Efficacy and safety of triplet chemotherapy plus anti-EGFR agents in metastatic colorectal cancer: a systematic review and meta-analysis

Qian Wu, Huan Wang, Suqin Zhang, Yifei Zeng, Wei Yang, Wenjun Pan, Guodai Hong and Wenbin Gao*

Abstract
Background: To date, the optimal treatment for potentially resectable metastatic colorectal cancer (mCRC) patients has yet to be determined. Encouraging results have been reported in studies exploring the efficacy of triplet chemotherapy plus anti-epidermal growth factor receptor (anti-EGFR) target agents. Thus, we conducted a meta-analysis to evaluate the efficacy and safety of triplet chemotherapy plus anti-EGFR target agents.

Methods: We systematically searched the PubMed, Embase, and Web of Science databases from December 2004 to October 2021 for studies examining the efficacy of triplet chemotherapy plus anti-EGFR target agents in mCRC patients. The primary outcomes were the objective response rate (ORR) and R0 resection rate (R0RR), and the secondary outcomes were median progression-free survival (mPFS), median overall survival (mOS), and toxicity. Data were analyzed with R software 4.1.2.

Results: Fourteen studies comprising 762 patients with mCRC were included in this meta-analysis. Analysis with a random effects model revealed that after treatment with triplet chemotherapy plus anti-EGFR target agents, the pooled ORR was 82% (95% CI = 76–88%, $I^2 = 76$%), and the pooled R0RR of colorectal liver metastasis (CLM) was 59% (95% CI = 49–68%, $I^2 = 60$%). The mPFS ranged from 9.5 to 17.8 months, and the mOS ranged from 24.7 to 62.5 months. A total of 648 grade 3 or 4 adverse events were reported; the most commonly reported events were diarrhea (174/648), neutropenia (157/648), and skin toxicity (95/648), which had pooled prevalence rates of 29% (95% CI = 20–39%, $I^2 = 84$%), 28% (95% CI = 20–37%, $I^2 = 77$%), and 17% (95% CI = 11–24%, $I^2 = 66$%), respectively.

Conclusions: Triplet chemotherapy plus anti-EGFR agents therapy seems to be capable of increasing the ORR of mCRC patients and the R0RR of CLM patients. The toxicity of this treatment is manageable. High-quality randomized controlled trial (RCT) studies are required for further validation.

Keywords: Metastatic colorectal cancer, Anti-EGFR, Triplet chemotherapy, Cetuximab, Panitumumab

Background
Colorectal cancer is the third most common malignancy and the second leading cause of cancer-related deaths worldwide. Approximately one-quarter of patients are unresectable or have metastatic colorectal cancer (mCRC) at the initial diagnosis [1]. The 5-year survival rate associated with mCRC is less than 20%, whereas the number is more than 80% in early-stage CRC patients [2].

With recent progress in cancer management, the median overall survival (mOS) of mCRC has widely improved from approximately 6 months (best supportive care) to nearly 30 months after standard systematic treatments in the past 20 years [3]. In addition to new drugs and novel technologies, these improvements are mainly attributed to biomarker-based patient selection

*Correspondence: drwenbingao@163.com

Department of Oncology, Shenzhen Luohu People’s Hospital, Shenzhen, Guangdong 518000, People’s Republic of China

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and effective therapeutic combination strategies [4, 5]. The first-line therapy plays a critical role in the successful treatment of patients with mCRC, especially for patients with potentially resectable metastases. Triplet chemotherapy, the combination of 5-fluorouracil, irinotecan, and oxaliplatin [2, 6], has been proven to be effective and tolerable in pancreatic cancer with characteristics of rapid tumor shrinkage and improved secondary surgery rate since 2010 [7–9]. This regimen is also gaining importance in the treatment of mCRC. The randomized, controlled, phase 3 TRIBE study compared FOLFOXIRI plus bevacizumab to FOLFIRI plus bevacizumab and showed a better objective response rate (ORR; 65 vs. 54%, \( P<0.05 \)) and mOS (29.8 vs. 25.8 months, hazard ratio [HR] 0.8, 95% confidence interval [CI] 0.65–0.98, \( P=0.03 \)) in the triplet plus bevacizumab arm without increasing intolerable toxicity [10]. This finding led to major guideline recommendations for this therapy as a first-line treatment for mCRC patients. Anti-epidermal growth factor receptor (anti-EGFR) target agents (e.g., cetuximab or panitumumab) also proved to have a high response rate in mCRC treatment. The FIRE-3 trial established that in comparison with FOLFIRI plus bevacizumab, a combination of FOLFIRI and cetuximab improved the ORR (77 vs. 65%, \( P=0.014 \)) and mOS (33 m vs. 26 m, HR=0.75, \( P=0.011 \)) in rat sarcoma (RAS) gene wild-type patients with left-side disease [11]. Since multiple studies revealed the advanced efficacy of both FOLFOXIRI and anti-EGFR agents (in RAS and BRAF wild-type patients) [12–14], one question was raised: in RAS and BRAF wild-type mCRC patients, will the combination of triplet chemotherapy and anti-EGFR agents improve the ORR or secondary resection rate? Although this regimen is not recommended in major guidelines, there are an increasing number of clinical trials exploring its efficacy and safety [15]. The POTHER trial, the first phase II prospective trial aiming to assess the effectiveness of cetuximab plus triplet chemotherapy in colorectal liver metastasis (CLM), achieved an ORR and secondary R0 resection rate (R0RR) of 79.1% and 60%, respectively, with tolerable toxicity [14]. The VOLFI trial compared the efficacy of panitumumab plus mFOLFOXIRI with FOLFOXIRI MAb C225 (Colorectal Cancer) OR (Colorectal Carcinoma) AND (Cetuximab OR Erbitux OR (IMC C225) OR (MAb C225) OR (C225) OR panitumumab OR (Human Panitumumab Antibody) OR (ABX-EGF MAb) OR (ABX EGF Monoclonal Antibody) OR Vectibix OR anti-EGFR) AND (FOLFOXIRI OR FOLFIRINOX OR (triplet chemotherapy))

It is generally acknowledged that meta-analysis is a powerful statistical tool to overcome the limitation of different sample sizes from individual studies and to generate the best estimation. Therefore, we conducted a meta-analysis of all eligible published studies to evaluate the efficacy and safety of triplet chemotherapy plus anti-EGFR agents in treating mCRC patients as a first-line regimen.

