Systematic Review and Meta-Analysis

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# Neoadjuvant therapy of cetuximab combined with chemoradiotherapy in rectal cancer

## A single-arm meta-analysis of noncomparative clinical studies and randomized controlled trials

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**Abstract**

**Objective:** Preoperative chemoradiotherapy combined with radical resection has reduced local recurrence rates in rectal cancer. Cetuximab shows improvement in rectal cancer treatment. But the role for neoadjuvant therapy of cetuximab combined with chenmoradiotherapy in rectal cancer remains unclear. The present study aimed to use meta-analytical techniques to assess its benefit and risk.

**Materials and Methods:** We searched PubMed, the Cochrane Library, Embase to identify the correlational non-comparative clinical studies and randomized controlled trials (RCTs). The primary endpoints of interest were pathological complete response (pCR), complete response (CR), partial response (PR), stable disease, progressive disease (PD), R0-resection, R1-resection, and R2-resection. The secondary included any grade of toxicity.

**Results:** Eleven investigations (9 noncomparative open-label cohort studies and 2 randomized controlled trials) involving 550 patients were ultimately included. The pooled estimates of pCR was 10% (95% confidence interval [CI]: 7%–13%, $I^2$ = 55.9%). Simultaneously, only a small amount of patients achieved CR (11%, 95% CI: 7%–15%, $I^2$ = 44.0%), which was consistent with pCR. Besides, R0 resection (93%, 95% CI: 90%–96%, $I^2$ = 16.5%) seemed to be increased but need further exploration. The safety was also calculated, and most of the toxicities were moderate.

**Conclusion:** Neoadjuvant therapy of cetuximab combined with chemoradiotherapy could not improve pCR. The raise of R0-resection rate needed to be verified by more high-quality and well-designed RCTs. Meanwhile, the morbidity of toxicity was relatively mild and acceptable.

**Abbreviations:** CIOMS = Counsil for International Organization of Medical Sciences, CR = complete response, EGFR = epidermal growth factor receptor, LARC = locally advanced rectal cancer, MCRC = metastatic colorectal cancer, nCRT = neoadjuvant chemoradiotherapy, NOS = Newcastle-Ottawa Quality Assessment Scale, OS = overall survival, pCR = pathological complete response, PD = progressive disease, PFS = progression-free survival, PR = partial response, RCT = randomized controlled trial, SD = stable disease.

**Keywords:** cetuximab, chemoradiotherapy, efficacy, neoadjuvant treatment, rectal cancer

## 1. Introduction

Rectal cancer is a common malignant tumor that seriously threatens human health. Global rectal cancer patients accounted for 10.2% of all cancer patients in 2018, ranking third, with a mortality rate of 9.2%.[1] Patients with locally advanced rectal cancer (LARC) are at tremendous risk of metastatic diseases due to high rates of local and distant recurrence.[2] Evidence from the previous investigations has proven the efficacy of neoadjuvant

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

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chemoradiotherapy (nCRT) in tumor downstaging and local control.[3,4] Unfortunately, distant metastases rate remains stable in the 25% to 35% range, which is the predominant mode of failure.[5] Efforts to improve preoperative treatment are aimed through integrating more effective systemic therapy into combined-modality protocols.

Targeted therapies, which are under active investigations in the neoadjuvant settings, have rapidly gained attention in the treatment of rectal cancer. Cetuximab, an epidermal growth factor receptor (EGFR) monoclonal antibody, is recommended by the National Comprehensive Cancer Network guidelines for patients with wild-type metastatic colorectal cancer of the *RAS* gene.[6] The role of cetuximab in nCRT for rectal patients has been researched by many investigators recently. Some have previously shown that the addition of cetuximab to nCRT failed to improve the efficacy.[7,8] But other correlative studies hold the different views or attempted to elicit molecularly defined subgroups that may benefit from the addition of cetuximab.[9,10] Therefore, the efficacy of adding ceutximab to the nCRT is still controversial.

Given a lack of clarity regarding the benefit of cetuximab combined with chemoradiotherapy for rectal carcinoma in neoadjuvant therapy, it is significant to establish whether or not it is appropriate. In this meta-analysis, we pooled the data extracted from the included studies to evaluate the efficacy and safety of adding ceutximab to the nCRT.

## 2. Materials and methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statements checklist[11] and registered with PROSPERO (International Prospective Register of Systematic Reviews, CRD42020189711). Since the meta-analysis did not involve individual patients, ethical approval was not required.

### 2.1. Search strategy

PubMed, the Cochrane Library, and Embase were searched for relevant publications up to May 31, 2020. The search strategy was based on the PICOS principle, using the combination of the medical subject heading (MeSH) terms and entry terms, including "Rectal Neoplasms", "Cetuximab", "Neoadjuvant Therapy", and "Randomized Controlled Trial". The reference lists of retrieved papers were further screened for additional eligible publications. There was no language restriction used during the search.

