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Chemotherapy plus bevacizumab as an optimal first-line therapeutic treatment for patients with right-sided metastatic colon cancer: a meta-analysis of first-line clinical trials

Xia-Hong You,[1] Yu-Huan Jiang,[2] Zhou Fang,[3] Fan Sun,[1] Yao Li,[3] Wei Wang,[3] Zi-Jin Xia,[3] Xiao-Zhong Wang,[1] Hou-Qun Ying [1,4]

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For numbered affiliations see end of article.

Correspondence to
Dr Hou-Qun Ying;
yinghouqun2013@163.com

ABSTRACT

Background Monoclonal antibodies of anti-epidermal growth factor receptor (EGFR) have been recommended as first-line therapy for patients with left-sided metastatic colorectal cancer (mCRC) with wild-type *RAS*. The effect of tumour laterality on antivascular endothelial growth factor antibody and how to optimise targeted therapies for the right-sided cases remain controversial.

Patients and methods A comprehensive meta-analysis enrolling 16 first-line clinical trials was performed to evaluate the efficacy of chemotherapy alone and chemotherapy plus targeted therapies for patients with mCRC with right primary tumour site, and we validated the results in metastatic setting (14 trials containing 4306 patients with unresectable mCRC).

Results Here, we found that progression-free survival (PFS) (combined HR 1.30, 95% CI 1.17 to 1.44) and overall survival (OS) (combined HR 1.46, 95% CI 1.32 to 1.62) of the right-sided patients were significantly inferior to the left-sided individuals receiving chemotherapy alone in overall population, regardless of race. Similar results were also observed in metastatic setting. OS of patients with left-sided mCRC receiving chemotherapy plus bevacizumab was superior to the right-sided individuals (combined median survival ratio (MSR)=1.23, 95% CI 1.08 to 1.39 for overall population; combined MSR=1.23, 95% CI 1.05 to 1.45 for metastatic setting), especially for wild-type *RAS* and mixed population. Moreover, the right-sided patients benefited more from chemotherapy plus bevacizumab comparing with chemotherapy alone in both overall population and metastatic setting. Importantly, the *RAS*-wild right-sided patients achieved longer PFS (combined HR 0.67, 95% CI 0.52 to 0.88) and OS (combined HR 0.74, 95% CI 0.56 to 0.98) from chemotherapy plus bevacizumab comparing with chemotherapy associated with anti-EGFR agents.

Conclusions Patients with right-sided mCRC show impaired chemosensitivity, and chemotherapy plus bevacizumab can be an optimal first-line therapeutic regimen for the *RAS*-wild patients with right-sided mCRC.

key questions

What is already known about this subject?

► Patients with left-sided metastatic colorectal cancer (mCRC) have superior survival than right-sided cases and the targeted drugs such as cetuximab and panitumumab have been proposed as first-line therapeutic defenses for the wild-type RAS patients with left-sided disease. But how to optimize targeted therapies for the right-sided cases remain unclear.

What does this study add?

► Here, we present results of the meta-analysis about the efficacy of chemotherapy alone and chemotherapy plus targeted therapies for mCRC patients with right-sidedness based on 16 first-line clinical trials. We found that overall survival of the right-sided patients was significantly inferior to the left-sided individuals receiving chemotherapy alone or chemotherapy plus bevacizumab. Importantly, The right-sided patients benefited more from chemotherapy plus bevacizumab comparing with chemotherapy alone or chemotherapy combined with anti-EGFR agents.

How might this impact on clinical practice?

► The results provide new evidence for clinical practice to precisely select optimal targeted therapeutic regimens for the patients with right-sided mCRC, and help to reduce medical costs and prolong the survival of those patients.

