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ORIGINAL ARTICLE

Cetuximab-based therapy versus non-cetuximab therapy for advanced cancer: a meta-analysis of 17 randomized controlled trials

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Abstract
Purpose To assess the efficacy and safety of cetuximab-based therapy versus non-cetuximab therapy for advanced cancer.
Methods A total of 7,954 patients from 17 randomized controlled trials are identified, with 3,965 patients in the cetuximab group and 3,989 patients in the non-cetuximab group. The outcome was progression-free survival (PFS), overall survival (OS), overall response rate (ORR), and grade 3/4 advent events.
Results There was a significant improvement of PFS (HR 0.83, 95%CI 0.78–0.88), OS (HR 0.89, 0.84–0.95), and ORR in the cetuximab group (OR 1.39, 1.22–1.58). In subgroup analysis, in colorectal cancer, there was a significant improvement of PFS (0.72, 0.66–0.78), OS (0.90, 0.81–1.00), and ORR in the cetuximab group (1.36, 1.15–1.60). In head and neck carcinoma, there was a significant improvement of PFS (0.63, 0.54–0.73), OS (0.78, 0.67–0.91), and ORR in the cetuximab group (1.57, 1.15–2.16). In non-small-cell lung cancer, there was a significant improvement of OS (0.86, 0.76–0.96) in the cetuximab group, and no difference on PFS (0.82, 0.64–1.07) and ORR (1.56, 0.85–2.88). In pancreatic cancer, there was no difference on PFS (1.11, 0.97–1.28), OS (1.07, 0.93–1.25), and ORR (0.94, 0.66–1.33). There were higher incidences of grade 3–4 toxicity (OR 1.84), skin-related toxicity (OR 31.80), acneiform rash (OR 30.14), and hypomagnesemia (OR 6.72) in the cetuximab group.
Conclusions Cetuximab-based therapy improved PFS and OS, and better ORR versus non-cetuximab therapy. The severe adverse events should be predictable and manageable.

Keywords Cetuximab · Advanced or metastasis cancer · Meta-analysis

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Introduction

Most cancers are diagnosed with unresectable advanced disease [1]. Systemic chemotherapy or radiotherapy is regarded as the principal treatment and patients show better survival [2, 3]. However, the value of chemoradiotherapy is counterbalanced by increased and prohibitive toxicity, particularly among patients with coexisting medical conditions and decreased performance status [4]. Therefore, novel treatments are needed.

The epidermal growth factor receptor (EGFR), a member of the ErbB family of receptor tyrosine kinases, is abnormally activated in epithelial cancers, including non-small-cell lung cancer [5], colorectal cancer [6], pancreatic cancer [7], and head and neck cancer [8]. The cells of almost all such neoplasms express high levels of EGFR, a feature associated with a poor clinical outcome [8, 9]. Chemoradiotherapy increases the expression of EGFR in cancer cells, and blockade of EGFR signaling sensitizes cells to the effects of chemoradiotherapy [10, 11]. The epidermal growth factor (EGF) is crucial for tumor cell proliferation, inhibition of apoptosis, and other processes important for cancer progression, including angiogenesis, invasion, and metastasis, making EGF a promising target for anticancer agents [12, 13].

Cetuximab (Erbitux, ImClone Systems), an IgG1 monoclonal antibody against the ligand-binding domain of EGFR, enhances the cytotoxic effects of chemoradiotherapy in EGFR expressing cell carcinoma [14]. Although it was approved by the Food and Drug Administration (FDA) for use in metastatic colorectal cancer in 2004 [15, 16]. The clinical efficacy of cetuximab is still undergoing evaluated in several randomized controlled trials (RCTs) with varying results, none of which was large enough to show a statistically significant effect. This meta-analysis was conducted to give an overview of all eligible RCTs comparing combined therapy with or without cetuximab, with the aim of investigating whether cetuximab-based therapy is more effective than non-cetuximab therapy for advanced or metastatic cancers. To our knowledge, so far there has been no meta-analysis with a greater power of the statistical comparisons to detect treatment differences.

Methods

Literature search

Pubmed, Embase, and The Cochrane Library were searched from January 1966 to December 2008 using keywords including "cetuximab" or "Erbitux." The search was conducted using these keywords alone and in combination with "cancer" to identify all eligible RCTs. In addition, we manually searched all abstracts that contained "cetuximab" presented at 2000–2008 American Society of Clinical Oncology (ASCO) annual meetings and the ASCO virtual meeting. The reference lists of all traced articles and general reviews of this topic were examined manually.

Study selection

Citations selected from this initial search were subsequently screened for eligibility using the follow criteria: (1) participating patients with metastatic or advanced cancer at baseline; (2) studies combined therapy with cetuximab versus without cetuximab; (3) original articles must have censored number of patients or Kaplan–Meier curve; and (4) RCTs. Reports were excluded by the following criteria: (1) phase I clinical trial; (2) retrospective trial; (3) any review, comment, and case report.

Data extraction

Two reviewers abstracted data independently and reached consensus on all items. The primary outcomes were progression-free survival (PFS) and overall survival (OS); secondary outcomes were overall response rate (ORR) and grade 3 or 4 advent events (AEs). Whenever reports pertained to sets of patients that overlapped, only the report with longest follow-up (having the largest number of events) was used in the final analysis. The following information were sought from each article, although some articles did not contain all the information as followed: type of cancer, first author, publication year, country, treatment regiment, patient number, age, gender rate, start accrual, treatment line, ECOG (Eastern Cooperative Oncology Group) performance status (PS) or WHO status or Karnofsky status (KPS), number of the patients eligible for response, median OS, PFS, ORR, AEs, specific Grade 3–4 toxicity data such as cetuximab-related skin toxicity, acneiform rash, hypomagnesemia, general symptoms (asthenia, infection, and infusion-related reactions), hematological system syndroma (neutropenia, thrombocytopenia, and anemia), digestive system syndroma (nausea/vomiting, diarrhea, and anorexia), and neuropathy. For trials included in this meta-analysis, if log hazard ratio (HR) and its variance was not presented explicitly, methods reported by Parmar et al. [17] was used to extract estimates of these statistics.

