World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i35.4944

World J Gastroenterol 2012 September 21; 18(35): 4944-4958
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer?

Chen Sun, Daniel Ansari, Roland Andersson, De-Quan Wu

Chen Sun, De-Quan Wu, Department of Surgery, Second Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang Province, China
Chen Sun, Daniel Ansari, Roland Andersson, Department of Surgery, Clinical Sciences Lund, Lund University, Skåne University Hospital, SE-22185 Lund, Sweden
Author contributions: Sun C and Ansari D performed the majority of the study and wrote the manuscript; Andersson R and Wu DQ conceived the study and finalized the revision; all authors read and approved the final manuscript.
Correspondence to: De-Quan Wu, MD, PhD, Department of Surgery, Second Affiliated Hospital of Harbin Medical University, Xuefu Road, Harbin 150086, Heilongjiang Province, China. dqwu56@163.com
Telephone: +86-451-86605535 Fax: +86-451-82524051
Received: December 17, 2011 Revised: February 1, 2012
Accepted: April 12, 2012
Published online: September 21, 2012

Abstract

AIM: To assess whether gemcitabine-based combination therapy improves the prognosis of unresectable pancreatic cancer compared with gemcitabine treatment alone.

METHODS: A quantitative up-to-date meta-analysis was undertaken to investigate the efficacy of gemcitabine-based combination treatment compared with gemcitabine monotherapy in locally advanced or metastatic pancreatic cancer. Inclusion was limited to high-quality randomized clinical trials.

RESULTS: Twenty-six studies were included in the present analysis, with a total of 8808 patients recruited. The studies were divided into four subgroups based on the different kinds of cytotoxic agents, including platinum, fluoropyrimidine, camptothecin and targeted agents. Patients treated with gemcitabine monotherapy had significantly lower objective response rate [risk ratio (RR), 0.72; 95% confidence interval (CI): 0.63-0.83; $P < 0.001$], and lower 1-year overall survival (RR, 0.90; 95%CI: 0.82-0.99; $P = 0.04$). Gemcitabine monotherapy caused fewer complications, including fewer grade 3-4 toxicities: including vomiting (RR, 0.75; 95%CI: 0.62-0.89; $P = 0.001$), diarrhea (RR, 0.66; 95%CI: 0.49-0.89; $P = 0.006$), neutropenia (RR, 0.88; 95%CI: 0.72-1.06; $P = 0.18$), anemia (RR, 0.96; 95%CI: 0.82-1.12; $P = 0.60$), and thrombocytopenia (RR, 0.76; 95%CI: 0.60-0.97; $P = 0.03$) compared with gemcitabine combination therapies.

CONCLUSION: Gemcitabine combination therapy provides a modest improvement of survival, but is associated with more toxicity compared with gemcitabine monotherapy.

Key words: Pancreatic cancer; Gemcitabine; Combination therapy; Outcome; Meta-analysis

Peer reviewers: Itaru Endo, MD, PhD, Professor and Chairman, Department of Gastroenterological Surgery, Yokohama City University, Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 2360004, Japan; Cuong D Tran, PhD, Research Fellow, Affiliate Lecturer, University of Adelaide, Gastroenterology Unit, Children, Youth and Women's Health Service, 72 King William Rd, North Adelaide, SA 5006, Australia

Sun C, Ansari D, Andersson R, Wu DQ. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? *World J Gastroenterol* 2012; 18(35): 4944-4958 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i35/4944.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i35.4944

INTRODUCTION

Pancreatic cancer is a highly lethal disease, and represents the fourth cause of cancer-related death in the Western

world. In the United States, the incidence of pancreatic cancer almost equals its mortality, with 43 140 estimated new cases and 36 800 deaths in 2010. Globally, the incidence of new cases is approximately 230 000 each year[1,2]. Despite advances in diagnosis, staging, and surgical management of the disease during the past decade, the 5-year survival rate in the United States, Europe, and Australia is less than 5%[3-5]. Pancreatic cancer is characterized by a rapid disease progression and highly invasive tumor phenotype, with most patients having unresectable disease at diagnosis, and chemotherapy being the only possible treatment option for these patients[6].

Gemcitabine is a pyrimidine antimetabolite and analog of deoxycytidine. It was approved by the Food and Drug Administration as a first-line treatment for patients with locally advanced (stage Ⅱ or stage Ⅲ disease when surgery is not an option) or metastatic (stage Ⅳ) cancer of the pancreas, and has been widely used during the last decade. However, because of high levels of intrinsic and acquired chemoresistance, a large number of patients do not respond to gemcitabine[7]. To improve clinical efficacy, systemically administered gemcitabine is often combined with a second cytotoxic agent, such as platinum analogs, fluoropyrimidine, or a targeted cytotoxic agent. Numerous clinical trials have aimed at proving the superiority of gemcitabine-based combination therapy over single-agent gemcitabine treatment. However, most of the results of clinical trials have important limitations, including lack of statistical power because of small study populations. Thus, there remain several areas of controversy and uncertainty concerning optimal treatment regimens.

In the present study, we undertook a quantitative up-to-date meta-analysis to investigate the efficacy of gemcitabine-based combination treatment in locally advanced or metastatic pancreatic cancer. The aim of this study was to assess whether gemcitabine-based combination therapy improves the prognosis compared with gemcitabine treatment alone and to discuss possible mechanisms.

MATERIALS AND METHODS

Literature search strategy

We carried out a comprehensive search of the literature, including PUBMED (http://www.ncbi.nlm.nih.gov/pubmed), EMBASE (http://www.embase.com/home), American Society of Clinical Oncology abstracts (http://www.asco.org), and the Cochrane Database (http://www.thecochranelibrary.com). The following keywords were used in the search: ("Gemcitabine" or "Gemzar"), and ("pancreatic cancer" or "pancreatic tumor" or "pancreatic carcinoma"), and ("clinical trial"). The deadline for a publication to be eligible for this study was November 5, 2011. In addition to the online search, references from reviews and original articles were also scanned manually to identify further trials that met the eligibility criteria. No language restrictions were applied.

Inclusion and exclusion criteria

Studies included in the analysis had to meet all of the following criteria: (1) prospective, randomized, controlled open or blinded trial; (2) patients with histologically confirmed locally advanced or metastatic pancreatic ductal adenocarcinoma; and (3) assessment of the efficacy of gemcitabine combination therapy *vs* gemcitabine alone. Non-randomized trials and quasi-randomized trials, studies of curatively aimed resection, and studies where patients had multiple cancers, were excluded to avoid clinical heterogeneities between different studies.

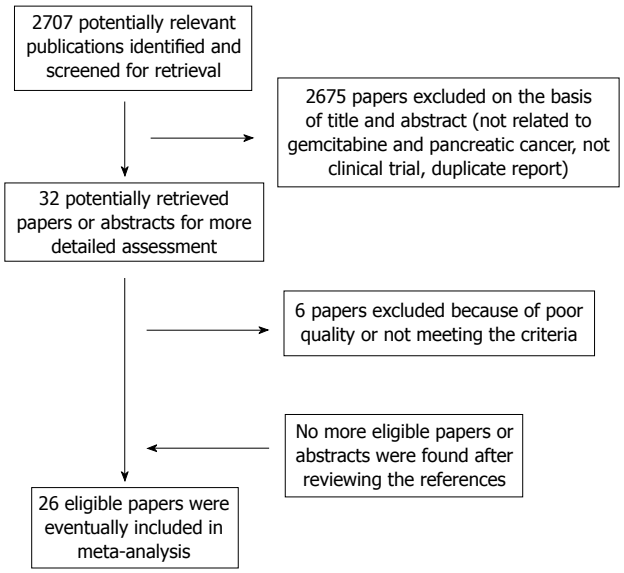

Figure 1 Flow chart of study selection.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by two reviewers (CS and DA). Any disagreements between the reviewers were discussed with a third reviewer (RA) to achieve a consensus. The data extracted from the eligible studies included: first author, year of publication, patient characteristics, intervention, and clinical outcome (toxicity, response rate, overall survival and progression-free survival). If the same trial appeared on sequential or multiple publications, the data from the most recent or comprehensive one was included.

The methodological quality of included studies was assessed using the "Jadad scale" or "Oxford quality scoring system"[8]. This tool is an evidence-based quality assessment tool. There are three items (randomization, double blinding, withdrawals and dropouts) directly related to bias reduction for assessment. Each item is given a score of 1 point for each "yes" or 0 points for each "no", and 1 additional point for appropriate randomization and double blinding. Every eligible study were assessed and given a score from 0-5.

