Systematic Review and Meta-Analysis

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Efficacy and safety of gemcitabine-capecitabine combination therapy for pancreatic cancer

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Recent randomized controlled trials revealed the combination of gemcitabine and capecitabine (GemCap) regime shows promising efficacy in pancreatic cancer patients. Here, we conducted a meta-analysis to compare the efficacy and safety of gemcitabine (Gem) with GemCap for pancreatic cancer.

Methods: The database of MEDLINE (PubMed), EMBASE, Cochrane Central Controster of Controlled Trials, Web of Science was searched for relevant randomized controlled trials before 8 April, 2020. The outcomes were overall survival (OS), 12-month survival rate, progress free survival (PFS), partial response rate (PRR), objective response rate (ORR), and Grade 3/4 toxicities.

Results: Five randomized controlled trials involving 1879 patients were included in this study. The results showed that GemCap significantly improves the OS (hazard ratio = 1.15, 95% CI: 1.037-1.276, $P = .008$), PFS (hazard ratio = 1.211, 95% CI 1.09-1.344, $P = 0$), PRR (relative risk (RR) = 0.649, 95% CI 0.488-0.862, $P = .003$), ORR (RR = 0.605, 95% CI 0.458-0.799, $P = 0$), and the overall toxicity (RR = 0.708, 95% CI 0.620-0.808, $P = .000$) compared to Gem alone. However, no significant difference was found in 12-month survival.

Conclusions: Despite a higher incidence of Grade 3/4 toxicity, GemCap was associated with better outcomes of OS, PFS, PRR, ORR, as compared with Gem, which is likely to become a promising therapy for pancreatic cancer.

Abbreviations: 5-FU = 5-fluorouracil, Gem = gemcitabine, GemCap = gemcitabine and capecitabine, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progress free survival, PRR = partial response rate, RCTs = recent randomized controlled trials, RR = relative risk.

Keywords: capecitabine, gemcitabine, meta-analysis, pancreatic cancer

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the world,[1] and the incidence of pancreatic cancer has been increasing rapidly in recent years. Almost 96% of pancreatic cancer was constituted with pancreatic ducal adenocarcinoma.[2] It is expected that pancreatic cancer will become the 2nd leading cause of cancer-related death by 2030.[3] The prognosis of pancreatic cancer was extremely poor with a 1-year survival rate was around 18% and 5-year survival rate was less than 8%.[4–6] Surgical resection remains the only treatment that can achieve long-term survival. Because the majority of patients are diagnosed with local advanced or metastatic, only 15% to 20% of patients are amenable to surgical resection.[7,8] Therefore, chemotherapy becomes the first-line treatment for advanced and metastatic pancreatic cancer.

Gemcitabine (Gem) was recommended as the gold standard treatment for pancreatic cancer due to a Phase III clinical trial that found Gem achieved a better survival rate and more clinical benefits than 5-fluorouracil (5-FU). Gem has acquired about a 20% increase in 1-year survival rate and a median overall survival of 5 to 7 months in metastatic pancreatic cancers.[9] However, the therapeutic effect of Gem monopoly is still not satisfactory,[9,10] it calls for the need of better treatment strategies for pancreatic cancer. To improve clinical benefit of pancreatic cancer, various anti-tumor agents combined with Gem were recently attempted in numerous clinical setting, such as Nab-paclitaxel and FOLFIRINOX (5-FU, Oxaliplatin, Irinotecan, folinic acid), cisplatin, oxaliplatin, docetaxel et al, but most studies cannot show a significant improvement in overall survival (OS) or a better tolerance of

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toxicities than Gem monopoly, except for combing capecitabine or erlotinib.[11–14]

Capecitabine is a designed oral fluoropyrimidine carbamate that is associated with a lower incidence of toxicities and achieved similar efficacy compared with intravenous 5-FU.[15] The convenience of oral administration makes capecitabine widely used in various tumors. Capecitabine is currently approved by the FDA for the treatment of breast cancer and colorectal cancer.[16] Capecitabine monopoly has been found to be safe and effective in advanced pancreatic cancer in a phase II study and demonstrated similar benefits in tumor-related symptoms with Gem.[9,17] Though capecitabine led to a modest clinical benefit, it failed to improve the terrible prognosis. To obtain better clinical benefits, various capecitabine-based schemes have been attempted in multiple clinical research.

Gemcitabine and capecitabine (GemCap) are both nucleoside analogs and the combination show synergism to antitumor. Furthermore, both drugs have nonoverlapped toxicity and are well tolerated.[16,18,19] Previous studies have shown Gem combined capecitabine improved overall survival rate, progression-free survival (PFS) and achieved a better tumor response than Gem alone.[11,16,19–21] However, some clinical benefit in the 5 studies are quite contrary. In this study, we conducted this systematic review and meta-analysis of the currently available randomized controlled studies to evaluate the efficacy and safety of the gemcitabine-capecitabine (Gem-Cap) and Gem alone for the patients of pancreatic cancer.

2. Methods

2.1. Search strategy

From inception to 8 April, 2020, comprehensive electronic searches were performed with the database of MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, Web of Science. The search terms and strategy are based on the combination of the following keyword: ("pancreatic cancer") AND ("gemcitabine" or "Gemzar") AND ("capecitabine" or "Xeloda") AND ("randomized controlled trial"). The searching language was restricted to English. This meta-analysis was conducted following the guidelines provided by the PRISMA statement.

