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The impact of combining cetuximab with the traditional chemotherapy regimens on clinical effectiveness in metastatic colorectal cancer: a systematic review and meta-analysis

Marryam Azeem[1], Anees ur Rehman[1*], Saba Rasheed[1], Aleena Shahzad[1], Muhammad Hamza Javed[1], Qurratul Ain Jamil[2], Hidayah Karuniawati[3] and Saleh Karamah Al-Tamimi[4*]

Abstract

Background Metastatic colorectal cancer (mCRC) poses a high rate of morbidity and mortality despite various treatment advances. Cetuximab, an anti-EGFR, has shown promising efficacy in improving outcomes when combined with chemotherapy. Understanding its efficacy is essential for optimizing treatment strategies in mCRC. This systematic review and meta-analysis aims to evaluate the effectiveness of combining cetuximab with chemotherapy in mCRC.

Methods PubMed and Google Scholar were systematically searched following the benchmarks indicated by PRISMA. The primary outcomes of the study were progression-free survival (PFS) and overall survival (OS). Statistical analyses were executed using Stata version 16.

Results The meta-analysis encompassed 25 studies involving 3788 mCRC patients. The median age spans from 18 to 77 years. The cetuximab plus chemotherapy exhibited a higher PFS and OS with a significant difference (PFS: HR = 0.79, 95% CI = 0.63–0.96, $p < 0.01$, $I^2 = 38\%$ and OS: HR = 0.78, 95% CI = 0.60–0.91, $p < 0.01$, $I^2 = 47\%$) compared to the control group. Subgroup analysis based on randomized controlled trials demonstrated consistent treatment effects for PFS (HR = 0.77, 95% CI = 0.62–0.93) and OS (HR = 0.76, 95% CI = 0.61–0.88) in the cetuximab treatment group.

Conclusions Combining cetuximab with chemotherapy offers a potential benefit in improving survival outcomes for metastatic colorectal cancer patients, as indicated by this study. These results suggest that cetuximab may be a valuable addition to mCRC treatment strategies, warranting further clinical investigation and integration into standard care.

Keywords Cetuximab, Chemotherapy, Anti-EGFR, Progression-free Survival, Overall Survival, Metastatic Colorectal Cancer, Systematic Review, Meta-analysis

*Correspondence:
Anees ur Rehman
aneesurrehmanr@gmail.com
Saleh Karamah Al-Tamimi
salehk810@gmail.com
Full list of author information is available at the end of the article

Background

Colorectal cancer (CRC) manifests the uncontrolled proliferation of cells in the colon or rectum [1]. CRC ranked third among cancers and stands as the second most common cause of death worldwide. CRC presented a serious health concern with over 1.9 million new cases and almost 904,000 deaths from CRC recorded globally in 2022. Based on incidence, it is the third most prevalent cancer in women and the second most common in males, demonstrating its substantial impact across genders [2].

CRC can be cured if diagnosed in its initial stages [3]. Metastasis is a major complication in CRC patients [4]. Almost, 15%–30% of CRC patients have metastases at the time of diagnosis and 20%–50% of CRC patients will eventually experience metastases. The 5-year survival rate for mCRC is typically 14%, while that of regional and localized CRC is 90% and 71%, respectively [5].

Over recent decades, significant advancements in CRC treatment have improved survival outcomes in patients with metastasis. These survival benefits are attributed to progress in early detection techniques and managing localized metastases by administering various immunotherapies, targeted therapies and monoclonal antibody protocols in mCRC [6].

Treatment approaches for mCRC are tailored to each patient, considering their tumour characteristics, life expectancy, overall health status and patient's personal preferences [7]. Primary treatments for mCRC typically include chemotherapy, targeted therapy or a combination of both approaches [8]. Chemotherapy is indicated as first-line therapy to eradicate or inhibit cancer cell proliferation in the mCRC and 5-Florouracil, folinic acid, oxaliplatin, irinotecan or capecitabine are used in combination with various chemotherapy regimens [9]. The combination regimens include FOLFIRI (5-fluorouracil and leucovorin with irinotecan), FOLFOX (5-fluorouracil and leucovorin with oxaliplatin), XELOX (capecitabine with oxaliplatin) and FOLFOXIRI (5-fluorouracil and leucovorin with oxaliplatin and irinotecan) [10]. For patients with mCRC, the combination of chemotherapy and targeted therapy is frequently employed as the initial course of treatment [11]. Targeted therapies can successfully treat malignant cells by interfering with the processes that allow them to proliferate and differentiate [12].

Various monoclonal antibodies have been approved as a targeted therapy to treat cancer patients [13]. These antibodies are derived from a single clone of B-cells, highly uniform and specifically target a single epitope. They provide greater therapeutic effects and are generally well-tolerated by patients, providing fewer adverse reactions than chemotherapeutic drugs [14]. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved the clinical use of two types of monoclonal antibodies for treating mCRC: anti-EGFR antibodies such as cetuximab and panitumumab, which act to inhibit the epidermal growth factor receptor and VEGF inhibitors like bevacizumab, which block vascular endothelial growth factor [15].

Cetuximab is an IgG1 type of monoclonal antibody that is chimeric, combining both human and murine antibody components, specifically targeting the epidermal growth factor receptor (EGFR) [13]. Cetuximab interacts with EGFR, effectively blocking its intracellular signaling. This leads to the inhibition of cell proliferation, angiogenesis and differentiation and apoptosis stimulation. Cetuximab also prevents the release of proteases and their inhibitors, thereby reducing the risk of metastasis [16]. Cetuximab triggers various immune responses in addition to EGFR signaling inhibition, including antibody-dependent cellular cytotoxicity (ADCC) through natural killer (NK) cells and complement-dependent cytotoxicity (CDC), leading to antitumour activity. Cetuximab also modulates the immune microenvironment by inducing cytotoxic T-cell activation, enhancing antigen presentation and reducing regulatory T-cells, thereby enhancing anti-tumour immunity and its therapeutic efficacy [17–19].

RAS family proteins, such as KRAS (Kirsten rat sarcoma viral oncogene homolog) and NRAS (Neuroblastoma RAS viral oncogene homolog), play crucial roles in intracellular signaling pathways mediated by EGFR. Mutations in RAS genes, commonly found in mCRC, frequently occur in 2, 3 and 4 exons. Among these, the mutation in KRAS exon 2 is the most prevalent [11]. Cetuximab improves progression-free survival (PFS) and overall survival (OS) in patients with wild-type KRAS genotypes, but it is thought to be ineffective in individuals with mutant KRAS. In first-, second- or third-line settings for mCRC patients carrying wild-type KRAS, cetuximab is recommended as monotherapy or in combination with chemotherapy in the world [20].

Cetuximab was approved for treating malignancies expressing EGFR after irinotecan therapy failure in 2004. Cetuximab was authorized as a first-line treatment for wild-type KRAS mCRC in 2008 and its application was broadened to encompass NRAS mCRC and wild-type KRAS in 2013 [21]. It has been demonstrated that patients with mCRC benefit from cetuximab when paired with chemotherapy therapies [22].

Cetuximab was shown to improve median PFS and to lower the risk of disease progression in patients with wild-type KRAS when added to the FOLFOX-4 regimen. Moreover, when cetuximab and chemotherapy were combined, OS was significantly longer than when chemotherapy was used alone [23]. Research showing robust evidence in PFS and OS endpoints, validates the use of

cetuximab in conjunction with FOLFOX chemotherapy as a first-line treatment regimen, for patients with wild-type RAS mCRC [24–26]. Those patients having RAS and KRAS wild-type metastasis experienced greater survival benefits in PFS and OS after administering cetuximab with FOLFIRI [27, 28]. Cetuximab has also demonstrated promising efficacy in mCRC patients when given as a first-line or second-line regimen along with XELOX or XELIRI chemotherapies [29–31].