Data analysis

The outcome measures were objective response rate [objective response rate (ORR) = complete response (CR) + partial response (PR)], as previously defined[9], 1-year overall survival (OS), median progression-free survival (PFS), median OS and toxicity. The analysis of ORR

Table 1 Characteristics of selected trials

Ref.	Intervention	*n*	Male (%)	Age (range)	Metastatic (%)	Response rate (%)	Median PFS (mo)	1-yr OS	Median OS (mo)	Quality
Louvet *et al*[15]	Gem	163	53	60.1 (22-75)	70	17.3	3.7	27.8	7.1	4
	Gem + Oxaliplatin	163	60	61.3 (35-77)	68	26.8	5.8	34.7	9.0	
Poplin *et al*[16]	Gem	275	56.4	64 (31-88)	90.2	6	2.6	16	4.9	4
	Gem + Oxaliplatin	272	45.6	63 (29-96)	89.3	9	2.7	21	5.7	
Heinemann *et al*[17]	Gem	95	61.9	66 (43-85)	78.9	9.0	3.1	24.7	6.0	4
	Gem + Cisplatin	95	65.3	64 (37-82)	80	11.5	5.3	25.3	7.5	
Colucci *et al*[18]	Gem	54	50	63 (43-75)	65	9.2	2	11	5	4
	Gem + Cisplatin	53	35	60 (33-71)	68	26.4	5	11.3	7.5	
Colucci *et al*[19]	Gem	199	56.8	63 (37-75)	82.9	10.1	3.9	34.0	8.3	4
	Gem + Cisplatin	201	62.2	63 (35-75)	84.6	11.4	3.8	30.7	7.2	
Kulke *et al*[20]	Gem	64	66	58.9 (31-81)		14	3.3	NR	6.4	4
	Gem + Cisplatin	66	56	58.9 (36-84)	100	13	4.5	NR	6.7	
	Gem + Irinotecan	64	68	60.8 (32-77)		14	4.0	NR	7.1	
Berlin *et al*[21]	Gem	162	53.7	64.3 (33-85)	90.1	5.6	2.2	NR	5.4	4
	Gem + 5-fluorouracil	160	51.8	65.8 (28-84)	89.4	6.9	3.4	NR	6.7	
Herrmann *et al*[22,24]	Gem	159	53	62 (36-84)	79	8	3.9	30	7.2	4
	Gem + Capecitabine	160	54	62 (27-83)	80	10	4.3	32	8.4	
Cunningham *et al*[23]	Gem	266	58	62 (26-83)	71	12.4	3.8	22.0	6.2	4
	Gem + Capeitabine	267	60	62 (37-82)	70	19.1	5.3	24.3	7.1	
Scheithauer *et al*[25]	Gem	42	55	66 (39-75)	100	14	4.0	37.2	8.2	4
	Gem + Capeitabine	41	66	64 (40-75)	100	17	5.1	31.8	9.5	
Costanzo *et al*[26]	Gem	49	48	64 (34-75)	73	8	3.5	18	7.75	4
	Gem + 5-fluorouracil	45	63	62 (44-75)	67	11	4.5	20	7.5	
Abou-Alfa *et al*[27]	Gem	174	57	62.3 (30-84)	78	5.7	3.8	21	6.2	4
	Gem + Exatecan	175	53	63.0 (36-85)	79	7.1	3.7	23	6.7	
Stathopoulos *et al*[28]	Gem	74	42	64 (44-83)	66	10	2.9	21.8	6.5	4
	Gem + Irinotecan	71	39	64 (31-84)	60	15	2.8	24.3	6.4	
Lima *et al*[29]	Gem	180	53.3	60.2 (32-82)	80.6	4.4	3.0	22	6.6	4
	Gem + Irinotecan	180	57.2	63.2 (38-81)	82.2	16.1	3.5	21	6.3	
Moore *et al*[38]	Gem	284	57	64 (36.1-92)	75.0	8.0	3.55	17	5.91	4
	Gem + Erlotinib	285	47.7	63.7 (37-84)	76.5	8.6	3.75	23	6.24	
Cutsem *et al*[39]	Gem	347	58	62 (30-88)	77	8	3.6	24	6.06	4
	Gem + Tipifarnib	341	57	61 (29-89)	76	6	3.7	27	6.43	
Eckhardt *et al*[40]	Gem	120	59	60 (35-86)	73	NR	3.03	NR	7.36	5
	Gem + Tipifarnib	124	64	63 (35-81)	71	NR	2.3	NR	6.73	
Philip *et al*[37]	Gem	371	54	64.3	78	7	3.0	NR	5.9	4
	Gem + cetuximab	372	51	63.7	79	8	3.4	NR	6.3	
Kindler *et al*[36]	Gem	300	51	65.0 (35-86)	85	10	2.9	NR	5.9	4
	Gem + Bevacizumab	302	58	63.7 (26-88)	84	13	3.8	NR	5.8	
Kindler *et al*[35]	Gem	316	59	62 (35-89)	72	1.6	4.4	NR	8.3	5
	Gem + Axitinib	316	61	61 (34-84)	72	4.9	4.4	NR	8.5	
Spano *et al*[41]	Gem	34	47	61.0 (36-78)	19	3	3.7	23.5	5.6	4
	Gem + Axitinib	69	51	65.0 (44-81)	40	7	4.2	36.8	6.9	
Friess *et al*[34]	Gem	43	42	66 (56-80)	91	14	3.83	0.24	7.7	4
	Gem + Cilengitide	46	57	68 (40-80)	94	17	3.66	0.15	6.7	
Richards *et al*[33]	Gem	44	72.7	64.1 (41-83)	86.4	5.3	3.0	17	5.1	4
	Gem + Enzastarin	86	53.5	68.3 (39-86)	90.7	8.6	3.4	19	5.6	
Bramhall *et al*[31]	Gem	119	71	62 (37-85)	62	16	3.2	17	5.46	5
	Gem + Marimastat	120	69	62 (32-83)	59	11	3.08	18	5.51	
Richards *et al*[32]	Gem	85	60.2	65 (36-83)	83.0	13.9	3.43	NR	7.13	5
	Gem + CA-994	85	59.3	62 (32-82)	82.6	11.8	3.06	NR	6.47	
Oettle *et al*[30]	Gem	282	53.5	63 (28-82)	91.1	7.1	3.3	20.1	6.3	4
	Gem + PPemetrexed	283	60.4	63 (27-82)	90.1	14.8	3.9	21.4	6.2	

NR: No record; PFS: Progression-free survival; OS: Overall survival.

(number of partial and complete responses, as defined by Response Evaluation Criteria in Solid Tumors[10]), PFS (time from randomization to progression or death) and OS (time from the date of random assignment until date of death or date last known to be alive) were based on the intent-to-treat population, consisting of all patients randomly assigned onto every study. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, and based on the safety population. The median PFS and median OS were assessed using the paired *t*-test. $P < 0.05$ was considered statistically significant.

Meta-analysis was performed using the Review Manager (version 5.1, provided by The Cochrane Collaboration). The strength of the associations between treatment and outcomes were estimated by risk ratio (RR, a ratio

Table 2 Grade 3 or 4 toxicity of selected clinical trials

Ref.	Intervention	Vomiting	Diarrhea	Neutropenia	Anemia	Thrombocytopenia
Louvet *et al*[15]	Gem	3.2	1.3	27.6	10.3	3.2
	Gem + Oxaliplatin	8.9	5.7	20.4	6.4	14.0
Poplin *et al*[16]	Gem	7	4	33	10	13
	Gem + Oxaliplatin	16	6	22	6	11
Heinemann *et al*[17]	Gem	5.9	4.7	NR	10.6	10.6
	Gem + Cisplatin	22.2	3.3	NR	13.3	4.4
Colucci *et al*[18]	Gem	2	0	9	4	2
	Gem + Cisplatin	2	4	18	6	2
Colucci *et al*[19]	Gem	< 1	1.5	13.7	1	18.9
	Gem + Cisplatin	2.6	< 1	24.7	4.8	15.3
Kulke *et al*[20]	Gem	24.1	NR	82.8	20	43.1
	Gem + Cisplatin	29	NR	74.2	25.8	79
	Gem + Irinotecan	16.7	NR	41.7	8.3	23.3
Berlin *et al*[21]	Gem	8	NR	5	10	11
	Gem + 5-fluorouracil	7	NR	7	10	19
Herrmann *et al*[22,24]	Gem	4	2	19	6	8
	Gem + Capeitabine	4	5	23	8	4
Cunningham *et al*[23]	Gem	6	4	22	6	6
	Gem + Capeitabine	6	5	35	4	11
Scheithauer *et al*[25]	Gem	0	0	7.6	0	2.5
	Gem + Capeitabine	0	5	10	5	0
Costanzo *et al*[26]	Gem	0	0	2	6	0
	Gem + 5-fluorouracil	2	0	2	7	2
Abou-Alfa *et al*[27]	Gem	3.1	< 1	14.6	7.6	4.4
	Gem + Exatecan	5.3	1.1	30.3	5.9	15.4
Stathopoulos *et al*[28]	Gem	1.4	2.8	15.7	4.2	0
	Gem + Irinotecan	1.6	3.2	26.6	5	5
Lima *et al*[29]	Gem	8.2	1.8	31.9	13	14.2
	Gem + Irinotecan	13.9	18.5	37.6	16.2	19.6
Moore *et al*[38]	Gem	NR	< 1	27%	NR	11%
	Gem + Erlotinib	NR	2	24%	NR	10%
Cutsem *et al*[39]	Gem	9	3	30	16	12
	Gem + Tipifarnib	7	4	40	20	15
Eckhardt *et al*[40]	Gem	9.3	0	33.9	11	15.3
	Gem + Tipifarnib	4	0	35.5	12.1	16.1
Philip *et al*[37]	Gem	2.2	2.5	23.9	6.2	8.5
	Gem + cetuximab	6.6	2.8	23.3	9.7	6.6
Kindler *et al*[36]	Gem	NR	NR	29	8	12
	Gem + Bevacizumab	NR	NR	33	5	12
Kindler *et al*[35]	Gem	3.2	1.6	< 1	< 1	< 1
	Gem + Axitinib	3.9	1.3	0	0	0
Spano *et al*[41]	Gem	10	0	33	17	13
	Gem + Axitinib	6	6	28	8	20
Richards *et al*[33]	Gem	0	2.6	28.2	5.1	25.6
	Gem + Enzastarin	2.4	3.7	18.3	3.7	14.6
Bramhall *et al*[31]	Gem	14%	NR	NR	7%	NR
	Gem + Marimastat	6%	NR	NR	3%	NR
Richards *et al*[32]	Gem	9	3	NR	5	11
	Gem + CA-994	9	5	NR	13	25
Oettle *et al*[30]	Gem	3.7	0.7	12.8	2.9	6.2
	Gem + Pemetrexed	3.3	2.9	45.1	13.9	17.9

NR: No record.

of the probability of the event occurring in the exposed group versus a non-exposed group) and 95% confidence interval (CI)[11]. The heterogeneities between different studies or different subgroups were estimated using Cochran's Q test[12,13]. In addition, the I^2 value was used for evaluating the extent of heterogeneity between studies or subgroups[14]. The I^2 index measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom by the Q value itself, and multiplied by 100. I^2 indicated the possibility of the variability among effect sizes caused by true heterogeneity between studies, not by sampling error[14]. If a significant Q test ($P < 0.1$) or $I^2 > 50\%$ indicated that heterogeneity existed between studies, the random effects model was used for meta-analysis, otherwise the fixed effects model was used. Publication bias was assessed by visual inspection of funnel plots.

