Is there an efficacy-effectiveness gap between randomized controlled trials and real-world studies in colorectal cancer: a systematic review and meta-analysis

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Background: To investigate whether patients with colorectal cancer (CRC) enrolled in randomized controlled trials (RCTs) and real-world studies (RWS) differ in terms of baseline characteristics, leading to an efficacy-effectiveness gap.

Methods: A systematic literature reviews was conducted to identify RCTs and RWS with CRC, treated with bevacizumab (BEV), cetuximab (CET) or oxaliplatin combined with capecitabine (XELOX). Using random-effects meta-analyses compared the baseline characteristics and treatment effects of RCTs and RWS, overall and by drug. Correlation between treatment effects and baseline characteristics and study types were estimated using meta-regression analyses.

Results: Two hundred and fifty-three studies were included. Compared with patients enrolled in RWS, the proportion of male patients in RCTs was 0.032 higher (P=0.004), the proportion of patients with Eastern Cooperative Oncology Group (ECOG) performance ≥2 was 0.085 less (P<0.001). No significant differences in treatment effects [progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR)] were found by overall analysis. But the OS of patients in RCTs was 4.184 higher (P=0.023) in the CET group. Meta-regression results showed that OS difference in the CET group was related to the difference in treatment lines, not related to other baseline characteristics and study types.

Conclusions: No efficacy-effectiveness gap was found in CRC between RCTs and RWS. CRC treatment effects Between RCTs and RWS had high consistency.

Keywords: Efficacy-effectiveness gap; randomized controlled trials (RCTs); real-world studies (RWS); colorectal cancer (CRC)

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Introduction

In the process of developing clinical diagnosis and treatment guidelines and healthcare policy, it is essential to obtain valid clinical trial evidence, in which randomized controlled trials (RCTs) are recognized as the gold standard for evaluating interventions (1). In most countries, such as the United Kingdom, Canada, and South Korea, the development of health decision-making and clinical practice guidelines are based on research-based RCTs (2). With the increasingly complicated situation and high cost of cancer treatment, the conducting clinical trials in cancer are facing more challenges. People have begun to realize that RCTs do not match the real-world environment and lack external validity, due to moderately and highly standardized trial
designs, strict patient inclusion and exclusion criteria, and short follow-up time (3). Unlike RCTs, real-world studies (RWS) are a type of research that reflects the actual clinical diagnosis and treatment process, based on the real-world data. Principles of its research design are mainly non-randomization, non-intervention, and openness, which are closer to the actual clinical treatment environment and have higher external validity. RWS have received an increasing amount of attention, since the United States Congress passed the 21st Century Cures Act in 2016, which made it clear that the FDA could use real-world data as evidence of approval for post-marketing research and new indications for medical devices and drugs, where appropriate. In 2018, the FDA announced Real-World Evidence Program, which presents a detailed standard for evaluating the quality of real-world evidence. Recently, the FDA approved a new indication for Pfizer’s Ibrance based on the real-world data, Oxaliplatin combined with capecitabine (XELOX), and targeted drugs [e.g., cetuximab (CET), bevacizumab (BEV)] combined with chemotherapy should be used as effective first- and second-line treatments for chemotherapy-resistant patients with metastatic CRC according to NCCN Clinical practice guidelines in oncology (version 1.2017) (19) and The Chinese Diagnosis and Treatment Specification of Colorectal Cancer (2017 edition) (20). Therefore, this study selected XELOX, CET monotherapy or combined chemotherapy, BEV monotherapy or combined chemotherapy as the therapeutic regimens.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2303).

## Methods

### Literature search strategy

We searched Medline and Embase to find relevant articles published from 20 September 2009 to 20 September 2019 in English using the main search terms “bevacizumab”, “cetuximab”, “XELOX” and “colorectal cancer”. Considering the incomplete development of real-world research methods, the database search was limited to last 10 years of research. In addition, references for secondary research were manually retrieved to supplement the original research literature. Specific search strategies show in Table 1.

### Study selection

Titles and abstracts of all retrieved literature were imported into the NoteExpress V3.2.0. The repeat literature was

| No. | Search strategy |
|-----|----------------|
| 1   | (colorectal cancer or CRC or Colorectal carcinoma or Colorectal neoplasms),ti,ab,ot,hw,rn. |
| 2   | (Cetuxim* or Erbitux),ti,ab,ot,hw,m. |
| 3   | (Bevacizum$b or CAPOX-B),ti,ab,ot,hw,rn. |
| 4   | (Oxaliplatin or L-OHP or OXA),ti,ab,ot,hw,m. |
| 5   | (capecitabine or Xeloda or ECX),ti,ab,ot,hw,rn. |
| 6   | 4 and 5 |
| 7   | XELOX or CapeOX.ti,ab,ot,hw,rn. |
| 8   | Or/6-7 |
| 9   | Or/2,3,8 |
| 10  | 1 and 9 |
| 11  | limit 10 to yr="2009-current" |
removed. Two reviewers (XZ and SF) independently performed the study selection, including screening titles and abstracts, and evaluating full-text eligibility of potentially eligible studies. Discussion or negotiation with a third party was implemented if there were divergences. If necessary, we contacted the original authors by email or phone to obtain unidentified information.

Included studies need to meet the following criteria: (I) studies that enrolled patients with CRC treated with BEV, CET or XELOX; (II) studies that reported on at least one of the following clinical outcomes: (i) primary outcomes: progression-free survival (PFS), overall survival (OS); (ii) secondary outcomes: response rate (RR) including disease control rate (DCR), objective response rate (ORR), complete response rate (CR), partial response rate (PR), and stable disease (SD) based on the measurement of cancer antigen 125 levels confirmed by radiological examination results or by combined Gynecologic Cancer InterGroup criteria.

Studies not meeting the inclusion criteria were excluded. Other exclusion criteria were: (I) studies in which BEV, CET or XELOX was used as neoadjuvant treatments; (II) studies with a sample size of less than 30; (III) non-English studies.