INTRODUCTION

Metastatic colorectal cancer (mCRC) is a refractory malignancy with remarkable heterogeneity,[1] and it accounts for approximately 40% of the newly diagnosed disease in clinic settings.[2] Although patients with the early-stage disease can receive radical resection and adjuvant chemotherapy, the majority of them frequently experience recurrence or distal metastasis after surgery. In regard to mCRC, palliative resection, radiochemotherapy, targeted therapy and immune checkpoint therapy are some of the clinical managements for these patients.[3 4] However,

responses of the patients to these treatments are variable. Moreover, inconsistent clinical benefits are also frequently dictated by their primary tumour sidedness.[4–6]

Studies suggest that patients with left-sided mCRC can benefit more from anti-epithelial growth factor receptor (EGFR) monocolonal antibodies (mAbs) compared with the right-sided cases.[7] Consequently, the targeted drugs such as cetuximab and panitumumab have been proposed as first-line therapeutic defenses for the wild-type *RAS* patients with left-sided disease.[8 9] Meanwhile, several clinical trials investigated the prognostic role of bevacizumab, the most commonly used antivascular endothelial growth factor (VEGF) mAb, in the treatment of patients with right-sided and left-sided mCRC.[10 11] Specifically, AGITG MAX and CALGB 80405 trials revealed no effect of tumour laterality on prognosis of the patients undergoing first-line chemotherapy plus bevacizumab.[7 12] In contrast, PROVETTA, AVF2107g and NO16966 trials identified improved outcome within bevacizumab-treated patients with left-sided mCRC compared with the right-sided cases.[5 13] Compared with the left-sided patients, favourable efficacy and prognosis were also observed in the right-sided patients with the treatment of first-line chemotherapy plus bevacizumab as reported in ITACa trial.[13] Overall, these trials highlighted an undergoing controversy regarding the efficacy and precise use of bevacizumab combined with chemotherapy. Importantly, there is no meta-analysis reported yet to evaluate the prognostic difference in patients with right-sided mCRC with first-line chemotherapy plus anti-EGFR mAbs or bevacizumab-based treatment.

Hence, a comprehensive meta-analysis with 16 first-line clinical trials was performed to investigate the effect of chemotherapy alone and chemotherapy plus either anti-EGFR mAbs or bevacizumab on prognosis of patients with right-sided mCRC, and to define which was more suitable as a first-line regimen for the patients.

PATIENTS AND METHODS

In the present study, we comprehensively screened and identified eligible studies to perform this meta-analysis in accordance with PRISMA guideline.[14] First of all, medical subject heading terms including "rectal, colon, colorectal"; "cancer, tumour, neoplasms or carcinoma"; "sided, sidedness, side, location, localization, site, right and left-side, laterality"; "prognosis, survival, outcome"; and "bevacizumab, cetuximab, panitumumab, EGFR, VEGF, anti-VEGF or EGFR" were selected to identify candidate articles by two independent investigators (X-HY and Y-HJ). The retrieval was conducted in the following databases: PubMed, Embase, Cochrane and ASCO meeting library as well as CNKI database (as of 15 March 2019). The actual retrieval strategy is described in online supplementary materials. Meanwhile, additional studies were also discovered by screening references of the relevant articles. Second, we identified relevant articles by reading the title of the candidate article, and those unrelated to any of the terms were excluded from the present study. Third, eligible studies were identified by careful examination of the abstract or the full text according to the following inclusion criteria: (1) clinical trial reported association between primary tumour location and survival of palliative patients with resected or unresectable mCRC with treatment of first-line chemotherapy or chemotherapy plus targeted agents; (2) the cancer arising from the appendix, caecum, ascending colon, hepatic flexure or transverse colon was classified as the right-sided disease, and the disease originating in splenic flexure, descending colon, sigmoid colon and rectum was defined as left-sided CRC; (3) each eligible study provided clinical baseline characteristics and outcome.

Two independent investigators (X-HY and ZF) extracted clinical baseline characteristics (name of clinical trial or the first author, study design, phase, country, race, recruitment time, *RAS* status, number of included patients with mCRC, palliative resection, therapeutic regimen and outcome), median progression-free survival (PFS) and overall survival (OS) or HR and 95% CI from each eligible study. All the relevant data were thoroughly checked by the third investigator (FS) who reread the full text.

Median survival ratio (MSR), HR and 95% CI were selected as the common measurements to assess the robust strength between tumour laterality and prognosis of patients with mCRC. Heterogeneity within the included studies was evaluated by Q test and estimated I^2, p_h <0.1 or I^2 >50% was recognised as indicative of substantial heterogeneity. Z test in fixed (p_h>0.1) or random (p_h<0.1) model was selected to investigate the combined effect. Sensitivity analysis was carried out to detect the robust result by stratified analysis and different pooled model. Publication bias within the included studies was evaluated by Egger's and Begg's test.[15 16] SPSS V.17.0 and Stata V.11.0 (Stata, College Station, TX, USA) software were used in all statistical analyses and p value <0.05 was considered as statistically significant.