RESULTS

Literature search and trial flow

The results of the literature search are depicted in Figure

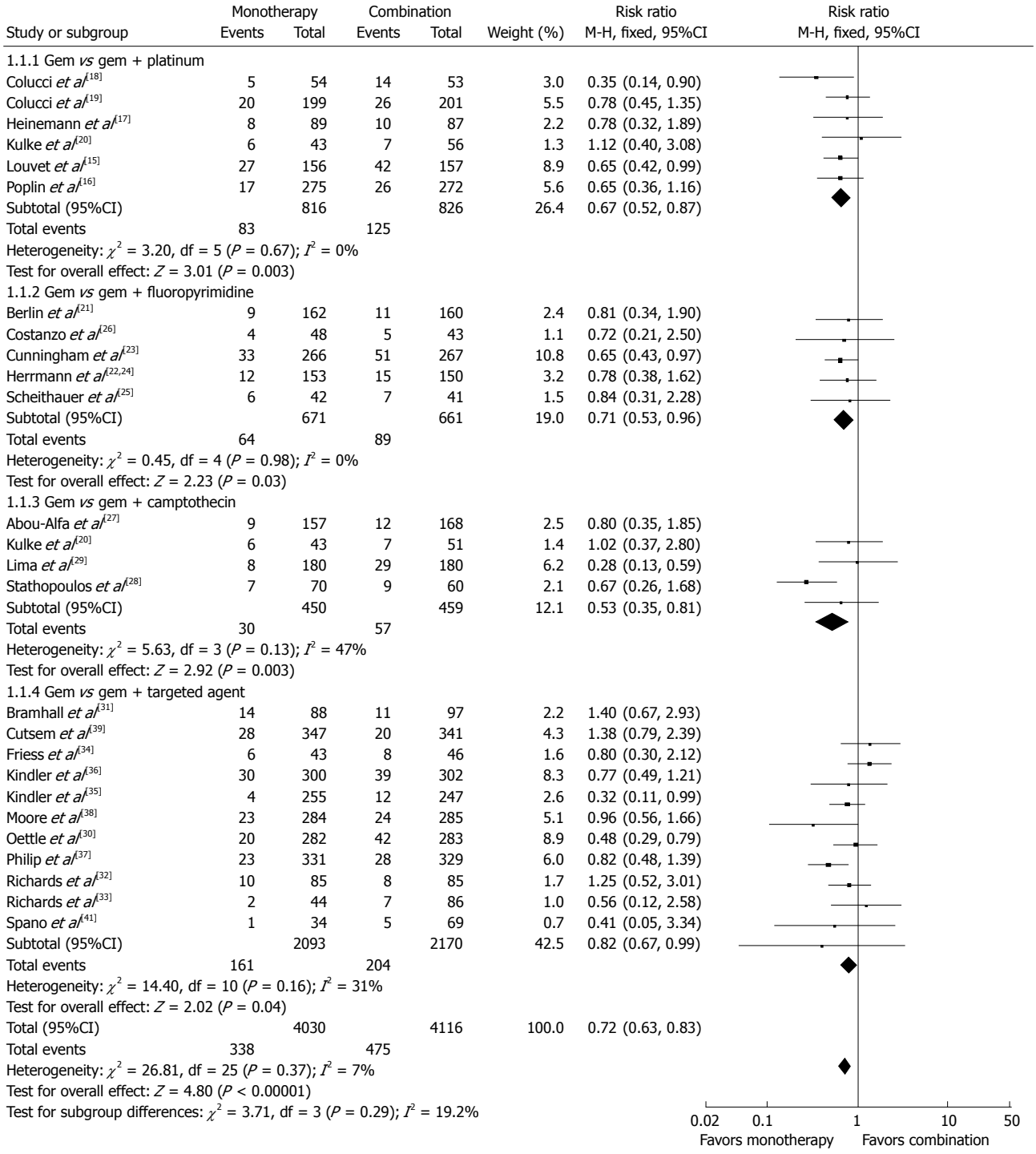

Figure 2 Fixed effect model of risk ratio of objective response rate. CI: Confidence interval.

1. Some 2707 studies were initially retrieved. After reading the title and abstract, 2675 studies were excluded, and 32 studies were left for further review. Six of these were excluded because of poor quality or failure to meet the inclusion criteria.

Characteristics of selected trials

The characteristics of the included studies are shown in Table 1. Twenty-six studies were included in the present analysis, with 8808 recruited patients. The studies were divided into four subgroups based on types of cytotoxic agents used, including platinum[15-20], fluoropyrimidine[21-26], camptothecin[21,27-29] and targeted agents[30-41]. All included studies enrolled patients that were ⩾ 18 years; had a histologically confirmed locally advanced or metastatic pancreatic cancer not amenable to surgical resection; no previous chemotherapy; a life expectancy of at least 12 wk; a Karnofsky performance status ⩾ 50, or World Health Organization performance status of 0-2; and adequate liver, renal, and hematopoietic functions.

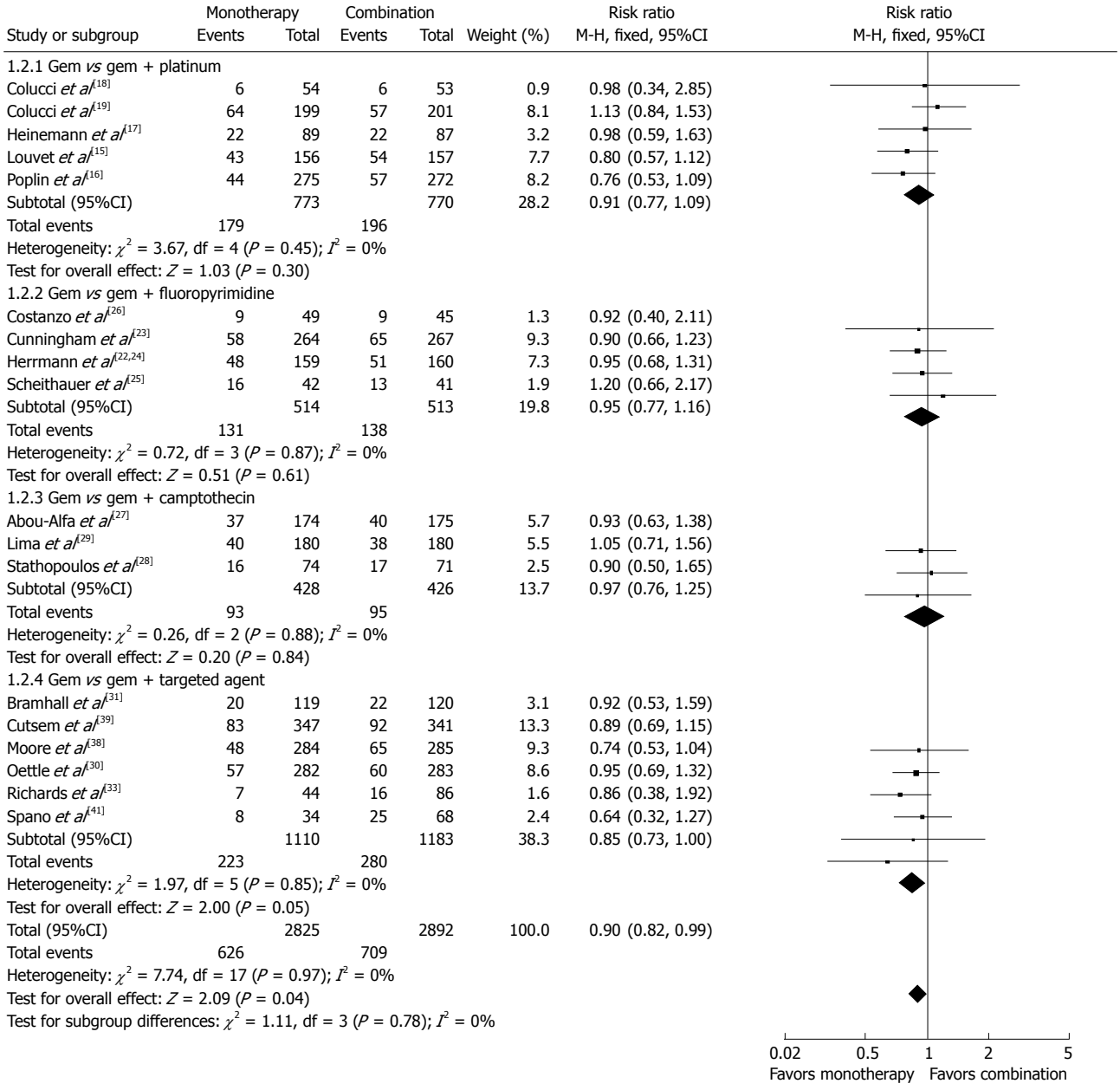

Figure 3 Fixed effect model of risk ratio of 1-year overall survival rate. CI: Confidence interval.