Data analysis

The outcomes used for this meta-analysis were OS, defined as the time from random assignment to death from any cause, censoring patients who had not died at the date last known alive, and PFS, defined as the time from random assignment to first documented progression, and ORR, defined as the sum of partial and complete response rates (according to the Response Evaluation Criteria in Solid Tumors (RECIST) [18, 19], and toxicity, which was graded according to the Common Toxicity Criteria version 2 (http://ctep.cancer.gov). The overall HR for OS and PFS, the relative risks (RRs) for ORR and odds ratios (ORs) for AEs and the treatment-related deaths were calculated using Stata version 9.0. Efficacy analysis was performed on the intent-to-treat population, defined as all randomly assigned patients. Safety analysis included all patients who received at least one dose of study drug. A statistical test with a P value less than 0.05 was considered significant. An RR >1 reflects a favorable outcome in the cetuximab arm for response rate, and an OR >1 indicates more toxicity or more treatment-related deaths in the cetuximab arm and vice versa. Pooled estimates of efficacy were calculated using a fixed-effects model [19]. If any heterogeneity existed, the following techniques were employed to explain it: (a) subgroup analysis; (b) sensitivity analysis performed by excluding the trials which potentially biased the results; and (c) the random effect model was used after efforts were made to explore the cause of the heterogeneity. Bias was studied using the weighted regression tests described by Egger et al. [20]. Findings of the meta-analysis are depicted in classical Forest plots, with point estimates and 95%

confidence interval (CI) for each trial and overall; size of the squares is proportional to the study size.

Assessment of study quality

The methodological quality of the studies included in the meta-analysis was scored using the Jadad composite scale [20, 21].

Result

Description of included trials

The search strategy generated 35 potential RCTs. From these, only 11 RCTs [22–32] compared cetuximab-based therapy with non-cetuximab therapy in advanced or metastatic cancer. From the abstracts published during ASCO annual meetings and virtual meeting from 2000 to 2008, we identified 100 abstracts that included cetuximab. After evaluating each abstract, we included six additional trials [33–38]. Finally, 17 RCTs [22–38] fulfilled the inclusion criteria of this meta-analysis. Among the 17 trials included, there were seven trials [22–26, 33, 34] on colorectal cancer, four trials [27, 28, 35, 36] on non-small-cell lung cancer, three trials [29–31] on head and neck squamous-cell carcinoma, and three trials [32, 37, 38] on pancreatic cancer. The flow chart is shown in Fig. 1.

A total of 7,954 patients from 17 clinical studies were available for analysis, with 3,965 patients in the cetuximab based group and 3,989 patients in the non-cetuximab group. The baseline characteristics of 17 studies are summarized in Table 1. The cetuximab was combined with regimens including best supportive treatment (BSC), XELOX, irinotecan, XELOX + bevacizumab, irinotecan + 5-FU/FA, radiotherapy, cisplatin, platinum + fluorouracil, gemcitabine + cisplatin + carboplatin, pemetrexed + carboplatin + thoracic radiation, cisplatin + vinorelbine, gemcitabine, irinotecan + docetaxel, and 5-FU/FA; the average median age was ranged from 56- to 66-years-old; the male patients were ranged from 38.5 to 92%; the total number of each trial varied from 74 to 1,298; and Jadad score ranged from 1 point to 5 points. The baseline ECOG status for most of the patients was between 0–1 and 2, while WHO status was between 0 and 1, and KPS was lower than 80 and 80–100. The median follow-up was ranged from 6.8 months to 54 months.

Efficacy

PFS

Twelve eligible RCTs [22–25, 27–33, 37] have the data of PFS which included 2,498 patients in the cetuximab group and 2,501 patients in the non-cetuximab group. There was a

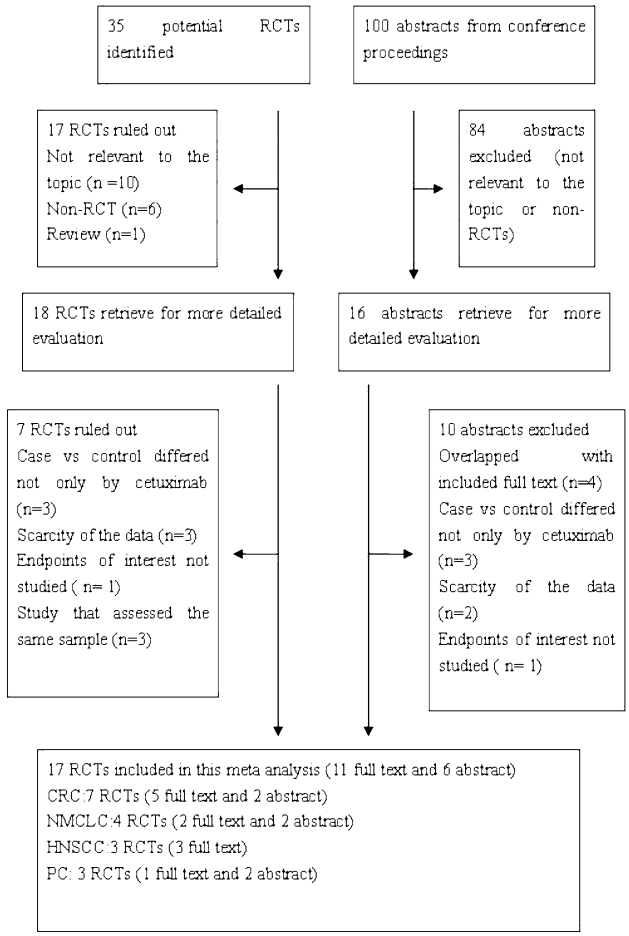


Fig. 1 The flow chart of the meta-analysis in this study

significant improvement of PFS in the cetuximab group (HR 0.83 95%CI 0.78–0.88). However, there was significant heterogeneity among studies ($P = 0.000$, $I^2 = 84.4\%$). Sensitivity analysis showed that the heterogeneity could be attributed mainly to two trials [33, 37]. After removing these two trails, there was a 29% reduction in the hazard of progression for cetuximab group (HR 0.71, 95%CI 0.66–0.76, heterogeneity $P = 0.089$, $I^2 = 40.3\%$) (Fig. 2).