**Methods**

This systematic review and meta-analysis is registered in the PROSPERO database (CRD42021289370, https://www.crd.york.ac.uk/PROSPERO/). It was performed following the meta-analysis (PRISMA) guideline (details were presented in Additional file 1).

**Search strategy**

We systematically searched the PubMed, Embase, and Web of Science databases for relevant studies published from December 2004 (date of cetuximab approval by the Food and Drug Administration [FDA]) to October 2021. Additionally, abstracts from the American Society of Clinical Oncology (ASCO) annual meeting (December 2004 to 2021), the European Society of Medical Oncology annual meeting (2004–2021), and the World Congress on Gastrointestinal Cancer (2004 to 2021) were screened. Reference lists of included studies were screened to identify other eligible studies. Abstracts from the meetings were searched through the meetings’ official websites to identify relevant citations.

Search strategies included the following:

The PubMed search terms were as follows:

- (Colorectal Neoplasm) OR (Colorectal Tumor) OR (Colorectal Cancer) OR (Colorectal Carcinoma)) AND (Cetuximab OR Erbitux OR (IMC C225) OR (MAb C225) OR (C225) OR panitumumab OR (Human Panitumumab Antibody) OR (ABX-EGF MAb) OR (ABX EGF Monoclonal Antibody) OR Vectibix OR anti-EGFR) AND (FOLFOXIRI OR FOLFIRINOX OR (triplet chemotherapy))

The Embase search terms were as follows:

- (‘colorectal neoplasm’ OR ‘colorectal tumor’ OR ‘colorectal cancer’ OR ‘colorectal carcinoma’) AND (‘c225’ OR ‘erbitux’ OR ‘imc 225’ OR ‘ly 2939777’ OR ‘Cetuximab’ OR ‘abx egf’ OR ‘panitumab’ OR ‘vectibex’ OR ‘vectibix’ OR ‘anti-EGFR’) AND (‘FOLFOXIRI’ OR ‘FOLFIRINOX’ OR ‘triplet chemotherapy’)

Search terms for the Web of Science were as follows:

- (Colorectal cancer) AND (cetuximab OR Erbitux OR (C225) OR panitumumab OR Vectibix OR anti-
EGFR) AND (FOLFOXIRI OR FOLFIRINOX OR (triplet chemotherapy))

Inclusion criteria

(1) Diagnosis: The studied patients were diagnosed with metastatic colorectal adenocarcinoma and pathologically confirmed.
(2) No restriction existed for patient racial/publication status (full text or meeting abstract) as long as data were completed.
(3) Patients were treated with triple chemotherapy (5-fluorouracil, irinotecan, and oxaliplatin/capecitabine) plus anti-EGFR (cetuximab or panitumumab) agent as a first-line chemotherapy.
(4) At least three of the treatment outcomes mentioned below were reported.
(5) The study design included RCTs, prospective non-randomized trials, and observational studies (prospective or retrospective) published from December 2004 to October 2021 with a sample size of at least 10 patients.

Exclusion criteria

(1) The studies were not written in English.
(2) All patients in the study had a RAS or BRAF mutation.
(3) The studies contained incomplete data on the outcome of interest.
(4) Studies with duplicate data or report analysis.

Data extraction

All candidate articles were evaluated and extracted by two independent authors (H Wang and SQ Zhang). If disagreement occurred, a third author (Q Wu) was consulted. Data were extracted from the eligible studies using a standardized extraction form.

For each study, the following data were extracted: first author, year of publication, country, study period, median age, total number of cases, sex ratio, study design, treatment strategy, RAS status, BRAF status, ORR, number of liver-limited patients, R0 resection rate (R0RR), mPFS, mOS, follow-ups, and grade 3/4 adverse effects. The characteristics of the selected studies are shown in Table 1.

The primary outcomes were ORR and R0RR in liver-limited mCRC patients. The secondary outcomes were mPFS, mOS, and grade 3/4 toxicity rate. ORR was defined as the ratio between the number of patients achieving an objective response (complete or partial response) and the total number of patients.

Quality assessment

Because both case series and cohort studies were included in this meta-analysis, the Methodological Index for Non-Randomized Studies (MINORS) was used by two independent authors (H Wang and SQ Zhang) to assess the quality of the studies. The MINORS comprises 12 methodological items with a maximum score of 24. The first eight items (i.e., a clearly stated aim, inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the aim of study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss to follow-up less than 5%, prospective calculation of the study size) apply to both comparative and noncomparative studies, whereas the remaining four items (i.e., an adequate control group, contemporary groups, baseline equivalence of groups, adequate statistical analyses) apply only to comparative studies. A score lower than 10 for a case-series study or lower than 16 for a cohort study indicates low quality, and studies with such scores were excluded. The MINORS scores of the included studies are shown in Table 1. None of the studies was excluded on the basis of their score. Details on the MINORS score of each study are presented in Table 2.

The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Statistical analysis

Statistical analyses were performed using the meta-package of R 4.1.2 software. After data evaluation, we chose Freeman-Tukey double arcsine transformation to process the data presented as proportions with ORR, R0RR, and any grade 3/4 toxicity rate. We then aggregated using the inverse variance random-effect method (DerSimonian–Laird estimate). CIs for the individual studies were calculated based on the Clopper-Pearson interval method. Cochrane’s Q test and Higgins I$^2$-squared statistic were used to assess the heterogeneity of the included trials. $P<0.1$ in the Q test or $I^2>50\%$ suggested significant heterogeneity. When significant heterogeneity was observed, the random effects model was used. Otherwise, the fixed effects model was adopted to evaluate the 95% CI. The sensitivity analysis was applied to explore the origin of heterogeneity. Publication bias was assessed by a visual inspection of the funnel plot, and the possibility of publication bias was assessed by Egger’s test.
Table 1 Summary of the study characteristic