RESULTS

The detailed search and selection procedure are depicted in figure 1. A total of 16 first-line trials,[5 7 17–24] including 4574 patients with mCRC, were ultimately fulfilled the inclusion criteria. The baseline characteristics within each eligible study are summarised in table 1. As shown in table 1, 4306 patients within 14 included trials were confirmed as unresectable mCRC cases, which composed the metastatic setting in our study. Eight trials with 3154 patients with mCRC[5 7 18 19 23 24] and 10 trials including 3247 patients with mCRC[5 7 17 20 22 25] reported the survival difference between the right-sided and left-sided patients receiving first-line chemotherapy alone and chemotherapy plus bevacizumab, respectively. Effects of bevacizumab within the left-sided and right-sided patients were examined in three trials.[5 17] Moreover, we also evaluated data of 273 patients with mCRC within three clinical

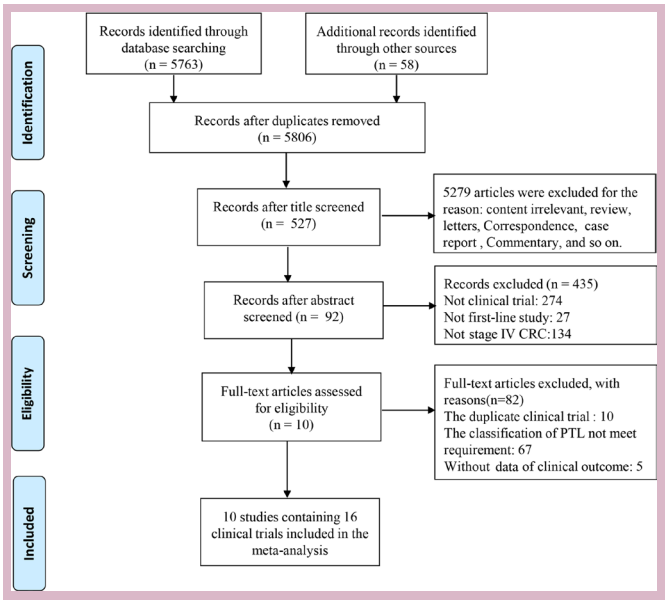

Figure 1 Selection procedure of eligible study in accordance with PRISMA guidelines. CRC, colorectal cancer; PTL, primary tumor location.

trials[7] to better understand the type of biological antibody that is more suitable for treatment of the right-sided RAS-wild patients.

The combined survival of patients with mCRC receiving first-line chemotherapy is described in figure 2 and online supplementary table 1. Prognosis of chemotherapy-treated right-sided patients was significantly worse than the left-sided cases (p_h=0.280, combined HR 1.30, 95% CI 1.17 to 1.44 for PFS; p_h=0.827, combined HR 1.46, 95% CI 1.32 to 1.62 for OS), regardless of race. A similar result was also observed in metastatic setting (p_h=0.567, combined HR 1.40, 95% CI 1.23 to 1.59 for PFS; p_h=0.661, combined HR 1.43, 95% CI 1.24 to 1.64 for OS). Stratifying according to *RAS* status, the right tumour origin was only significantly associated with poor OS (p_h=0.756, combined HR 1.32, 95% CI 1.02 to 1.72) in wild-type *RAS* subgroup.

In analysis of patients with mCRC treated with first-line chemotherapy plus bevacizumab, combined OS (p_h<0.001, combined MSR=1.23, 95% CI 1.08 to 1.39 for overall population; p_h<0.001, combined MSR=1.23, 95% CI 1.05 to 1.45 for metastatic setting) of the left-sided patients was obviously longer than the right-sided cases (figure 3), particularly in the *RAS*-wild individuals (p_h=0.169, combined MSR=1.11, 95% CI 1.01 to 1.21 for PFS; p_h=0.045, combined MSR=1.29, 95% CI 1.12 to 1.48 for OS) and mixed population (p_h=0.189, combined MSR=1.18, 95% CI 1.13 to 1.22 for PFS; p_h<0.001, combined MSR=1.29, 95% CI 1.10 to 1.51 for OS) (online supplementary table 2).