Sub-group analysis

CRC (colorectal cancer)

Five eligible RCTs [22–25, 33] have the data of PFS which included 1,506 patients in the cetuximab group and 1,505 patients in the non-cetuximab group. The pooled analysis of PFS showed a significant heterogeneity ($P = 0.000$, $I^2 = 88.9\%$). Sensitivity analysis showed that the heterogeneity could be ascribed to Punt et al. [33]. After removing the trial [33], there was a 17% reduction in the hazard of progression for the cetuximab group (HR 0.72, 95%CI 0.66–0.78, heterogeneity $P = 0.130$, $I^2 = 46.8\%$).

Table 1 Baseline characteristics of included patients

Type	Author, year	Country	Treatment	*n*	Age (years)	Male (%)	Start accrual	Treatment line	ECOG performance status—no. (%)		Follow-up (month)	Jadad score
									0-1	2		
CRC	Cutsem et al. [34]	Belgium	Ir + 5-FU/FA + Ce	608	61	730 (60)	August 2004 to October 2005	First	1,186 (97.5)	43 (3.5)	\	1
			Ir + 5-FU/FA	609								
CRC	Jonker et al.[24]	Canada	BSC + Ce	287	63	186 (64.8)	December 2003 to August 2005	First	220 (76.7)	67 (23.3)	14.6	4
			BSC	285	63.6	182 (63.9)			218 (76.5)	67 (23.5)		
CRC	Bokemeyer et al. [22]	US	FOLFOX-4 + Ce	169	62	89 (53)	July 2005 to March 2006	First	154 (91.1)	15 (9)	\	4
			FOLFOX-4	168	60	92 (55)			151(89.9)	17 (10)		
CRC	Sobrero et al. [23]	US	Ir + Ce	648	61	405 (62.5)	May 2003 to February 2006	First	608 (93.8)	35 (5.4)	Every 3 months	2
			Ir	650	62	411 (63.2)			611 (94.0)	35 (5.4)		
HNSCC	Burtness et al. [30]	US	Ci + Ce	57	60.6	41(71.9)	June 1999 to June 2001	First and Second	57 (100)	0 (0)	31	5
			Ci + placebo	60	58.3	50 (83.3)			60 (100)	0 (0)		
NMCLC	Butts et al. [27]	US	Ge + Ci/Ca +Ce	65	66	25 (38.5)	\	First	64 (98.5)	2 (1.5)	\	2
			Ge + Ci/Ca	66	64	33 (50)			65 (98.5)			
NMCLC	Pirker et al. [35]	\	Ce + Ci/Vi(CV)	557	59	788 (70)	\	First	934 (83)	\	\	1
			Ci/Vi (CV)	568								
PC	Philip et al. [37]	\	Ge + ce	367	64	375 (51)	January 2004 to April 2006	\	\	96 (13)	\	2
			Ge	368								
PC	Pirker et al. [35]	\	Ir/Do + Ce	43	60.6	24 (55)	\	\	19 (44)	\	\	2
			Ir/Do	44	60.2	36 (86)			19 (43)			
PC	Cascinu et al. [32]	Italy	Ge + Ci + Ce	42	61	22 (52.4)	May 2005 to Sept 2006	First	38 (90.5)	4 (9.5)	11.8	4
			Ge + Ci	42	64	29 (69.0)			38 (90.5)	4 (9.5)		
									WHO performance status—no. (%)			
									0	1		
CRC	Tol et al. [26]	Netherlands	Ca + Ox + Be + Ce	192	61.5	121 (63)	June 2005 to September 2007	First	122 (64)	65 (34)	6.8	3
			Ca + Ox + Be	197	62	103 (52)			115 (58)	79 (40)		
CRC	Borner et al. [25]	Switzerland	XELOX + Ce	37	60	23 (62)	June 2004 to October 2005	First	22 (59)	15 (41)	17.2	3
			XELOX	37	63	21 (57)			21 (57)	16 (43)		

Table 1 continued

									Karnofsky performance status (KPS)—no. (%)		
									<80	80–100	
HNSCC	Bonner et al. [29]	US	Ra + Ce	211	56	171(81)	April 1999 to March 2002	First	21 (9.6)	189 (89.6)	54	3
			Ra	213	58	169 (79)			22 (10.3)	190 (89.2)		
HNSCC	Vermorken et al. [31]	US	Pl-Fl + Ce	222	56	197 (89)	December 2004 to December 2005	First	27 (12)	195 (88)	19.1	3
			Pl-Fl	220	57	202 (92)			25 (11)	195 (89)	18.2	
NMCLC	Rosell et al. [28]	Spain	Ci + Vi + Ce	43	58	33 (76.7)	February 2002 to May 2003	First	3 (7)	39 (93)	Every 2 months	2
			Ci + Vi	43	57	31 (72.1)			3 (7)	39 (93)		
CRC	Punt et al. [33]	Netherlands	Ca + Ox + Be + Ce	365	62	\	June 2005 to December 2006	First	\	\	14.7	3
			Ca + Ox + Be	365								
NMCLC	Bogart et al. [36]	\	Pe + Ca + Ra +Ce	52	64.5	65 (61)	September 2005 to December 2007	Second	\	\	\	2
			Pe + Ca + Ra	54								

Ir irinotecan, *Ce* cetuximab, *Ci* cisplatin, *Ge* gemcitabine, *Ca* carboplatin, *Vi* vinorelbine, *Do* docetaxel, *Ox* oxaliplatin, *Be* bevacizumab, *Pl–Fl* platinum–fluorouracil, *Pe* pemetrexed

HNSCC (head and neck squamous-cell carcinoma)

Three eligible RCTs [29–31] have the data of PFS which included 490 patients in the cetuximab group and 493 patients in the non-cetuximab group. Patients in the cetuximab group has the remarkable PFS benefit (HR 0.63, 95%CI 0.54–0.73, heterogeneity $P = 0.148$, $I^2 = 47.7\%$).