| Author/ year | Country/ period of study | Trial name | Study design | Total patients | Gender(M/F) | Median age (years, range) | Primary Location | RAS wt/mt/ unknown | BRAF wt/mt/ unknown | Primary endpoint | ORR (%) | mPFS (month) | mOS (month) | CLM/RRR | in CLM | mfollow-up (month, range) | MINORS |
|--------------|--------------------------|------------|--------------|----------------|-------------|----------------------------|-----------------|---------------------|---------------------|------------------|----------|---------------|--------------|---------|-------|-----------------------------|-------|
| Garufi C [14]/2010 | Italy/2006–2008 | POCHER | Pros-case series | 43 | 27/16 | 61 (33–75) | 34/9 | 3.0/7/6 | NA | ORR | 79.1% | 14 | 37 | 43/60% | 22 (1–43) | 16 |
| Souglakos I [16]/2011 | Greece/2007–2010 | - | Pros-case series | 30 | 16/14 | 64 | NA | 3.0/0/3 | NA | ORR | 70% | 11 | NR | 16/5/7% | 15.1 (NA) | 14 |
| ERC-ASCENAT [17]/2011 | France/2006–2008 | ERBRINOX | Pros-case series | 42 | 22/20 | 60 (32–76) | 30/12 | 24/16/2 | NA | CRR | 80.90% | 9.5 | 24.7 | 15/NA | 18.1 (04–39) | 16 |
| Z Saridaki [18]/2012 | Greece/2007–2010 | - | Pros-case series | 30 | 14/16 | 64 (36–70) | 22/8 | NA | NA | ORR | 70% | 10.2 | 30.3 | 16/6/2% | 31 (13–37) | 16 |
| Folprecht, G [19]/2013 | Germany/2014–2018 | CELUM2 | Pros-cohort | 28 | NA | NA | NA | 28/0/3 | 28/0/0 | ORR | 86% | 15 | 55 | NA | NA | 22 |
| Fornaro, L [20]/2013 | Italy/2010–2011 | TRIP | Pros-case series | 37 | 21/16 | 63 (33–72) | 26/11 | 37/0/4 | 37/0/0 | ORR | 89% | 13.3 | NR | 12/75% | 17.7 (NA) | 16 |
| Bendell, J C [21]/2016 | USA/NA | - | Pros-case series | 15 | 13/2 | 55 (39–70) | NA | 8/0/7 | NA | ORR | 60% | 13.3 | NR | 15/6/7% | 15 (NA) | 16 |
| Pietrantoni [22]/2017 | Italy/NA | - | Pros-case series | 31 | NA | NA | NA | NA | NA | ORR | 87% | 17.8 | 62.5 | 31/8/4% | 48 (NA) | 14 |
| Cremolini, C [23]/2018 | Italy/2011–2015 | MACBETH | Pros-multi-center, cohort | 116 | 82/34 | 59.5 (53–67) | 95/23 | 116/0/0 | 116/0/0 | 10mPFR | 71.60% | 10.1 | 33.2 | 52/5/19% | 44 (30.5–52.1) | 24 |
| D Modest [24]/2019 | Germany/NA | VOLIR | RCT, multi-center, cohort | 63 | 41/22 | 5.8 (31–76) | 53/10 | 63/0/0 | 43/7/13 | ORR | 87.3% | 9.7 | 35.7 | NA | 44.2 (NA) | 14 |
| Ogata, T [25]/2019 | Japan/2014–2017 | - | Retro-cohort | 17 | NA | 60 | 14/3 | 17/0 | NA | ORR | 100% | 13.1 | NR | NA | 18.4 (NA) | 21 |
| E Samalin [26]/2019 | NA | ESTER | Retro-case series, multi-center | 70 | 43/27 | 5.8 (40–74) | 57/13 | 70/0 | NA | PFS | 85.70% | 13.3 | 48.5 | 68/7/5% | 49.2 (12–135) | 13 |
| Deng, Y [27]/2020 | China/2014–2019 | FOCULM | Pros-case series, multi-center | 67 | 58/9 | 5.2 (28–70) | 66/1 | 67/0/0 | 67/0/0 | Rate of NED | 95.50% | 15.5 | NR | 67/46.3% | 22.6 (NA) | 16 |
| Akihito Tsuji [28]/2021 | Japan/2015–2019 | DEEPER | RCT | 173 | NA | 65 | NA | 173/0/0 | NA | mDpR | 69.10% | 12.7 | 37.6 | NA | NA | 22 |

* All included patients were diagnosed as liver-limited colorectal cancer; *colon/rectum, *left/right, *14 patients with cetuximab, 3 patients with panitumumab; *only KRAS; *time to progression, TTP; wt, wild-type, mt, mutant-type, ORR objective response rate, mPFS median progression-free survival, mOS median overall survival, CLM colorectal liver-limited metastases, RRR R0 resection rate, mDpR median depth of response. 
**Results**

**Search results and study characteristics**

A flow chart of the search strategies and reasons for exclusion is shown in Fig. 1.

In total, 577 potential articles were initially identified through the database, 266 articles were eliminated because of duplicate data, and 285 articles were removed after screening the title and abstract. The remaining 31 articles were retrieved for further assessment. Finally, 14 studies comprising 762 patients with mCRC were included in this meta-analysis. Among them, five studies were only described in conference abstracts.