Data extraction

Data from each included paper were extracted into a standardized spreadsheet developed for this project by two reviewers independently with adjudication by a third reviewer: study characteristics (e.g., title, author, publication year, study design, country, study horizon, follow-up time, trial name, and registration number); treatments (e.g., drug, dose, frequency, and cycle); patient characteristics (e.g., sample size, age, gender, Eastern Cooperative Oncology Group (ECOG), treatment line, tumor location, and transfer); treatment effects (e.g., PFS, OS, RR, DCR, ORR, CR, PR, and SD). We extracted frequency number and percentages. All patients included in the study were fully enrolled in the primary studies, and nowitching over treatment or treatment discontinuation.

Data synthesis and statistical analysis

Data on patient baseline characteristics (age, proportions of male, proportion of patients with ECOG ≥2, proportion of patients with second-line and above second-line treatment) and treatment effects (PFS, OS, ORR, DCR) were finally analyzed. The ORR = CR + PR and DCR = ORR + SD were used to process the tumor response results. The methods described by Wan et al. (21) were used to convert the mean and range of continuous variables such as age, PFS, and OS into mean and standard deviation, whereas the other variables were presented as ratios. We first combine the baseline characteristics and treatment effects of CRC patients in RCTs and RWS using random-effect meta-analyses, and subsequently to compare the difference of the combined results.

We used meta-regression analyses to assess the heterogeneity by including the baseline characteristics as covariates, the study design as a dichotomous covariate, and treatment effects as dependent variables. We used restricted maximum-likelihood estimation to assess between-study variance (tau-squared) and applied the Knapp-Hartung adjustment (22).

Considering the follow-up time, treatment cycle and duration would have a major impact on the treatment effects, a comparative analysis of follow up time, treatment cycle and duration between RCT and RWS was added. All analyses were done in the Stata SE15.

Results

Characteristics of included studies

We identified 6,147 records through database searching, and 2 potentially eligible studies through other sources. After duplicate checking and title and abstract screening, 369 full-text articles assessed for eligibility. Finally, 369 full-text articles assessed for eligibility. Finally, 201 articles were eventually included: 117 RCTs including 94 phase II clinical trials, 6 phase III clinical trials, and 17 unknown phase clinical trials; 84 RWS including 36 case series, 13 registry, 20 cohort, and 15 unknown category of studies. There were 102 studies on BEV treatment, 54 studies on CET treatment, and 45 studies on XELOX treatment. A total of 37,479 patients were included, with 13,889 patients in RCTs and 23,590 patients in RWS. The process and results of article selection show in Figure 1. The main characteristics of all studies show in Tables 2,3.

Comparison of patient characteristics

Compared with patients enrolled in RWS, the proportion of male patients in RCTs was 0.032 higher (0.613, 0.598 to 0.628 vs. 0.581, 0.565 to 0.597; P=0.004), the proportion of patients with ECOG ≥2 was 0.085 less (0.005, 0.003 to 0.006 vs. 0.090, 0.078 to 0.103; P<0.001). No significant
differences in age and treatment line were found (Figure 2).

Subgroup analysis by drug showed that differences generally were in the same direction for the three drugs: the proportion of male patients in RCTs was 0.060 higher than those in RWS (0.622, 0.580 to 0.664 vs. 0.562, 0.524 to 0.600; P=0.038) in the XELOX group; the proportion of patients with ECOG ≥2 in RCTs was 0.075 less than those in RWS (0.006, 0.003 to 0.008 vs. 0.081, 0.065 to 0.98; P<0.001) in the BEV group, and similar results was also found in the CET group [0.175 less than those in RWS (0.006, 0.003 to 0.009 vs. 0.181, 0.118 to 0.245; P<0.001)]. Furthermore, patients in RCTs were 1.304 years older than those in RWS (59.205, 58.520 to 59.890 vs. 57.901, 56.839 to 58.963; P=0.043) in the BEV group; the proportion of patients with second-line and above second-line treatment in RCTs was 0.350 lower than those in RWS (0.281, 0.136 to 0.427 vs. 0.631, 0.403 to 0860; P=0.012) in the CET group (Figure 2). More detailed results show in Table S1 and Figures S1−S8.

Comparison of treatment effects

Primary outcomes

No significant differences were found in OS and PFS between RCTs and RWS by overall analysis. The results of subgroup analysis by drug were mostly consistent with the overall analysis, no significant differences were found in the BEV group and XELOX group, but patients in the CET group of RCTs had an OS of 4.184 months higher than that of patients in the CET group of RWS (17.432 months, 15.118 to 19.745 vs. 13.248, 11.281 to 15.215; P=0.023) (Figure 3).
Table 2 Baseline characteristics of RCTs