### 2.2. Selection criteria

The predefined criteria for eligible studies were as follows:

1. Patients with histologically confirmed rectal carcinoma;
2. Treatment: nCRT combined with cetuximab;
3. Endpoints of interest included pathological complete response (pCR), complete response (CR), partial reponse (PR), stable disease (SD), progressive disease (PD), R0~R2 resection rates, and toxicity.
4. Study types included noncomparative open label studies and RCTs.

### 2.3. Data extraction

Two independent reviewers (QY and J-jZ) assessed the titles, abstracts, and full texts from each included study and extracted the following information respectively: first author, publication year, phase of clinical study, number of participants enrolled, participant characteristics, tumor stage, clinical setting, endpoint, corresponding provided outcome, operation time after treatment, and study design. Total summarized data were extracted from noncomparative studies, and intervention groups results of RCTs. The primary endpoints of interest were pCR, CR, PR, SD, PD, and R0~R2 resection rates. The secondary was any grade of toxicity. The third investigator (F-mZ) resolved disagreements between the 2 reviewers.

### 2.4. Quality assessment

The Newcastle-Ottawa quality assessment scale (NOS) was applied to evaluate the quality of eligible studies for meta-analysis.[12] Studies scored ≥5 were regarded as moderate-quality trials and those with ≥7 were high-quality studies.

### 2.5. Statistical analysis

All statistical analyses were performed by using STATA version 15.0. Meta-analyses were conducted by calculating the pooled estimates of pCR, CR, PR, SD, PD, R0~R2 resection rates and any grade of toxicity. Random-effect model was used which provides more conservative estimates for the inevitable heterogeneity of included studies.[13] To evaluate heterogeneity, the Cochrane $Q$ test and inconsistent index ($I^2$) were performed.[14] Studies with an $I^2$ statistic of 25% to 50%, 50% to 75%, and >75% were deemed to have low, moderate, and high heterogeneity, respectively.[14] Sensitivity analysis and funnel plots (Begg funnel plot and Egger linear regression test) were applied to detect the publication biases.

## 3. Results

### 3.1. Study identification

After an initial database search, we identified 309 potentially relevant publications. 46 were excluded for duplication. A total of 237 were excluded for the following reasons: irrelevant studies (n=218); meta-analysis (n=5); clinical study protocols (n=14). Finally, 26 were assessed through full-text review, and 15 of them were excluded due to proceedings (n=13) and unable to extract data (n=2). The remaining 11 articles were eligible for our meta-analysis. The whole selection process is presented in a flow diagram (Fig. 1).

### 3.2. Study characteristics

The meta-analysis included a total 11 studies involving 550 participants[7–10,15–21]; Table 1 describes the characteristics and main outcome indicators of the included studies. These studies were all published in English. Two were RCTs[9,10] and 9 were noncomparative studies.[7,8,15–20,21] One was phase I study,[15] 3 were phase I/II studies,[16,17,20] 5 were phase II studies,[7,9,18,19,21] and 2 did not indicate it.[8,10] Eleven studies reported the time of surgery after neoadjuvant therapy,[7–10,15–20,21] and the average is 6 weeks. Two studies included rectal cancer patients with only KRAS wild-type,[8,10] 5 involved with KRAS wild-type and KRAS mutation-type,[9,18–21] and 4 did not indicate KRAS status.[7,15–17] Eleven studies added cetuximab to nCRT (Chemotherapy involved XELOX,[8,9,17,20] XELIRI,[7,15] FOLFOX6[10] and capecitabine[16,18,19,21]). Table 2 shows the NOS