2.2. Inclusion and exclusion criteria

Trials, were included in this meta-analysis should fulfill the following criteria: The study was randomized controlled trials (RCTs; Phase II or III) with Gem and GemCap treatment. Cytologically or histologically ascertained pancreatic cancer; Age was between 18 and 85 years; Karnofsky performance status score $\geq$50% (or WHO Health Organization performance status $\leq$2), adequate bone marrow, hepatic, and renal functions; No previous chemotherapy or radiotherapy.

The exclusions are as follows: Studies were not RCTs such as reviews and case reports, full text unavailable and non-published conference was also excluded. For Duplicate publications, the most comprehensive article was selected. Single-arm studies.

2.3. Data extraction

The data extracted and quality assessment was performed independently by 2 authors (i.e., GQOY and WC L). Any disagreement between 2 authors was resolved after discussing with a third reviewer (YRW) and a consensus was achieved. The following data were extracted: The first author's name, year of publication, gender distribution, study design, treatment group, number of patients, patient characteristics. The outcome of treatment, such as CRR, objective response rate (ORR), partial response rate (PRR), OS, PFS, toxicities. If the same trail reported in different publications, the most recent publication or comprehensive one was chosen. If log hazard ratio (HR) and its variance of overall survival or forgeprogression-free survival was not provided directly in the text but only in figures, Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) was used to read the Kaplan-Meier curves.

2.4. Quality assessment

The Jadad score was used to assess the quality of the included RCTs. The 3 items of Jadad are as follows: randomization, double blinding, withdrew wals and dropouts. Jadad score ranged from 0 to 5, and $\geq$3 was considered high-quality literature.[22]

2.5. Statistical analysis

All analyses were performed with Stata version 12.0 software (Stata Corporation, College Station, TX) according to the Cochrane Handbook for Systematic Review. The primary endpoint of this meta-analysis was included OS and PFS. OS was defined as the time between date of random assignment and the date of death from any cause. PFS was defined as the time by random assignment to disease progression. The second endpoints included 12 months survival rate, ORR, PRR, CRR, Grade 3-4 toxicities. The HRs with 95% CIs were used to express the results of OS and PFS. The pooled odds ratio with 95% CI was calculated for the second point. The χ^2-based Q-test and I^2 statistics were used to assess the heterogeneity. If there were statistical differences in terms of heterogeneity ($I^2 > 50\%$, $P < .10$), a random effects model was used[23]; otherwise, a fixed effects model was selected. A P value less than .05 was considered statistically significant. The possibility of publication bias was ascertained by visually funnels plots.

2.6. Ethical statement

The data analyzed in this study was extracted from previously published studies, and therefore ethical approval was not necessary.

3. Results

3.1. Literature search

After searching literature within several databases, a total of 1382 potentially relevant studies was eventually identified for screening (Fig. 1). After duplicating and screening the titles and abstracts, 15 studies were enrolled for full-text screening. Of the 15 remaining studies, 8 were excluded because they were non-randomize trials and 2 were excluded because they were single-arm control study. Finally, 5 RCTs compared Gem alone with GemCap in pancreatic cancer were included in this meta-analysis.[11,16,19–21]