| No. | Reference          | Year | Study phase | Country/region | Sample size | Drug | Characteristics | Outcomes | Registration number   |
|-----|--------------------|------|-------------|----------------|-------------|------|-----------------|----------|-----------------------|
| 1   | Kim et al. (23)    | 2019 | Phrase II   | Korea          | 60          | BEV  | 1,2,3,4         | 5,7,8    | NCT02026583           |
| 2   | Cremolini et al. (24) | 2019 | Phrase II   | Italy          | 117         | BEV  | 1,2,4           | 5,7,8    | NCT02271464           |
| 3   | Suzuki et al. (25) | 2019 | Phrase II   | Japan          | 51          | BEV  | 1,2,3,4         | 6,8      | UMIN000009280         |
| 4   | Nakayama et al. (26) | 2018 | Phrase II   | Japan          | 54          | BEV  | 1,2,4           | 5,6,7,8  | UMIN000006478         |
| 5   | Oki et al. (27)    | 2018 | Phrase II   | Japan          | 69          | BEV  | 1,2,3,4         | 5,6,7    |                      |
| 6   | Jonker et al. (28) | 2018 | Phrase I/II | Canada         | 51          | BEV  | 1,2,3,4         | 8        | NA                    |
| 7   | Satake et al. (29) | 2018 | Phrase II   | Japan          | 62          | BEV  | 1,2,3,4         | 5,6,7    | NA                    |
| 8   | Matsuda et al. (30) | 2018 | Phrase II   | Japan          | 51          | BEV  | 1,2,3,4         | 5,6,8    | NA                    |
| 9   | Ulivi et al. (31)  | 2018 | Phrase I/II | Italy          | 65          | BEV  | 1,2,4           | 5,7,8    | NA                    |
| 10  | Venook et al. (32) | 2017 | NA          | USA            | 559         | BEV  | 1,2,3,4         | 5,8      | NCT00265850           |
| 11  | Nakayama et al. (33) | 2017 | Phrase II   | Japan          | 52          | BEV  | 1,2,3,4         | 5         | UMIN000006478         |
| 12  | Apsangikar et al. (34) | 2017 | NA          | India          | 33          | BEV  | 1,2,3,4         | 5,8      | NA                    |
| 13  | Zhao et al. (35)   | 2017 | Phrase II   | China          | 122         | BEV  | 1,2,3,4         | 5,8      | NA                    |
| 14  | Baba et al. (36)   | 2017 | Phrase I/II | Japan          | 256         | BEV  | 1,2,3,4         | 4,7,8    | NA                    |
| 15  | Matsui et al. (37) | 2016 | Phrase II   | Japan          | 51          | BEV  | 1,2,3,4         | 5,7      | NA                    |
| 16  | Ogata et al. (38)  | 2016 | NA          | Japan          | 47          | BEV  | 1,2,3,4         | 5,6,7    | NA                    |
| 17  | Yamazaki et al. (39) | 2016 | Phrase I/II | Japan          | 197         | BEV  | 1,2,3,4         | 8        | UMIN000001396         |
| 18  | van Hazel et al. (40) | 2016 | Phrase I/II | Australia      | 263         | BEV  | 1,2,3,4         | 5         | NA                    |
| 19  | Stintzing et al. (41) | 2016 | Phrase I/II | Germany        | 201         | BEV  | 1,2,3,4         | 5,7,8    | NA                    |
| 20  | Shitara et al. (42) | 2016 | Phrase II   | Japan          | 58          | BEV  | 1,2,3,4         | 8        | NA                    |
| 21  | Hagman et al. (43) | 2016 | NA          | Sweden         | 35          | BEV  | 1,2,3,4         | 8        | NCT01229813           |
| 22  | Benson et al. (44) | 2016 | Phrase II   | USA            | 88          | BEV  | 1,2,3,4         | 5        | NCT01478594           |
| 23  | Shimomura et al. (45) | 2016 | Phrase II   | Japan          | 55          | BEV  | 1,2,3,4         | 5,6,7,8  | NA                    |
| 24  | Passardi et al. (46) | 2015 | Phrase I/II | Italy          | 176         | BEV  | 1,2,4           | 5,7,8    | NCT01878422           |
| 25  | Antonuzzo et al. (47) | 2015 | Phrase I/II | Italy          | 197         | BEV  | 1,2,3,4         | 5,7,8    | NCT00577031           |
| 26  | Iwamoto et al. (48) | 2015 | Phrase I/II | Japan          | 181         | BEV  | 1,2,3,4         | –        | UMIN000002557         |
| 27  | Hegewisch et al. (49) | 2015 | Phrase I/II | Germany        | 158         | BEV  | 1,2,3,4         | 8        | NCT00973609           |
| 28  | Masi et al. (50)   | 2015 | Phrase I/II | Italy          | 92          | BEV  | 1,2,3,4         | 5,6,8    | NCT00720512           |
| 29  | Cao et al. (51)    | 2015 | Phrase II   | China          | 65          | BEV  | 1,2,4           | 5,6,8    | NA                    |
| 30  | Wang et al. (52)   | 2015 | NA          | China          | 114         | BEV  | 1,2,3,4         | 5,6,8    | NA                    |
| 31  | Garcia et al. (53) | 2015 | Phrase II   | Spain          | 77          | BEV  | 1,2,3,4         | 5,6,7,8  | NCT00875771           |
| 32  | Liu et al. (54)    | 2015 | Phrase II   | China          | 30          | BEV  | 1,2,3,4         | 5,8      | NA                    |
| 33  | Nakayama et al. (55) | 2015 | Phrase II   | Japan          | 40          | BEV  | 1,2,3,4         | 5,6,7,8  | UMIN000001127         |
| 34  | Heinemann et al. (56) | 2014 | Phrase I/II | Germany        | 295         | BEV  | 1,2,3,4         | 5,7,8    | NCT00433927           |
Table 2 (continued)