Next, we investigated the efficacy of the addition of bevacizumab to chemotherapy as compared with chemotherapy only or chemotherapy treatment plus anti-EGFR mAbs in patients with right-sided mCRC. In first-line chemotherapy plus bevacizumab-treated subgroup, PFS within the right-sided patients was obviously longer than those undergoing chemotherapy only (p_h=0.009, combined MSR=1.40, 95% CI 1.15 to 1.71 for overall population; p_h=0.369, combined MSR=1.57, 95% CI 1.39 to 1.77 for metastatic setting). Moreover, significantly improved OS was also observed in the right-sided patients (p_h=0.658, combined MSR=1.21, 95% CI 1.11 to 1.31 for overall population; p_h=0.363, combined MSR=1.20, 95% CI 1.06 to 1.36 for metastatic setting) (figure 4A and online supplementary table 3). Interestingly, the prognosis of *RAS*-wild right-sided patients receiving first-line chemotherapy plus bevacizumab was obviously superior to the patients undergoing chemotherapy plus anti-EGFR mAbs (p_h=0.552, combined HR 0.67, 95% CI 0.52 to 0.88 for PFS; p_h=0.966, combined HR 0.74, 95% CI 0.56 to 0.98 for OS) (figure 4B and online supplementary table 4).

In our study, the relative symmetric funnel plots were observed in prognostic comparisons of the right-sided and left-sided patients receiving chemotherapy or chemotherapy combined with bevacizumab; p values of Egger's and Begg's tests were greater than 0.05 in each comparison (online supplementary figure 1).

DISCUSSION

Studies demonstrate a lack of consensus regarding to which kind of biological antibody is more effective to improve prognosis of patients with right-sided mCRC.[22 26] In the present study, we specifically observed that survival of the right-sided patients was inferior to the left-sided individuals with first-line chemotherapy alone or chemotherapy plus bevacizumab, respectively. Whereas, the right-sided patients could benefit significantly from first-line chemotherapy plus bevacizumab, and also achieved strikingly improved prognosis from first-line chemotherapy plus bevacizumab in comparison with combined therapeutic regimen of chemotherapy and anti-EGFR mAbs.

Over the recent decade, targeted therapy has been emerging as an optimal therapeutic option for the treatment of patients with refractory mCRC.[27 28] Notably, clinical responses to treatments with anti-EGFR and VEGF mAbs are inconsistent across patients with different primary tumour locations.[29 30] In the current study, we found that the outcome of patients with left-sided mCRC was superior to the right-sided patients who received first-line chemotherapy with or without bevacizumab. The results revealed that primary tumour sidedness was linked to the efficacy of chemotherapy. Right-sided mCRC might induce impaired sensitivity to common chemotherapy, leading to different benefits from first-line chemotherapy between the right-sided and left-sided cases. The finding was consistent with our previous study.[31] A recent study by Loupakis and his coworkers reported that the right-sided and left-sided patients could significantly benefit from the treatment of chemotherapy plus bevacizumab, especially in the left-sided cases.[13] In our study, remarkable PFS and OS improvements were also observed in the

Table 1 Characteristics of 16 eligible first-line trials included in the meta-analysis