The characteristics and study quality of all the included studies were evaluated by the MINORS and are presented in Table 2. Twelve studies were prospective, four were two-arm comparative cohort studies, ten were prospective/retrospective case series, four were multicenter investigations, and five were available only as conference abstracts or posters. A total of 762 patients were included across 14 studies. The median age range was 52–64 years (available in 11 studies), and the overall sex distribution was 338/175 (10 studies). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1. RAS and BRAF mutations were detected in 701 and 311 patients, respectively. Among the 701 patients who accepted the RAS mutation test, 157 were KRAS wild-type, 390 were RAS wild-type (all tests were amended to the RAS test after the FDA changed its instructions for cetuximab), and 23 were KRAS mutants (all participated before the discovery of the negative role played in anti-EGFR agent treatment). Tumor primary locations were presented in 316 patients from 10 studies: 48 patients with tumors in the colon (side unspecified), 35 patients with tumors in the right colon, and 233 patients with tumors in the left colon or rectum. All patients were treated by a triplet chemotherapy (combination of 5-fluorouracil, irinotecan, and oxaliplatin/capecitabine) plus anti-EGFR agents (cetuximab or panitumumab). Details of the regimen in each study are shown in Table 3. Median cycles of chemotherapy were reported in eight studies with a range of 1–12. The metastasis location of 321 patients from 10 studies was limited to the liver; secondary R0RR in patients diagnosed with unresectable colorectal liver metastases (CLM). After accepting triplet chemotherapy plus an anti-EGFR agent therapy, 179 out of 321 CLM patients achieved R0RR. The range of R0RR was 46.3 to 84%, and the pooled R0RR was 59% with a random effects model (95% CI=50–69%, \( I^2 = 60\% \)). The forest plots of ORR and R0RR are shown in Figs. 2 and 3, respectively.

**Secondary outcomes**

**Median progression-free survival and median overall survival**

The mPFS and mOS were obtained in 14 and 9 studies, respectively. The median PFS ranged from 9.5 to 17.8 months, and the mOS ranged from 24.7 to 62.5 months (Table 1).

**Grade 3/4 adverse events**

Thirteen studies reported grade 3/4 adverse events. In these studies, 648 grade 3/4 adverse events were observed among 731 patients who accepted triplet chemotherapy plus anti-EGFR agent therapy. One study reported a treatment-related toxic death related to neutropenic septicemia. The grade 3/4 toxicities described the most were diarrhea (174/648), neutropenia (157/648), and skin toxicity (95/648). The pooled rates were 29% (95% CI=20–39%, \( I^2 = 86\% \)), 28% (95% CI=20–37%, \( I^2 = 77\% \)), and 17% (95% CI=11–24%, \( I^2 = 66\% \)), respectively. A forest plot of each is shown in Figs. 4, 5, and 6. Toxicity profiles were not completed in five studies that were only available as a conference abstract. Most of the side effects were treatable. There were three studies that reduced the dose for a high incidence of adverse events (two because of diarrhea; one because of febrile neutropenia). All of them observed a significant decrease in toxicity after reduction. The toxicity profile is presented in Table 4.

**Publication bias**

As shown in Figs. 7 and 8, the possible publication bias of the included studies was assessed by the funnel plot test and Egger’s linear regression test. No significant publication bias was detected from statistical tests based on ORR (t=1.33, \( P = 0.2083 \)).

**Discussion**

To the best of our knowledge, our study is the first meta-analysis evaluating the efficacy of triplet chemotherapy plus anti-EGFR agent therapy. Nevertheless, there are multiple reviews and studies of this topic, which implies
Table 2 MINORS checklist for included studies

| Study          | Garufi | Sougklakos | ASSENAT | Saridaki | Folprecht | Fornaro | Bendell | Pietrantonio | Cremolini | Modest | Ogata | Samalin | Deng | Tsuji |
|----------------|--------|------------|---------|----------|-----------|---------|---------|--------------|-----------|--------|-------|--------|------|-------|
| **Methodological items for non-randomized studies** |        |            |         |          |           |         |         |              |           |        |       |        |      |       |        |        |        |        |        |        |        |        |        |
| A clearly stated aim | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Inclusion of consecutive patients | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Prospective collection of data | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Endpoints appropriate to the aim of study | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Unbiased assessment of the study endpoint | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Follow-up period appropriate to the aim of the study | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Loss to follow up less than 5% | 2      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| Prospective calculation of the study size | 0      | 2          | 2       | 2        | 2         | 2       | 2       | 2             | 2          | 2      | 2     | 2      | 2    | 2     | 2      | 2      |        |        |        |        |        |        |        |
| **Additional criteria for comparative studies** |        |            |         |          |           |         |         |              |           |        |       |        |      |       |        |        |        |        |        |        |        |        |        |        |
| An adequate control group | -      | -          | -       | -        | 2         | -       | -       | -             | 2          | -      | 2     | -      | -    | -     | 2      | 2      |        |        |        |        |        |        |        |
| Contemporary groups | -      | -          | -       | -        | 2         | -       | -       | -             | 2          | -      | 2     | -      | -    | 2     | -      | -      |        |        |        |        |        |        |        |
| Baseline equivalence of groups | -      | -          | -       | -        | 2         | -       | -       | -             | 2          | 2      | 2     | -      | 2    | -     | 2      | 2      |        |        |        |        |        |        |        |
| Adequate statistical analyses | -      | -          | -       | -        | 2         | -       | -       | -             | 2          | -      | 2     | -      | -    | 2     | -      | -      |        |        |        |        |        |        |        |
| **Total** | 16     | 14          | 16       | 16       | 22         | 16       | 16       | 14             | 24          | 14      | 21     | 13      | 16    | 22     |        |        |        |        |        |        |        |        |        |        |        |        |        |
that researchers have devoted considerable attention to this important issue. Our meta-analysis combined the outcomes of 762 mCRC patients treated with triple chemotherapy plus anti-EGFR therapy from 14 studies, indicating that the treatment can improve the ORR to 82% and improve the secondary R0 rate without increasing the G3/4 adverse effect.

Despite the large number of studies comparing the efficacy of different regimens in mCRC first-line treatment, the optimal therapy is still controversial [29, 30], especially in CLM patients or potentially resectable mCRC patients who may need more intensive treatment to achieve distinct tumor shrinkage to purchase the chance of secondary surgery [31]. Since both FOLFOXIRI and anti-EGFR target therapy were considered to be related to more rapid tumor responses, we conducted this meta-analysis to assess the efficacy and safety of their combination.

In our meta-analysis, the pooled ORR of patients who accepted triplet chemotherapy plus anti-EGFR therapy was 82% (95% CI=76–88%, I²=76%), ranging from 60 to 100%. For comparison, we summarized several meta-analyses of important studies in mCRC treatment. Details are presented in Table 5. This result clearly dominates the efficacy of all the other treatments. This indicates that triplet chemotherapy plus anti-EGFR therapy conspicuously increases the chance of secondary resection in mCRC patients. The same advantages can be observed in other outcomes, such as the R0RR of CLM, mPFS, and mOS. A possible explanation of such a remarkable improvement is discussed below.