Previous studies have demonstrated promising efficacy with the administration of cetuximab in combination with chemotherapy in mCRC management. However, there has been variability in the findings of individual trials and the significant differences in the combining pattern of cetuximab with different chemotherapies. Considering the use of cetuximab, we aim to investigate its efficacy and survival benefits in terms of PFS and OS outcomes through a comprehensive literature review. By synthesizing data from multiple studies, the study endeavors to comprehensively bridge the gap between the findings of individual research studies and their effective application in real-world clinical practice, ultimately enhancing the evidence-based findings in mCRC. Through its systematic approach, this review will also provide a comprehensive overview that can guide oncologists in decision-making and provide future cancer research directions.

Methods

This systematic review and meta-analysis was carried out under PRISMA standards [32] and the protocol is filed in the PROSPERO database with registration number CRD42023456714 [33].

Search strategy

A thorough search was conducted using electronic databases, such as PubMed and Google Scholar, to find pertinent studies. The following search terms were utilized in the PubMed search: "colorectal cancer", "colorectal carcinoma", "colorectal neo-plasm", "colorectal tumour", "monoclonal antibody", "anti-EGFR", "cetuximab", "treatment outcomes", "treatment efficacy". These search phrases were concatenated using Boolean operators (AND, OR) to ensure comprehensive study retrievals. The reference lists of the shortlisted research were also manually searched, to find pertinent papers. The literature search was restricted to English-language works. The literature search was conducted between December 18, 2002 and October 15, 2023, to identify relevant published studies. Initially, M.A. systematically searched the literature to explore the relevant studies. S.R. carried out an independent validation of the search to ensure its comprehensiveness. This validation involved re-executing the search strategy using the same terms and criteria, ensuring no potential study was overlooked.

Study selection and criteria

All of the citations discovered through database searches were assembled into an electronic library using Endnote bibliographic software, which was also used to eliminate duplicate citations. Initially, search results were screened through the titles and abstracts for the potentially eligible studies, these were further assessed for full-text using previously defined inclusion and exclusion criteria. The studies were considered for inclusion if these had histologically and pathologically confirmed diagnoses of metastatic in colorectal cancer patients, patients aged ≥ 18 years, observational studies, non-randomised clinical trials or randomised controlled trials, patients receiving cetuximab in addition to conventional chemotherapy regimens and providing sufficient data on patient outcomes and treatment efficacy and patient's life expectancy > 3 months.

Unavailable studies, non-human studies, invitro pharmacokinetic and pharmacodynamics studies, case reports, editorials, conference abstracts, reviews and studies not reporting desired outcomes were excluded.

Study outcomes

Our review's main findings were progression-free survival (PFS) and overall survival (OS). The term "progression-free survival" describes the time interval between the start of a therapy or its randomisation and the onset of a disease or death [34]. Overall survival describes the time from the diagnosis to death [35]. PFS and OS definitions and reporting practices slightly varied between studies. Different terms and definitions used for reporting PFS and OS survival metrics across the included studies were synchronized to synthesize the survival outcomes. Progression-free survival and alternative outcomes such as time to tumour progression (TTP) were grouped under PFS and overall survival and median survival times were under the term OS. This approach was employed to reduce the potential bias and inconsistency in the survival outcomes.

Data extraction form

A typical format sheet was designed using MS Word to integrate all the data from the retrieved studies. Title, the first author, journal name, publication year, objective, study design, duration, study population, median age, gender ratio, therapy protocols, follow-up data, median PFS, median OS and their corresponding hazard ratios (HRs) with 95% confidence interval (CI) and *p*-values were among the extracted data. Two reviewers, M.A. and S.R. independently retrieved these data from

encompassed studies. Disagreements regarding data extraction occurred, primarily related to study design, study duration, patient population details, sample size, treatment protocols, outcome measures and subgroup categorization. The extent of these discrepancies varied, minor issues such as sample size, study duration and treatment protocols were resolved immediately by M.A. and S.R. through meaningful dialogue. The substantial discrepancies regarding the study design, population details, outcomes measures and subgroup categorization were settled through detailed discussion or involving a third reviewer, A.U.R. All discrepancies were documented and consensus was reached through insightful conversation, ensuring the final extracted data set was accurate and being agreed by all reviewers.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was employed to appraise the studies [36]. Two reviewers, M.A. and S.R. independently assess the quality of studies, following pre-defined criteria. Discrepancies regarding the quality assessments were brought to another reviewer to reach a consensus, ensuring a robust evaluation of studies. NOS contains three main criteria: study selection group, comparability group and outcome/exposure determination. Higher rankings indicate a higher quality and a lesser chance of bias. The scores range from 0 to 9 stars. A study receiving seven to nine stars was seen as having a low risk of bias, a study receiving four to six stars was regarded as having a moderate risk of bias and a study receiving fewer than four stars was evaluated as having a high risk of bias. NOS ensured a systematic assessment of the quality of the included research.

Statistical analysis

Pooled estimates were calculated using either a fixed-effects model or a random-effects model, depending on the level of heterogeneity observed among the studies. We evaluated homogeneity using I^2 statistics. The fixed-effects model was employed for $I^2 < 50\%$ to account for low heterogeneity, otherwise the random-effects model was for considerable heterogeneity, $> 50\%$. Based on I^2 values, studies were grouped into having low (25–50%), moderate (50–75%) and high heterogeneity ($> 75\%$) [37]. The subgroup analysis was conducted to determine how the study design affected the PFS and OS study outcomes and to address potential heterogeneity. The forest plots were constructed to display the pooled findings of the PFS and OS, providing a visual summary of the data. Publication bias was assessed through funnel plots, where the standard error of the log HR of each study was plotted against the corresponding hazard ratio (HR), to visualize the relationship between effect estimates and the study precision. A two-sided *P*-value less than 0.05 was used to determine statistical significance. Stata, version 16 was employed to execute all the statistical analysis (Stata Corp, College Station, TX).

Results

Literature search and study characteristics

Initially, systematically searching the selected databases produced 709 studies. After removing duplicates, 651 studies underwent the title and abstract screening. After reviewing these, 560 studies were primarily excluded: review articles, irrelevant studies, non-CRC studies and case reports, resulting in 91 studies for further full-text evaluation based on the pre-defined criteria. Among them, 84 articles were excluded and the final analysis contained 25 potential studies [21, 22, 26, 30, 38–58]. The systematic review included studies with various methodologies, 6 were phase II & III randomised controlled trials, with a high level of evidence through their comparative groups, 6 were multicenter phase II clinical trials, 4 were phase I & II prospective trials, 4 were prospective cohort and 6 were retrospective studies. This diverse range of studies contributed to a comprehensive analysis of our study. Figure 1 shows the selection process of studies using PRISMA.

Patient characteristics

The included trials comprised a total of 3788 cases of mCRC, of which 1421 were in the chemotherapy group and 2367 were in the cetuximab with chemotherapy group. The median age of patients ranges from 18 to 77 years. Included patients have either an ECOG performance status of ≤ 2 or a WHO score of ≤ 2 or a Karnofsky performance status score of ≥ 70. Anti-EGFR cetuximab was administered to each patient along with one or more chemotherapy regimens. Cetuximab-based chemotherapy combinations were XELOX/CAPOX, FOLFIRI, FOLFIXIRI, mFOLFOXIRI, FOLFOX and mFOLFOX. Treatment regimens include median cycles of 1 to 12. The median follow-up data was reported by 18 studies and ranged from 2–72 months. The characteristics of the included studies are shown in Table 1 and the characteristics of the patients are described in the supplementary Table S1.