The details of toxicity assessment are shown in Table 2 (only grade 3 and 4 toxic effects are presented), including vomiting, diarrhea, neutropenia, anemia and thrombocytopenia.

The methodological quality of selected studies was high. Most trials had a Jadad score of 3, while three studies had a score of 4. Methods of double blinding were infrequently reported.

Gemcitabine combination therapy improves objective response rate compared with gemcitabine treatment alone

This analysis evaluated 26 trials (8146 patients) comparing gemcitabine monotherapy with the combination of gemcitabine and some other cytotoxic agent. Based on all studies, patients treated with gemcitabine monotherapy had a significantly lower ORR than gemcitabine combination therapy (RR, 0.72; 95%CI: 0.63-0.83; $P < 0.001$). The RRs in the different subgroups were 0.67, 0.71, 0.53 and 0.82, for platinum, fluoropyrimidine, camptothecin and targeted agents, respectively. All RRs in the subgroups were also significant. Data are shown in Figure 2.

Gemcitabine combination therapy improves 1-year overall survival rate compared with gemcitabine alone

5717 patients from 18 trials were included in this meta-analysis comparing gemcitabine monotherapy with combination therapies for 1-year overall survival. The RRs of 1-year overall survival were analyzed both totally and in the different subgroups. Subgroup analysis showed that the RRs of the monotherapy-based 1-year overall survival were lower than for the combination groups (RR:

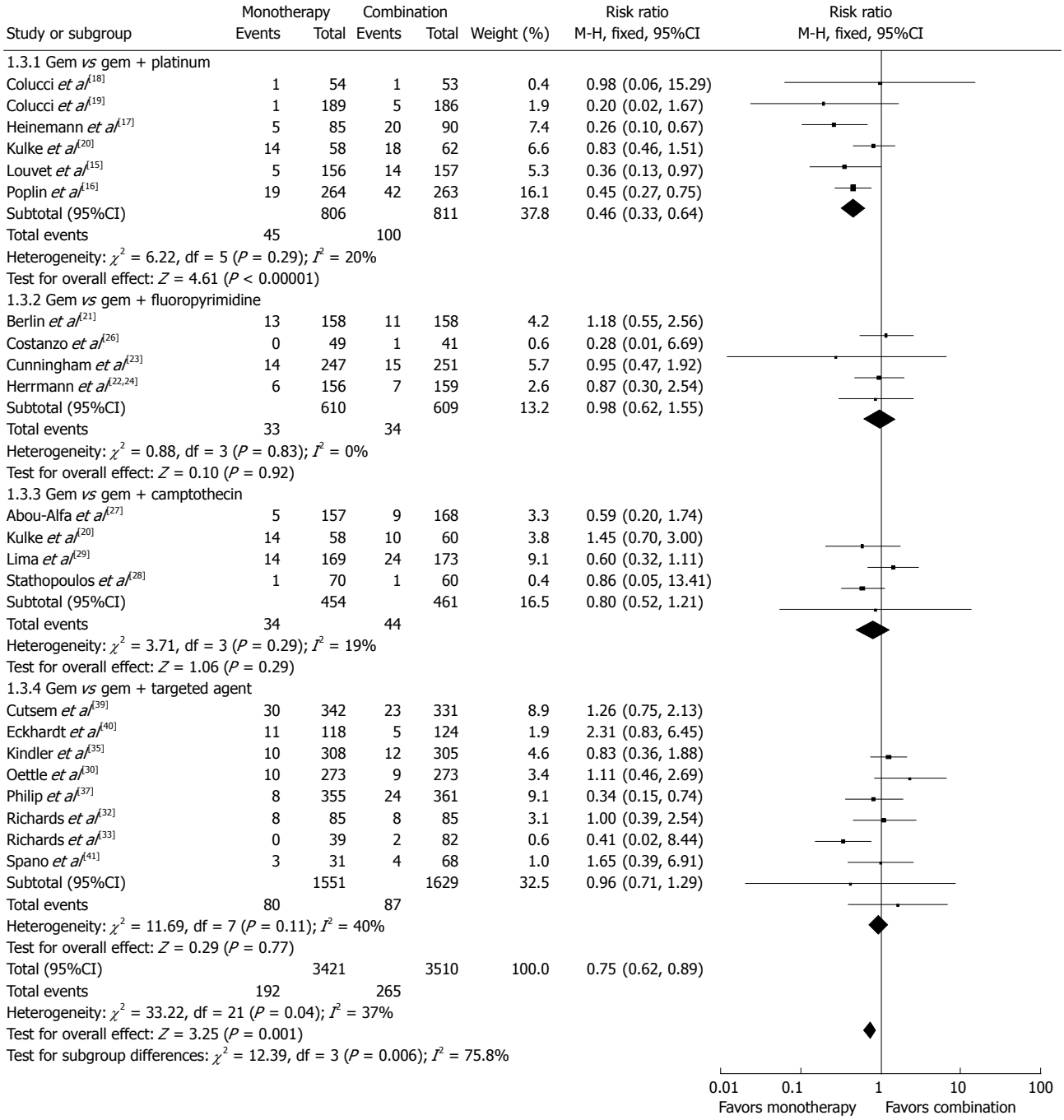

Figure 4 Fixed effect model of risk ratio of grade 3 or 4 vomiting. CI: Confidence interval.

0.91, 0.95, 0.97 and 0.85, for platinum, fluoropyrimidine, camptothecin and targeted agents, respectively), but no significant differences were found. When analyzed in terms of total events, the RR shown in Figure 3 was 0.90 [(95%CI: 0.82-0.99); P = 0.04]. The result showed that the 1-year overall survival rate of gemcitabine monotherapy was almost 90% of that of the combination therapy.

Gemcitabine combination therapy increases the toxicity effect compared with gemcitabine alone

Outcomes of the meta-analysis of the main toxicities are presented in Figures 4-8. All RRs with grade 3-4 toxicities analyzed in this study were lower in the gemcitabine monotherapy group than in the combination group. The incidence of vomiting (RR, 0.75; 95%CI: 0.62-0.89; P = 0.001), diarrhea (RR, 0.66; 95%CI: 0.49-0.89; P = 0.006) and thrombocytopenia (RR, 0.76; 95%CI: 0.60-0.97; P = 0.03) were all significantly different between the treatment groups, while no significant difference was noted regarding neutropenia (RR, 0.88; 95%CI: 0.72-1.06; P = 0.18) and anemia (RR, 0.96; 95%CI: 0.82-1.12; P = 0.60).

In subgroup analysis, the RRs were 0.46-0.98 for vomiting, 0.65-0.70 for diarrhea, 0.70-1.03 for neutropenia, 0.87-1.09 for anemia and 0.65-0.85 for thrombocy-