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**Fig. 1** Flow diagram of literature search and study selection
RAS and BRAF mutation status

KRAS codons 12 and 13, 61, HRAS, NRAS, and BRAF V600E mutations are the most important and widely studied biomarkers for anti-EGFR agents. Both RAS and BRAF mutations have been proven to be prognostic factors associated with worse survival [36]. Because anti-EGFR target therapy is not recommended for patients with RAS or BRAF mutations, there were notable differences in patient baseline gene status selection in the included studies. In our meta-analysis, among the 701 patients who accepted the RAS mutation test, 157 were KRAS wild-type, 390 were RAS wild, and three were KRAS mutants. Among the 311 patients who accepted the BRAF mutation test, 291 were wild-type, and seven were mutant. It is assumed that the impressive efficacy was associated with the large number of RAS and BRAF wild-type patients.

Table 3  Summary of dose used in studies

| Study                        | Treatment/median cycles (range) | Dose Anti-EGFR | L-OHP (mg/m²) | CPT-11 (mg/m²) | 5-FU (mg/m²) | Dose reduction or dose intensity |
|------------------------------|---------------------------------|----------------|---------------|----------------|-------------|---------------------------------|
| C Garufi/2010 [14]          | Cet+Chrono-IFLO/6 (3–15)        | Cet (400mg/m² initial, 250 weekly mg/m²) | 80           | 130           | 2400        | L-OHP:60mg/m², CPT-11:110mg/m², 5-FU:2200mg/m² |
| Souglakis, I/2011 [16]       | Cet+FOLFOXIRI/NR                | Cet 500mg/m²   | 65           | 150           | 600+400 (bolus) | NA |
| ERIC ASSENAT/2011 [17]       | Cet+FOLFIRINOX/9 (1–12)        | Cet (400 initial/250 weekly) | 85           | 180           | 2400+400 (bolus) | 76%required dose reduction, overall dose intensity was >90% |
| Z Saridaki/2012 [18]         | Cet+FOLFOXIRI/12 (1–16)        | Cet 500mg/m²   | 65           | 150           | 1200+400 (bolus) | NA |
| Folpecht, G/2013             | Cet+FOLFOXIRI/11 (3–16)        | Cet 500mg/m²   | 85           | 125           | 3200        | NA |
| Fornaro, L/2013 [20]         | Pan+FOLFIRINOX/11 (3–16)       | Pan 6mg/kg     | 85           | 150           | 3000        | Relative dose intensity: L-OHP 75%, CPT-11 74%, 5-FU 76% |
| Bendell, J. C./2016 [21]     | Pan+FOLFOXIRI/NA                | Pan 6mg/kg     | 85           | 125           | 3200        | NA |
| Pietrantonio, F/2017 [2017]  | Cet+COI-E/NA                   | Cet 500mg/m²   | 85           | 180           | 1000 twice d2-5² | NA |
| Cremonini, C./2018 [23]      | Cet+FOLFOXIRI/8 (6–8)          | Cet 500mg/m²   | 85           | 130           | 2400        | NA |
| D Modest/2019 [24]           | Pan+FOLFIRINOX/11 (2–12)       | Pan 6mg/kg     | 85           | 165           | 3200        | NA |
| Ogata, T./2019 [25]          | Cet+FOLFOXIRI/7 (1–14)         | Cet (400mg/m² initial, 250 weekly mg/m²) | 85           | 125/150/165² | 3200        | NA |
| E. Samalin/2019/2020         | Cet+FOLFIRINOX/10 (2–12)       | NA             | NA           | NA            | NA         | NA |
| Deng, Y/2020                 | Cet+mFOLFIRIX/10 (2–12)        | Cet 500mg/m²   | 85           | 165           | 2800        | Relative dose intensity: L-OHP 96%, CPT-11 96%, 5-FU 96% |
| Akihito Tsuji/2021 [28]      | Cet+mFOLFIRIX/10 (1–12)        | Cet 500mg/m²   | 85           | 150           | 2400        | NA |

* Modified on UGT1A1 status; *²capcitabine; Cet, cetuximab; Pan, panitumumab; CPT-11, irinotecan; L-OHP, oxaliplatin; 5-FU, 5-fluorouracil; mFOLFOXIRI, modified FOLFOXIRI; COI-E, irinotecan+oxaliplatin+capcitabine; NA, not available

Primary tumor side

There is now a consensus that the primary tumor side of mCRC is biologically distinct [37]. The CALGB/SWOG 80405 study presented a significantly longer mPFS and mOS of the left side than the right side (mOS 33.3 months vs. 19.4 months, P<0.001) [38]. Subgroup analysis showed that in left-side-originated mCRC patients, compared with doublet chemotherapy plus bevacizumab, the combination of doublet chemotherapy and cetuximab was associated with a significantly longer mOS (36 vs. 31.4 months, P=0.018). This advantage was not reflected in the right-side originated mCRC patients; the mOS of cetuximab-arm and bevacizumab-arm were 16.7 vs. 24.2 months, P=0.065 [39]. The same tendency was found in the sub-analysis of trials FIRE-3 and PEAK [9, 40]. Based on this evidence, guidelines recommended treatment separately according to the primary tumor side.
Anti-EGFR-targeted therapy is only recommended in left-side colon cancer combined with doublet chemotherapy, including FOLFOX, FOLFIRI, and XELOX [41]. In our meta-analysis, among the 762 patients included, tumor primary location was reported for 316 patients from five studies, including 48 patients with tumors in the colon, 35 patients with tumors in the right colon, and 233 patients with tumors in the left colon or rectum. Thus, a large proportion of left colon or rectal cancer patients may be one reason for our high ORR.