Outcomes measures

Efficacy of cetuximab plus chemotherapy on survival outcomes

Median PFS (mPFS) was reported in 25 studies and it ranges from 3.0–15.7 months. The median overall survival (mOS) obtained from 23 studies, ranges from 11.2–32.6 months. However, the meta-analysis was conducted on 24 PFS and 21 OS studies providing data

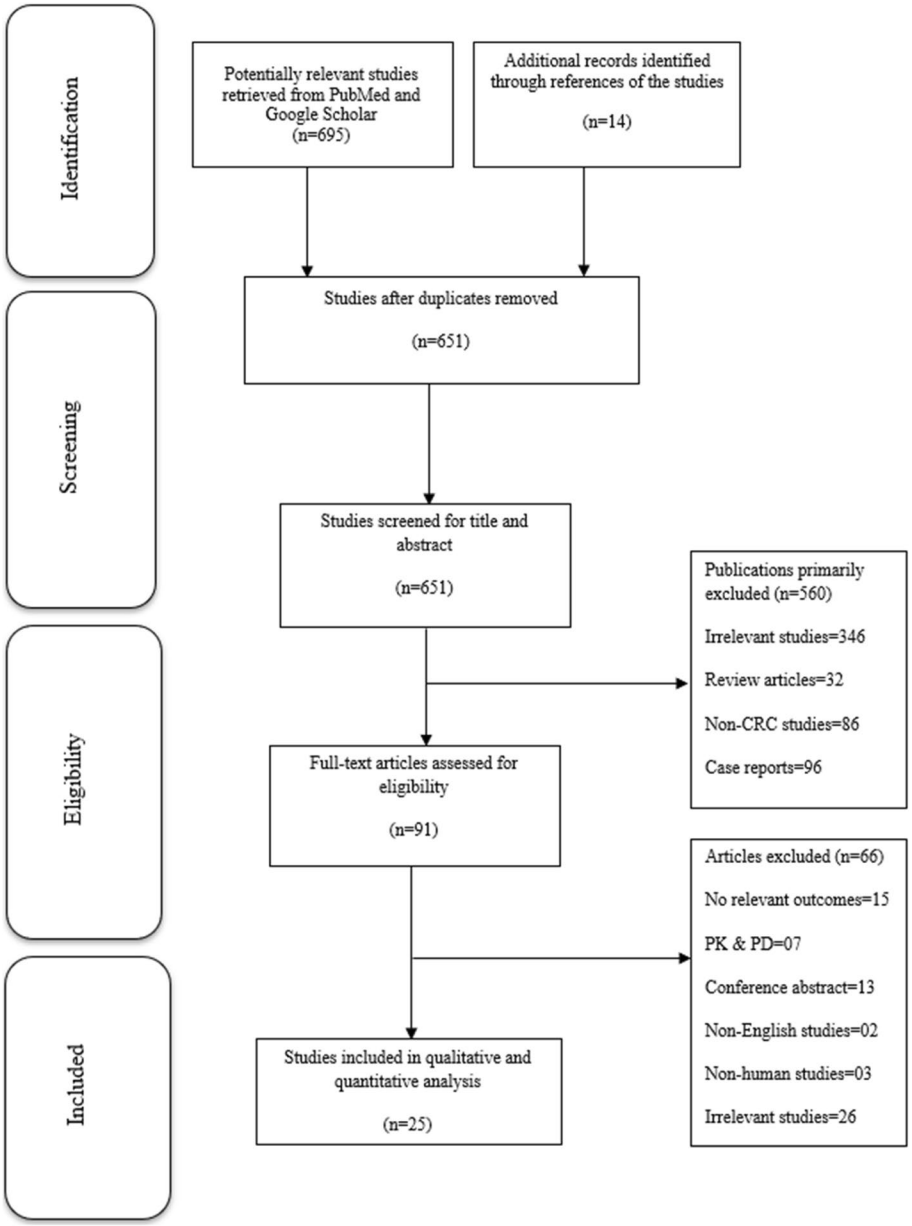

Fig. 1 Studies selection process using PRISMA

on HR with corresponding CI and *P*-values. The fixed effect model was employed to calculate the PFS and OS log HR values. The PFS findings demonstrated that adding cetuximab to chemotherapy has significantly lowered the risk of disease progression in mCRC resulting in improved progression-free survival (HR = 0.79, 95% CI = 0.63–0.96, $p < 0.01$). The statistical findings (Z = 53.2, $I^2 = 38$) highlight the therapeutic advantage of cetuximab with chemotherapy in prolonging disease-free survival compared to chemotherapy alone, as shown in Fig. 2. The OS meta-analysis showed that the group receiving cetuximab with chemotherapy had considerably better results than the chemotherapy-alone receiving group (HR = 0.78, 95% CI = 0.60–0.91, $p < 0.01$). Figure 3 illustrates the significant effect of adding cetuximab to chemotherapy in terms of enhancing patient survival, despite the moderate heterogeneity reported in these results (I2 = 47%, Z = 43.92). The fixed-effects model was considered appropriate over the random-effects model as I^2 values were less than the 50% threshold, indicating moderate heterogeneity for estimating minimal variability between studies.

Table 1 Characteristics of the Included Studies

Study	Publishing year, Country	Study design	Phase	No. of Patients		Therapy Protocol		Median Follow-up (months)	Study Outcomes	median PFS (months)			median OS (months)		
				C	E	C	E			C	E	*P*-value	C	E	*P*-value
Stintzing, Heinrich et al. [38]	2023, Germany	RCT	II	30	59	Bevacizumab + FOLFOX	Cetuximab + FOLFOX	2.0	PFS OS	12.4	7.6	0.003	22.9	15.2	0.14
Kang, Lee et al. [39]	2023, Korea	Retrospective	-	26	19	Bevacizumab + FOLFOX-6	Cetuximab FOLFOX-6 +	27.6	PFS OS	11.5	11.1	0.92	25.6	32.4	0.92
Wu, Wang et al. [40]	2021, China	Retrospective	-	78	58	mFOLFOX/ XELOX/ FOLFIRI	Cetuximab + mFOLFOX/ XELOX/ FOLFIRI	21.0	PFS OS	7.4	9.5	0.013	19.8	25.1	0.038
Huang, Gu et al. [41]	2021, China	Retrospective	-	104	100	Bevacizumab + FOLFOXIRI	Cetuximab + FOLFOXIRI	27.0	PFS OS	8.4	10.7	0.02	11.7	17.7	0.07
Kadowaki, Masuishi et al. [42]	2021, Japan	Prospective	Ib	_	9	_	Cetuximab FIOLFOXIRI +	29.8	PFS	_	11.8	_	_	_	_
Heinemann, von Weikersthal et al. [43]	2021, Germany	RCT	III	183	169	Bevacizumab + FOLFIRI	Cetuximab + FOLFIRI	72.0	PFS OS	10.4	10.3	0.71	25.6	31.1	0.012
Sagawa, Sato et al. [44]	2020, Japan	Retrospective	-	60	50	Bevacizumab + FOLFOX/ FOLFIRI	Cetuximab + FOLFOX/ FOLFIRI	25.1	PFS OS	10.2	12.6	0.06	25.6	38	0.0584
Jiang, Chen et al. [45]	2020, China	Prospective cohort	-	28	44	Cetuximab + FOLFIRI	Cetuximab + FOLFIRI followed by maintenance cetuximab + irinotecan	18.0	PFS	13	19	< 0.001	_	_	_
Kasper, Meiler et al. [46]	2020, Germany	Multicenter trial	II	_	57	_	Cetuximab + FOLFOX-6	42.9	PFS OS	_	10.1	_	_	28.7	_
Wei, Chen et al. [47]	2020, China	Prospective cohort	-	55	55	Cetuximab	Cetuximab + Oxaliplatin/ 5-Fluorouracil/ capcitabine	C = 48.7 E = 44.4	PFS OS	7.4	11.2	0.003	12.3	16.8	0.007
Qin, Li et al. [26]	2018, China	RCT	III	200	193	FOLFOX-4	Cetuximab + FOLFOX-4	_	PFS OS	7.4	9.2	0.004	17.8	20.7	0.02
Rouyer, François et al. [21]	2018, France	Retrospective	-	_	389	_	Cetuximab + Irinotecan/oxaliplatin	24.0	PFS OS	_	9.2	_	_	23	0.48
Hazama, Maeda et al. [30]	2016, Japan	Multicenter trial	II	_	40	_	Cetuximab + XELOX	_	PFS OS	_	6.5	_	_	24.3	_
Uemura, Kim et al. [48]	2016, Japan	Prospective cohort	-	_	64	_	Cetuximab + FOLFOX/ FOLFIRI/ XELOX	36.4	PFS OS	_	11.9	_	_	39.6	_