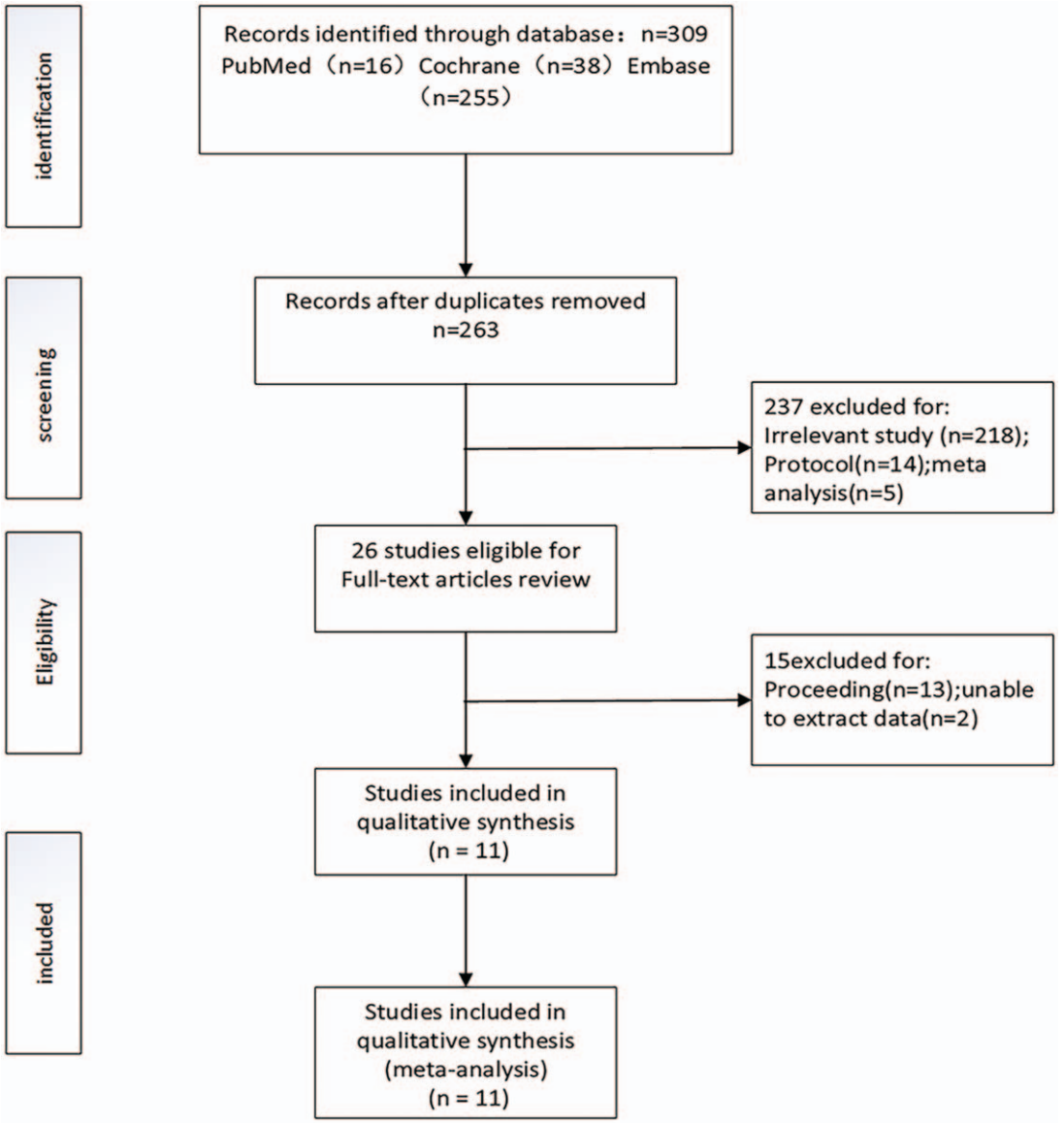


**Figure 1.** Selection of studies. Flowchart showing the selection process for the included studies.

quality evaluation of the enrolled studies. Two investigations with 7 scores were judged as high quality. The remaining 9 with 6 scores were regarded as moderate quality.

### 3.3. Main outcomes

***3.3.1. pCR.*** Eight studies reported the outcomes of pCR, the pooled estimate of pCR was 10% (95% confidence interval [CI]: 7%–13%, $I^2=55.9\%$) (Fig. 2). Compared to the actual clinical practice, the addition of cetuximab to the nCRT might not improve pCR for rectal cancer patients. Evidence of moderate heterogeneity was present across the 8 studies ($I^2=55.9\%$).

***3.3.2. CR, PR, SD, and PD.*** Four studies reported the outcomes of CR, PR, and SD; the pooled estimates were 11% (95% CI: 7%–15%, $I^2=44.0\%$), 52% (95% CI: 46%–58%, $I^2=89.4\%$), and 16% (95% CI: 12%–21%, $I^2=80.4\%$), respectively. Three studies reported PD and the pooled estimate was 3% (95% CI: 1%–5%, $I^2=91.5\%$) (Fig. 3). CR, PR, SD, and PD were also the indicators of clinical efficacy. The results showed that most patients only achieved PR, whereas CR was not improved significantly. Besides, the single-arm meta-analysis was inherently less stable than the 2-arm,[22] which was one of the reasons for the high heterogeneity in this study.

***3.3.3. R0-resection, R1-resection, and R2-resection.*** Five studies reported the outcomes of R0-resection and the pooled estimate was 93% (95% CI: 90%–96%, $I^2=16.5\%$). Three studies reported the outcomes of R1-resection and R2-resection, the pooled estimates were 2% (95% CI: 0–3%, $I^2=0$) and 4% (95% CI: 1%–6%, $I^2=46.1\%$), respectively (Fig. 4). It seemed that neoadjuvant therapy of cetuximab combined with chemo-radiotherapy could improve the R0 resection significantly with low heterogeneity ($I^2=16.5\%$).

***3.3.4. Toxicity.*** As shown in Table 3, the incidences of any-grade toxicities associated with the addition of cetuximab to nCRT were listed to understand the increased risk of clinical related toxicities.