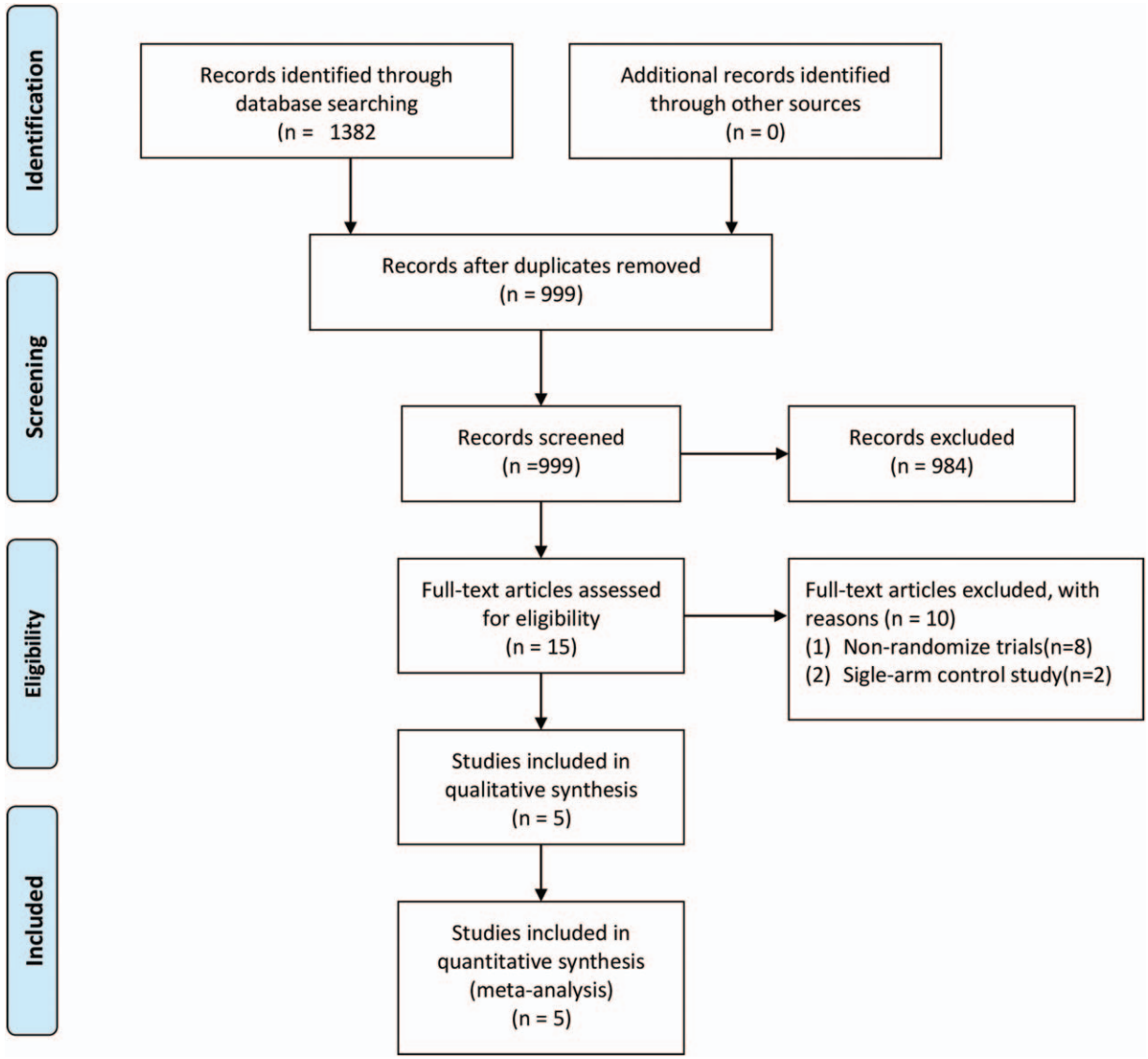

Figure 1. Flow diagram for identifying and including studies in the meta-analysis.

3.2. Study characteristics

The baseline characteristic of the enrolled studies is summarized in Table 1. Five studies including a total of 1879 patients with pancreatic cancer were included in the final analysis, 939 patients were assigned to the Gem group and 940 to the GemCap group. All included trials were considered high qualities, with a score of 3 in Jadad score. Of the 5 trials, 4 were randomized phase II trials and 1 were phase II trial. The patient of these trials came from the UK, Germany, France, Sweden, Austria, Italy, Switzerland, and South Korea. Four studies were done in Europe and 1 in Asia. The

Table 1

Characteristics of 5 included trials in the meta-analysis.

Studies	Year	Publication type	Inclusion period	Total number	Male/female		Median age (range)		Jadad score
					Gem	GemCap	Gem	GemCap	
Scheithauer W	2003	Phase 2	1996.6-2001.5	83	23/19	27/14	66 (39-75)	66 (40-75)	3
Herrmann R	2007	Phase 3	2001.6-2004.6	319	85/74	86/74	NA	NA	3
Cunningham D	2009	Phase 3	2002.2-2005.1	533	153/113	160/167	62 (26-83)	62 (37-82)	3
Lee HS	2017	Phase 3	NA	214	57/49	63/45	64 (43-85)	64 (37-80)	3
Neoptolemos JP	2017	Phase 3	2008.11-2014.9	730	212/154	202/162	65 (37-80)	65 (39-81)	3

Gem = gemcitabine, GemCap = gemcitabine plus capecitabine, NA = not available.