| No. | Reference                  | Year | Study phase     | Country/region | Sample size | Drug | Characteristics | Outcomes | Registration number |
|-----|----------------------------|------|-----------------|----------------|-------------|------|-----------------|----------|---------------------|
| 35  | Duran et al. (57)          | 2014 | NA              | Turkey         | 298         | BEV  | 2,3,4           | 5,7,8    | NA                  |
| 36  | O’Neil et al. (58)         | 2014 | Phrase II       | USA            | 49          | BEV  | 1,2,3,4         | 5        | NA                  |
| 37  | Uygun et al. (59)          | 2013 | NA              | Japan          | 64          | BEV  | 1,2,3,4         | 5,8      | NA                  |
| 38  | Schmiegel et al. (60)      | 2013 | Phrase II       | Germany        | 127         | BEV  | 1,2,3,4         | 7,8      | NA                  |
| 39  | Kochi et al. (61)          | 2013 | Phrase II       | Japan          | 39          | BEV  | 1,2,3,4         | 5,6,7    | NA                  |
| 40  | Bennouna et al. (62)       | 2013 | Phrase I/II     | France         | 409         | BEV  | 1,2,3,4         | 5,8      | NCT00700102         |
| 41  | Ducreuex et al. (63)       | 2013 | Phrase II       | France         | 72          | BEV  | 1,2,3,4         | 5,7,8    | NA                  |
| 42  | Cunningham et al. (64)     | 2013 | NA              | UK             | 66          | BEV  | 2,3,4           | 5,8      | NA                  |
| 43  | Yalcin et al. (65)         | 2013 | Phrase I/II     | Turkey         | 62          | BEV  | 1,2,3,4         | 5,7,8    | NA                  |
| 44  | Johnsson et al. (66)       | 2013 | Phrase I/II     | Sweden         | 80          | BEV  | 1,2,3,4         | 8        | NCT00598156         |
| 45  | Hong et al. (67)           | 2013 | Phrase II       | Korea          | 57          | BEV  | 1,2,3,4         | 5,8      | NA                  |
| 46  | Stintzing et al. (68)      | 2012 | NA              | Germany        | 46          | BEV  | 1,2,3,4         | 5,6,7,8  | NCT00433927         |
| 47  | Pectasides et al. (69)     | 2012 | Phrase I/II     | Australia, New Zealand | 143 | BEV  | 1,2,3,4         | 5,7,8    | NA                  |
| 48  | Diaz-Rubio et al. (70)     | 2012 | Phrase I/II     | Spain          | 241         | BEV  | 1,2,3,4         | 5,7,8    | NA                  |
| 49  | Hurwitz et al. (71)        | 2012 | Phrase II       | USA            | 217         | BEV  | 2,3,4           | 5,8      | NCT00159432         |
| 50  | Renouf et al. (72)         | 2012 | Phrase II       | Canada         | 50          | BEV  | 1,2,3           | 5,6      | NA                  |
| 51  | Wolff et al. (73)          | 2012 | Phrase II       | USA            | 58          | BEV  | 1,2,3,4         |          | NA                  |
| 52  | Tang et al. (74)           | 2012 | Phrase II       | NA             | 51          | BEV  | 1,2,3           | 8        | NA                  |
| 53  | Yamada et al. (75)         | 2012 | Phrase II       | Japan          | 51          | BEV  | 1,2,3           | 5,6      | NA                  |
| 54  | Wong et al. (76)           | 2011 | Phrase I/II     | NA             | 31          | BEV  | 2               |          | NA                  |
| 55  | Guan et al. (77)           | 2011 | Phrase I/II     | China          | 139         | BEV  | 1,2,3,4         | 5,7,8    | NCT00642577         |
| 56  | Altmare et al. (78)        | 2011 | Phrase II       | USA            | 50          | BEV  | 1,2,4           | 8        | NCT00597506         |
| 57  | Kopetz et al. (79)         | 2010 | Phrase II       | USA            | 43          | BEV  | 1,2,4           | 5,8      | NA                  |
| 58  | Bruera et al. (80)         | 2010 | Phrase II       | NA             | 50          | BEV  | 1,2,4           | 5,8      | NA                  |
| 59  | Masi et al. (81)           | 2010 | Phrase II       | Italy          | 57          | BEV  | 1,2,3,4         | 5,6,7,8  | NCT01163396         |
| 60  | Tebbutt et al. (82)        | 2010 | Phrase I/II     | Australia, New Zealand | 157 | BEV  | 1,2,3,4         | 5,7,8    | NA                  |
| 61  | Aranda et al. (83)         | 2018 | Phrase II       | NA             | 129         | CET  | 1,2,3,4         | 7        | NA                  |
| 62  | Kotake et al. (84)         | 2017 | Phrase II       | Japan          | 60          | CET  | 1,2,3,4         | 5,6,7    | NA                  |
| 63  | Kataoka et al. (85)        | 2017 | Phrase II       | Japan          | 32          | CET  | 2,3,4           | 5,6      | NA                  |
| 64  | Stintzing et al. (41)      | 2016 | Phrase I/II     | NA             | 199         | CET  | 2,3             | 5,8      | NA                  |
| 65  | Hazama et al. (86)         | 2016 | Phrase II       | Japan          | 40          | CET  | 1,2,3,4         | 5,6,7,8  | NA                  |
| 66  | Bowles et al. (87)         | 2016 | Phrase II       | NA             | 43          | CET  | 1,2,3           | 5,6,8    | NA                  |
| 67  | Ciardiello et al. (88)     | 2016 | Phrase II       | Italy          | 74          | CET  | 1,2,4           | 5,6,8    | NA                  |
| No. | Reference          | Year | Study phase | Country/region | Sample size | Drug | Characteristics | Outcomes | Registration number |
|-----|--------------------|------|-------------|----------------|-------------|------|----------------|----------|-------------------|
| 68  | Eng et al. (89)    | 2016 | Phrase II   | NA             | 60          | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 69  | Soda et al. (90)   | 2015 | Phrase II   | Japan          | 62          | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 70  | Sclafani et al. (91)| 2015 | Phrase I/II | UK             | 119         | CET  | 2,3,4          | 5,6      | NA                |
| 71  | Do et al. (92)     | 2015 | Phrase II   | USA            | 30          | CET  | 1,2,4          | 5,7      | NA                |
| 72  | Élez et al. (93)   | 2015 | NA          | NA             | 72          | CET  | 1,2,3          | 5,8      | NA                |
| 73  | Fernandez et al. (94)| 2014 | Phrase II   | Spain          | 99          | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 74  | Heinemann et al. (56)| 2014 | Phrase I/II | Germany        | 297         | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 75  | Iwamoto et al. (95) | 2014 | Phrase II   | Japan          | 60          | CET  | 1,2,3,4        | 5,6,8    | NA                |
| 76  | Douillard et al. (96)| 2014 | Phrase II   | USA            | 150         | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 77  | Ye et al. (97)     | 2014 | Phrase II   | NA             | 70          | CET  | 1,2,3          | 5,6,8    | NA                |
| 78  | Siu et al. (98)    | 2013 | NA          | China          | 374         | CET  | 1,2,3          | 5,6,8    | NA                |
| 79  | Brodowicz et al. (99)| 2013 | NA          | NA             | 75          | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 80  | Hong et al. (100)  | 2013 | NA          | NA             | 40          | CET  | 1,2,3,4        | 5,6,8    | NA                |
| 81  | Assenat et al. (101)| 2011 | Phrase II   | France         | 42          | CET  | 1,2,3,4        | 5,6,7    | NA                |
| 82  | Kullmann et al. (102)| 2011 | Phrase II   | NA             | 62          | CET  | 1,2,4          | 5,6,7,8  | NA                |
| 83  | Lim et al. (103)   | 2011 | Phrase II   | Asian, Australia| 123        | CET  | 1,2,4          | 5,6,8    | NA                |
| 84  | Van et al. (104)   | 2011 | Phrase I/II | Europe         | 599         | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 85  | Moosmann et al. (105)| 2011 | Phrase II   | Germany        | 89          | CET  | 1,2,4          | 5,6      | NA                |
| 86  | Wong et al. (106)  | 2011 | Phrase II   | USA            | 30          | CET  | 1,2,3          | 5,6      | NA                |
| 87  | Shitara et al. (107)| 2011 | NA          | NA             | 30          | CET  | 1,2,3,4        | 5,6,7    | NA                |
| 88  | Saridaki et al. (108)| 2012 | Phrase II   | USA            | 30          | CET  | 1,2,3          | 5,6,8    | NA                |
| 89  | Stintzing et al. (68)| 2012 | Phrase I/II | Germany        | 50          | CET  | 1,2,3,4        | 5,6,7,8  | NA                |
| 90  | Shitara et al. (109)| 2012 | Phrase II   | Japan          | 30          | CET  | 1,2,3,4        | 5,6      | NA                |
| 91  | Tveit et al. (110) | 2012 | Phrase I/II | Europe         | 194         | CET  | 1,2,3,4        | 5,6,8    | NA                |
| 92  | Mrabti et al. (111)| 2009 | Phrase I/II | Morocco        | 32          | CET  | 1,2,4          | 5        | NA                |
| 93  | Mizushima et al. (112)| 2019 | Phrase II   | Japan          | 107         | XELOX| 1,2,3          | –        | NA                |
| 94  | Yoshimatsu et al. (113)| 2019 | Phrase II   | Japan          | 57          | XELOX| 1,2            | –        | ID:00005427      |
| 95  | Nishimura et al. (114)| 2018 | Phrase II   | Japan          | 42          | XELOX| 1,2,3          | –        | NA                |
| 96  | Larsen et al. (115) | 2017 | Phrase II   | NA             | 52          | XELOX| 1,2,3          | –        | NCT00964457      |
| 97  | Danno et al. (116) | 2017 | Phrase II   | Japan          | 190         | XELOX| 1,2,3          | 5        | ID:00006742      |
| 98  | Azria et al. (117) | 2017 | NA          | France         | 291         | XELOX| 1,2            | –        | NA                |
| 99  | Liu et al. (118)   | 2016 | Phrase II   | China          | 47          | XELOX| 1,2            | 5,6      | NCT02415829      |
| 100 | Pilanci et al. (119)| 2016 | Phrase II   | Turkey         | 30          | XELOX| 1,2,3          | 5,8      | NO:44140529      |
| 101 | Feng et al. (120)  | 2016 | Phrase III  | China          | 224         | XELOX| 1,2            | –        | NCT00714077      |
Table 2 (continued)