**R0 resection rate and conversion therapy**

Conversion therapy is a standard therapy for mCRC patients, especially for patients with CLM. Recent studies verified that CLM is a particular type of mCRC that is heterogeneous to other mCRC patients [37]. Convincing
evidence has proven that the R0RR of CLM can significantly increase the 5-year survival rate and mOS [42]. This inspiring discovery reflects the importance of seeking optimal treatment for the appropriate patients. The new treatment goal of CLM is currently to maximize the possibility of eradicating all LM lesions, which require rapid and distinct tumor shrinkage [43]. In our meta-analysis, the pooled R0RR in CLM patients was 60% with a random effects model (95% CI=49–70%, $I^2=69\%$). Among the 14 included studies, five studies were designed specifically to evaluate the R0RR of CLM after treatment with triplet chemotherapy plus anti-EGFRs agent, and the R0RR ranged from 60 to 84%. Despite these encouraging results, there were an additional 14 patients from two studies who accepted R1 resection (two patients) or R2 resection (12 patients). Other important indices for conversion therapy include early tumor shrinkage and depth of response (DpR),

**Table 1**

| Study                  | Events | Total | Proportion | 95%–CI       | Weight (common) | Weight (random) |
|------------------------|--------|-------|------------|--------------|-----------------|-----------------|
| C Garufi/2010          | 15     | 43    | 0.35       | [0.21; 0.51] | 6.1%            | 8.4%            |
| Souglakos, I./2011     | 16     | 30    | 0.53       | [0.34; 0.72] | 4.3%            | 7.9%            |
| ERIC ASSENAT/2011      | 22     | 42    | 0.52       | [0.36; 0.68] | 6.0%            | 8.4%            |
| Z Saridaki/2012        | 16     | 30    | 0.53       | [0.34; 0.72] | 4.3%            | 7.9%            |
| Fornaro, L./2013       | 13     | 37    | 0.35       | [0.20; 0.53] | 5.3%            | 8.2%            |
| Bendell, J. C./2016    | 5      | 15    | 0.33       | [0.12; 0.62] | 2.2%            | 6.5%            |
| Cremolini, C./2018     | 21     | 116   | 0.18       | [0.12; 0.26] | 16.4%           | 9.4%            |
| Diminik P. Modest./2018| 16     | 63    | 0.25       | [0.15; 0.38] | 9.0%            | 8.9%            |
| Ogata, T./2019         | 2      | 17    | 0.12       | [0.01; 0.36] | 2.5%            | 6.7%            |
| E. Samalin/2019        | 22     | 70    | 0.31       | [0.21; 0.44] | 9.9%            | 9.0%            |
| Deng, Y./2020          | 5      | 67    | 0.07       | [0.02; 0.17] | 9.5%            | 9.0%            |
| Akhiito Tsuji/2021     | 21     | 173   | 0.12       | [0.08; 0.18] | 24.5%           | 9.7%            |

**Fig. 4** Forest plot of grade 3/4 diarrhea in mCRC patients treated with triplet chemotherapy plus anti-EGFR. ORR, objective response rate; mCRC, metastatic colorectal cancer

| Study                  | Events | Total | Proportion | 95%–CI       | Weight (common) | Weight (random) |
|------------------------|--------|-------|------------|--------------|-----------------|-----------------|
| C Garufi/2010          | 2      | 43    | 0.05       | [0.01; 0.16] | 7.7%            | 8.6%            |
| Souglakos, I./2011     | 7      | 30    | 0.23       | [0.10; 0.42] | 5.4%            | 7.9%            |
| ERIC ASSENAT/2011      | 16     | 42    | 0.38       | [0.24; 0.54] | 7.5%            | 8.6%            |
| Z Saridaki/2012        | 7      | 30    | 0.23       | [0.10; 0.42] | 5.4%            | 7.9%            |
| Folprecht, G./2013     | 13     | 28    | 0.46       | [0.28; 0.66] | 5.1%            | 7.8%            |
| Fornaro, L./2013       | 18     | 37    | 0.49       | [0.32; 0.66] | 6.6%            | 8.4%            |
| Bendell, J. C./2016    | 2      | 15    | 0.13       | [0.02; 0.40] | 2.7%            | 6.3%            |
| Cremolini, C./2018     | 36     | 116   | 0.31       | [0.23; 0.40] | 20.7%           | 9.9%            |
| Diminik P. Modest./2018| 10     | 63    | 0.16       | [0.08; 0.27] | 11.3%           | 9.2%            |
| Ogata, T./2019         | 10     | 17    | 0.59       | [0.33; 0.82] | 3.1%            | 6.6%            |
| E. Samalin/2019        | 15     | 70    | 0.21       | [0.13; 0.33] | 12.5%           | 9.4%            |
| Deng, Y./2020          | 21     | 67    | 0.31       | [0.21; 0.44] | 12.0%           | 9.3%            |

**Fig. 5** Forest plot of grade 3/4 neutropenia in mCRC patients treated with triplet chemotherapy plus anti-EGFR. ORR, objective response rate; mCRC, metastatic colorectal cancer.
The anti-EGFR agents significantly increased the pos-
demonstrated that the use of triplet chemotherapy plus
CI
R0RR were presented in the POCHER trial (60%, 95%
55.2% and 29.4%, respectively [27]. Consistent results of
P
= 0.012), and the overall resection rates were
the addition of cetuximab improved the DpR from 44
20–39%, \( I^2 = 86\)%, 28% (95% CI=20–37%, \( I^2 = 77\)%), and 17% (95% CI=11–24%, \( I^2 = 66\)%)
for diarrhea, neutropenia, and skin toxicity, respectively.
Three studies reported a dose reduction after a high inci-
dence of toxicity, mainly because of diarrhea and neu-
ropenia. After a dose adjustment, all studies considered
the side effects manageable through symptomatic meas-
ures. The detailed dosage of each drug is presented in
Table 2. Two studies pointed out that dose reduction did
not influence efficacy. The results should be interpreted
discreetly due to the retrospective design and small sam-
ple size. It should also be noted that nearly all included
patients had an ECOG performance score of 0–1.