NSCLC (non-small-cell lung cancer)

Two eligible RCTs [27, 28] have the data of PFS which included 108 patients in cetuximab group and 109 patients in non-cetuximab group. No significant difference was noted in PFS between two groups (HR 0.82, 95%CI 0.64–1.07, heterogeneity $P = 0.547$, $I^2 = 0.0\%$).

PC (pancreatic cancer)

Two eligible RCTs [32, 37] have the data of PFS which included 394 patients in cetuximab group and 394 patients in non-cetuximab group. No PFS benefit was observed for the cetuximab group (HR 1.11, 95%CI 0.97–1.28, heterogeneity $P = 0.512$, $I^2 = 0.0\%$).

OS

Eleven eligible RCTs [23–25, 27–32, 35, 37] have reported OS which included 2,521 patients in the cetuximab group and 2,536 patients in the non-cetuximab group (HR 0.89, 95%CI 0.84–0.95, heterogeneity $P = 0.127$, $I^2 = 33.9\%$) (Fig. 3).

Sub-groups analysis:

CRC

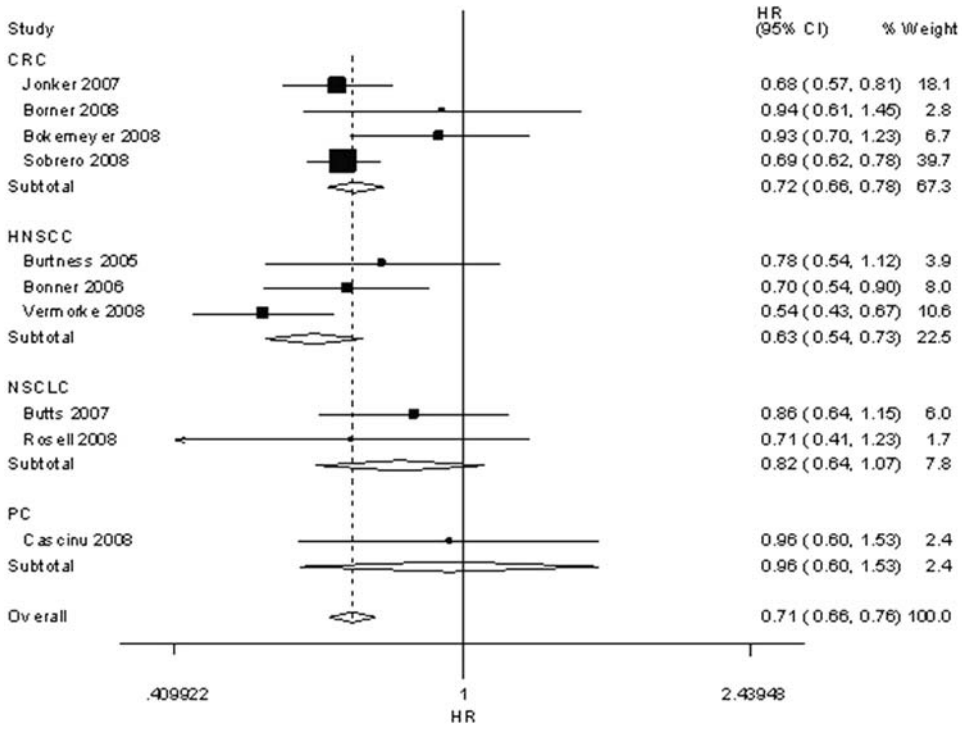
Three eligible RCTs [23–25] have the data of OS which included 972 patients in the cetuximab group and 972 patients in the non-cetuximab group with a marginal effect of HR equal to 0.90 and 95%CI of 0.81–1.00. Heterogeneity existed among studies ($P = 0.120$, $I^2 = 52.8\%$).

HNSCC

Three eligible RCTs [29–31] have the data of OS which included 490 patients in the cetuximab group and 493 patients in the non-cetuximab group (HR 0.78, 95%CI 0.67–0.91, heterogeneity $P = 0.868$, $I^2 = 0.0\%$).

NSCLC

Three eligible RCTs [27, 28, 35] have the data of OS which included 665 patients in the cetuximab group and 677



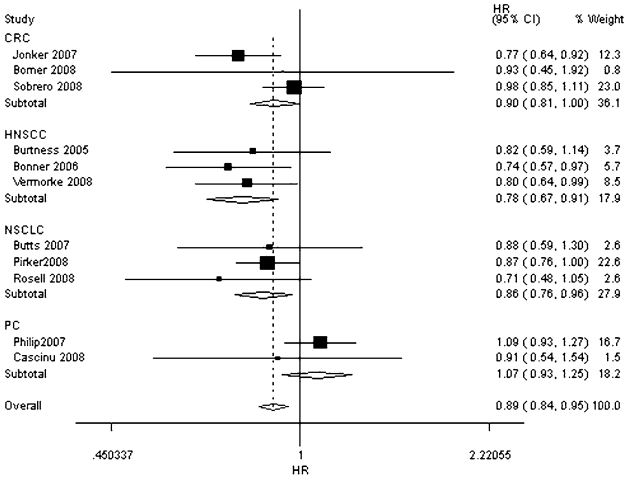


Fig. 2 Progression free survival

Fig. 3 Overall survival

patients in the non-cetuximab group (HR 0.86, 95%CI 0.76–0.96, heterogeneity $P = 0.622$, $I^2 = 0.0\%$).

PC

Two eligible RCTs [32, 37] have the data of OS which included 394 patients in the cetuximab group and 394 patients in the non-cetuximab group with an HR equal to 1.07 and 95%CI of 0.93–1.25 and P value equal to 0.347. There was no heterogeneity across studies ($P = 0.520$, $I^2 = 0.0\%$).