Clinical trials	Design	Phase	Race	Recruitment time	*RAS* status	Palliative resection	Therapeutic regimen	Total	Left	Right	Outcome
Negri *et al*[24]	Prospective RCT	NA	Caucasian	1992–1998	NA	No	5-FU*†	135	96	39	OS
FFCD[23]	Prospective RCT	III	Caucasian	1997–2001	NA	No	LV5FU2*†	172	110	62	OS, PFS
ITACa[17]	Prospective RCT	III	Caucasian	2007–2013	NA	No	FOLFOX4, FOLFIRI+BEV†‡§	122	71	51	OS, PFS
PROVETTA[5]	Prospective RCT	NA	Mixed	NA	NA	No	CT+BEV‡	200	144	56	OS, PFS
AVF2107g[5]	Retrospective RCT	III	Mixed	2000–2002	NA	No	CT, CT+BEV*	559	353	206	OS, PFS
FIRE1[18]	Retrospective RCT	III	Caucasian	2000–2004	NA	No	FuFIRI/mIROX*†	423	341	82	OS, PFS
NO16966[5]	Retrospective RCT	III	Mixed	2004–2005	NA	No	CT, CT+BEV*	1268	935	333	OS, PFS
CRYSTAL[7]	Retrospective RCT	III	Caucasian	2004–2005	*RAS* WT	No	FOLFIRI*†	189	138	51	OS, PFS
PRIME[7]	Retrospective RCT	III	Mixed	2006–2008	*RAS* WT	No	FOLFOX4*†	208	159	49	OS, PFS
PEAK[7]	Retrospective RCT	II	Caucasian	2009–2011	*RAS* WT	NA	FOLFOX6+BEV, FOLFOX6+Pani‡¶	68	54	14	OS, PFS
FIRE 3[7]	Retrospective RCT	III	Caucasian	2007–2012	*RAS* WT	No	FOLFIRI+BEV, FOLFIRI+CET‡	199	149	50	OS, PFS
CALGB 80405[7]	Retrospective RCT	III	Mixed	2005–2012	*RAS* WT	No	FOLFIRI/FOLFOX6+BEV, FOLFIRI/FOLFOX6+CET†‡¶	230	152	78	OS, PFS
DREAM[20]	Retrospective RCT	III	Caucasian	2005–2012	*RAS* WT mutation	No	CT+BEV†‡	172	124	48	OS
MAVERICC[21]	Retrospective RCT	II	Mixed	2011–2015	NA	No	mFOLFOX6/FOLFIRI+BEV†‡	376	212	154	OS, PFS
NCT01311050[22]	Prospective trial	I–II	Asian	2009–2011	NA	No	XELOXIRI+BEV‡	53	42	11	OS, PFS
NCT01282658[19]	Prospective trial	NA	Asian	2010–2014	NA	NA	FOLFIRI*	200	NA	NA	OS

*Enrolled into the subgroup analysis (right-sided vs left-sided) in patients with mCRC with only chemotherapy treatment.
†Enrolled into the metastatic setting.
‡Enrolled into the subgroup analysis (right-sided vs left-sided) in patients with mCRC with chemotherapy plus bevacizumab treatment.
§Enrolled into the subgroup analysis (CT+BEV vs CT) in patients with right-sided mCRC.
¶Enrolled into the subgroup analysis (CT+BEV vs CT+anti-EGFR) in patients with right-sided mCRC.
BEV, bevacizumab; CET, cetuximab; CT, chemotherapy; FOLFIRI/FuFIRI, fluorouracil, leucovorin and irinotecan; FOLFOX, fluorouracil, leucovorin and oxaliplatin; FU, fluorouracil; LV, leucovorin;mCRC, metastatic colorectal cancer; mIROX, irinotecan and oxaliplatin; NA, not available; OS, overall survival; Pani, panitumumab; PFS, progression-free survival;RCT, randomised controlled trial; RAS/BRAF WT, RAS/BRAF wild-type; XELOXIRI, capecitabine, oxaliplatin and irinotecan.

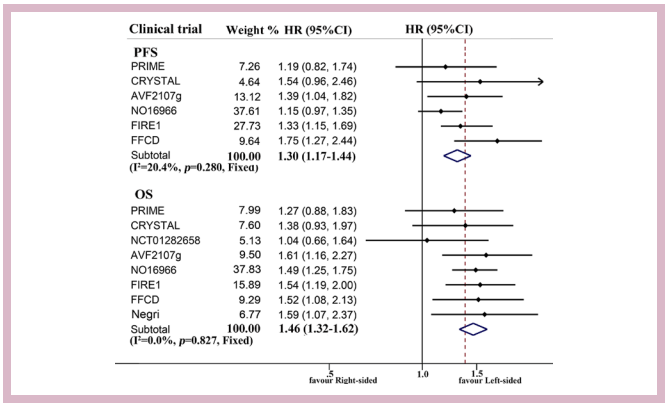

Figure 2 Forest plots of survival comparison between individuals with right-sided and left-sided metastatic colorectal cancer receiving first-line chemotherapy (right vs left). OS, overall survival; PFS, progression-free survival.