| No. | Reference                  | Year | Study phase | Country/region | Sample size | Drug | Characteristics | Outcomes | Registration number |
|-----|----------------------------|------|-------------|----------------|-------------|------|-----------------|----------|--------------------|
| 102 | Sclafani et al. (121)      | 2016 | Phrase II   | UK             | 50          | XELOX| 1,2,3,4         | 5,7,8    | NCT00958737        |
| 103 | Kim et al. (122)           | 2015 | Phrase II   | Korea          | 44          | XELOX| 1,2,3,4         | 5,7,8    | NCT00677144        |
| 104 | Wong et al. (123)          | 2015 | Phrase II   | USA            | 52          | XELOX| 1,2,3           | 7,8      | NA                 |
| 105 | Kim et al. (124)           | 2014 | Phrase III  | Korea          | 172         | XELOX| 1,2,3,4         | 7,8      | NA                 |
| 106 | Zhu et al. (111)           | 2013 | Phrase II   | China          | 32          | XELOX| 1,2,3,4         | 7,8      | NA                 |
| 107 | Gérard et al. (125)        | 2012 | NA          | France         | 299         |      |                 |          | NA                 |
| 108 | Salazar et al. (126)       | 2012 | Phrase II   | Spain          | 45          | XELOX| 1,2,3           | 7,8      | NA                 |
| 109 | Arbea et al. (127)         | 2012 | Phrase II   | Spain          | 100         | XELOX| 1,2,3,4         | 7,8      | NA                 |
| 110 | Schou et al. (128)         | 2012 | NA          | Denmark        | 84          | XELOX| 1,2,3,4         | 7,8      | NA                 |
| 111 | Ducreux et al. (129)       | 2011 | Phrase III  | France         | 156         | XELOX| 1,2,3,4         | 5,7,8    | NA                 |
| 112 | Haller et al. (130)        | 2011 | Phrase III  | 29 countries   | 944         | XELOX| 1,2,3           |          | NO16968            |
| 113 | Waddell et al. (131)       | 2011 | Phrase II   | UK             | 45          | XELOX| 1,2,3,4         | 5,7,8    | NA                 |
| 114 | Baraniskin et al. (132)    | 2011 | Phrase III  | Germany        | 190         | XELOX| 1,2,3,4         | 5,7,8    | NA                 |
| 115 | Cassidy et al. (133)       | 2011 | Phrase III  | UK             | 317         | XELOX| 1,2,3,4         | 8        | NO16966            |
| 116 | Li et al. (134)            | 2010 | NA          | France         | 124         | XELOX| 1,2,3,4         | 5,7,8    | NA                 |
| 117 | Qvortrup et al. (135)      | 2010 | Phrase II   | Denmark        | 70          | XELOX| 1,2,3,4         | 8        | NA                 |

Age =1; gender =2; ECOG =3; treat-line =4; ORR =5; DCR =6; PFS =7; OS =8. UK, United Kingdom; USA, the United States of America; NA, not available; BEV, bevacizumab; CET, cetuximab; XELOX, oxaliplatin combined with capecitabine; ECOG, Eastern Cooperative Oncology Group.