Table 1 (continued)

Study	Publishing year, Country	Study design	Phase	No. of Patients		Therapy Protocol		Median Follow-up (months)	Study Outcomes	median PFS (months)			median OS (months)		
				C	E	C	E			C	E	*P*-value	C	E	*P*-value
Wasan, Meade et al. [49]	2014, United Kingdom	RCT	II	112	114	Intermittent cetuximab + Intermittent chemotherapy (FOLOX)	Continuous cetuximab + Intermittent chemotherapy (FOLFOX)	Intermittent cetuximab = 32.8 Continuous cetuximab = 34.2	PFS OS	3.1	5.8	_	16.8	22.2	_
Fernandez-Plana, Pericay et al. [50]	2014, Spanish	Multicenter trial	II	_	99	_	Biweekly cetuximab + FOLFOX-4	17.8	PFS OS	_	10.1	_	_	20.8	_
Chen, Chiang et al. [22]	2013, Taiwan	Retrospective	-	10	40	_	Cetuximab + FOLFOX-4/ FOLFIRI	_	PFS OS	4.1	12.13	0.257	15.13	28.77	0.014
Sastre, Grávalos et al. [51]	2012, Spain	Prospective cohort	-	_	66	_	Cetuximab + capcitabine	_	PFS OS	_	7.1	_	_	16.1	_
Maughan, Adams et al. [52]	2011, United Kingdom	RCT	III	815	815	Oxaliplatin plus Fluoropyrimidine chemotherapy	Cetuximab + Oxaliplatin plus Fluoropyrimidine chemotherapy	_	PFS OS	8.6	8.6	0.6	17.9	17	0.67
Shitara, Yokota et al. [53]	2011, Japan	Multicenter trial	II	_	30	_	Cetuximab + Irinotecan combination chemotherapy	_	PFS OS	_	5.8	_	_	NR	_
Colucci, Giuliani et al. [54]	2010, Italy	Multicenter trial	II	_	67	_	Cetuximab + FOLFOX-4	10.1	PFS OS	_	10	_	_	22	_
Bokemeyer, Bondarenko et al. [55]	2009	RCT	II	168	169	FOLFOX-4	Cetuximab + FOLFOX-4	_	PFS	7.2	7.2	0.617	_	_	_
Tabernero, Van Cutsem et al. [56]	2007	Multicenter trial	II	_	43	_	Cetuximab + FOLFOX-4	30.5	PFS OS	_	12.3	_	_	30	_
Koo, Lee et al. [57]	2007, Korea	Prospective	II	_	31	_	Cetuximab + Biweekly FOLFIRI	13.2	PFS OS	_	2.9	_	_	10.9	_
Souglakos, Kalykaki et al. [58]	2007, Greece	Prospective	II	_	40	_	Cetuximab + CAPOX	8.1	PFS OS	_	2.9	_	_	10.7	_

CAPOX/XELOX Capcitabine plus oxaliplatin, *C* Control Group, *E* Experimental Group, *FOLFIRI* 5-FU and folinic acid with irinotecan, *FOLFOX* folinic acid and 5-FU with oxaliplatin, *FOLFOXIRI* 5-FU and folinic acid with irinotecan and oxaliplatin, *mFOLFOXIRI* 5-FU and folinic acid with modifies irinotecan and oxaliplatin, *OS* Overall Survival, *PFS* Progression-Free Survival, *RCT* Randomised Controlled Trial

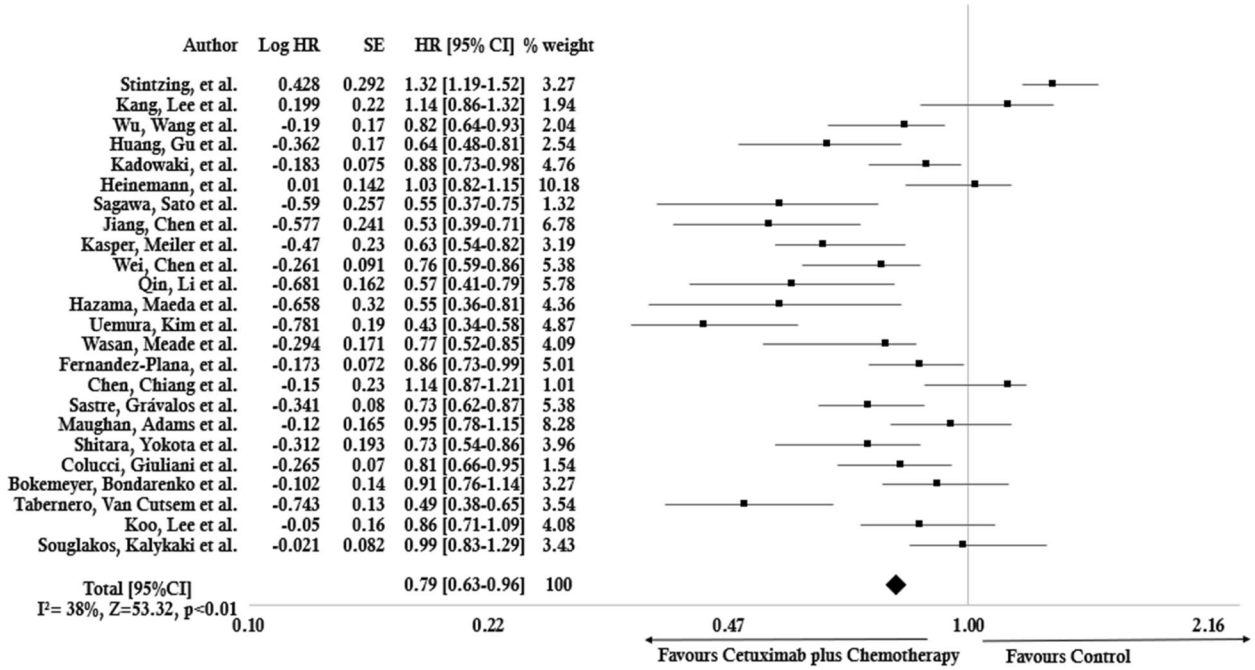

Fig. 2 Forest Plot of PFS for cetuximab plus chemotherapy regimens using fixed effect model