right-sided patients with treatment of first-line chemotherapy plus bevacizumab comparing with chemotherapy only. Moreover, we found that prognosis of patients with left-sided mCRC was superior to the right-sided patients receiving chemotherapy plus bevacizumab. These results suggest that bevacizumab improves the prognosis of patients with mCRC; however, impaired chemosensitivity restricts the survival benefit from bevacizumab plus chemotherapy, resulting in poor prognosis in the right-sided mCRC cases. The latest meta-analysis performed by Holch and his coworkers identified significant survival benefit from anti-EGFR mAbs compared with bevacizumab when added to standard chemotherapy in *RAS*-wild patients with left-sided mCRC.[32] Interestingly, the drastically improved prognosis was examined in patients with right-sided mCRC receiving first-line chemotherapy plus bevacizumab comparing with the patients undergoing chemotherapy plus anti-EGFR mAbs in our study.

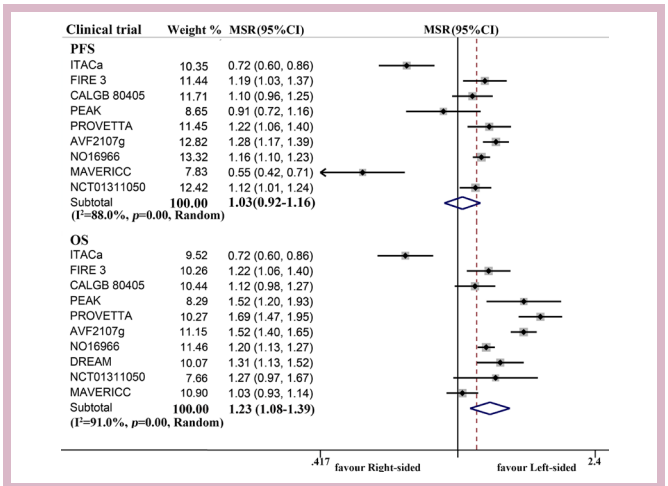

Figure 3 Forest plots of survival comparison between individuals with right-sided and left-sided metastatic colorectal cancer receiving first-line chemotherapy plus bevacizumab (left vs right). MSR, median survival ratio; OS, overall survival; PFS, progression-free survival.

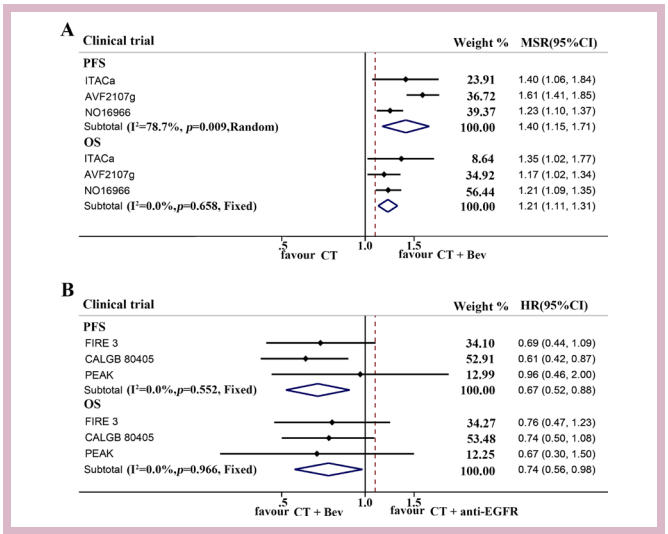

Figure 4 Forest plots of survival comparison in patients with right-sided metastatic colorectal cancer receiving first-line chemotherapy or chemotherapy plus targeted mAbs. (A) Chemotherapy (CT) vs chemotherapy plus bevacizumab (CT+Bev) in the right-sided patients. (B) Adjuvant chemotherapy plus bevacizumab (CT+Bev) vs adjuvant chemotherapy plus anti-EGFR antibody (CT+anti EGFR) in *RAS*-wild right-sided patients. EGFR, epithelial growth factor receptor; mAbs, monoclonal antibodies; MSR, median survival ratio; OS, overall survival; PFS, progression-free survival.

It indicates that first-line chemotherapy combined with bevacizumab is an optimal clinical treatment of patients with right-sided mCRC to achieve a satisfactory prognosis.