Table 3 Baseline characteristics of RWS

| No. | Reference                  | Year | Study design | Country/region | Sample size | Drug | Characteristics | Outcomes |
|-----|----------------------------|------|--------------|----------------|-------------|------|-----------------|----------|
| 1   | Houts et al. (136)         | 2019 | Case series  | USA            | 264         | BEV  | 2,4             | 7,8      |
| 2   | Degirmencioğlu et al. (137)| 2019 | Case series  | Turkey         | 114         | BEV  | 4               |          |
| 3   | Khakoo et al. (138)        | 2019 | Case series  | UK             | 714         | BEV  | 1,2,3,4         | 7,8      |
| 4   | Ogata et al. (139)         | 2019 | NA           | Japan          | 55          | BEV  | 1,2,3,4         | 5,6,8    |
| 5   | Ottaiano et al. (140)      | 2019 | Registry     | NA             | 31          | BEV  | 1,2,3,4         | 5,6,8    |
| 6   | Devaux et al. (141)        | 2019 | NA           | France         | 99          | BEV  | 1,2,3,4         | 5,6,8    |
| 7   | Turpin et al. (142)        | 2018 | NA           | France         | 216         | BEV  | 1,2,4           | 7,8      |
| 8   | Matsusaka et al. (143)     | 2017 | NA           | Japan          | 424         | BEV  | 1,2,4           | 8        |
| 9   | Hasegawa et al. (144)      | 2017 | NA           | Japan          | 58          | BEV  | 1,2,4           | 5,8      |
| 10  | Sun et al. (145)           | 2017 | Case series  | China          | 217         | BEV  | 2,3,4           | 5,6,8    |
| 11  | Bennouna et al. (146)      | 2017 | Cohort       | France         | 521         | BEV  | 1,2,3,4         | 8        |
| 12  | Chapman et al. (147)       | 2016 | Case series  | Australia      | 292         | BEV  | 2,4             | 8        |
| 13  | Bai et al. (148)           | 2016 | Registry     | China          | 188         | BEV  | 1,2,3,4         | 5,7,8    |
| 14  | Dionisio de Sousa et al. (149)| 2016 | Case series  | France         | 41          | BEV  | 1,2,4           | 5,8      |
Table 3 (continued)