**Table 1**

**Characteristics of included studies.**

| Study | Patients | Age, y | Male | Quit | Phase | Drug | Combined with | Outcomes | Operation time after treatment | Study design |
|---|---|---|---|---|---|---|---|---|---|---|
| Hofheinz et al, 2006[15] | 20 | 56 (41–75) | 16 | 1 | I | Cetuximab (400 mg/m$^2$ on day 1 and 250 mg/m$^2$ on days 8, 15, 22, and 29) | XELIRI regimen, radiation | AEs, pCR | 4–5 wk | Noncomparative open-label nonsquamous |
| Machiels et al, 2007[16] | 37 | 61 (34–78) | 30 | 3 | I/II | Cetuximab (400 mg/m$^2$ day-7 followed by 250 mg/m$^2$/wk for 5 wk) | Capecitabine, radiation | AEs, pCR | 6–8 wk | Noncomparative open-label nonsquamous |
| Rodel et al, 2008[17] | 58 | 61 (35–83) | 38 | 2 | I/II | Cetuximab (initial dose of 400 mg/m$^2$ 7 days before the start of RT, and then at 250 mg/m$^2$ once weekly) | XELOX regimen, radiation | AEs, pCR, CR, PR, SD, PD, R0∼R2 resection rates | 6 wk | Noncomparative open-label nonsquamous |
| Horisberger et al, 2009[7] | 50 | 57 (33–80) | 33 | 0 | II | Cetuximab (400 mg/m$^2$ day 1, 250 mg/m$^2$ days 8, 15, 22, 29) | XELIRI, regimen, radiation | pCR | 4–6 wk | Noncomparative open-label nonsquamous |
| Dewdney et al, 2012[9] | 81 | 61 (31–75) | 54 | 1 | II | Cetuximab (400 mg/m$^2$ on day 1 followed by 250 mg/m$^2$/wk) | XELOX regimen, radiation | CR, PR, SD, PD, R0∼R2 resection rates | 4–6 wk | Randomized open-label study |
| Sun et a, 2012[18] | 63 | 64 (50–77) | 39 | 0 | II | Cetuximab (as a loading dose 400 mg/m$^2$, 250 mg/m$^2$ weekly) | Capecitabine, radiation | pCR | 6–8 wk | Noncomparative open-label nonsquamous |
| Velenik et al, 2012[19] | 36 | NR | NR | 11 | II | Cetuximab (as a loading dose 400 mg/m$^2$, 250 mg/m$^2$ weekly) | Capecitabine, radiation | pCR | 6 wk | Noncomparative open-label nonsquamous |
| Fokas et al, 2013[20] | 53 | 60 (35–83) | 34 | 7 | I/II | Cetuximab (NR) | XELOX regimen, radiation | pCR, CR, PR, SD, PD, R0∼R2 resection rates | 6 wk | Noncomparative open-label Nonsquamous |
| Eisterer et al, 2014[21] | 31 | 61 (41–80) | 20 | 0 | II | Cetuximab (400 mg/m$^2$ body surface on day 1, followed by 250 mg/m$^2$ body surface on days 8, 15, 22 and 29) | Capecitabine, radiation | AEs, R0 resection rates | 6–8 wk | Noncomparative open-label nonsquamous |
| Leichman et al, 2017[8] | 75 | 56.4 (25.5–77.6) | 53 | 11 | NR | Cetuximab (400 mg/m$^2$ on day 1 followed by 250 mg/m$^2$) | XELOX regimen, radiation | pCR | 3–8 wks | Noncomparative open-label nonsquamous |
| Yang et al, 2017[10] | 46 | NR | 30 | 0 | NR | Cetuximab (500 mg/m$^2$ intravenous infusion once every 2 wk) | FOLFOX6 regimen, radiation | AEs, CR, PR, SD, PD, R0 resection rates | 8–10 wk | Randomized open-label study |

AEs = treatment-related adverse events, CR = complete response, FOLFOX6 = oxaliplatin + leucovorin + fluorouracil, NR = not reported, pCR = pathological complete response, PD = progressive disease, PR = partial response, SD = stable disease, XELIRI = irinotecan + capecitabine, XELOX = capecitabine + oxaliplatin.

**Table 2**

**The NOS quality of enrolled investigations.**

| | Selection | | | | Comparability | | Outcome | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | REC | SNEC | AE | DO | SC | AF | AO | FU | AFU | Total | Quality |
| Hofheinz et al, 2006[15] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Machiels et al, 2007[16] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Rodel et al, 2008[17] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Horisberger et al, 2009[7] | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 | High |
| Dewdney et al, 2012[9] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Sun et al, 2012[18] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Velenik et al, 2012[19] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Fokas et al, 2013[20] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Eisterer et al, 2014 | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Leichman et al, 2017[8] | 1 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 6 | Moderate |
| Yang et al, 2017[10] | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 7 | High |

AE = ascertainment of exposure, AF = study controls for any additional factors, AFU = adequacy of follow-up of cohorts, AO = assessment of outcome, DO = demonstration that outcome of interest was not present at start of study, FU = follow-up long enough for outcomes to occur, NOS = Newcastle-Ottawa Quality Assessment Scale, REC = representativeness of the exposed cohort, SC = study controls for age, sex, SNEC = selection of the nonexposed cohort. "1" means that the study satisfies the item and "0" means the opposite situation.