Tumour laterality is one of the most debated topics in treatment of CRC.[6 33 34] There is significant heterogeneity in genetic alteration and tumour microecology in right-sided and left-sided cancer.[35 36] High CpG island methylator phenotype and microsatellite instability as well as hypermutation within DNA mismatch repair (MMR), MAPK, TGF-β and insulin signalling pathways are prevalent in the right-sided disease compared with its counterpart.[22 37–39] The MMR-deficient status impairs genomic stability, leading to carcinogenesis, chemoresistance and progression of the disease.[40 41] Meanwhile, chromosome instability, mutations of *APC*, *SMAD4* and *P53* as well as *EGFR* amplification are frequently detected within the left-sided CRC,[42 43] while the low instability of genome-wide copy number alterations within right-sided mCRC confers no additional benefit from bevacizumab, resulting in drug resistance.[44] Moreover, relatively abundant *Prevotella*, *Pyramido-bacterium*, *Selenomonas* and *Peptostreptococcus* with low infiltration of activated CD8+ T cell and T helper type 1 cell as well as high infiltration of neutrophils and regulatory T cells are commonly observed in the right-sided disease.[45 46] Combination of the environmental factors cross-talk with the cancer cell to release various cytokines such as IL-6, CXCL8 and MIP-1α, creating excessive inflammatory microenvironment in the right-sided disease.[47] Our previous study also

identified severe inflammation in the right-sided mCRC, and severe inflammation was also linked with resistance to chemotherapy, leading to poor clinical response and prognosis.[31] In addition, VEGF expression is relatively high in the left-sided cancer comparing with the right-sided disease.[48 49] The right-sided patients often present with inactive EGFR pathway and low expressions of EGFR endogenous ligands such as epiregulin and amphiregulin,[42] resulting in resistance to EGFR inhibition in these patients.[50] These differences can likely explain the survival differences between the right-sided and left-sided patient receiving the same therapeutic regimen. Specifically, we come closer to understanding why the prognosis of the bevacizumab-treated right-sided patients is superior to the patients receiving anti-EGFR mAbs-based therapy.

This work, to the best of our knowledge, is the first comprehensively designed study examining clinical responses and survival differences in the right-sided patients treated with chemotherapy or chemotherapy plus biological antibodies. Moreover, our work first provides the evidence illustrating first-line bevacizumab-based treatment, instead of chemotherapy plus anti-EGFR mAbs, is likely more suitable for patients with right-sided mCRC. Only the first-line clinical trials were examined in our study, so as to arrive at accurate and robust conclusions.

The following limitations should be addressed to fully understand the findings in our study. The sample size of enrolled studies relating to comparison of the two kinds of biological therapies was small; our findings should be validated by large sample size and multicentre clinical trials. It is also important to emphasise that the majority of examined studies are from Caucasian population. and we do not know the role of primary tumour sidedness in Asian population, especially in Chinese. Finally, there was only one eligible study concerning *RAS*-mutated population, so we could not specifically examine the prognostic difference in *RAS*-mutated patients with right-sided and left-sided mCRC.

In summary, right tumour sidedness confers impaired sensitivity to chemotherapy, and chemotherapy plus bevacizumab can be selected as an optimal first-line therapeutic regimen for the treatment of *RAS*-wild patients with right-sided mCRC. The results provide new evidence for clinical practice to precisely select optimal targeted therapeutic regimens for patients with right-sided mCRC and also help to reduce medical costs and prolong the survival of those patients. Further studies are warranted to validate the findings in Asian population and to explore effective biomarkers to predict the prognosis of the patients.

Author affiliations
[1]Department of Clinical Laboratory, Jiangxi Province Key Laboratory of Laboratory Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[2]Department of Clinical Laboratory, First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
[3]Department of Laboratory Medicine, Nanchang University Medical College, Nanchang, Jiangxi, China
[4]Department of Nuclear Medicine, Jiangxi Province Key Laboratory of Laboratory Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Contributors X-HY screened and selected the eligible study in the meta-analysis, and performed all the statistics. Y-HJ and ZF contributed to select and identify the eligible study, and extract the data of enrolled studies. FS, YL and Z-JX contributed to data extraction. X-ZW contributed to examining the data. H-QY provided the idea, established the study design, and revised and approved the manuscript.

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ORCID iD
Hou-Qun Ying http://orcid.org/0000-0003-3858-4761

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