| No. | Reference                | Year | Study design | Country/region | Sample size | Drug | Characteristics | Outcomes |
|-----|--------------------------|------|--------------|----------------|-------------|------|----------------|----------|
| 15  | Kotaka et al. (150)      | 2016 | Cohort       | Japan          | 40          | BEV  | 1,2,3,4         | 5        |
| 16  | Wong et al. (151)        | 2016 | Registry     | Australia      | 206         | BEV  | 2,3,4           | –        |
| 17  | Cabart et al. (152)      | 2016 | NA           | France         | 164         | BEV  | 1,2,3,4         | 8        |
| 18  | Kocakova et al. (153)    | 2015 | Registry     | Czech          | 357         | BEV  | 1,2,3,4         | 6,8      |
| 19  | Hammerman et al. (154)   | 2015 | Cohort       | Israel         | 1,052       | BEV  | 2,4             | 8        |
| 20  | Stein et al. (155)       | 2015 | Cohort       | Germany        | 1,777       | BEV  | 1,2,3,4         | 5,6,8    |
| 21  | Bai et al. (156)         | 2015 | Cohort       | China          | 175         | BEV  | 1,2,3,4         | 5,6,8    |
| 22  | Bencsikova et al. (157)  | 2015 | NA           | Czech          | 964         | BEV  | 1,2,3,4         | 7,8      |
| 23  | Tahover et al. (158)     | 2015 | Cohort       | Israel         | 216         | BEV  | 1,2,4           | 5,6,7,8  |
| 24  | Kubáčková et al. (159)   | 2015 | Registry     | Czech          | 981         | BEV  | 1,2,4           | 5,6,7,8  |
| 25  | Cheng et al. (160)       | 2015 | NA           | China          | 69          | BEV  | 2,4             | 5,6,8    |
| 26  | Ohhara et al. (161)      | 2015 | Cohort       | Japan          | 85          | BEV  | 1,2,4           | 5,6      |
| 27  | Yang et al. (162)        | 2014 | Case series  | Taiwan         | 95          | BEV  | 2,4             | 5,6,8    |
| 28  | Fourrier-Réglat et al. (163)| 2014 | Cohort       | France         | 411         | BEV  | 1,2,3,4         | 5,7,8    |
| 29  | Hofheinz et al. (164)    | 2014 | Cohort       | Germany        | 1,297       | BEV  | 1,2,3,4         | –        |
| 30  | Suenaga et al. (165)     | 2014 | Cohort       | Japan          | 85          | BEV  | 1,2,4           | 5,6,7,8  |
| 31  | Uchima et al. (166)      | 2014 | NA           | Japan          | 40          | BEV  | 1,2,4           | 5,6,7    |
| 32  | Yin et al. (167)         | 2014 | Case series  | China          | 87          | BEV  | 1,2,4           | 7        |
| 33  | Hurwitz et al. (168)     | 2014 | Cohort       | USA            | 1,550       | BEV  | 1,2,3,4         | 7,8      |
| 34  | Kiss et al. (169)        | 2014 | Registry     | Czech          | 3,990       | BEV  | 1,2,4           | 5,7,8    |
| 35  | Turan et al. (170)       | 2014 | Case series  | Turkey         | 52          | BEV  | 2               | –        |
| 36  | Moscetti et al. (171)    | 2013 | Case series  | NA             | 220         | BEV  | 1,2,3,4         | 5        |
| 37  | Cvetanovic et al. (172)  | 2013 | Case series  | NA             | 51          | BEV  | 2,4             | 6,7      |
| 38  | Wu et al. (173)          | 2013 | Case series  | China          | 36          | BEV  | 1,2,3,4         | 6,7,8    |
| 39  | Meyerhardt et al. (174)  | 2012 | Registry     | USA            | 1,589       | BEV  | 2,3,4           | 5,8      |
| 40  | Ghiringhelli et al. (175)| 2012 | Case series  | France         | 49          | BEV  | 1,2,3           | 8        |
| 41  | Yildiz et al. (176)      | 2010 | NA           | NA             | 40          | BEV  | 2,3             | 5,8      |
| 42  | Dranitsaris et al. (177) | 2010 | Case series  | Holland        | 43          | BEV  | 1,2,4           | 8        |
| 43  | Rouyer et al. (178)      | 2018 | Cohort       | France         | 389         | CET  | 1,2,3,4         | 7,8      |
| 44  | Wu et al. (179)          | 2018 | Case series  | China          | 34          | CET  | 1,2,4           | 5,7,8    |
| 45  | Chapman et al. (147)     | 2017 | Case series  | Australia      | 134         | CET  | 2               | 8        |
| 46  | Jerzak, et al. (180)     | 2017 | Registry     | Canada         | 278         | CET  | 2,4             | 8        |
| 47  | Kim et al. (181)         | 2017 | NA           | Korea          | 147         | CET  | 1,2,4           | 8        |
| 48  | Ozaslan et al. (182)     | 2017 | Case series  | NA             | 40          | CET  | 1,2,4           | 5,6,8    |
| 49  | Bai et al. (148)         | 2016 | Registry     | China          | 101         | CET  | 1,2,3,4         | 5,6,7,8  |
| No. | Reference                  | Year | Study design | Country/region | Sample size | Drug | Characteristics | Outcomes |
|-----|---------------------------|------|--------------|----------------|-------------|------|-----------------|----------|
| 50  | Derangère et al. (183)    | 2016 | Cohort       | France         | 52          | CET  | 2,3             | -        |
| 51  | Pinto et al. (184)        | 2016 | Case series  | Italy          | 225         | CET  | 2,3,4           | 5,6,7,8  |
| 52  | Uemura et al. (185)       | 2016 | Case series  | Japan          | 64          | CET  | 1,2,3,4         | 5,6      |
| 53  | Yamaguchi et al. (186)    | 2016 | Case series  | Japan          | 97          | CET  | 1,2,3,4         | 5,8      |
| 54  | Feng et al. (187)         | 2016 | Cohort       | China          | 102         | CET  | 2,3,4           | 5,6,8    |
| 55  | Sato et al. (188)         | 2015 | NA           | Japan          | 109         | CET  | 1,2,4           | 8        |
| 56  | Wang et al. (189)         | 2015 | NA           | China          | 110         | CET  | 2,3,4           | 5,6      |
| 57  | Giampieri et al. (190)    | 2015 | Case series  | Italy          | 46          | CET  | 2               | 5,6,8    |
| 58  | Yang et al. (162)         | 2014 | Case series  | Taiwan         | 63          | CET  | 2,4             | 5,6,7,8  |
| 59  | Jahn et al. (191)         | 2014 | Registry     | Germany        | 247         | CET  | 2               | 5,6      |
| 60  | Kennecke et al. (192)     | 2013 | Registry     | Canada         | 37          | CET  | 1,2,3           | 8        |
| 61  | Chen et al. (193)         | 2013 | Case series  | Taiwan         | 50          | CET  | 1,2,4           | 5,6      |
| 62  | Santos-Ramos et al. (194) | 2013 | Case series  | Spain          | 81          | CET  | 2,3,4           | -        |
| 63  | Jahn et al. (195)         | 2012 | NA           | Germany        | 309         | CET  | 1,2,3,4         | -        |
| 64  | Bouchahda et al. (196)    | 2011 | Case series  | Europe         | 91          | CET  | 1,2,3,4         | 5,8      |
| 65  | Xu et al. (197)           | 2019 | Case series  | NA             | 108         | XELOX| 1               | -        |
| 66  | Loree et al. (198)        | 2018 | Registry     | Canada         | 151         | XELOX| 1,2,3           | -        |
| 67  | Sha et al. (199)          | 2018 | NA           | NA             | 95          | XELOX| 2,3             | -        |
| 68  | van et al. (200)          | 2017 | Case series  | Holland        | 191         | XELOX| 2               | -        |
| 69  | Nakanishi et al. (201)    | 2016 | Case series  | Japan          | 53          | XELOX| 1,2             | -        |
| 70  | Karin et al. (202)        | 2016 | Registry     | NA             | 51          | XELOX| 2               | 8        |
| 71  | Spada et al. (203)        | 2016 | Case series  | Italy          | 78          | XELOX| 1,2,3           | 5,8      |
| 72  | Osawa et al. (204)        | 2014 | Case series  | Japan          | 41          | XELOX| 1,2,3           | -        |
| 73  | Osawa et al. (204)        | 2014 | Case series  | Japan          | 41          | XELOX| 1,2             | -        |
| 74  | Loree et al. (205)        | 2014 | Cohort       | Canada         | 83          | XELOX| 2,3             | 8        |
| 75  | Chiu et al. (206)         | 2014 | Case series  | Hong Kong      | 110         | XELOX| 1,2,3           | -        |
| 76  | Loree et al. (207)        | 2014 | Cohort       | Canada         | 76          | XELOX| 1,2             | -        |
| 77  | Boisen et al. (208)       | 2014 | Cohort       | Denmark        | 211         | XELOX| 1,2,3           | 8        |
| 78  | Qiu et al. (209)          | 2014 | Cohort       | China          | 64          | XELOX| 1,2,4           | 7,8      |
| 79  | Fukuchi et al. (210)      | 2013 | Case series  | Japan          | 108         | XELOX| 1,2,3           | 5,6      |
| 80  | Constantinidou et al. (211)| 2013 | Case series  | UK             | 34          | XELOX| 1,2             | -        |
| 81  | Hansen et al. (212)       | 2012 | Cohort       | Denmark        | 89          | XELOX| 2               | -        |
| 82  | Satram-Hoang et al. (213) | 2013 | Cohort       | USA            | 122         | XELOX| 2               | 8        |
| 83  | Hansen et al. (212)       | 2012 | Case series  | Denmark        | 89          | XELOX| 2,4             | 8        |
| 84  | Karacetin et al. (214)    | 2009 | Case series  | Turkey         | 34          | XELOX| 1,2,3           | 8        |

**Age = 1; gender = 2; ECOG = 3; treat-line = 4; ORR = 5; DCR = 6; PFS = 7; OS = 8. UK, United Kingdom; USA, the United States of America; NA, not available; BEV, bevacizumab; CET, cetuximab; XELOX, oxaliplatin combined with capecitabine; ECOG, Eastern Cooperative Oncology Group.**
Secondary outcomes

No differences in ORR and DCR were found between RCTs and RWS by overall analysis and subgroup analysis in the BEV group and CET group. However, in the XELOX group, the ORR of patients in RCTs was 0.251 higher than that of patients in RWS (0.563, 0.457 to 0.669 vs. 0.312, 0.214 to 0.410; P=0.001), and DCR was also 20.6% higher than that of patients in RWS (0.936, 0.857 to 1.016 vs. 0.730, 0.646 to 0.814; P=0.001) (Figure 3). More detailed results show in Table S2 and Figures S9–S16.
According to the meta-analysis results, there were OS differences between RCT and RWS in the CET group, and ORR and DCR differences in the XELOX group.