ORR

ORR data were available from 14 RCTs [22–25, 27–34, 37, 38]. The ORR was 901 (28.6%) for 3,149 patients in the cetuximab group and 671 (21.3%) for 3,154 patients in non-cetuximab group showing a statistically significant difference in favor of the former (OR 1.56, 95% CI 1.38–1.77). However, significant heterogeneity existed among trials ($P = 0.000$, $I^2 = 73.8\%$). According to the results of sensitivity analysis, one trial [23] was excluded. Afterwards, there was a higher response rate in the cetuximab group (795/2,501) than that in the non-cetuximab group (644/2,504) (OR 1.39, 95%CI 1.22–1.58, heterogeneity $P = 0.037$, $I^2 = 45.6\%$) (Fig. 4).

Sub-groups analysis

CRC

Six RCTs [22–25, 33, 34] reported response rate including 666 (31.5%) of 2,144 patients in the cetuximab group and 476 (22.5%) of 2,144 patients in the non-cetuximab group. However, the pooled analysis of ORR showed a significant heterogeneity ($P = 0.000$, $I^2 = 86.7\%$). According to the result of sensitivity analysis, two trials [23, 24] were excluded. Afterwards, there was a higher response rate in the cetuximab group (569/1,466) than that in the non-cetuximab group (449/1,464) (OR 1.36, 95%CI 1.15–1.60, heterogeneity $P = 0.136$, $I^2 = 45.9\%$).

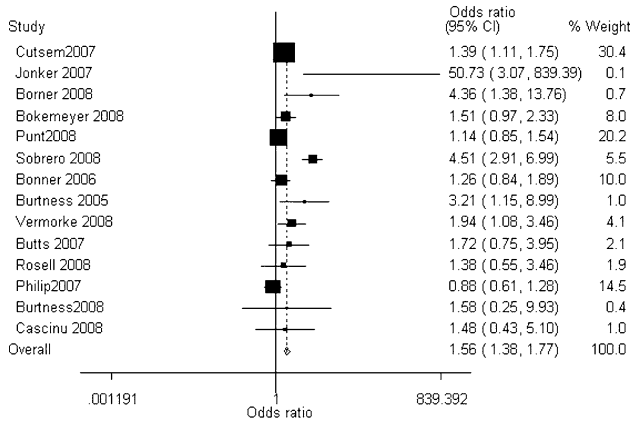


Fig. 4 Overall response rate

HNSCC

Three RCTs [29–31] reported ORR including 125 (25.5%) of 490 patients in the cetuximab group and 90 (18.3%) of 493 patients in the non-cetuximab group (OR 1.57, 95%CI 1.15–2.16, heterogeneity $P = 0.174$, $I^2 = 42.9\%$).

NSCLC

Two RCTs [27, 28] reported ORR including 33 (30.6%) of 108 patients in the cetuximab group and 24 (22.0%) of 109 patients in the non-cetuximab group (OR 1.56, 95%CI 0.85–2.88, heterogeneity $P = 0.728$, $I^2 = 0.0\%$).

PC

Three RCTs [32, 37, 38] reported ORR including 77 (17.6%) of 437 patients in the cetuximab group and 81 (18.5%) of 438 patients in the non-cetuximab group (OR 0.94, 95%CI 0.66–1.33, heterogeneity $P = 0.629$, $I^2 = 0.0\%$).

Safety

1. *Grade 3–4 toxicity*: Eight RCTs [22–24, 26, 33, 34] reported grade 3–4 toxicity including 1,813 (63.2%) of 2,868 patients in the cetuximab group and 1,378 (48.4%) of 2,845 patients in the non-cetuximab group. The pooled analysis of grade 3–4 toxicity showed a significant heterogeneity ($P = 0.003$, $I^2 = 68\%$). According to the result of sensitivity analysis, Cutsem et al. [34] were excluded. Afterwards, there was a higher morbidity in the cetuximab group (1,444/2,260) than that in the non-cetuximab group (1,171/2,236) (OR 1.84, 95%CI 1.61–2.11, heterogeneity $P = 0.136$, $I^2 = 38.4\%$).
2. *Skin-related toxicity*: Fourteen RCTs [22–34, 36] reported skin-related toxicity including 898 (30.1%) of 2,983 patients in the cetuximab group and 458 (15.4%) of 2,969 patients in the non-cetuximab group. The pooled analysis of skin-related toxicity showed a significant heterogeneity ($P = 0.000$, $I^2 = 82.8\%$). According to the result of sensitivity analysis, two trials [25, 26] were excluded. Afterwards, there was a much higher morbidity in the cetuximab group (699/2,583) than that in the non-cetuximab group (344/2,560) (OR 31.80, 95%CI 18.62–54.30, heterogeneity $P = 0.145$, $I^2 = 30.8\%$) (Fig. 5).
3. *Acneiform rash*: Ten RCTs [23–25, 27–30, 33, 36] reported rash including 280 (14.6%) of 1,922 patients in the cetuximab group and 10 (0.5%) of 1,906 patients in the non-cetuximab group (OR 30.14, 95%CI 16.60–54.72, heterogeneity $P = 0.840$, $I^2 = 0.0\%$) (Fig. 6).
4. *Hypomagnesemia*: Six RCTs [23, 24, 26, 27, 30, 31] reported hypomagnesemia including 48 (4.5%) of 1,061 patients in the cetuximab group and 6 (0.6%) of 959 patients in the non-cetuximab group (OR 6.72, 95%CI 3.01–14.98, heterogeneity $P = 0.621$, $I^2 = 0.0\%$).
5. *General symptoms*:

(1) *Asthenia*: Eleven RCTs [22, 24, 25, 27–31, 33, 36] reported asthenia including 258 (12.1%) of 2,141 patients in the cetuximab group and 212 (10.0%) of 2,121 patients in the non-cetuximab group (OR 1.25, 95%CI 1.02–1.53, heterogeneity $P = 0.239$, $I^2 = 21.50\%$).

(2) *Infection*: Seven RCTs [24, 25, 27–31] reported infection including 61 (5.7%) of 1,071 patients in the cetuximab group and 15 (1.2%) of 1,214 patients in the non-cetuximab group (OR 2.87, 95%CI 1.47–5.62, heterogeneity $P = 0.211$, $I^2 = 23.5\%$).