Future prospects
With the development of surgery and toxicity man-
agement, the role of conversion therapy has become
increasingly important in colorectal cancer treatment,
especially in CLM patients. Thus, anti-EGFR plus tri-
plet chemotherapy, which is considered to be able
to increase the secondary surgery rate, has attracted
researchers’ attention. However, despite the inspir-
results mentioned above, several questions still
should be answered. First, we discuss the dose and the
treatment schedule of this therapy. It should be noted
that the drug dose and treatment cycles in each clini-
trial were not completely in accordance. Patients in
several trials experienced dose reduction. In addi-
tion, there were also apprehensions about the adjuvant

which were verified as capable of predicting treatment
outcomes and cetuximab efficacy [44, 45]. Two studies
used these indices as end points. The FOCULM study
demonstrated that compared with mFOLFOXIRI alone,
was slightly different from that of triplet chemotherapy
plus anti-VEGF therapy, in which neutropenia was the
most frequently observed grade 3/4 adverse event, with
an incidence of 45.8%, and the incidence of diarrhea was
only 17.8% [30]. In our meta-analysis, the pooled rates
an incidence of 45.8%, and the incidence of diarrhea was
20–39%,

| Study            | Events | Total | Proportion | 95%–CI     | Weight (common) | Weight (random) |
|------------------|--------|-------|------------|------------|----------------|----------------|
| C Garufi/2010    | 6      | 43    | 0.14       | [0.05; 0.28]| 7.5%           | 10.1%          |
| Sougklokos, I./2011 | 13     | 30    | 0.43       | [0.25; 0.63]| 5.2%           | 8.8%           |
| ERIC ASSENAT/2011 | 14     | 42    | 0.33       | [0.20; 0.50]| 7.3%           | 10.0%          |
| Z Saridaki/2012  | 1      | 30    | 0.03       | [0.00; 0.17]| 5.2%           | 8.8%           |
| Folprecht, G./2013| 5      | 28    | 0.18       | [0.06; 0.37]| 4.9%           | 8.6%           |
| Fornaro, L./2013 | 5      | 37    | 0.14       | [0.05; 0.29]| 6.4%           | 9.6%           |
| Bendell, J. C./2016 | 3      | 15    | 0.20       | [0.04; 0.48]| 2.7%           | 6.3%           |
| Cremolini, C./2018| 18     | 116   | 0.16       | [0.09; 0.23]| 20.0%          | 12.8%          |
| Diminik P.Modest./2018 | 9      | 63    | 0.14       | [0.07; 0.25]| 10.9%          | 11.3%          |
| Akhito Tsuji/2021| 21     | 173   | 0.12       | [0.08; 0.18]| 29.8%          | 13.6%          |
| **Common effect model** | **577** | **577** | **0.15** | **[0.12; 0.19]** | **100.0%** | --- |
| **Random effects model** | **577** | **577** | **0.17** | **[0.11; 0.24]** | --- | **100.0%** |

Heterogeneity: \( I^2 = 66\)%, \( \tau^2 = 0.0112, p < 0.01 \)

**Fig. 6** Forest plot of grade 3/4 skin toxicity in mCRC patients treated with triplet chemotherapy plus anti-EGFR. ORR, objective response rate; mCRC, metastatic colorectal cancer

Toxicity and dose adjustment
The most commonly observed adverse event in our
study was diarrhea (174/648), followed by neutropenia
(157/648) and skin toxicity (95/648). The toxicity profile
was slightly different from that of triplet chemotherapy
plus anti-VEGF therapy, in which neutropenia was the

| Weight (common) | Weight (random) |
|-----------------|-----------------|
| 0.1             | 0.2             |
| 0.3             | 0.4             |
| 0.5             | 0.6             |
### Table 4  Summary of grade 3/4 toxicity in patients treated by triplet chemotherapy plus anti-EGFR agents

| Author                  | Total | Neutropenia | FN  | Thrombopenia | Diarrhea | Nausea/vomiting | Anorexia | Stomatitis | Asthenia | Skin toxicity | Neurotoxicity | HFS | Hypomagnesemia | Others |
|-------------------------|-------|-------------|-----|--------------|----------|-----------------|----------|-------------|----------|---------------|---------------|-----|----------------|--------|
| C Garufi                | 43    | 2           | -   | -            | 15       | 4               | -        | 3           | 6        | -             | -             | -   | -              | 3      |
| Sougklakos, Ia¹         | 30    | 7           | NA  | NA           | 16       | NA              | NA       | NA          | NA       | 13            | 5             | NA  | NA             | NA     |
| ERIC ASSENIAT           | 42    | 16          | 2   | 5            | 22       | 4               | 10       | -           | 13       | 14            | 8             | 4   | -              | 4      |
| Z Saridaki              | 30    | 7           | 1   | 2            | 16       | 5               | -        | 3           | -        | 1             | -             | 1   | -              | 1      |
| Folprecht, G³           | 28    | 13          | NA  | NA           | NA       | NA              | NA       | NA          | NA       | NA            | NA            | NA  | NA             | NA     |
| Formaro, L              | 37    | 18          | 2   | -            | 13       | 5               | -        | 5           | 10       | 5            | 3             | 1   | 5              | -      |
| Bendell, J. C           | 18    | 2           | -   | 1            | 5        | 1               | 2        | -           | 3        | 3             | -             | 1   | 1              | 2      |
| Cremolini, C            | 116   | 36          | 4   | -            | 21       | 3               | 4        | 7           | 11       | 18            | -             | -   | -              | -      |
| D Modest                | 63    | 10          | -   | -            | 16       | 6               | -        | 6           | 5        | 9             | 2             | 4   | 3              | 17     |
| Ogata, T                | 17    | 10          | -   | -            | 2        | 1               | -        | -           | -        | -             | -             | -   | 2              | -      |
| E Samalina³             | 70    | 15          | 2   | NA           | 22       | NA              | NA       | NA          | NA       | NA            | NA            | NA  | NA             | NA     |
| Deng, Y                 | 67    | 21          | 2   | 1            | 5        | 1               | -        | 1           | 1        | -             | 3             | -   | -              | 6      |
| Akihito Tsuji³          | 173   | NA          | NA  | NA           | 21       | NA              | NA       | NA          | NA       | NA            | NA            | NA  | 7              | NA     |
| Total                   | 731   | 157         | 13  | 9            | 174      | 30              | 16       | 22          | 48       | 95            | 21            | 21  | 11             | 18     |