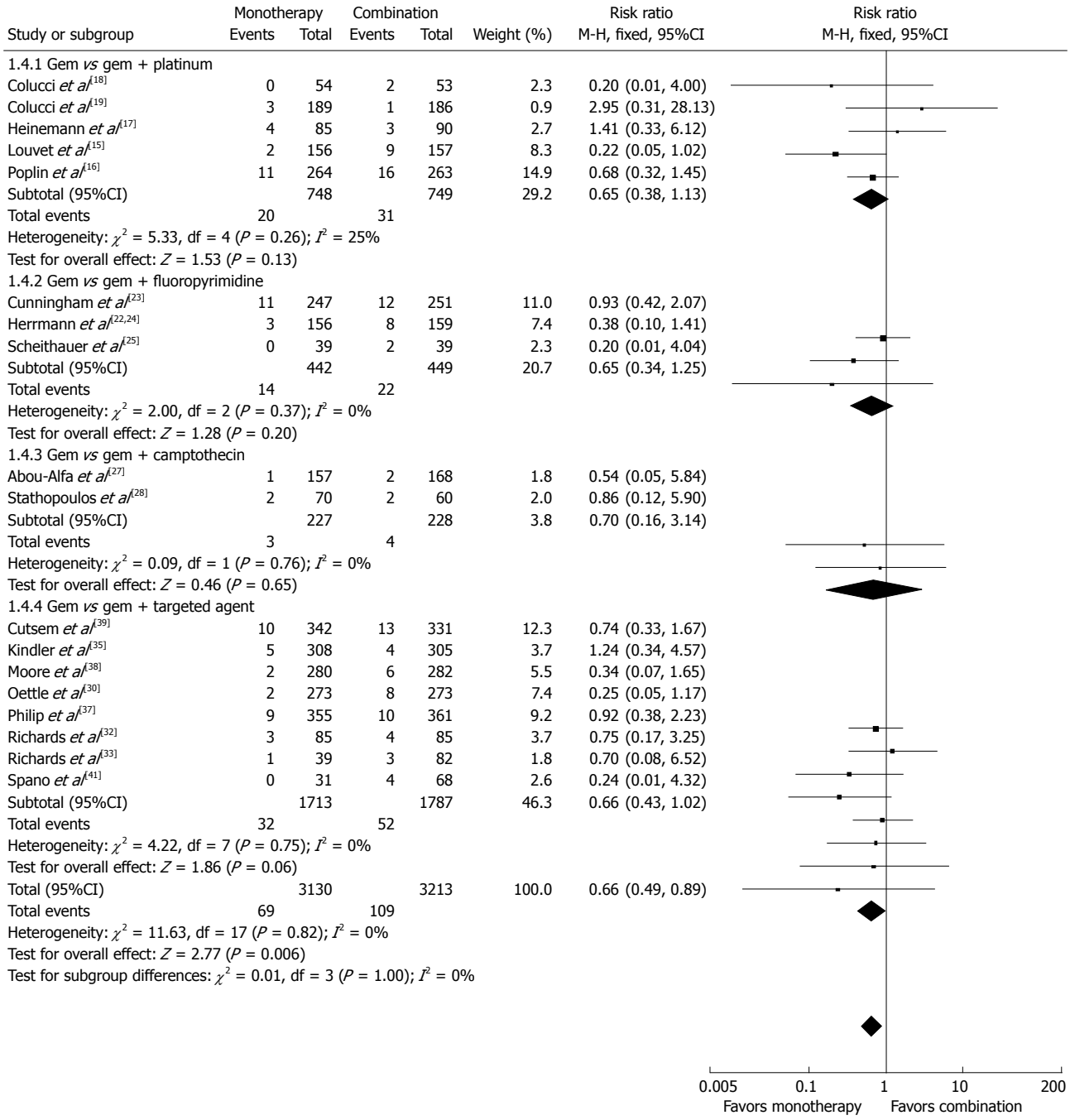

Figure 5 Fixed effect model of risk ratio of grade 3 or 4 diarrhea. CI: Confidence interval.

topenia, respectively. No subgroup differences in overall toxic outcomes, expect for vomiting, were found between the gemcitabine monotherapy group and the combination groups. Gemcitabine monotherapy decreased the incidence rate of vomiting by more than 50% compared with the gemcitabine plus platinum subgroup (RR, 0.46; 95%CI: 0.33-0.64; $P < 0.001$), while no significant differences for other subgroups was seen. In addition, the results showed that gemcitabine plus fluoropyrimidine therapy significantly increased the incidence of neutropenia (RR, 0.70; 95%CI: 0.55-0.88; $P = 0.002$).

The median PFS and median OS between gemcitabine monotherapy and combination therapies

The data of median PFS and OS in every study were extracted and assessed by a paired *t*-test. The results showed that only gemcitabine plus fluoropyrimidine significantly increased the median PFS (3.480 *vs* 4.520; $P = 0.045$) and median OS (6.950 *vs* 7.840; $P = 0.038$). Data are shown in Figure 9.

Publication bias

The funnel plots are shown in Figure 10. There was no

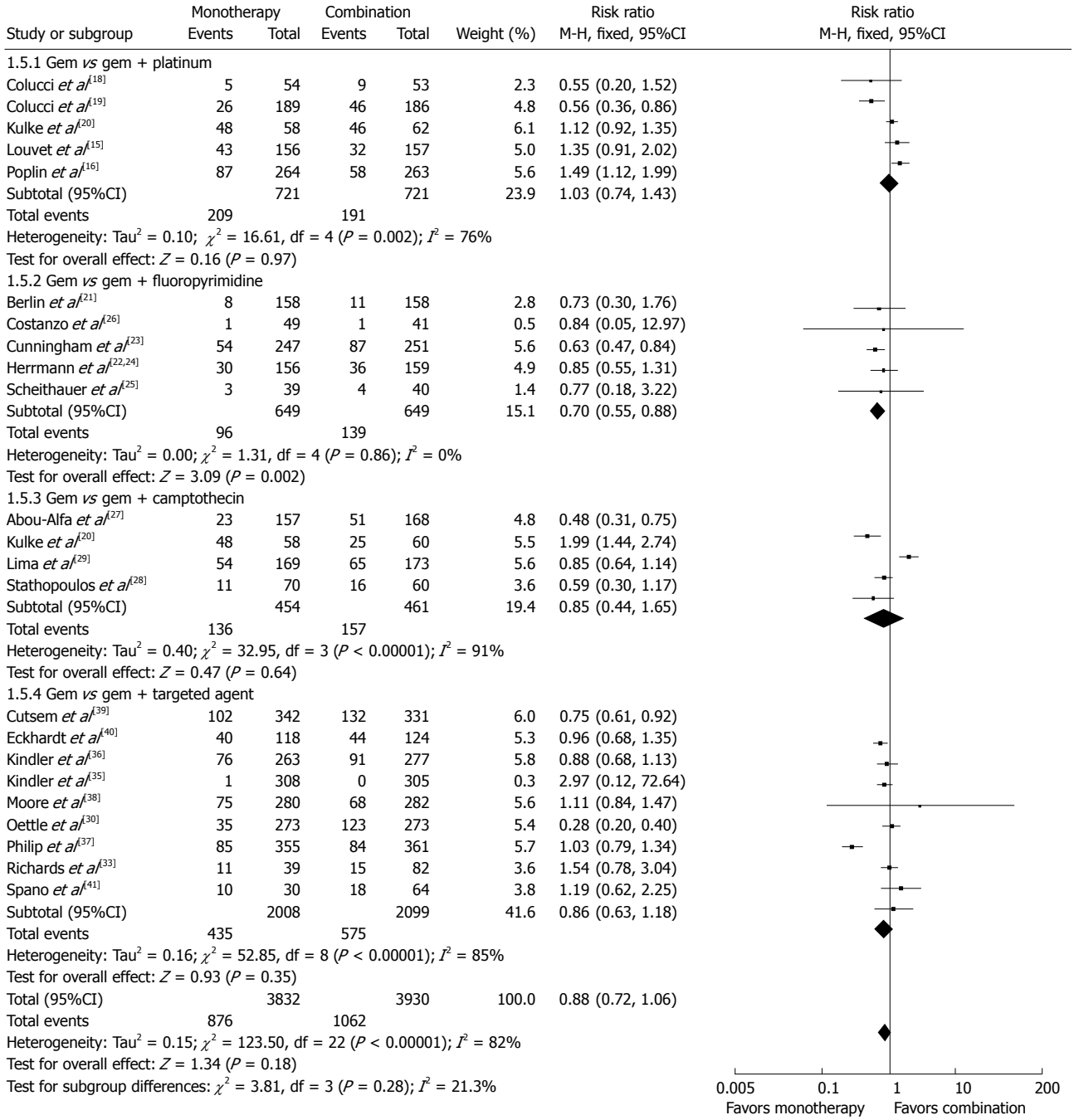

Figure 6 Random effect model of risk ratio of grade 3 or 4 neutropenia. CI: Confidence interval.

obvious publication bias found in the analysis.

DISCUSSION

Pancreatic cancer is a devastating disease with a dismal prognosis. Most of patients present with locally advanced or metastatic disease and are thus not candidates for surgical resection, thereby having to rely on palliative chemotherapy as the only treatment option. In this situation, the goals of chemotherapy should be to control tumor progression, decrease toxicity, and improve the survival rate. At present, gemcitabine monotherapy remains the standard treatment for patients with locally advanced or metastatic pancreatic cancer, but its efficacy is unsatisfactory. During the last decade, several randomized controlled clinical trials have evaluated gemcitabine in combination with various agents in an attempt to improve the prognosis of pancreatic cancer. The aim of this meta-analysis was to compare the therapeutic efficacy of gemcitabine-based combination treatments with gemcitabine alone in patients with locally advanced or metastatic pancreatic cancer. The results of this study showed that various combination therapies overall did not provide any major benefit compared with gemcitabine monotherapy.

Moreover, gemcitabine monotherapy had an almost 30% lower ORR than combination therapy regimens, but