According to the frequency of adverse drug reaction recommended by Counsil for International Organization of Medical Sciences (CIOMS), the incidence of diarrhea (70%, 95% CI: 66%–77%, $I^2 = 26.8\%$), anemia (64%, 95% CI: 57%–71%, $I^2 = 97.7\%$), acne-like rash (97%, 95%CI: 93%–101%, $I^2 = 52.9\%$), leukocytopenia (38%, 95% CI: 26%–49%, $I^2 = 0$), nausea and vomiting (34%, 95% CI: 25%–43%, $I^2 = 56.6\%$), hand-foot syndrome (14%, 95% CI: 8%–19%, $I^2 = 33.4\%$), proctitis (20%, 95% CI: 11%–30%, $I^2 = 57.5\%$), fatigue/asthenia (19%, 95% CI: 11%–28%, $I^2 = 91.9\%$), and infection/fever (14%, 95% CI: 6%–21%, $I^2 = 87.9\%$) were very common. Although the incidence of stomatitis (6%, 95% CI: 1%–10%, $I^2 = 0$), thrombocytopenia (8%, 95% CI: 2%–13%, $I^2 = 89.6\%$), obstipation/ileus (4%, 95% CI: 0–8%, $I^2 = 0$), and sensory neuropathy (8%, 95% CI: 3%–14%, $I^2 = 92.1\%$) were common.

*3.3.5. Evaluation of publication bias.* To evaluate publication bias, we performed Begg test and Egger test. The *P* values of Begg test and Egger test for the pooled pCR of the 8 studies[7,8,15–20] were 0.902 and 0.581, indicating there was no significant publication bias (see Figure S1, http://links.lww.com/MD/F729, Supplemental Digital Content, which illustrates the Begg funnel plots and the Egger publication bias plot concerning the pCR for the enrolled studies). Besides, to further evaluate the potential publication bias detected from the pooled pCR, we performed sensitivity analysis, the results are shown in Supplemental Digital Content (Figure S2, http://links.lww.com/MD/F730) (see Figure S2, http://links.lww.com/MD/F730 Supplemental Digital Content, which demonstrates the results of the sensitivity analysis concerning the pCR for the included studies). It was further confirmed that no obvious bias was among the studies.

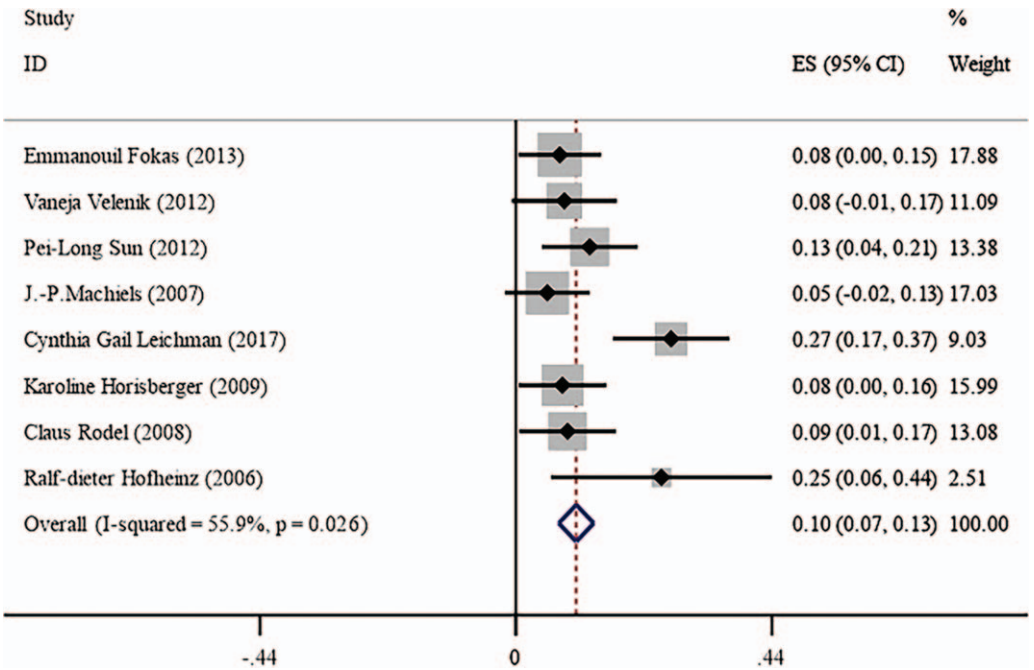


**Figure 2.** The pooled estimate of pCR for the rectal cancer patients from included studies. The size of each square is proportional to the study's weight. Horizontal lines indicate 95% confidence interval (CI). Diamonds indicate pooled incidence rate with its corresponding 95% CI. pCR = pathological complete response.