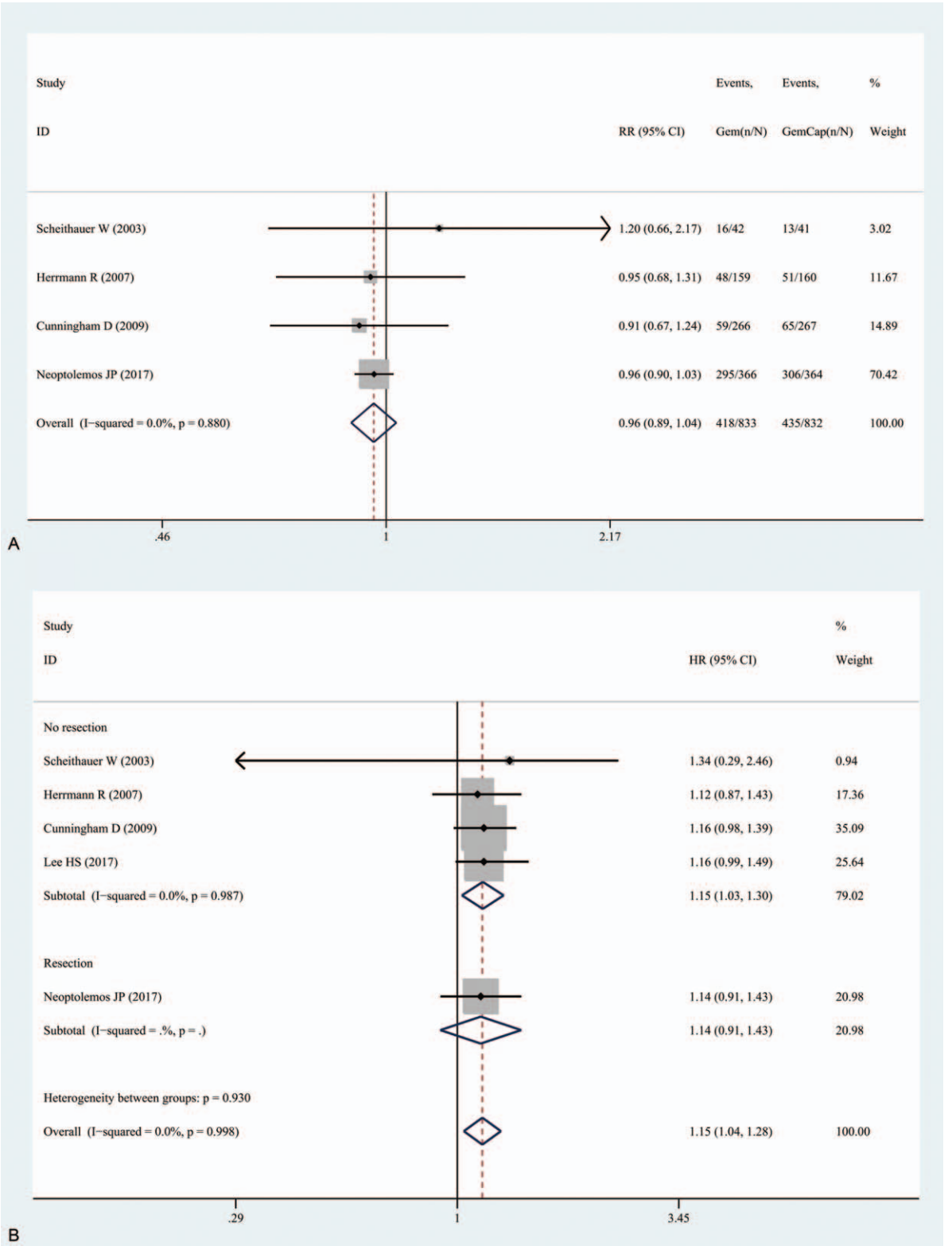

Figure 2. A: Twelve-month survival rate results are not associated with the Gem group and the GemCap group. B: Meta-analysis of OS results for the Gem group and the GemCap group. CI = confidence interval, Gem = gemcitabine, GemCap = gemcitabine and capecitabine, HR = hazard ratio, RR = relative risk.

period of publication ranged from 2003 to 2017. The ratio of male/female in the Gem group was 530/409 and in GemCap group was 538/402.

3.3. Twelve-month survival rate and overall survival

The 12-month survival data were reported for 4 trials. A total of 1665 pancreatic cancer patients from these 4 trials, 833 from the

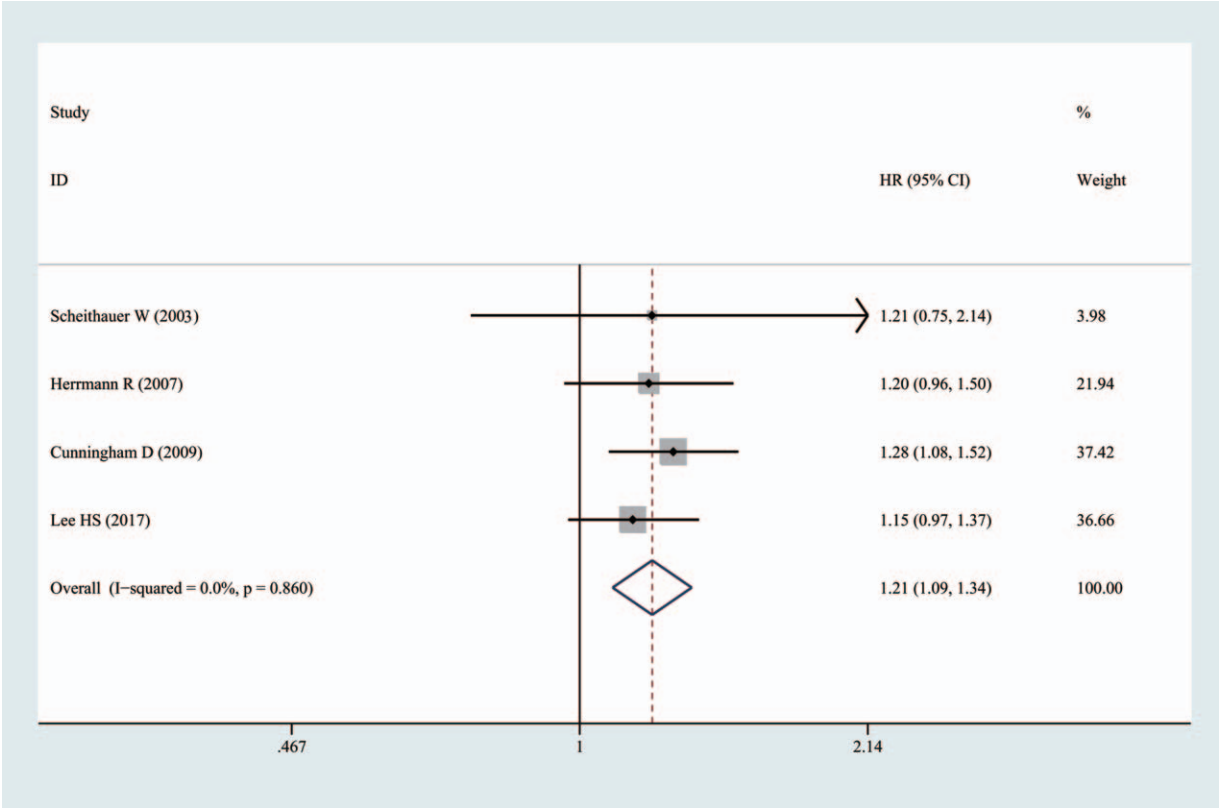

Figure 3. Meta-analysis of PFS results for the Gem group and the GemCap group. CI = confidence interval, Gem = gemcitabine, GemCap = gemcitabine and capecitabine, HR = hazard ratio, PFS = progress free survival.