Based on the previous analysis, we found no differences in age, gender, ethnicity and other baseline characteristics of the CET group, except for ECOG and treatment line. To explore the reason for OS differences, we performed meta-regression analysis by including ECOG and treatment line.
as covariates, OS as dependent variables in the CET group. We extracted the proportion of patients with ECOG score $\geq 2$, and the proportion of patients with second-line or above treatment, based on baseline data from the original study. And there were only gender differences in the XELOX group, so we included the proportion of male patients as covariates, ORR and DCR as the dependent variable in the XELOX group. To explore the impact of study design on results, included the study design as a dichotomous covariate in both groups.

The regression results showed that OS differences in the CET group were related to the difference of treatment line and were not related to ECOG and study type (Table 4). In the XELOX group, differences in treatment outcomes were independent of baseline characteristics and study type (Tables 5, 6).

In addition, although the case number of RWS reporting follow-up time, treatment cycle, and duration was lower than that of RCT, the $t$-test results for mean follow-up time, treatment cycle, and duration between RCT and RWS showed no significant difference (Table 7).

**Discussion**

**Key findings**

In this systematic review and meta-analysis, we found that there were slight systematic differences in patient characteristics between RCTs and RWS in CRC. The differences in baseline characteristics mainly included a higher proportion of male patients, a lower proportion of patients with ECOG score $\geq 2$, and a lower proportion of second-line and above-second-line treatments in RCT. The reasons for these differences may be as follows: For gender, data on CRC patients collected from the Medicare

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**Table 4** Regression analyses of OS in the CET group

| OS                      | Coef.     | Std. Err. | t     | P      | 95% CI               |
|-------------------------|-----------|-----------|-------|--------|----------------------|
| Study type              | 2.924438  | 2.812611  | 1.04  | 0.314  | –3.038031 to 8.886906 |
| Treatment line          | 10.29738  | 2.341684  | –4.4  | 0.000  | –15.26153 to –5.333236 |
| ECOG                    | 2.644013  | 10.23937  | –0.26 | 0.800  | –24.3505 to 19.06248  |
| _cons                   | 21.47765  | 1.143907  | 18.78 | 0.000  | 19.05267 to 23.90262  |

OS, overall survival; CET, cetuximab; Coef., coefficient; Std. Err., standard error; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

**Table 5** Regression analyses of ORR in the XELOX group

| ORR                      | Coef.     | Std. Err. | t     | P      | 95% CI               |
|--------------------------|-----------|-----------|-------|--------|----------------------|
| Study type               | –0.2529   | 0.112954  | –2.24 | 0.052  | –0.50842 to 0.002623 |
| Gender                   | 0.422701  | 0.484584  | 0.87  | 0.406  | –0.673505 to 1.518906 |
| _cons                    | 0.262381  | 0.294841  | 0.89  | 0.397  | –0.404595 to 0.929357 |

ORR, objective response rate; XELOX, oxaliplatin combined with capecitabine; Coef., coefficient; Std. Err., standard error; CI, confidence interval.

**Table 6** Regression analyses of DCR in the XELOX group

| DCR                      | Coef.     | Std. Err. | t     | P      | 95% CI               |
|--------------------------|-----------|-----------|-------|--------|----------------------|
| Study type               | 0.0055461 | 0.0924147 | 0.06  | 0.962  | –1.168694 to 1.179786 |
| Gender                   | 1.428532  | 0.4492353 | 3.18  | 0.194  | –4.279555 to 7.136596 |
| _cons                    | 0.1183735 | 0.3428134 | –0.35 | 0.788  | –4.475501 to 4.238754 |

DCR, disease control rate; XELOX, oxaliplatin combined with capecitabine; Coef., coefficient; Std. Err., standard error; CI, confidence interval.
database show that the proportion of men with CRC is generally higher than that of women, however, as the sample size increases, the difference will be narrowed, since the sample size of RWS is much larger than that of RCT, the proportion of male patients in RWS is closer to 50%. In addition, according to a study, men are more likely to participate in RCTs than women (215), which also led to a higher proportion of male patients in RCT than RWS. For ECOG score and treatment line, RCT has more strict inclusion and exclusion criteria for patients. Patients with high ECOG score and above-second-line treatments may be excluded due to poor health status and complex medical history. Therefore, the proportion of patients with ECOG score ≥2 and second-line and above-second-line treatments in RCT is lower.

Although there were slight differences in baseline characteristics, it did not lead to any difference in treatment outcomes by overall analysis, indicating that the results of RCT and RWS were highly consistent. As for the partial differences in subgroup analysis, a further meta-regression analysis showed that the higher OS value in the CET group of RCTs were due to the inclusion of more patients who are treated in frontlines, that can be reasonably interpreted as patients treated in frontlines were in better health. But no reason was found for the difference between ORR and DCR in XELOX group due to the small number of studies and the serious lack of clinical outcome data. We suggest conducting high-quality XELOX RWS for CRC patients in the future to supplement the deficiencies of the existing research.

**Strengths and implications**

This comparative study focused on cancer, the anticancer treatment process had relatively high standardization in drug regimens, drug compliance, and strict monitoring measures of toxicity and adverse reaction (216,217), which greatly reduced the differences in intervention measures and patients’ drug compliance and also lowered the bias of the results. Compared with several studies in the past, regression analysis was added in this study to determine the correlation between differences in baseline characteristics and differences in treatment effects, and rule out the effect of study design on the results. We believe that the differences between RCTs and RWS in different disease areas cannot be generalized. This study will be more applicable to clarify the external validity of RCTs results for CRC in real-world applications, help understanding the current status in CRC, improving research design and providing decision-making references for health decision-making departments.

**Limitations**

Given that this study mainly focused on the differences in patient characteristics between RCTs and RWS rather than the results of clinical trials, we did not perform quality assessment on the literature, the RWS across different countries may result in potential confounding factors. Since the OS value did not reach the upper limit in some studies, we used conservative estimation in the analysis to assume the OS values as the longest follow-up time in this study, which may lead to the underestimation of the OS values. Due to the limitations of study time, study number, and quality of the included studies, the conclusion herein need further verification.

**Conclusions**

No efficacy-effectiveness gap was found in CRC between
RCTs and RWS. The treatment effects of RCTs and RWS in CRC patients were highly consistent, and the results of RCTs have high external validity.

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