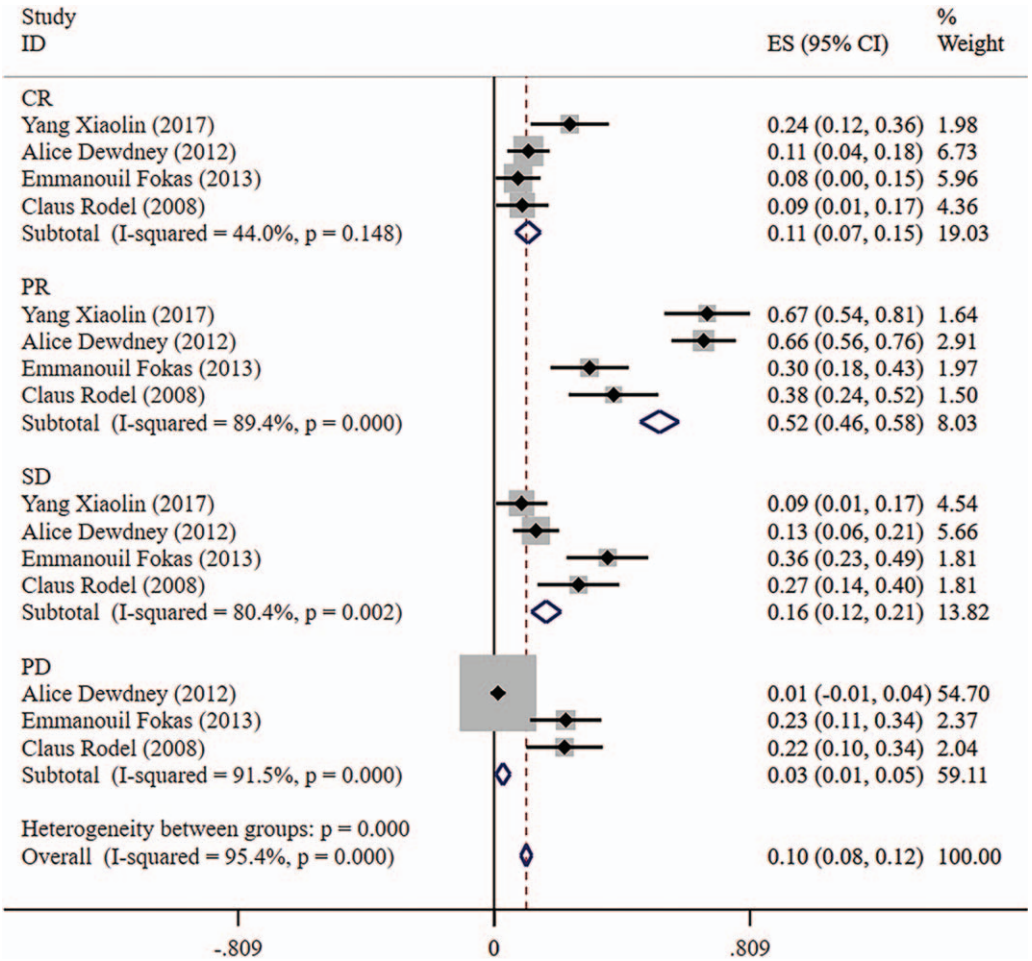


**Figure 3.** The pooled estimates of CR, PR, SD, and PD for the rectal cancer patients from included studies. The size of each square is proportional to the study's weight. Horizontal lines indicate 95% CI. Diamonds indicate pooled incidence rate with its corresponding 95% CI. CI = confidence interval, CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease.

## 4. Discussion

At present, radical resection after preoperative chemoradiotherapy has become the standard treatment for rectal cancer, especially the LARC. To some extent, nCRT can effectively control the local tumor, make the tumor shrink, improve the resection rate, and anus preservation rate.[23,24] But the patients with rectal cancer still have a potential risk of recurrence. Recently, the mode of targeted agent combined with nCRT has been studied in pursuit of higher efficacy and lower recurrence.

EGFR has been reported to be overexpressed in 49% to 82% of rectal tumors,[25–28] and its expression level is closely related to tumor stage and prognosis. Cetuximab is a monoclonal antibody against EGFR. It can inhibit the binding of EGFR and its ligands, block the downstream signaling, promote cell cycle arrest and apoptosis.[29] Cetuximab has been shown to be a potent radiosensitizing agent[30,31] and many studies have also proven that it can significantly improve the objective response rate, progression-free survival (PFS), and overall survival (OS) in patients with RAS wild-type metastatic colorectal cancer (MCRC).[32,33] More recently, many scholars have paid their attentions to the protocol of ceutximab combined with nCRT.[34] However, whether or not the addition of ceutximab to the nCRT provides increased efficacy remains controversial and requires further investigation.