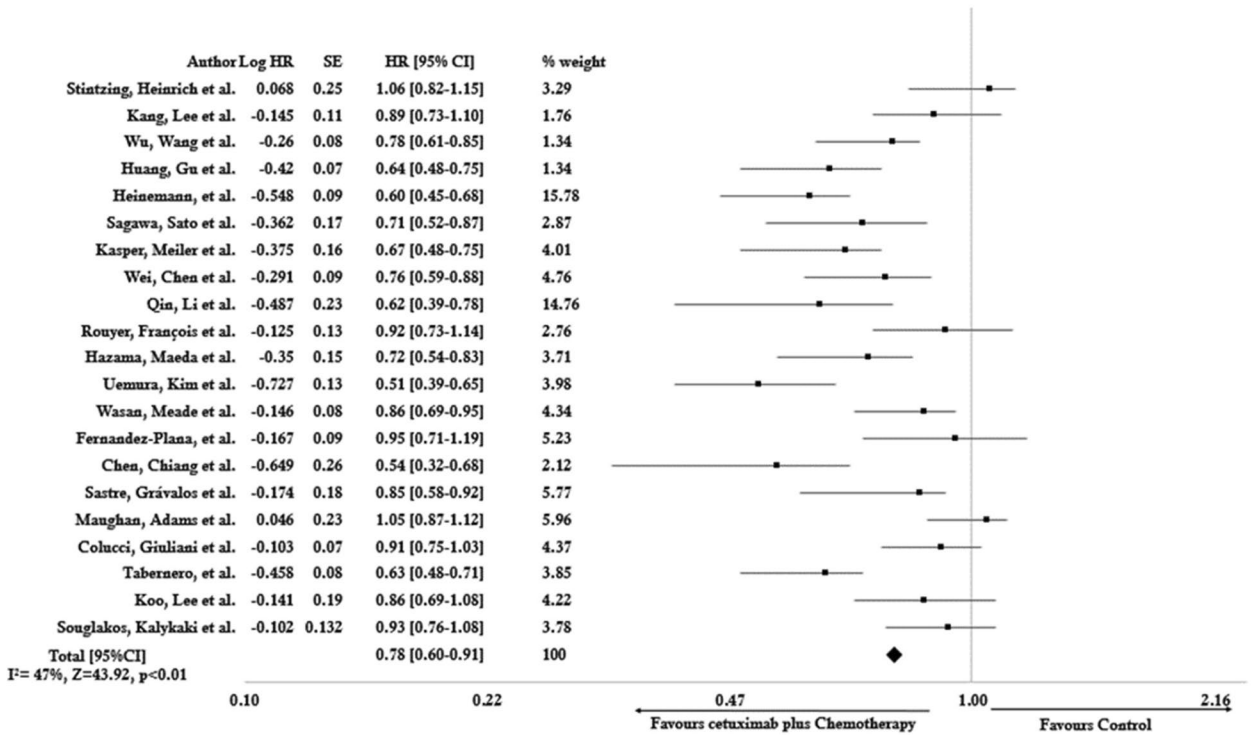

Fig. 3 Forest Plot of OS for cetuximab plus chemotherapy regimens using fixed effect model

Subgroup analysis of survival outcomes

Subgroup analysis based on study design was conducted to determine whether the treatment effect varies significantly or consistently between the studies or not. A fixed effect model was used to compute the PFS and OS subgroup findings. Moreover, sub-group analysis

based on the study design showed mild heterogeneity (I2 = 17% for PFS and I2 = 23% for OS), justifying the choice of a fixed-effects model over random effect to generate precise pooled estimates. The subgroup analysis of PFS in RCTs suggested a statistically significant and consistent treatment effect across the studies ($I^2 = 17\%$, Z = 58.51, $p < 0.01$, HR = 0.77, 95% CI = 0.62–0.93). As for OS, the moderate heterogeneity (I2 = 23%) suggests some variability in effect sizes across the studies, but the high Z-score and low p-value reinforce the strength of the treatment effect among the studies (Z = 48.15, $p < 0.01$, HR = 0.76, 95% CI = 0.61–0.88). The subgroup meta-analysis indexed to PFS and OS presented on forest plots favours the cetuximab plus chemotherapy arm shown in Figs. 4 and 5, respectively.

Risk of bias assessment

The NOS assessed the methodological quality of each included study. Among them, six studies scored 9 stars, nine scored 8, six received 7 and four studies scored 6 stars on the NOS scale. The mean score was 7, indicating overall high study quality and low risk of bias. Hence, this distribution of scores showed that 60% of the studies have a low risk of bias, while 40% have a moderate risk of bias, ensuring a robust methodological quality. Some confounding factors might have influenced the pooled findings of our meta-analysis, despite its high methodological quality. To acknowledge and mitigate the impact of these factors on our pooled estimates, a subgroup analysis was conducted. The subgroup analysis effectively compacted the high risk of bias by stratifying the studies based on study design, which was deemed to be a significant cofounder. So, potential bias was addressed in a structured way through subgroup analysis and no differential weighting based on NOS scores was applied. The quality assessment of the included is shown in Table 2.

Publication bias

Publication bias is the potential source of biases in the meta-analysis, defining how the unpublished data could contradict the findings of published studies. The funnel plot provides a visual assessment of the publication bias. The central line indicates the pooled estimate hazard ratio, while the sloping lines represent the expected 95% confidence intervals for a given standard error, assuming no heterogeneity between studies. PFS and OS were indexed to generate an inverted funnel plot for possible publication bias. Figures 6 and 7 showed funnel plots for PFS and OS respectively. Visual inspection of the PFS funnel plots showed no significant asymmetry, indicating no evidence of obvious publication bias. While funnel plot for OS suggested a potential bias, as indicated by the slight asymmetry in the distribution of the studies around the central line (HR = 0.78). Hence, publication bias has a mild effect on the robustness of our findings.

Discussion

Monoclonal antibodies are effective therapeutic options in mCRC treatment. Cetuximab, an anti-EGFR monoclonal antibody, demonstrated a significant advancement in managing mCRC when combined with various chemotherapy regimens. When used in conjunction

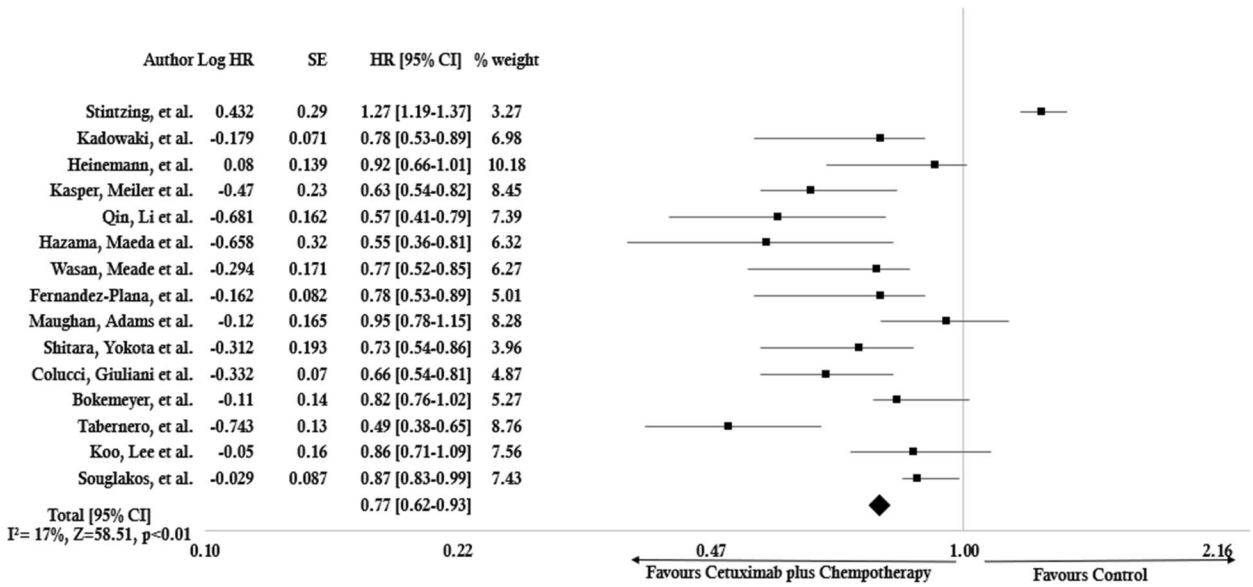

Fig. 4 Forest Plot of PFS Subgroup analysis for cetuximab plus chemotherapy regimens using fixed effect model