Gem group and 832 from the GemCap group, was enrolled in our meta-analysis. The consequences of this meta-analysis shows that no statistically significant difference was found in the 12-month survival rate between 2 groups (relative risk (RR) = 0.958, 95% CI 0.886-1.035, P=.278) (Fig. 2A). And no inter-group significant heterogeneity was detected in the 12-months survival rate (I^2 = 0, P=.88).

HR and its 95% CI for OS was available in all included studies. After performing a meta-analysis, the pooled HR between the Gem group and the GemCap group was 1.15 (95% CI: 1.037-1.276, P=.008) (Fig. 2B). The result revealed that Gem group was associated with a statistically significant 19% increase in HR for OS than the GemCap group. There was no significant heterogeneity has observed in the OS (I^2= 0, P=.998,), so a fixed-effects model was employed to pool the data.

3.4. Progression-free survival

The relevant PFS data were reported for 4 trials. A total of 1073 patients from these 4 studies, 537 from the Gem alone group and 576 from the GemCap group, was enrolled in this meta-analysis. After pooling the data, no heterogeneity among the studies was detected (I^2 = 0, P=.86); therefore, a fixed-effects model was used. There was a significant difference exist between Gem-alone groups and GemCap groups. The overall meta-analysis revealed that Gem increase 21.1% of HR for PFS (HR = 1.211, 95% CI 1.09-1.344, P=.860) (Fig. 3).

3.5. Partial response rate and objective response rate

In this meta-analysis, both PRR and ORR were analyzed, whereas CRR was not analyzed because of data deficient. Four studies involving a total of 1133 patients compared the PRR and ORR between the Gem alone group and the GemCap group. After pooling the data, the results revealed that GemCap group significantly improved the PRR than in the Gem-alone group (RR = 0.649, 95% CI 0.488-0.862, P=.003) (Fig. 4A), and there was no heterogeneity was detected regarding the outcome of PRR (I^2 = 16.3%, P=.31), a fixed-effects model was employed. The combined group of GemCap was associated with higher ORR than Gem monopoly (RR = 0.605, 95% CI 0.458-0.799, P=0), and fixed-effects model was used because no heterogeneity was found (I^2 = 0, P=.44) (Fig. 4B).

3.6. Toxicity

Five trials reported the incidence of Grade 3/4 neutropenia, anemia, and diarrhea[11,16,19–21]; 4 trials reported the incidence of Grade 3/4 thrombocytopenia and stomatitis.[11,16,20,21] Three trials reported the incidence of Grade 3/4 Nausea[11,16,21] and febrile neutropenia.[16,20,21]

The Grade 3/4 toxic effects were calculated with dichotomous data (RR, 95% CI) and the results of 2 arms were summarized in Table 2. As shown in Table 2, the most common toxicity of 2 arms was neutropenia (25.8%), and the incidence of the remaining toxicity was all below 7%. After pooling the data, there was no heterogeneity was found except for thrombocyto-