(3) *Infusion-related reactions*: Five RCTs [24, 25, 27, 29–31] reported infusion-related reactions including 33 (4.2%) of 788 patients in the cetuximab group and 3 (0.4%) of 778 patients in the non-cetuximab group (OR 8.37, 95%CI 2.90–24.17, heterogeneity $P = 0.358$, $I^2 = 8.4\%$).

6. *Hematological system syndroma*:

(1) *Neutropenia*: Eleven RCTs [22, 23, 25–28, 30–32, 34, 36] reported neutropenia including 601 (28.6%) of 2,101 patients in the cetuximab group and 505 (24.2%) of 2,084 patients in the non-cetuximab group. However, the pooled analysis showed a significant heterogeneity ($P = 0.002$, $I^2 = 64.3\%$). According to the result of sensitivity analysis, Rosell et al. [28] were excluded. Afterwards, there was a higher morbidity in the cetuximab group (566/2,059) than that in the non-cetuximab group (490/2,041) (OR 1.22, 95%CI 1.05–1.41, heterogeneity $P = 0.157$, $I^2 = 31.4\%$).

(2) *Thrombocytopenia*: Nine RCTs [22, 23, 25, 27, 28, 30–32, 36] reported thrombocytopenia including 128

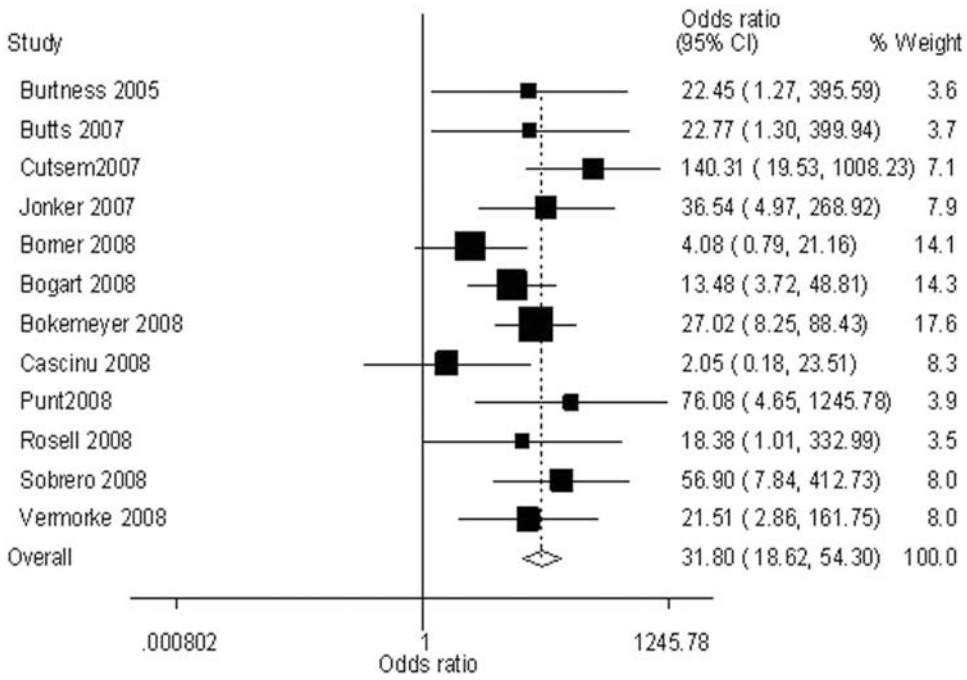


Fig. 5 Grade 3/4 skin-related toxicity

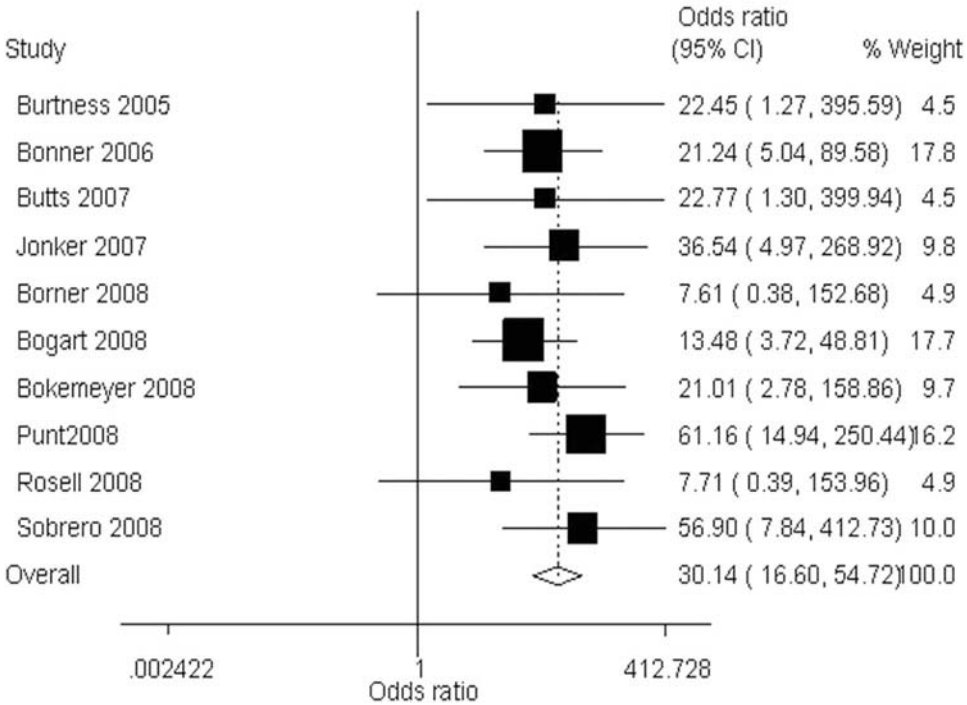


Fig. 6 Grade 3/4 acneform rash

(9.9%) of 1,299 patients in the cetuximab group and 100 (7.8%) of 1,277 patients in the non-cetuximab group (OR 1.49, 95%CI 1.08–2.06, heterogeneity $P = 0.474$, $I^2 = 0.0\%$).