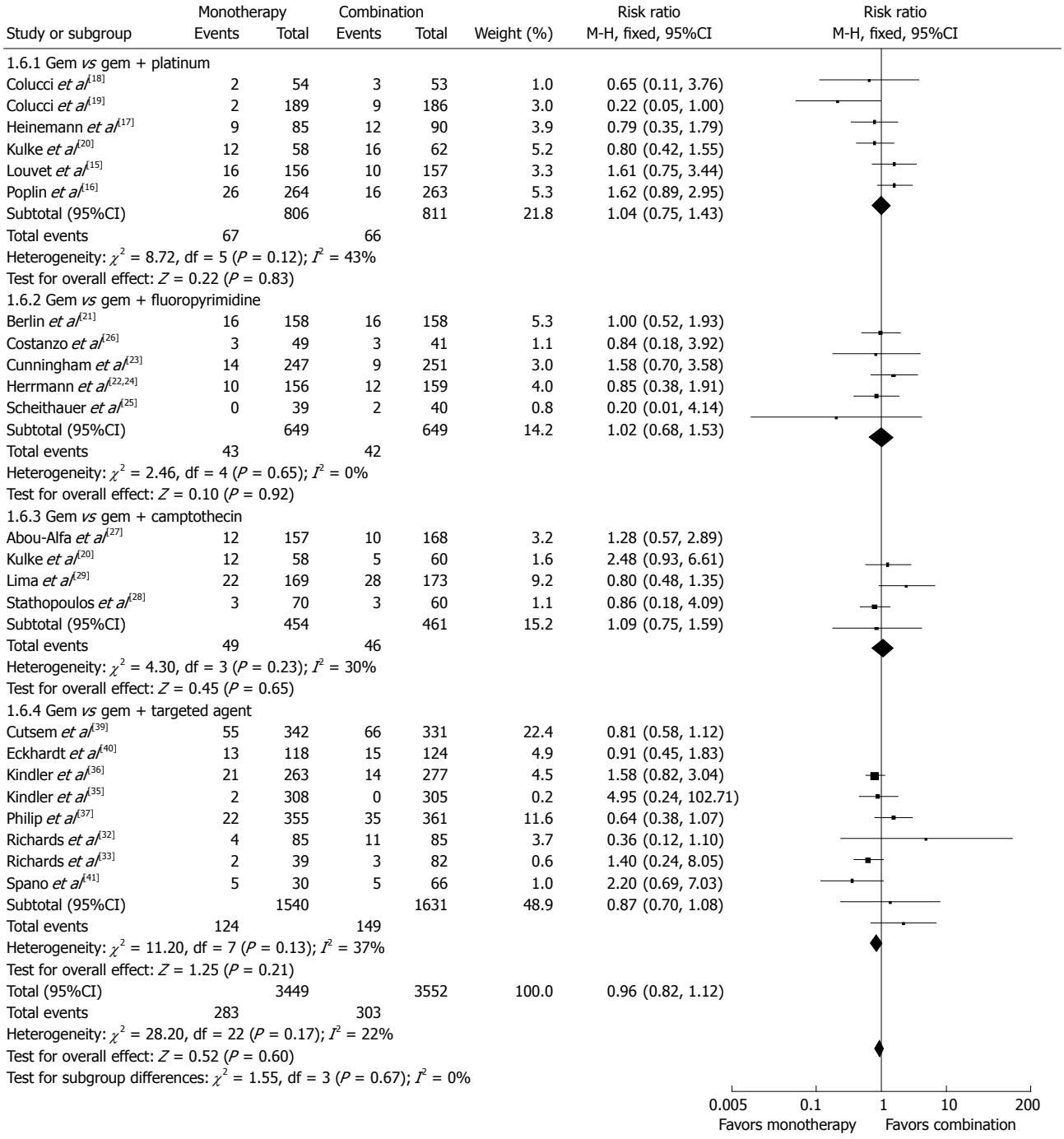

Figure 7 Fixed effect model of risk ratio of grade 3 or 4 anemia. CI: Confidence interval.

only had a 10% lower 1-year OS than combination therapy. According to the present data, 1-year OS in advanced or metastatic pancreatic cancer was low (less than 20%) after gemcitabine monotherapy; therefore, the combination therapy options studied did not improve outcome in a substantial way, the prognosis still being poor[21,31,42]. In addition, there were no significant improvements found in this analysis in median PFS and median OS after combination therapy compared with monotherapy, except for gemcitabine plus fluoropyrimidine treatment. Our results are similar to previously published analyses[23,43,44]. We also assessed the five most common toxicities related to chemotherapeutic treatment of locally advanced or metastatic pancreatic cancer, including hematological and gastrointestinal side effects. Grade 3-4 toxicities tended to be higher following combination therapy compared with monotherapy, and three of the five investigated toxicities reached significant differences. The RRs of vomiting, diarrhea, and thrombocytopenia in the monotherapy group were about 70% of that noted in the combination therapy group. Furthermore, subgroup analysis showed that the RR of vomiting after treatment with gemcitabine plus platinum was twice that of monotherapy. The results presented here showed that combination therapy induced

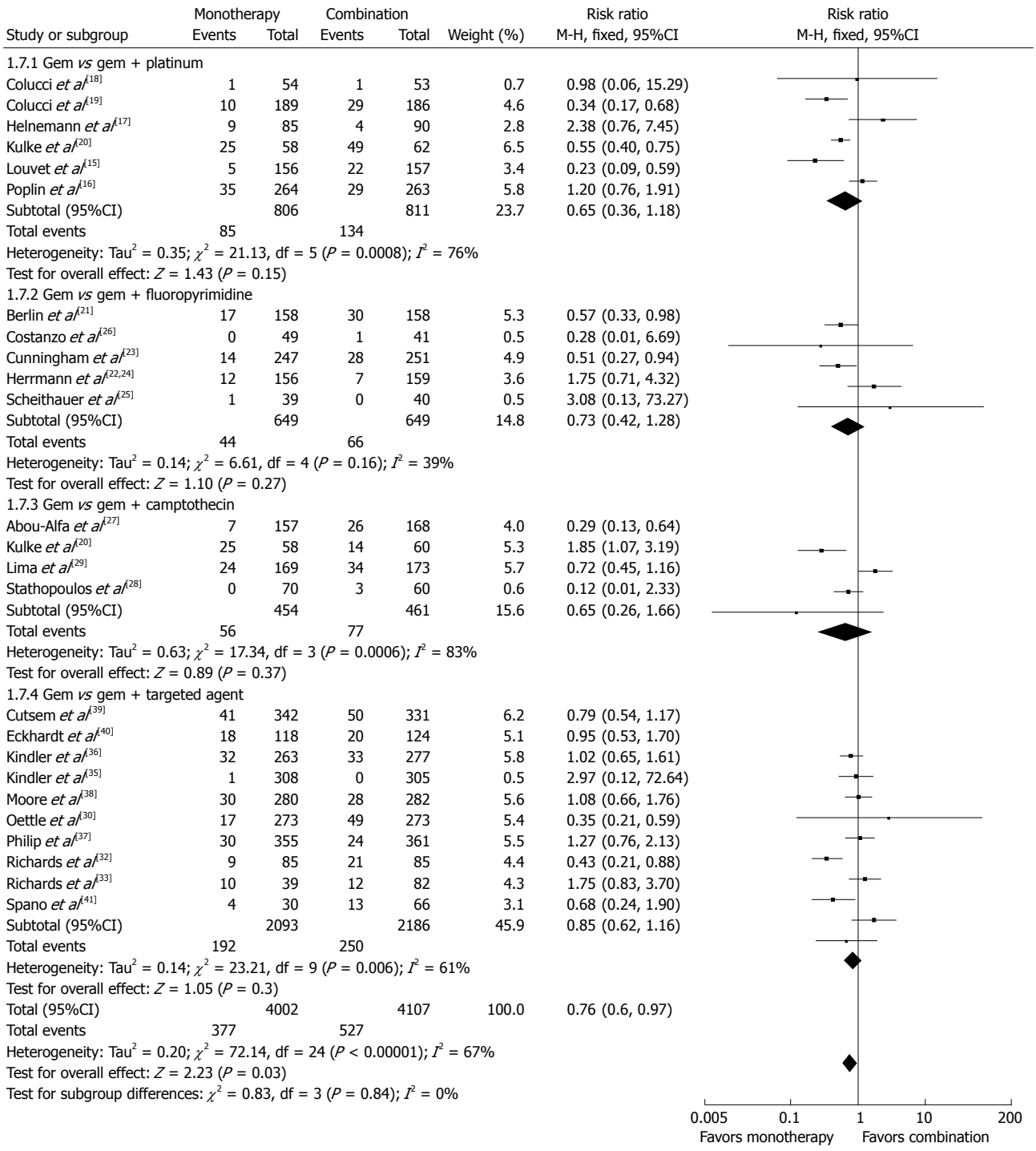

Figure 8 Random effect model of risk ratio of grade 3 or 4 thrombocytopenia. CI: Confidence interval.

more toxicity than gemcitabine alone. Similar results were found in a previous study[45]. This finding might explain why combination therapy received higher ORR, but without affecting the overall prognosis, as toxicities counterbalanced the positive effects.

In the present analysis, we included several kinds of combination therapies with gemcitabine, which could provide different anti-tumor effects and different uptake and toxicity profiles, including platinum based agents, topoisomerase inhibitors, taxanes, bevacizumab, cetuximab and other biologically targeted agents. However, no significant differences were found between the subgroups, except for side-effects (vomiting). In addition, the analysis of heterogeneity was not significant in most subgroups. This is interesting, and indicates that effectiveness of the different combinations regarding outcomes could not clearly be shown. There are two possible reasons that could explain these results. One is related to gemcitabine-uptake receptors. The other one could be the inherent drug-resistant character of pancreatic carcinoma cells and

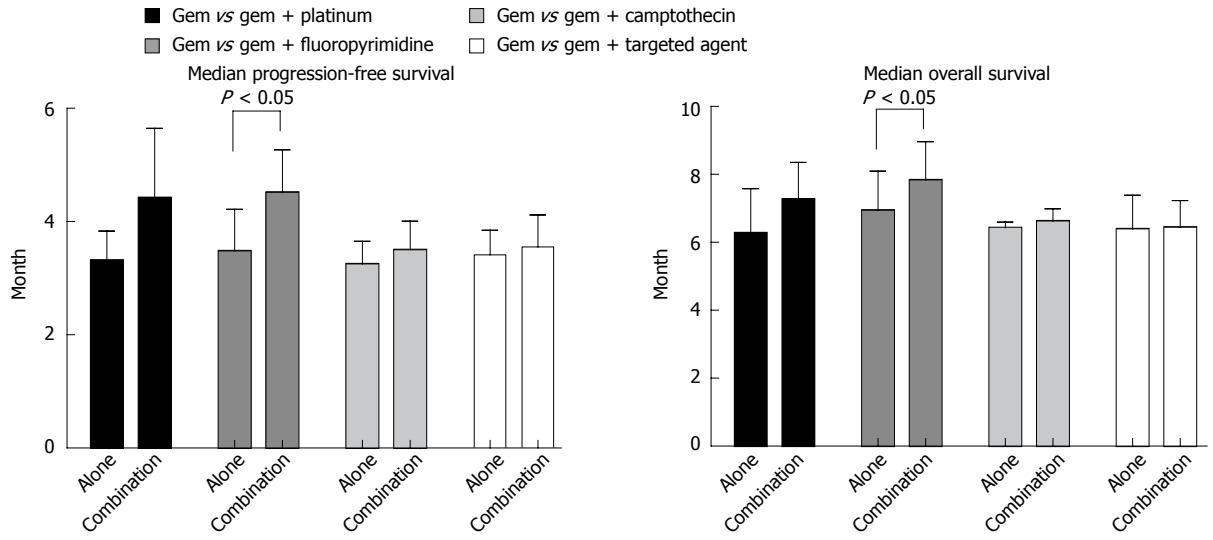

Figure 9 Median progression-free survival and overall survival between gem-monotherapy and combination therapy.