To date there have been limited RCTs or clinical controlled trials investigating the roles of ceutximab in nCRT regimens for rectal cancer patients, and most were single-arm phase II studies. However, this type of the clinical trials usually lacks a putative benchmark and evaluates the efficacy by comparing their outcomes with their predefined goal or the results in other researches. To assess the efficacy of adding ceutiximab to the nCRT, we established a benchmark by quantitatively synthesizing the outcomes of nCRT regimens without targeted agents. We extracted the results of pCR, R0-R1 resection from 10 cohorts which met our enrollment criteria and without any targeted agents in their nCRT regimens from the pooled analysis of Petrelli et al.[35] The baseline characteristics are shown in Supplemental Digital Content (Table S1, http://links.lww.com/MD/F734) (see Table S1, http://links.lww.com/MD/F734, Supplemental Digital Content, which illustrates the data from Petrelli et al's pooled analysis) and the NOS quality assessment is presented in Supplemental Digital Content (Table S2, http://links.lww.com/MD/F735) (see Table S2, http://links.lww.com/MD/F735, Supplemental Digital Content, which illustrates the NOS quality from Petrelli F et al's pooled analysis). The pooled estimates of pCR, R0 and R1 resection rates of these cohorts was 14% (95% CI, 10%–20%), 73% (95% CI, 67%–78%), 7% (95% CI, 4%–11%), respectively (see Figure S3-

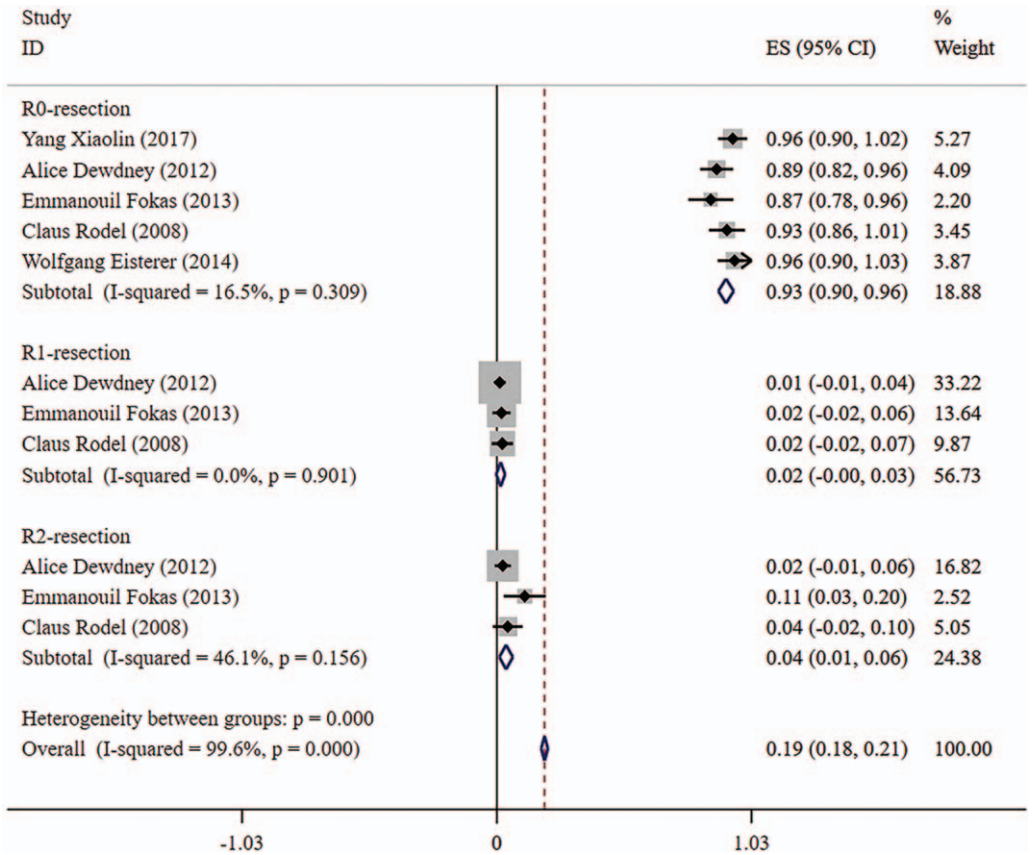


**Figure 4.** The pooled estimates of R0-R2 resection for rectal cancer patients from included studies. The size of each square is proportional to the study's weight. Horizontal lines indicate 95% CI. Diamonds indicate pooled incidence rate with its corresponding 95% CI. CI = confidence interval.

S5, http://links.lww.com/MD/F731, http://links.lww.com/MD/F732, http://links.lww.com/MD/F733, Supplemental Digital Contents, which indicate the pooled estimates of pCR, R0 and R1 resection rates from Petrelli et al's analysis), which were also in the range reported in some other previous researches.[36,37] Hence, we convinced that the above values are adequate benchmarks which can help reasonably evaluate the role of ceutiximab in the nCRT schedule.