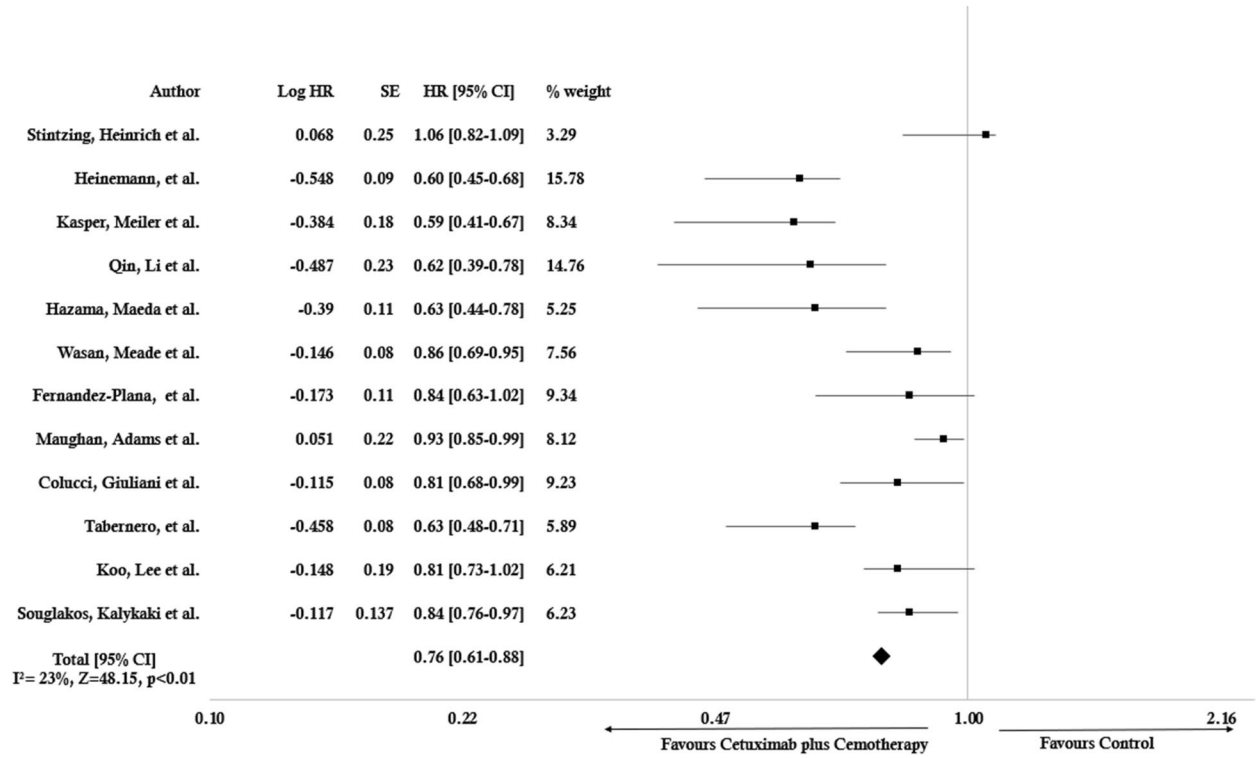

Fig. 5 Forest Plot of OS Subgroup analysis for cetuximab plus chemotherapy regimens using fixed effect model

with chemotherapy, cetuximab had a better prognosis for patients with CRC who had metastases by improving both overall and progression-free survival. Our meta-analysis encompassed 3788 mCRC patients from 25 comprehensive studies, receiving cetuximab in addition to various chemotherapy combinations. Compared to chemotherapy alone, cetuximab in plus chemotherapy has provided robust treatment efficacy in patients with metastasis in managing their disease effectively, improving quality of life and living longer. This personalized treatment paradigm has also provided the benefit of survival rates and disease progression. The use of cetuximab in conjunction with chemotherapies has been validated by our findings, primarily demonstrating statistically and clinically substantial improvements in the PFS and OS outcomes in mCRC patients. When cetuximab was added to chemotherapy, the PFS findings demonstrated a 21% reduction in the probability of tumour progression when compared to the group receiving chemotherapy alone. Similarly, combined OS data also showed that adding cetuximab to chemotherapy reduced the risk of death by 22%. The metastatic patients in the cetuximab and chemotherapy group experienced longer OS periods than those in the control group, resulting in a reduction of disease progression. Therefore, the pooled findings of our study emphasize the value of using cetuximab in addition to chemotherapy treatments in managing mCRC.

Our findings aligned with the meta-analysis conducted by Cao, Xu et al. which included 2,977 patients and examined how different KRAS statuses and tumour locations affected the efficacy of cetuximab-based chemotherapies. In terms of survival outcomes, the study consistently reported treatment effects that aligned with our findings. This demonstrates how using cetuximab, an anti-EGFR, in conjunction with chemotherapy lowers the chance of disease progression and improves survival rates in mCRC [59].

The pooled finding of Li, Liang et al. meta-analysis through 12 randomised controlled trials treating 7108 mCRC patients, closely aligns with our study treating 3788 mCRC patients. The study has demonstrated the superiority and promising efficacy of cetuximab-based regimens for PFS [14]. Our pooled outcomes were in line with the findings of Colucci, Giuliani et al. [54] results, which showed clinically relevant benefits in the PFS, resulting in prolonging the OS time. This multicenter phase II trial administered cetuximab with FOLFOX-4 as a first-line chemotherapy regimen in all the metastatically confirmed colorectal patients.

A prospective analysis of Uemura, Kim et al.'s [48] study, was not concordant with our pooled data and used

Table 2 Quality assessment of the included studies

Author	Year	NOS Scale for evaluating the quality of case–control and cohort studies			Total score	Risk of bias
		Selection	Comparability	Outcome/ exposure		
Stintzing, Heinrich et al	2023	****	**	**	8/9	Low
Kang, Lee et al	2023	****	*	***	8/9	low
Wu, Wang et al	2021	****	*	***	8/9	low
Huang, Gu et al	2021	****	**	***	9/9	low
Kadowaki, Masuishi et al	2021	***	*	***	7/9	low
Heinemann, von Weikersthal et al	2021	****	**	***	9/9	low
Sagawa, Sato et al	2020	****	**	***	9/9	low
Jiang, Chen et al	2020	***	**	***	8/9	low
Kasper, Meiler et al	2020	**	**	**	6/9	Moderate
Wei, Chen et al	2020	****	**	***	9/9	low
Qin, Li et al	2018	****	*	**	7/9	low
Rouyer, François et al	2018	***	**	***	8/9	low
Hazama, Maeda et al	2016	****	**	***	9/9	low
Uemura, Kim et al	2016	****	*	***	8/9	low
Wasan, Meade et al	2014	****	**	***	9/9	low
Fernandez-Plana, Pericay et al	2014	**	**	***	7/9	low
Chen, Chiang et al	2013	***	**	***	8/9	low
Sastre, Grávalos et al	2012	***	**	***	8/9	low
Maughan, Adams et al	2011	****	**	**	8/9	low
Shitara, Yokota et al	2011	**	**	**	6/9	Moderate
Colucci, Giuliani et al	2010	**	**	**	6/9	Moderate
Bokemeyer, Bondarenko et al	2009	****	**	**	7/9	low
Tabernero, Van Cutsem et al	2007	***	**	*	6/9	Moderate
Koo, Lee et al	2007	***	**	**	7/9	low
Souglakos, Kalykaki et al	2007	***	**	**	7/9	low