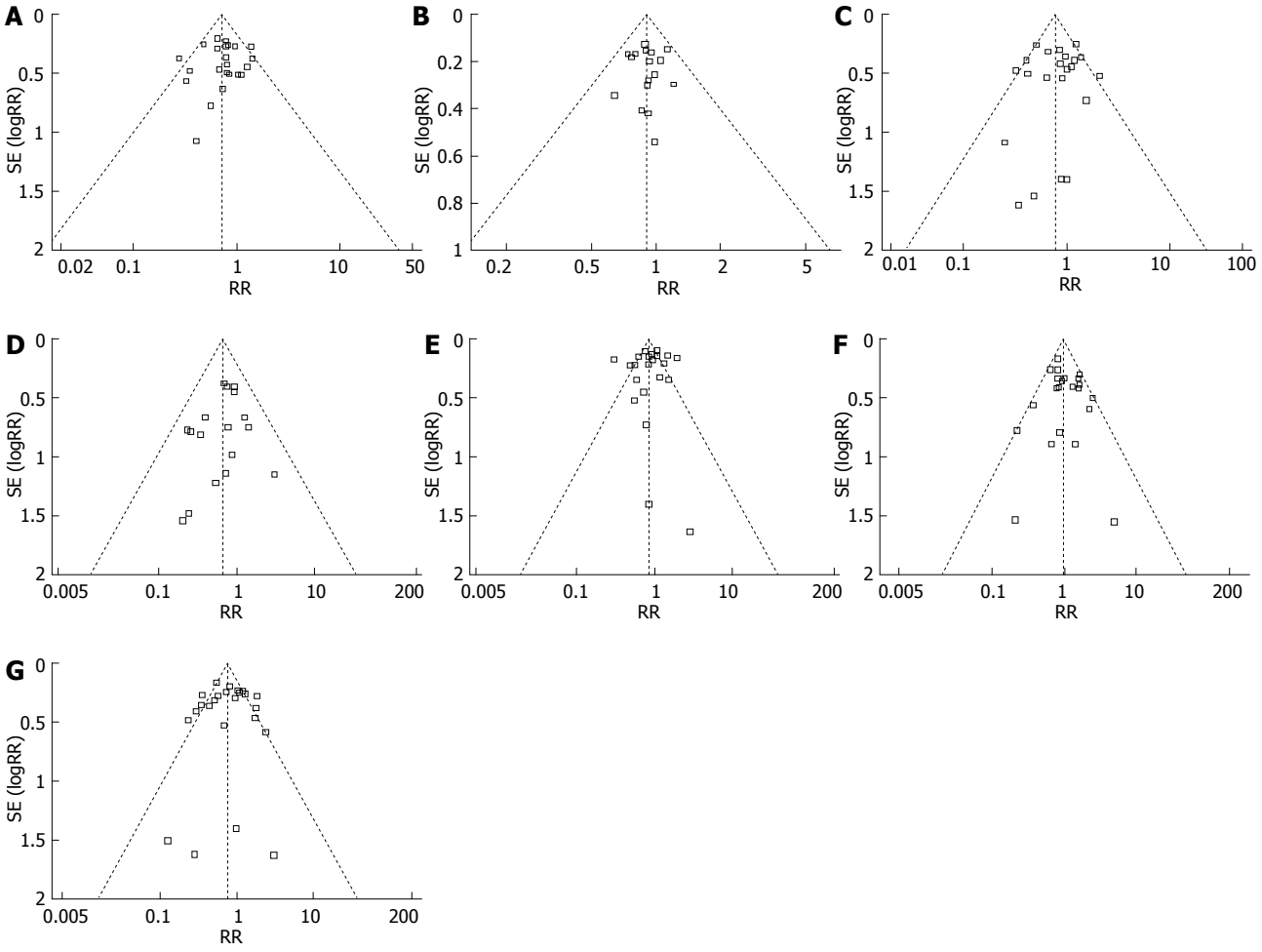

Figure 10 Funnel plots. A: Objective response rate; B: 1-year overall survival rate; C: Vomiting; D: Diarrhea; E: Neutropenia; F: Anemia; G: Thrombocytopenia. RR: Risk ratio.

the effect of the surrounding stroma.

Human equilibrative nucleoside transporter-1 (hENT-1) is the main membrane channel responsible for intracellular bioavailability of gemcitabine. Preclinical and clinical data have revealed that only a minority of patients have high hENT1 expression and reduced levels of hENT-1 expression correlate with increased resistance to gemcitabine[7]. To increase gemcitabine efficiency and

avoid overtreatment, determination of the hENT1 status at the time of diagnosis and modifying gemcitabine to allow it to bypass the receptor may represent a future mode of overcoming gemcitabine resistance[7]. Multidrug resistance proteins, including ABC transporters, have also been implied in drug resistance in pancreatic cancer and limit the efficacy of gemcitabine[46]. The pancreatic stellate cell has a key role in stroma formation and secretes factors that promote pancreatic tumor growth and resistance to radiation and gemcitabine chemotherapy[47]. The hypoxic stroma could be a physical barrier preventing chemotherapeutic drugs from reaching the pancreatic cancer cells per se, and depletion of the stroma could enhance cancer drug delivery[48]. Recently, cancer stem cells and epithelial to mesenchymal transition (EMT)-type cells have been implicated in metastasis formation and drug resistance[49]. Selective targeting of cancer stem cells and EMT-type cells might represent a future strategy to enhance chemosensitivity. The plasma circulating time of gemcitabine is short and its rapid metabolism thus limits tumor uptake. Using novel formulas such as PEGylated gemcitabine may result in a prolonged circulation time, and possibly inducing cytotoxicity at lower concentrations than those required with treatment with the native drug[50]. Pancreatic cancer, including its concurrent stroma, is complex; therefore, treatment with a single anti-tumor agent may not be effective enough. Determining the underlying mechanisms of drug resistance in pancreatic cancer will provide ways of overcoming chemoresistance and provide a foundation for novel therapies.

During the last decade, several meta-analyses have focused on the efficacy of combination therapy in locally advanced or metastatic pancreatic cancer[43,44,51-54]. Most of these studies have reported positive trends or have concluded that combination treatments may improve outcome, but only a limited number of the studies have reported toxicity data, or have only focused on one anti-tumor agent. In the present study, we collected and analyzed the outcomes in different chemotherapeutic subgroups, as well as toxicity, to make the result more comprehensive and convincing. However, several limitations in this analysis should still be considered. Firstly, some endpoints were not evaluated in all of the included randomised controlled trials. Secondly, heterogeneity of certain endpoints in some subgroups might limit the comparability between studies and affect the validity, despite the use of randomized models.

In conclusion, we compared the outcomes of different combination therapies with gemcitabine monotherapy, including ORR, OS, PFS and major toxicity. The results showed that gemcitabine combination therapy leads to a modest improvement in survival, though with more toxicity reported compared with gemcitabine monotherapy.

COMMENTS

Background

Pancreatic cancer is a devastating disease with a dismal prognosis. The majority of patients (80%-90%) have unresectable disease at diagnosis and have to rely on palliative chemotherapy alone. In this situation, the goals of chemotherapy should be to control tumor progression and improve the survival rate with minimal toxicity.

Research frontiers

Gemcitabine has long been the first-line chemotherapeutic agent in pancreatic cancer. However, because of high levels of intrinsic and acquired chemoresistance, a large number of patients do not respond to the drug. In an attempt to improve clinical efficacy, systemically administered gemcitabine has been combined with a second cytotoxic agent, such as platinum analogs, fluoropyrimidine, or a targeted cytotoxic agent. However, the added value of these additive agents is unknown.

Innovations and breakthroughs

The present meta-analysis included 26 high-quality randomized trials comparing gemcitabine monotherapy with gemcitabine combination therapy. The primary outcome variables evaluated were objective response rate, overall survival, progression-free survival and major toxicity. The results showed that gemcitabine combination therapy was associated with only a modest improvement in survival, though with more toxicity reported, compared with gemcitabine monotherapy.

Applications

The results of this study imply that current treatments for unresectable pancreatic cancer are not sufficiently effective. Further research concerning the mechanisms involved in drug resistance in pancreatic cancer could discover ways of overcoming chemoresistance and lead to novel types of therapy.

Peer review

This is a meta-analysis concerning combination chemotherapy with Gemcitabine unresectable pancreatic cancer. The manuscript is well written and represents elaborative work.