(3) *Anemia*: Nine RCTs [22, 23, 25, 27–32] reported anemia including 91 (62.4%) of 1,458 patients in the cetuximab group and 109 (75.9%) of 1,437 patients in the non-cetuximab group (OR 0.81, 95%CI 0.60–1.09, heterogeneity $P = 0.091$, $I^2 = 41.5\%$).

7. *Digestive system syndroma*:

(1) *Nausea/vomiting*: Twelve RCTs [23–33, 36] reported nausea/vomiting including 231(10.5%) of 2,205 patients in the cetuximab group and 238 (10.9%) of 2,192 patients in the non-cetuximab group. The pooled

analysis showed a significant heterogeneity ($P = 0.000$, $I^2 = 81.5\%$). According to the result of sensitivity analysis, two trials [23, 29] were excluded. Afterwards, there was a higher morbidity in the cetuximab group (162/1,359) than that in the non-cetuximab group (187/1,860) (OR 1.69, 95%CI 1.25–2.28, heterogeneity $P = 0.437$, $I^2 = 0.1\%$).

(2) *Diarrhea*: Eight RCTs [23, 25–27, 29, 32–34] reported diarrhea including 429 (19.9%) of 2,154 patients in the cetuximab group and 282 (13.1%) of 2,157 patients in the non-cetuximab group. The pooled analysis showed a significant heterogeneity ($P = 0.000$, $I^2 = 85.4\%$). Owing to heterogeneity can not be eliminated by sensitivity analysis, random-effect model was performed with an outcome of OR equal to 1.59 and 95% CI of 0.75–3.38 and P value equal to 0.225.

(3) *Anorexia*: Seven RCTs [23–25, 27, 29–31] reported anorexia including 69 (4.6%) of 1,512 patients in the cetuximab group and 38 (2.3%) of 1,645 patients in the non-cetuximab group (OR 1.88, 95%CI 1.26–2.81, heterogeneity $P = 0.063$, $I^2 = 49.8\%$).

8. *Neuropathy*: Five RCTs [23, 25, 26, 30, 33] reported neuropathy including 52 (6.3%) of 822 patients in the cetuximab group and 64 (7.8%) of 825 patients in the non-cetuximab group (OR 0.80, 95%CI 0.55–1.17, heterogeneity $P = 0.751$, $I^2 = 0.0\%$).

Table 2 lists the results of this meta-analysis.

Publication bias

There was no publication bias among these studies according to Fig. 7.

Discussion

This article is the first meta-analysis to evaluate the efficacy and safety of cetuximab based therapy and non-cetuximab therapy for advanced cancer. A total of 7,954 intent-to-treat patients from 17 RCTs, with 3,965 patients in cetuximab arm and 3,989 patients in non-cetuximab arm, were analyzed.

The traditional endpoint for efficacy is OS, but OS requires prolonged follow-up and the impact of first-line therapy on OS may be confounded by the effect of second-line therapies. PFS offers a direct measure of regimen activity that is not obscured by subsequent therapies; PFS is advised to act as a surrogate marker of survival. In the pooled analysis, cetuximab based therapy confers a clinically meaningful and statistically significant improvement OS and PFS with an 11% higher improvement of survival and a 29% lower risk of progression, respectively. Our data on ORR reinforces further the survival results because there was a higher response rate in the cetuximab group than that in the non-cetuximab group (OR 1.39, 95%CI 1.22–1.58).

For the subgroup analysis based on the type of tumor, treatment benefits are also significant with CRC and HNSCC in favor of the cetuximab-based therapy. However, survival gains are more modest and less definitive in NSCLC because only OS benefit (HR 0.86, 95%CI 0.76–0.96) was noted and neither PFS nor ORR benefit were noted in the cetuximab arm. As for pancreatic cancer, no treatment benefits were noted in the cetuximab-treated patients. We acknowledge that, for pancreatic cancer, the data were immature to make an exact conclusion and more evidences from RCTs are needed to appraise the therapeutic effect of cetuximab. And for advanced colorectal cancer, a recent study [39] manifested that the therapeutic efficacy of cetuximab may be associated with the mutation status of the K-ras gene. The mutation status of the K-ras gene in the tumor can affect the response to cetuximab and have treatment-independent prognostic value. They suggested that patients with a colorectal tumor bearing mutated K-ras did not benefit from cetuximab, whereas patients with a tumor bearing wild-type K-ras did benefit from cetuximab.

The meta-analysis suggests that the addition of cetuximab results in a meaningful increases in grade 3 and 4 toxicity including cetuximab-related skin toxicity, acneiform rash, hypomagnesemia, asthenia, infection, infusion-related reactions, neutropenia, thrombocytopenia, nausea/vomiting, and anorexia. One of the most common and severe adverse effects associated with cetuximab is skin toxicity, especially acneiform rash. The accurate mechanism for the acneiform rash is still not clear, although it is agreed that it is a consequence of inhibition of EGFR signaling on epidermal and adnexal epithelium. An interesting and much debated finding following analysis of trials for cetuximab is that the rash may be an important clinical surrogate of antitumor activity or therapeutic efficacy.

Another common and severe grade 3 or 4 adverse event is cetuximab-related hypomagnesemia, to which little attention has been paid. We found that the incidence of hypomagnesemia was 3.9% higher in the cetuximab arm than in the non-cetuximab arm. The association of cetuximab based therapy with hypomagnesemia might be related to a direct effect of cetuximab on the distal convulted tubule. Magnesemia transport has long been poorly understood, recently, TRPM6 and TRPM7 are now well accepted as important regulators of magnesium homeostasis. TRPM6 and TRPM7 are localized in the kidney tubule and vascular smooth muscle cells [40]. And EGFR is also highly expressed in the kidney tubule. The symptoms of hypomagnesemia can be very nonspecific, the irritability, paresthesia, and severe fatigue that some patients could easily have