Following the Newcastle–Ottawa Scale (NOS) criteria, a study may be assigned a maximum of one star in each selection and outcome/exposure category and a maximum of two stars in the comparability category

different first-line chemotherapies with cetuximab. The PFS findings predicted greater benefits in the intervention group, giving about 57% lower disease progression events while our study provided a 21% reduction in disease progression in mCRC patients. This disparity in our pooled hazard ratio might be attributed to evaluating the efficacy of various pre-defined chemotherapy regimens with cetuximab. A multicenter phase II non-randomised trial [56], has evaluated how well cetuximab and oxaliplatin-based FOLFOX-4 chemotherapy works to inhibit EGFR metastasis. The pooled analysis has documented that the frequency of potential benefits in the downsizing of tumours was the same as the experiencing of disease-related events by using this therapy in mCRC patients.

Heinemann, von Weikersthal et al. [43], a phase III RCT, has predicted the benefits in the PFS findings. Irinotecan-based FOLFIRI chemotherapy was compared with bevacizumab and cetuximab arms, respectively. There was not much contrary in the lengthening of PFS in the chemotherapy and cetuximab plus chemotherapy groups, respectively, 10.4 months and 10.3 months. The similar efficacy in both groups and not supporting a single group is likely to be attributed to the large number of trial centers.

The Trotta, Ottaiano et al. study has evaluated the correlation between cetuximab-mediated antibody-dependent cell toxicity (ADCC) and the Fcy polymorphism in mCRC, illustrating that patients having specific Fcy receptor polymorphism exhibited a substantially higher ADCC level and improved PFS. Additionally, the enhanced activity of natural killer cells demonstrates a promising response. These findings suggested the potential for genetic profiling and immune response activity characterization as a valuable predictor of cetuximab's effectiveness in mCRC [60].

The subgroup analysis based on RCTs has provided further insights into the impact of combining cetuximab with chemotherapy in mCRC patients. The low