REFERENCES

1 **Parkin DM**, Bray FI, Devesa SS. Cancer burden in the year 2000. The global picture. *Eur J Cancer* 2001; **37** Suppl 8: S4-66
2 **Jemal A**, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010; **60**: 277-300
3 **Fryer RA**, Galustian C, Dalgleish AG. Recent advances and developments in treatment strategies against pancreatic cancer. *Curr Clin Pharmacol* 2009; **4**: 102-112
4 **Jonckheere N**, Fauquette V, Stechly L, Saint-Laurent N, Aubert S, Susini C, Huet G, Porchet N, Van Seuningen I, Pigny P. Tumour growth and resistance to gemcitabine of pancreatic cancer cells are decreased by AP-2alpha overexpression. *Br J Cancer* 2009; **101**: 637-644
5 **O'Reilly EM**, Abou-Alfa GK. Cytotoxic therapy for advanced pancreatic adenocarcinoma. *Semin Oncol* 2007; **34**: 347-353
6 **Yeo CJ**, Cameron JL. Improving results of pancreaticoduodenectomy for pancreatic cancer. *World J Surg* 1999; **23**: 907-912
7 **Andersson R**, Aho U, Nilsson BI, Peters GJ, Pastor-Anglada M, Rasch W, Sandvold ML. Gemcitabine chemoresistance in pancreatic cancer: molecular mechanisms and potential solutions. *Scand J Gastroenterol* 2009; **44**: 782-786
8 **Jadad AR**, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1-12
9 **Miller AB**, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47**: 207-214
10 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216
11 **Case LD**, Kimmick G, Paskett ED, Lohman K, Tucker R. Interpreting measures of treatment effect in cancer clinical trials. *Oncologist* 2002; **7**: 181-187

12 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560
13 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558
14 **Huedo-Medina TB**, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 2006; **11**: 193-206
15 **Louvet C**, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; **23**: 3509-3516
16 **Poplin E**, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27**: 3778-3785
17 **Heinemann V**, Quietzsch D, Gieseler F, Gonnermann M, Schönekäs H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006; **24**: 3946-3952
18 **Colucci G**, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, Cigolari S, Testa A, Maiello E, Lopez M. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002; **94**: 902-910
19 **Colucci G**, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010; **28**: 1645-1651
20 **Kulke MH**, Tempero MA, Niedzwiecki D, Hollis DR, Kindler HL, Cusnir M, Enzinger PC, Gorsch SM, Goldberg RM, Mayer RJ. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009; **27**: 5506-5512
21 **Berlin JD**, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002; **20**: 3270-3275
22 **Herrmann R**, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, Saletti P, Bauer J, Figer A, Pestalozzi B, Köhne CH, Mingrone W, Stemmer SM, Tàmas K, Kornek GV, Koeberle D, Cina S, Bernhard J, Dietrich D, Scheithauer W. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007; **25**: 2212-2217
23 **Cunningham D**, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; **27**: 5513-5518
24 **Bernhard J**, Dietrich D, Scheithauer W, Gerber D, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, Saletti P, Bauer J, Figer A, Pestalozzi BC, Köhne CH, Mingrone W, Stemmer SM, Tàmas K, Kornek GV, Koeberle D, Herrmann R. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial--SAKK 44/00-CECOG/PAN.1.3.001. *J Clin Oncol* 2008; **26**: 3695-3701
25 **Scheithauer W**, Schüll B, Ulrich-Pur H, Schmid K, Raderer M, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Kornek GV. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol* 2003; **14**: 97-104
26 **Di Costanzo F**, Carlini P, Doni L, Massidda B, Mattioli R, Iop A, Barletta E, Moscetti L, Recchia F, Tralongo P, Gasperoni S. Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). *Br J Cancer* 2005; **93**: 185-189
27 **Abou-Alfa GK**, Letourneau R, Harker G, Modiano M, Hurwitz H, Tchekmedyian NS, Feit K, Ackerman J, De Jager RL, Eckhardt SG, O'Reilly EM. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006; **24**: 4441-4447
28 **Stathopoulos GP**, Syrigos K, Aravantinos G, Polyzos A, Papakotoulas P, Fountzilas G, Potamianou A, Ziras N, Boukovinas J, Varthalitis J, Androulakis N, Kotsakis A, Samonis G, Georgoulias V. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006; **95**: 587-592
29 **Rocha Lima CM**, Green MR, Rotche R, Miller WH, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004; **22**: 3776-3783
30 **Oettle H**, Richards D, Ramanathan RK, van Laethem JL, Peeters M, Fuchs M, Zimmermann A, John W, Von Hoff D, Arning M, Kindler HL. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 2005; **16**: 1639-1645
31 **Bramhall SR**, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JA. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer* 2002; **87**: 161-167
32 **Richards DA**, Boehm KA, Waterhouse DM, Wagener DJ, Krishnamurthi SS, Rosemurgy A, Grove W, Macdonald K, Gulyas S, Clark M, Dasse KD. Gemcitabine plus CI-994 offers no advantage over gemcitabine alone in the treatment of patients with advanced pancreatic cancer: results of a phase II randomized, double-blind, placebo-controlled, multicenter study. *Ann Oncol* 2006; **17**: 1096-1102
33 **Richards DA**, Kuefler PR, Becerra C, Wilfong LS, Gersh RH, Boehm KA, Zhan F, Asmar L, Myrand SP, Hozak RR, Zhao L, Gill JF, Mullaney BP, Obasaju CK, Nicol SJ. Gemcitabine plus enzastaurin or single-agent gemcitabine in locally advanced or metastatic pancreatic cancer: results of a phase II, randomized, noncomparative study. *Invest New Drugs* 2011; **29**: 144-153
34 **Friess H**, Langrehr JM, Oettle H, Raedle J, Niedergethmann M, Dittrich C, Hossfeld DK, Stöger H, Neyns B, Herzog

P, Piedbois P, Dobrowolski F, Scheithauer W, Hawkins R, Katz F, Balcke P, Vermorken J, van Belle S, Davidson N, Esteve AA, Castellano D, Kleeff J, Tempia-Caliera AA, Kovar A, Nippgen J. A randomized multi-center phase II trial of the angiogenesis inhibitor Cilengitide (EMD 121974) and gemcitabine compared with gemcitabine alone in advanced unresectable pancreatic cancer. *BMC Cancer* 2006; **6**: 285

35 **Kindler HL**, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, Springett GM, Wasan HS, Trask PC, Bycott P, Ricart AD, Kim S, Van Cutsem E. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011; **12**: 256-262

36 **Kindler HL**, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; **28**: 3617-3622

37 **Philip PA**, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fenoglio-Preiser CM, Abbruzzese JL, Blanke CD. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; **28**: 3605-3610

38 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966

39 **Van Cutsem E**, van de Velde H, Karasek P, Oettle H, Vervenne WL, Szawlowski A, Schoffski P, Post S, Verslype C, Neumann H, Safran H, Humblet Y, Perez Ruixo J, Ma Y, Von Hoff D. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 2004; **22**: 1430-1438

40 **Eckhardt SG**, De Porre P, Smith D, Maurel J, Steward WP, Bouche O, van de Velde H, Michiels B, Bugat R. Patient-reported outcomes as a component of the primary endpoint in a double-blind, placebo-controlled trial in advanced pancreatic cancer. *J Pain Symptom Manage* 2009; **37**: 135-143

41 **Spano JP**, Chodkiewicz C, Maurel J, Wong R, Wasan H, Barone C, Létourneau R, Bajetta E, Pithavala Y, Bycott P, Trask P, Liau K, Ricart AD, Kim S, Rixe O. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet* 2008; **371**: 2101-2108

42 **Burris HA**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413

43 **Hu J**, Zhao G, Wang HX, Tang L, Xu YC, Ma Y, Zhang FC. A meta-analysis of gemcitabine containing chemotherapy for locally advanced and metastatic pancreatic adenocarcinoma. *J Hematol Oncol* 2011; **4**: 11

44 **Xie DR**, Liang HL, Wang Y, Guo SS, Yang Q. Meta-analysis on inoperable pancreatic cancer: a comparison between gemcitabine-based combination therapy and gemcitabine alone. *World J Gastroenterol* 2006; **12**: 6973-6981

45 **Xie de R**, Liang HL, Wang Y, Guo SS. Meta-analysis of inoperable pancreatic cancer: gemcitabine combined with cisplatin versus gemcitabine alone. *Chin J Dig Dis* 2006; **7**: 49-54

46 **Hagmann W**, Jesnowski R, Löhr JM. Interdependence of gemcitabine treatment, transporter expression, and resistance in human pancreatic carcinoma cells. *Neoplasia* 2010; **12**: 740-747

47 **Hwang RF**, Moore T, Arumugam T, Ramachandran V, Amos KD, Rivera A, Ji B, Evans DB, Logsdon CD. Cancer-associated stromal fibroblasts promote pancreatic tumor progression. *Cancer Res* 2008; **68**: 918-926

48 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461

49 **Shah AN**, Summy JM, Zhang J, Park SI, Parikh NU, Gallick GE. Development and characterization of gemcitabine-resistant pancreatic tumor cells. *Ann Surg Oncol* 2007; **14**: 3629-3637

50 **Vandana M**, Sahoo SK. Long circulation and cytotoxicity of PEGylated gemcitabine and its potential for the treatment of pancreatic cancer. *Biomaterials* 2010; **31**: 9340-9356

51 **Sultana A**, Tudur Smith C, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer: results of secondary end points analyses. *Br J Cancer* 2008; **99**: 6-13

52 **Heinemann V**, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; **8**: 82

53 **Bria E**, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, Carlini P, Nisticò C, Terzoli E, Cognetti F, Giannarelli D. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. *Cancer* 2007; **110**: 525-533

54 **Sultana A**, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; **25**: 2607-2615

S- Editor Cheng JX **L- Editor** Stewart GJ **E- Editor** Zhang DN