Table 2 Results of this meta-analysis

Outcome	OR	HR	95%CI	*P* value	Heterogeneity	
					P	I^2 (%)
(a)						
Efficiency						
Progression-free survival	\	0.71	0.66–0.76	0.000	0.089	40.30
Overall survival	\	0.89	0.84–0.95	0.001	0.127	33.90
Overall response rate	1.39	\	1.22–1.58	0.000	0.037	45.60
Toxicity						
Grade 3–4 toxicity	1.84	\	1.61–2.11	0.000	0.136	38.40
Skin-related toxicity	31.8	\	18.62–54.30	0.000	0.145	30.80
Hypomagnesemia	7.01	\	3.16–15.56	0.000	0.559	0.00
Asthenia	1.25	\	1.02–1.53	0.03	0.239	21.50
Infection	2.87	\	1.47–5.62	0.03	0.211	23.50
Infusion-related reactions	8.37	\	2.90–24.17	0.000	0.358	8.40
Neutropenia	1.22	\	1.05–1.41	0.009	0.157	31.40
Thrombocytopenia	1.49	\	1.08–2.06	0.016	0.474	0.00
Anemia	0.81	\	0.60–1.09	0.162	0.091	41.50
Nausea/vomiting	1.69	\	1.25–2.28	0.001	0.437	0.10
Diarrhea	1.59	\	0.75–3.38	0.225	0	85.40
Anorexia	1.88	\	1.26–2.81	0.002	0.063	49.80
Neuropathy	0.8	\	0.55–1.17	0.257	0.751	0.00

Tumor type	Progression-free survival	Overall survival	Overall response rate
(b) Efficiency among different tumor			
CRR			
HR	0.72	0.9	1.36
95%CI	0.66–0.78	0.81–1.00	1.05–1.60
P value	0.000	0.048	0.000
HNSCC			
HR	0.63	0.78	1.57
95%CI	0.54–0.73	0.67–0.91	1.15–2.16
P value	0.000	0.002	0.005
NSCLC			
HR	0.82	0.86	1.560
95%CI	0.64–1.07	0.76–0.96	0.85–2.88
P value	0.143	0.011	0.154
PC			
HR	1.11	1.07	0.94
95%CI	0.97–1.28	0.93–1.25	0.66–1.33
P value	0.131	0.347	0.727

been attributed to the underlying tumor or to previous chemotherapy regimens [41]. Hypomagnesemia is often ignored in many studies, so serum magnesemia levels should be monitored better when cetuximab based therapy were performed for advanced cancer.

Another severe grade 3 or 4 adverse events are the cetuximab-related infectious complications. A previous systematic review [42] has reported that cetuximab in addition to chemotherapy increased the incidence of high-grade infections compared with chemotherapy alone. This is coincided with our results and we further support their findings by giving the exact data of the incidence of infectious complications. Our analysis show that the incidence of infections was 4.5% higher in the cetuximab arm than the non-cetuximab arm with an OR equal to 2.87 and 95%CI of 1.47–5.62. Although no death related to severe infection was reported in trials contained in this study. Infection can be life threatening when severe, therefore, nurses must

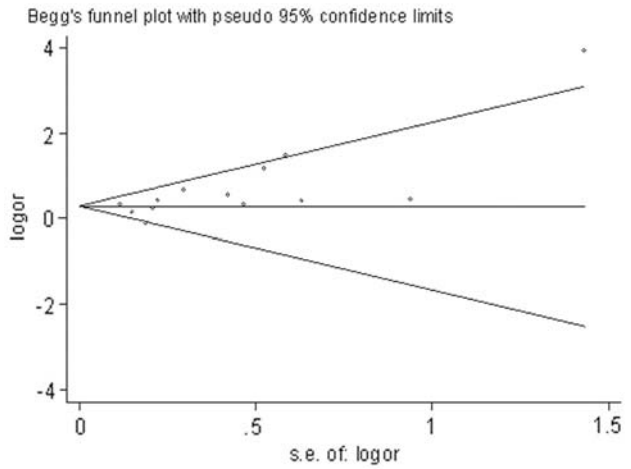


Fig. 7 Funnel plot

administer prophylactic treatment with antibiotic agent to prior to infusion and actively manage cetuximab-related infections when they occur.

Eventually, the incidence of grade 3 or 4 infusion-related reactions increased by 3.8% resulting from the use of cetuximab. Infusion reactions usually are mild to moderate (grade 1 or 2), but severe reactions are potentially fatal. We suggest that baseline vital sign measurements should be taken, and patients should be premedicated with an H1 antagonist before administration begins. Moreover, patients should be monitored carefully, and administration should be interrupted if symptoms of infusion reactions are detected. Administration should resume only if an infusion reaction was mild to moderate, and the rate of infusion should be reduced [43].

As for asthenia, neutropenia, thrombocytopenia, nausea/vomiting, and anorexia whether these increases are due to cetuximab, or a byproduct of the higher cumulative some chemotherapeutic agent (such as irinotecan, oxaliplatin) dose with the combination, is unclear, and these findings warrant careful evaluation of the patients appropriate for this regimen. Cetuximab did not increase the incidence of grade 3–4 anemia, diarrhea, and neuropathy.

Several limitations of our analysis worth consideration: first, as with every meta-analysis, results are affected by the quality of individual trials. Second, treatments were involved in a few trials based on the different tumor types; third, not all articles have the available data of OS, PFS, ORR, and some adverse effects. Fourth, more evidences from randomized studies are needed to evaluate the therapeutic efficacy of cetuximab for pancreatic cancer. Finally, the heterogeneity of the data exists in some outcomes in this meta-analysis, which may be mainly attribute to the difference of patient populations, concurrent radiochemotherapies, follow-up durations, lengths of treatment and tumor performance status (i.e., ECOG status or WHO status or KPS status) across included trials.

In conclusion, our data showed that cetuximab-based therapy improved PFS, OS, and result in better ORR versus non-cetuximab therapy, irrespective of tumor type. For pancreatic cancer, the data were immature to make an exact conclusion and more evidences from randomized studies are needed to appraise the effect. Meanwhile, the most common and severe adverse events associated with cetuximab are skin toxicity, rash, hypomagnesemia, infection, and infusion-related reaction which are predictable and manageable. We recommend this drug used as first or second line treatment for advanced or metastatic colorectal cancer and head and neck squamous cell carcinoma, but early monitor and effective management should be taken to prevent these severe adverse events in order to improve esthetic and functional impairment.

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