* Toxicity profile uncompleted; FN febrile neutropenia, HFS hand/foot syndrome, NA not available
or second-line treatment selection. The second question relates to treatment endpoints. Since one of the important objectives of anti-EGFR plus triplet chemotherapy treatment was to enhance the R0RR, some clinical trials chose ETS and DpR as primary endpoints instead of the ORR, which is the most frequently used endpoint. These indices might be easier for readers to interpret. However, we should not neglect our ultimate purpose, which is to prolong overall survival. Thus, complete follow-up is necessary for the final evaluation of this treatment. Third, the optimal criteria for patient selection remain unclear. It remains unclear how we can identify suitable treatment for patients according to their gene status, original side, metastatic condition, and so on. Fortunately, there are several ongoing RCTs, including DEEPER (mFOLFOXIRI+cetuximab vs. mFOLFOXIRI+bevacizumab, NCT02515734), TRIPLETE (mFOLFOXIRI+panitumumab vs. mFOLFOX6+panitumumab, NCT03231722), and PANIRINOX (mFOLFIRINOX+panitumumab vs. mFOLFOX6+panitumumab, NCT02980510), which aim to compare the efficacy of different combinations of doublet or triplet chemotherapy plus different target agents, and their results may be helpful in this regard.

Limitations
This study has several limitations that should be recognized. First, the eligible studies and the sample sizes of the included studies were relatively small. Heterogeneity between studies was relatively high, which may bias the results. Despite the utility of sensitivity analysis, the origin of heterogeneity could not be fully traced. Second, most of the studies were case series or retrospective studies, which may influence the accuracy of the results (especially in the assessment of adverse events). Third, a portion of the studies were only obtainable as conference abstracts. Despite efforts made to get in touch with authors for complete results, there remained crucial data uncollected. Fourth, the dosage of each study was not consistent; one of the included studies used capecitabine instead of 5-fluorouracil, affecting the outcome of the study and toxicity evaluation. Finally, this study was constrained to studies published in the English language only. Thus, the potential for publication bias cannot be ignored.
Table 5 Summary of related meta-analysis for a first-line treatment of mCRC

| Meta-analysis    | Included studies | Treatment | ORR       | mPFS (month) | mOS (month) | SRR     | Grade 3/4 toxicity                  | Neutropenia | Diarrhea | Febrile stomatitis |
|------------------|------------------|-----------|-----------|--------------|-------------|---------|-----------------------------------|-------------|----------|-------------------|
| Cremolini C [32] | CHARTA, OLIVIA, STEAM, TRIBE, TRIBE2 | bev+3-CT vs bev+2CT[^a^] | 64.5 vs 53.6% OR 1.57, P < 0.001 | 12.2 vs 9.9 HR 0.74, P < 0.001 | 28.9 vs 24.5 HR 0.81, P < 0.001 | 16.4 vs 11.8% OR 1.48, P = 0.007 | Neutropenia 45.8 vs 21.5% P < 0.001 FN 6.3 vs 3.7% P = 0.019 Diarrhea 17.8 vs 8.4% P < 0.001 |
| C Bokemeyer [33] | CRYSTAL, OPUS | Cet+2CT vs 2CT | 60.7 vs 40.9% OR 2.27, P < 0.0001 | 10.9 vs 7.7 HR 0.64, P < 0.0001 | 24.8 vs 21.1 HR 0.84, P = 0.0048 | NA | NA |
| F Pietrantonio [34] | Valentino, TRIBE, STEAM, CHARTA | pan+3CT vs bev+3CT | 73 vs 77% OR 0.79, P = 0.4 | 11.4 vs 13.3 HR 0.83, P = 0.11 | 30.3 vs 33.1 HR 0.8, P = 0.14 | 22 vs 18% P = 0.51 | Neutropenia 26 vs 48% P = 0.001 Diarrhea 14 vs 6%, P = 0.82 Febrile stomatitis 8 vs 6%, P = 0.67 |
| G Tomasello [35] | 11 studies | Bev+3CT | 69% (95%CI, 65–72%) | 12.4 (95%CI, 10–14.3) | 30.2 (95%CI, 26.5–33.7) | 36.6% (95%CI, 34.6–50.5%) | NA |

[^a^]: All KRAS and BRAF wild type; ORR Objective response rate, SRR Secondary resection rate, mPFS Median progression-free survival, mOS Median overall survival, 2CT Doublet chemotherapy, 3CT Triplet chemotherapy, FN Febrile neutropenia
Conclusion

Triplet chemotherapy plus anti-EGFR therapy seems to be capable of increasing the ORR of mCRC patients and R0RR of CLM patients. The toxicity of this treatment is manageable. High-quality RCT studies are required for further validation.

Abbreviations
mCRC: Metastatic colorectal cancer; anti-EGFR: Anti-epidermal growth factor receptor; ORR: Objective response rate; R0RR: R0 resection rate; mPFS: Median progression-free survival, mOS: Median overall survival, RCT: Randomized controlled trial, CLM: Colorectal liver metastasis; HR: Hazard ratio; CI: Confidence interval; RAS: Rat sarcoma; FDA: Food and Drug Administration; ASCO: American Society of Clinical Oncology; MINOS: Methodological Index for Non-Randomized Studies; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumors; OP: Depth of response; TTP: Time to progression; wt: Wild-type; mt: Mutant-type; pro.: Prospective study; retro.: Retrospective study; NA: Not available; NR: Not reached; CRR: Complete response rate; Cet: Cetuximab; Pan: Panitumumab; CPT-11: Irinotecan; L-OHP: 5-Fluorouracil; 5-FU: 5-Fluorouracil; FN: Febrile neutropenia; HFS: Hand/foot syndrome; SRR: Secondary resection rate; 2CT: Doublet chemotherapy; 3CT: Triplet chemotherapy.

Supplementary Information
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Additional file 1.

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Authors’ contributions
Conceptualization: QW, GDH. Methodology: WJP, QW. Software: WJP, QW. Supervision: WBG. Writing: QW, YFZ. The author(s) read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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