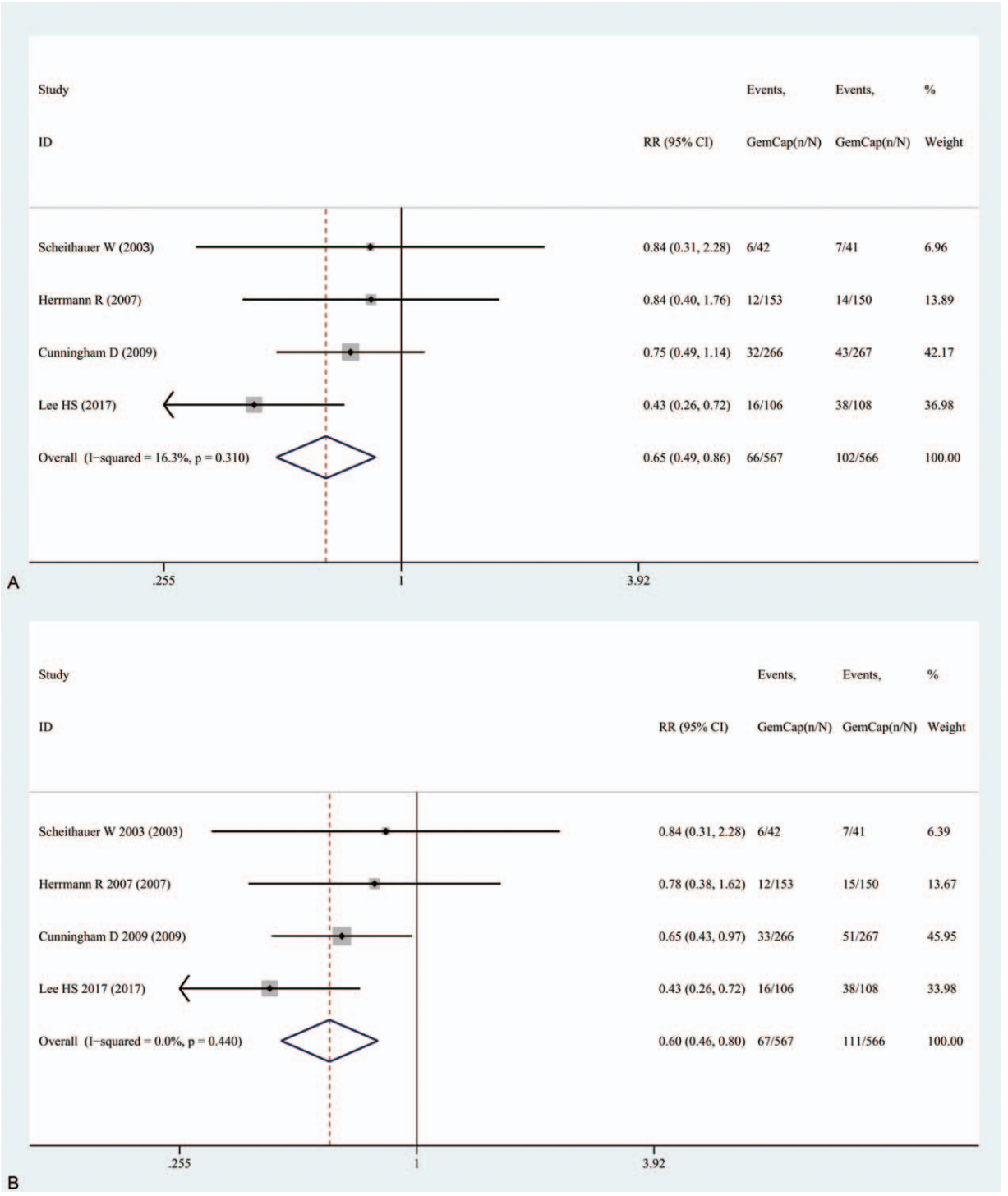

Figure 4. A: Meta-analysis of PRR results for the Gem group and the GemCap group. B: Meta-analysis of ORR results for the Gem group and the GemCap group. CI = confidence interval, Gem = gemcitabine, GemCap = gemcitabine and capecitabine, ORR = objective response rate, PRR = partial response rate, RR = relative risk.

penia while the I^2 was 62.6% (Table 2). Therefore, thrombocytopenia used a random effect model and the other 6 toxic events used the fixed-effects model. The pooled results show that as compared with Gem alone, GemCap group significantly increased the incidence of neutropenia, diarrhea; whereas no significant difference was found in the incidence of anemia, neubrimbocytopenia, febrile neutropenia, nausea, diarrhea between 2 groups (as shown in Table 2). The results of this meta-analysis based on the merging of the 7 toxic events revealed that Gem alone associate with lower toxicity than the GemCap group (RR = 0.708, 95% CI 0.620-0.808, P=.000) (Fig. 5).

Table 2

Toxicities of Gem and GemCap.

Toxicity	Gem n/N	GemCap n/N	RR	95% CI	I^2	P
Neutropenia	188/909	282/912	0.667	0.569-0.781	0	.818
Anemia	42/909	36/912	1.174	0.762-1.809	0	.481
Thrombocytopenia	32/543	38/553	1.083	0.396-2.961	62.6%	.046
Febrile neutropenia	4/296	7/302	0.614	0.197-1.913	0	.693
Diarrheas	20/909	43/912	0.479	0.288-0.799	6.5%	.370
Nausea	22/442	25/450	0.895	0.513-1.561	0	.993
Stomatitis	3/543	11/553	0.367	0.126-1.071	0	.506

CI = confidence interval, Gem = gemcitabine, GemCap = gemcitabine plus capecitabine, RR = relative ratios.

3.7. Publication bias

Begg funnel plot and Egger test were used to evaluating the potential publication bias of the included studies. The result indicated that there was no obvious publication bias for OS, analysis (Bgger test: $P = .806$ for OS) (Fig. 6A). The Egger test did not demonstrate any publication bias ($P = .373$ for OS) (Fig. 6B).

4. Discussion

Pancreatic cancer is one of the most fatal malignant neoplasms with an overall 5-year survival rate for all stages is no more than 8% and the ratio of mortality/incidence is 98%.[6,24] Although surgical resection is the only way to provide curative treatment, more than 80% of patients with pancreatic cancer are ineligible to be resected at diagnosed, because they usually metastasize to the distant organ or invading the major vessel when diagnosed.[25] Therefore, chemotherapy has become an alternative choice for pancreatic cancer patients. Since 1997, Gem has become the mainstay for the treatment of pancreatic cancer.[9] After that, Gem has become cornerstone treatment for patients with pancreatic cancer. In recent years, many randomized controlled trials have aimed at assessing the potential benefits of Gem-based combination over Gem monopoly. According to meta-analysis, Gem-based combination chemotherapy significantly improved the OS, ORR, and PFS in advancer pancreatic cancer patients. However, the combined group was associated with increased toxicity.[26] Capecitabine is widely used in many solid malignancies, particularly in gastrointestinal and breast