In our article, we achieved a pooled R0 resection rate (93%) over the benchmark (73%), which seemed as an appreciable efficacy of the ceutiximab combined with nCRT for rectal patients. However, only 2 studies from the benchmark involved the R0 resection rate. Bujko's study enrolled 235 patients and Moore's only 24, which might bias the result.[35] Generally, pCR is applied to predict tumor downstaging and success of radical surgery. The pooled estimate of pCR rate (10%) in this

**Table 3**

**The pooled incidences of AEs at any grade for rectal cancer patients from included studies.**

| Adverse events | No. of studies | ES (95% CI) | Heterogeneity $I^2$ (%) | Heterogeneity *P* | Effects model |
|---|---|---|---|---|---|
| Diarrhea | 4 | 0.70 (0.66–0.77) | 26.8 | .251 | Random |
| hand-foot syndrome | 4 | 0.14 (0.08–0.19) | 33.4 | .212 | Random |
| Anemia | 3 | 0.64 (0.57–0.71) | 97.7 | <.0001 | Random |
| Nausea and vomiting | 3 | 0.34 (0.25–0.43) | 56.6 | .1 | Random |
| Stomatitis | 3 | 0.06 (0.01–0.10) | 0 | .434 | Random |
| Proctitis | 2 | 0.20 (0.11–0.30) | 57.5 | .125 | Random |
| Leukocytopenia | 2 | 0.38 (0.26–0.49) | 0 | .35 | Random |
| Fatigue/astenia | 2 | 0.19 (0.11–0.28) | 91.9 | <.0001 | Random |
| Acne-like skin rash | 2 | 0.97 (0.93–1.01) | 52.9 | .117 | Random |
| Thrombocytopenia | 2 | 0.08 (0.02–0.13) | 89.6 | .002 | Random |
| Obstipation/ileus | 2 | 0.04 (0–0.08) | 0 | .826 | Random |
| Sensory neuropathy | 2 | 0.08 (0.03–0.14) | 92.1 | <.0001 | Random |
| Infection/fever | 2 | 0.14 (0.06–0.21) | 87.9 | .004 | Random |

AEs = adverse events, CI = confidence interval, ES = effect size.

study is less than the baseline (14%), suggesting that rectal patients could not benefit from the neoadjuvant therapy of cetuximab combined with nCRT. Besides, as we know, the efficacy of anti-EGFR treatment strictly depends on the RAS or BRAF gene status.[38–41] In this study, most of the enrolled publications did not report the pCR rates in accordance with RAS status. Consequently, the inadequate pooled pCR rate may be owing to the lack of published mutation status. On the basis of the analysis above, more high-quality phase III clinical trials are essential to explore the efficacy of cetuximab combined with nCRT specifically for the rectal cancer patients with RAS and BRAF wild-type. Moreover, we analyzed the rates of CR, PR, SD, and PD, which were also the indicators of curative effect. The pooled estimate of CR (11%) was consistent with pCR (10%).

As is known to all, chemotherapy and radiation can lead to adverse reactions. More attention should be paid to the extra toxicity induced by ceutiximab combined with nCRT. Since the studies we enrolled reported few Grade 3/4 toxicity, the data about any-grade toxicities were analyzed. Compared with the definition of adverse drug reaction frequency recommended by CIOMS, we found that it might induce relatively higher incidence of diarrhea, anemia, acne-like rash, leukocytopenia, nausea and vomiting, hand-foot syndrome, proctitis, fatigue, and infection. In addition, stomatitis, thrombocytopenia, obstipation/ileus, and sensory neuropathy were comparatively common. However, most of the above-mentioned toxicities were at Grade 1/2, which were relatively mild. We speculated that the safety of adding ceutiximab to the nCRT might be acceptable. Reports of toxicities are still correspondingly few; more importance should be attached to this field to verify our outcomes.

There still exist several limitations in our research. First, this meta-analysis was conducted in a single-arm setting owing to the lack of RCTs. Secondly, the efficacy of cetuximab combined with nCRT for the rectal cancer patients with RAS mutation and RAS wild-type status could not be evaluated due to the lack of relevant data included in the studies. Thirdly, we gathered information from the publications rather than the individual patient data. Fourthly, despite we focus on the some other indicators, such as the rates of CR, PR, SD, PD, R0-R2 resection and any grade of toxicity, there is little statistical analysis on the above-mentioned indicators in the existing literature. Finally, OS, PFS, and disease-free survival (DFS) cannot be statistically analyzed caused by the lack of high-quality RCTs. We cannot assess the role of cetuximab in nCRT regimens accurately.

## 5. Conclusion

In general, our study indicated that the addition of cetuximab to the nCRT cannot improve pCR for rectal cancer patients. Although it seems to improve the R0 resection, more RCTs are needed for further validation due to the limited literatures. What's more, the relationship between RAS status and cetuximab combined with nCRT still remains inconclusive, which should be attached more importance by RCTs with larger scale and better study design.

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## Author contributions

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**Data curation:** Qi Yan.
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