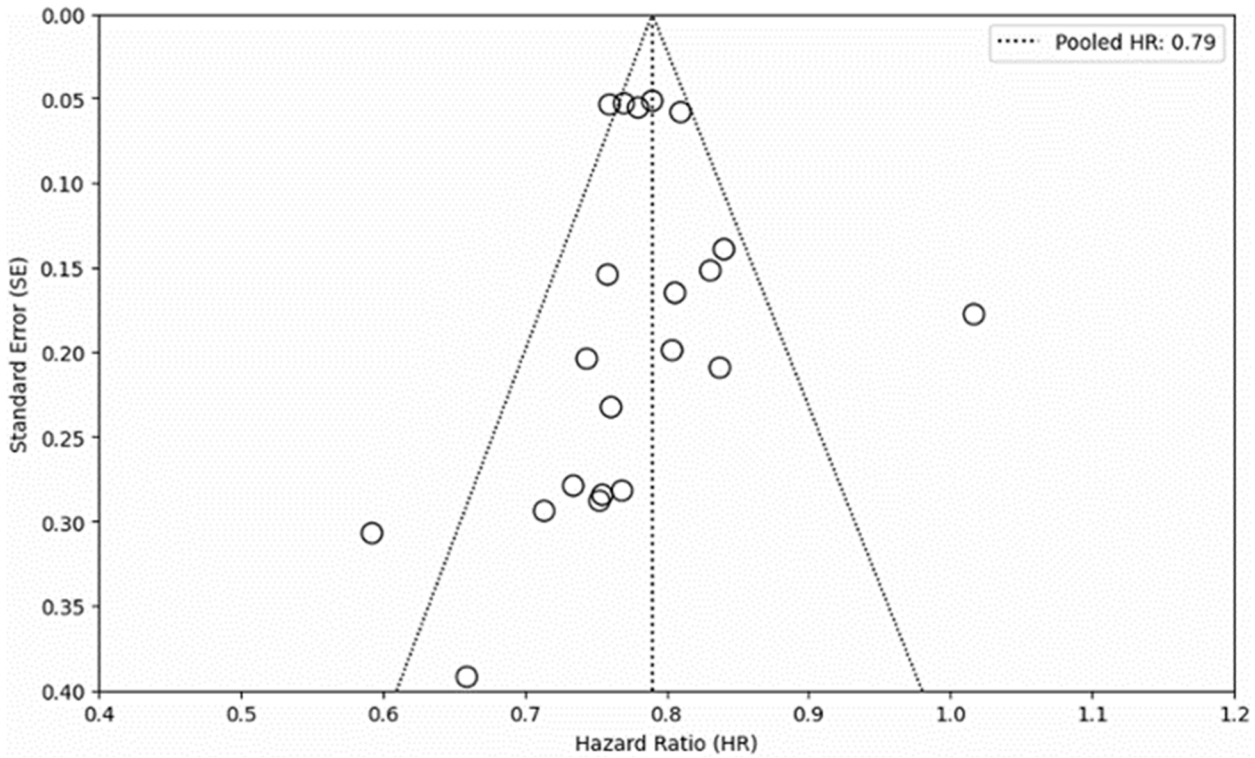

Fig. 6 Evaluating publication bias for PFS in mCRC through funnel plot

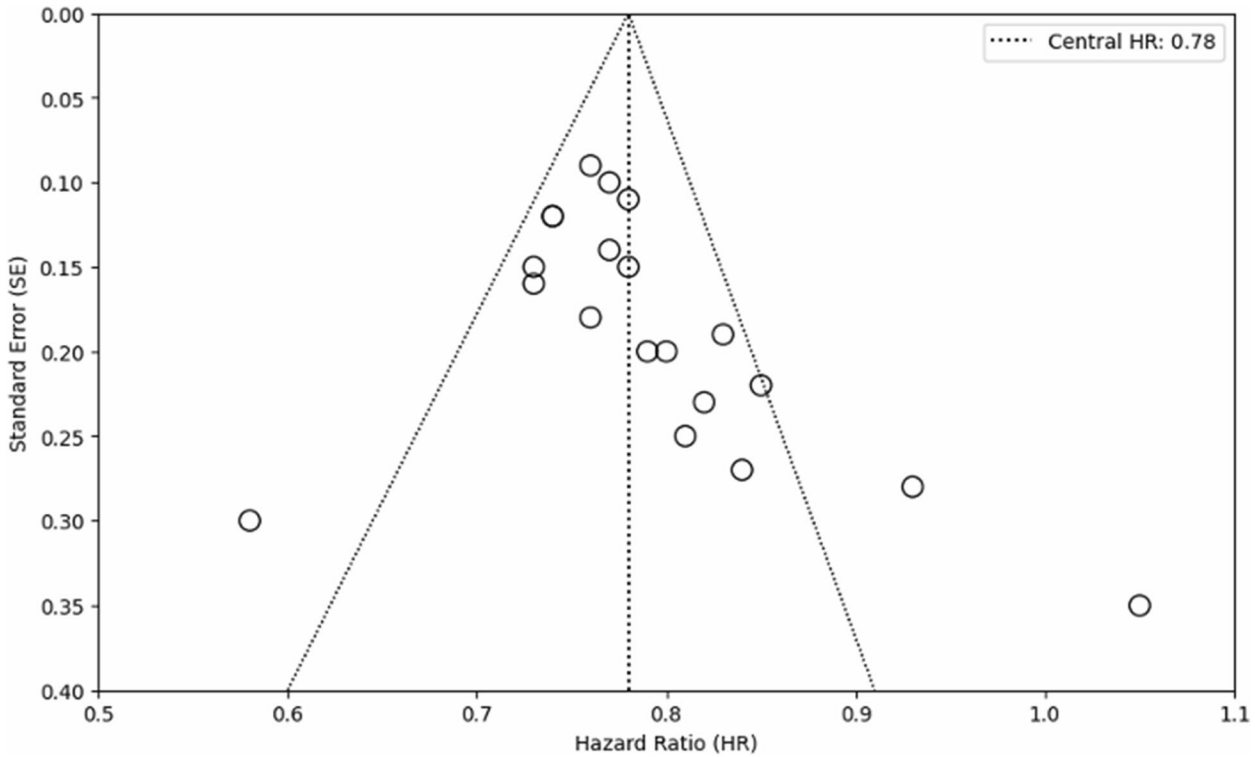

Fig. 7 Evaluating publication bias for OS in mCRC through funnel plot

heterogeneity among the RCTs reinforced the robustness of subgroup findings, underscoring the use of cetuximab-based chemotherapy approaches. The subgroup analysis of PFS in randomised controlled trials showed a 23% lower hazard of disease progression or death for the cetuximab treatment group compared to the chemotherapy group. In the overall analysis, there was moderate heterogeneity, while in the subgroup analysis, there was lower heterogeneity. The difference in interpretation suggested that the subgroup analysis may have more significant findings, a consistent effect across the studies and a substantially relevant effect on the PFS endpoint. However, both analyses demonstrate a protective effect with HRs less than 1, showing a reduced risk of the events.

In a retrospective study, Wu, Wang et al. [40], indicated a hazard ratio that was concordant with our pooled data and reported a greater overall survival period in the cetuximab with chemotherapy group. This result encourages the use of the cetuximab combination as a targeted therapy in cancer metastasis. A prospective cohort study's [47] findings were also consistent with our findings that used either oxaliplatin or fluoropyrimidine or capcitabine with a cetuximab group and cetuximab as an alternative. This analysis reported a lengthening of overall survival among the KRAS-mutated CRC patients in the interventional arm who received cetuximab combined with a single chemotherapeutic agent.

Oxaliplatin plus fluoropyrimidine-based chemotherapy, with or without cetuximab, was employed in a phase III RCT research conducted by Maughan, Adams et al. [52] to treat patients with mCRC. Their analysis was inconsistent with our PFS as well as OS findings, showing no significant differences, respectively as (8.6 vs. 8.6 months) and (17.9 vs. 17 months). This discrepancy might be due to including a large sample population drawn from 110 study centers, compared to those where recruitment is only from a few selected sites.

Our meta-analysis has demonstrated the overall effectiveness of cetuximab in mCRC, recently a CIFRA study explores the role of FcγRIIIa genetic polymorphisms in predicting response to cetuximab combined with irinotecan and fluorouracil in advanced CRC. This study provides an understanding of the Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) mechanism of cetuximab in the treatment efficacy by focusing on the high-affinity FcγRIIIa V/V genotype. Moreover, the study emphasizes that cetuximab's anti-tumour activity may also depend on interactions within the tumour microenvironment, particularly with natural killer (NK) cells and tumour-associated macrophages (TAMs). These findings underscore the potential for combining immunomodulatory agents with cetuximab to enhance ADCC, particularly in patients who exhibit resistance while using anti-EGFR alone [61].

When comparing the cetuximab treatment group to the control group, the OS subgroup analysis indicated a 24% decrease in the mortality risk. Similar to the PFS analysis, the OS interpretation may provide more significant results with lower heterogeneity and a narrower confidence interval for HR. Both overall and subgroup analyses, show a consistent trend of a reduced risk of the event of interest, suggesting a potential improvement in overall survival.

The assessment of publication bias is considered crucial in meta-analyses. We have employed funnel plots to determine publication bias in our study. The graphic representation of plots indicated no significant asymmetry, demonstrating a minimal risk of bias. Overall, these results provided that the publication bias had a mild influence on our pooled findings, affirming the robustness of the meta-analysis. However, the moderate heterogeneity among the included studies might be due to variability in patient populations, methodologies and potential confounders that could influence the outcomes. The probability of residual confounding remained, despite our efforts to reduce bias. The potential factors Contributing to this variability might be differences in study populations, such as geographic area, age and ethnicity and variations in research design and the method of defining or measuring outcomes. Funnel plots for OS indicate slight bias, so the possibility of unpublished negative studies cannot be entirely ruled out.

Including various cetuximab-based chemotherapy regimens provides a comprehensive assessment of mCRC treatment protocols across diverse clinical settings, ensuring broad clinical applicability and relevance. The integration of real-world evidence alongside clinical trials highlights the effectiveness of cetuximab in routine colorectal cancer practices. The evaluation of PFS and OS outcomes from extended follow-up periods indicates the durability of long-term survival benefits, which are crucial for optimizing patient care. Executing the fixed effect model with statistical heterogeneity provides a reliable PFS and OS estimation, strengthening the robustness of the findings. Furthermore, subgroup analysis based on research designs offers valuable insights into our meta-analysis of how cetuximab impact varies between randomised and non-randomised studies. Adhering to transparent search strategies and bias assessment of the review principles, this meta-analysis enhances confidence in its conclusions. These aspects significantly strengthen the study.

Our meta-analysis has some limitations that should be considered. Firstly, the included studies with small sample sizes might bias the outcomes. Second, the accuracy

of the results may have been impacted by the inclusion of some retrospective and prospective studies in the meta-analysis. Third, the heterogeneity in the findings of the meta-analysis might also be due to the methodological characteristics of the studies such as differences in research design, location, baseline characteristics of the patients, treatment regimens, follow-up data or selection of studies. Fourth, this analysis was restricted to publications that were in English, so the phenomenon of publication bias cannot be ignored. Lastly, our research yielded findings based on hazard ratios. Not all the included studies have reported hazard ratios with corresponding CIs, particularly for OS, as reported by a few studies, which might bias the reliability of our findings.

Conclusions

Our findings demonstrate the significant benefits of combining cetuximab with chemotherapy in metastatic colorectal cancer treatment (mCRC). The cetuximab-based therapy is associated with a substantial improvement in progression-free survival and overall survival compared to chemotherapy alone. Our meta-analysis justifies the useful addition of cetuximab to standard chemotherapy regimens for mCRC. This approach could improve patient outcomes and provide a valuable addition to current treatment strategies. Future research is needed to confirm its clinical efficacy, identify patient subgroups that are most likely to benefit and explore its impact on survival and quality of life for optimal integration into clinical practice. The findings underscore the cetuximab-chemotherapy combination as a promising first-line protocol for mCRC.

Abbreviations

CRC	Colorectal cancer
ECOG performance status	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptors
mCRC	Metastatic colorectal cancer
OS	Overall survival
PFS	Progression-free survival

Supplementary Information

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Supplementary Material 1.

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None

Authors' contributions

MA, AUR, SR, AS, HMJ, QAJ, HK and SKAT made substantial contributions to the conception and design of the study and its analysis and interpretation of the data. All the authors drafted the manuscript or revised it critically for important intellectual content. All authors reviewed, critiqued and approved the final version submitted for publication.

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Data availability

Data will be available on request from the corresponding author.

Declarations

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Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pharmacy Practice, Faculty of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan. [2]Department of Pharmacy Practice, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan. [3]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Muhammadiyah Surakarta, Surakarta, Indonesia. [4]Faculty of Pharmacy, University of Aden, Aden, Yemen.

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