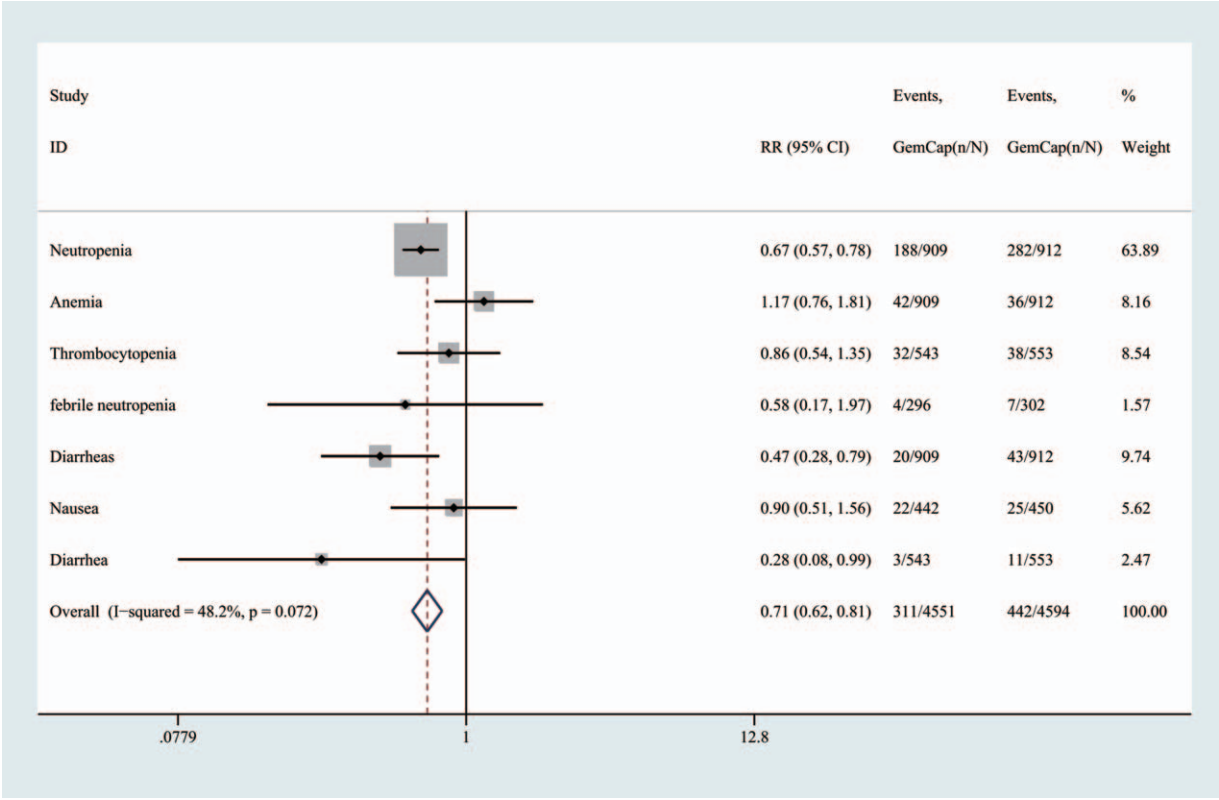

Figure 5. Meta-analysis of toxicity results in the Gem group and the GemCap group. CI = confidence interval, Gem = gemcitabine, GemCap = gemcitabine and capecitabine, RR = relative risk.

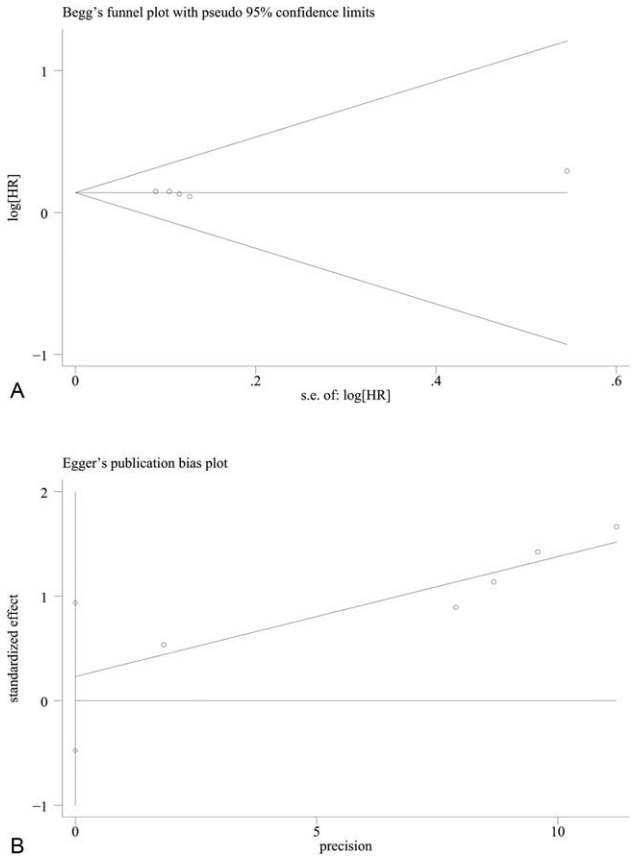

Figure 6. A: Begg funnel plot of publication bias test. B: Egger publication bias plot. HR = hazard ratio.

tumors, but also in pancreatic cancer.[27] The question of whether GemCap can achieve a better benefit than Gem alone is still unclear.

We performed the present meta-analysis to compare the efficacy and tolerability of GemCap vs Gem alone for pancreatic cancer patients. Five randomized trials include a total of 1879 patients enrolled into this study. Our pooled analysis revealed that Gem alone may lower the RR for 12-month survival rate than GemCap; however, no significant difference was found and heterogeneity was detected ($I^2=0$, $P=.88$). It was indicated that the combination group could not prolong the 12-months survival rate. The pooled HR for OS in our analysis was 1.19, indicating a 19% decline in the risk of death in pancreatic cancer patients treated with GemCap regimen. The median OS reported by the included 5 studies varied from 6.2 to 25.5 months in Gem group and from 7.1 to 28.0 months in GemCap regimen. However, Neoptolemos JP[19] reported the median OS in Gem and GemCap was 25.5 months and 28.0 months which was higher than the rest of the 4 studies. The difference between the included articles was due to the fact that the patients included in Neoptolemos JP[19] research were undergo surgical resection, while the enrolled patients of other studies were metastatic or advanced pancreatic cancer. As a result, we performed a subgroup analysis based on whether conducted resection and find that resection did not affect the result of OS between Gem and GemCap group (HR 1.15, $P=.008$). The median PFS in Gem alone group ranged from 3.8 to 5.3 months and 4.3 to 6.2 months in the GemCap group. The result shows that GemCap significantly reduces the hazard of death by 21.1% compared to Gem alone. Our results were also consistent with those of Cunningham D's study.[11] A meta-analysis[28] that reported Gem-based combination therapy could improve the OS and PFS, but not the 12-months survival rate was similar to our study. Based on the above results, though GemCap might not achieve a better outcome in 12-months survival rate, the OS and PFS were superior in GemCap compared to Gem alone. Thus, Gem plus capecitabine is more recommended over Gem monopoly.

The present meta-analysis showed that GemCap significantly increases PRR and ORR by 35.1% and 39.5% as compared with Gem monopoly. Our previous meta-analysis compared Gem plus cisplatin vs Gem alone revealed that the combination regime improves the outcome of ORR.[29] It was indicated that Gem combines with capecitabine or cisplatin might achieve synergistic effects. Another meta-analysis also suggested that Gem-based combination therapy increased 58% of ORR than Gem monotherapy, especially when combined with Gem or oxaliplatin; moreover, the combinations of Gem plus platinum fluoropyrimidine improved ORR by 47% as compared with Gem alone.[30] Capecitabine is an oral fluoropyrimidine seems to be a substitute intravenous 5-Fu, with the advantage of no need injection.[27] Lee et al[20] reported that GemCap significantly improved ORR (43.7% vs 17.6%; $P=.001$), but fail to improve OS (HR, 0.82; 95% CI, 0.67-1.01; $P=.06$) and PFS (HR, 0.87; 95% CI, 0.73-1.03; $P=.08$) compared with Gem monopoly. Some of the above results are different from ours because we found that GemCap not only improves not ORR but also improves OS and PFS.

In the present study, we found that the GemCap was associated with higher odds for Grade 3/4 toxic effects compared with Gem alone. Pooled adverse data significantly increased by 29.2% in GemCap over Gem alone (RR = 0.708, 95% CI 0.620-0.808, $P=.000$).

Previous studies proved that several new combination chemotherapies offer superior survival outcome and PFS than Gem alone regimens; however, it could not apply to all pancreatic cancer patients due to its severe toxicity.[31–33] The incidence rate of toxicity was under 7% except for neutropenia (25.8%); nevertheless, the incidence of neutropenia is still very low when compared to Gem plus S-1(63.3%).[34] It is well known that if patients experience serious adverse events during chemotherapy, the physician may reduce the dosage or even stop the chemotherapy, so lower toxicity effects were important for pancreatic cancer patients to improve the tolerance of chemotherapy.

Our meta-analysis reveals a statistically significant greater incidence of grades III/IV toxic effects in the GemCap regime, the 12-months survival, OS, PFS, PRR, and ORR, however, significantly increased may make the adverse events generally tolerable and reversible. However, due to the specific data that could not be obtained, more studies are required to further verify the greatest beneficiary from this treatment.

There are some limitations in the present meta-analysis and there were: our study only enrolled 5 RCTs and the sample size of each regimen relatively too small to provide sufficient evidence for the safety and efficiency of pancreatic cancer between GemCap and Gem alone. Therefore, more RCTs with larger sample sizes are required. Our study was based on literature and was associated with publication bias; the present meta-analysis was an inference from published abstracted data rather than individual patient profiles. Different dose and modification

schemes of Gem or capecitabine may generate divergent outcomes. The status of pancreatic cancer in 4 included studies was advanced or metastasis and only treated with chemotherapy, however, the status in Neoptolemos JP[19] was resected pancreatic cancer and patients were conducted surgical resection before chemotherapy. We hope further RCTs may resolve the above problems and provide much more high-quality clinical evidence.

5. Conclusions

This meta-analysis of randomized control studies revealed that GemCap significantly improves OS, PFS, PRR, ORR; however, no significant difference was found in the 12-months survival rate. Though the incidence of Grade 3/4 toxicity was higher in GemCap compared with Gem alone, the adverse events of GemCap were tolerable. In conclusion, Gem plus capecitabine may be considered as promising chemotherapy for pancreatic cancer. However, owing to the above limitations, more convincing large-scale RCTs are needed.

Author contributions

Conceptualization: Guoqing Ouyang, Guangdong Pan.
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Writing – review & editing: Guangdong Pan

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