World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i46.17648

World J Gastroenterol 2014 December 14; 20(46): 17648-17655
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

Is concomitant radiotherapy necessary with gemcitabine-based chemotherapy in pancreatic cancer?

Xin Zhang, He-Jing Huang, Dan Feng, De-Jun Yang, Chang-Ming Wang, Qing-Ping Cai

Xin Zhang, De-Jun Yang, Chang-Ming Wang, Qing-Ping Cai, Department of Gastrointestinal Surgery, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China
He-Jing Huang, Department of Hematology, Changzheng Hospital, Second Military Medical University, Shanghai 200003, China
Dan Feng, Department of Oncology, Changhai Hospital, Second Military Medical University, Shanghai 200433, China
Author contributions: Zhang X, Huang HJ and Feng D contributed equally to this work; all authors contributed to the manuscript.
Supported by National Natural Science Foundation of China, No. 81402359 and No. 81372670
Correspondence to: Qing-Ping Cai, Professor, Department of Gastrointestinal Surgery, Changzheng Hospital, Second Military Medical University, No. 415 Fengyang Road, Huangpu District, Shanghai 200003, China. caiqp1969@hotmail.com
Telephone: +86-21-81885601 Fax: +86-21-81885601
Received: March 25, 2014 Revised: June 5, 2014
Accepted: July 29, 2014
Published online: December 14, 2014

Abstract

AIM: To evaluate the efficacy and safety of gemcitabine (GEM) plus radiotherapy compared with GEM alone for pancreatic cancer (PC).

METHODS: A systematic search for eligible studies comparing gemcitabine plus radiotherapy with gemcitabine alone for PC was performed using MEDLINE, EMBASE, and the Cochrane Library. A quality assessment was performed in each study. Meta-analyses were performed to study the pooled effects of relative risk with 95% confidence interval (CI).

RESULTS: A total of 336 participants from four original studies were included. Gemcitabine plus radiotherapy resulted in comparable overall survival (HR = 0.84, 95%CI: 0.53-1.34, *P* = 0.48) and progress free survival (HR = 0.99, 95%CI: 0.97-1.01, *P* = 0.36) to gemcitabine alone. Moreover, concomitant radiotherapy was associated with a significantly higher incidence of severe (grade 3 or greater) toxicities, mainly anemia, leukocytopenia, thrombocytopenia, anorexia, nausea/vomiting, and asthenia/fatigue.

CONCLUSION: Radiotherapy is not beneficial with gemcitabine-based chemotherapy for PC. Further exploration for better radiotherapy approaches and therapeutic regimens for the treatment of PC is warranted.

Key words: Pancreatic cancer; Radiotherapy; Chemotherapy; Gemcitabine; Meta-analysis

Core tip: We performed this meta-analysis to evaluate the efficacy and safety of gemcitabine plus radiotherapy compared with gemcitabine alone for pancreatic cancer (PC). A total of 336 participants from four original studies were included. Gemcitabine plus radiotherapy resulted in comparable survival results to gemcitabine alone. Moreover, concomitant radiotherapy was associated with a significantly higher incidence of severe (grade 3 or greater) toxicities, mainly anemia, leukocytopenia, thrombocytopenia, anorexia, nausea/vomiting, and asthenia/fatigue. Therefore, radiotherapy is not beneficial with gemcitabine-based chemotherapy for PC. Further exploration for better radiotherapy approaches and therapeutic regimens in the treatment of PC is still warranted.

Zhang X, Huang HJ, Feng D, Yang DJ, Wang CM, Cai QP. Is concomitant radiotherapy necessary with gemcitabine-based chemotherapy in pancreatic cancer? *World J Gastroenterol* 2014; 20(46): 17648-17655 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i46/17648.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i46.17648

INTRODUCTION

Pancreatic cancer (PC) is a highly malignant disease and the fourth cause of cancer-related death worldwide[1,2]. Radical surgery is regarded as the only possible cure. A high rate of locoregional as well as distant recurrence has been observed after surgical resection with curative intent in PC[3]. Therefore, adjuvant therapies, including chemotherapy (CT), radiotherapy (RT), and chemoradiotherapy (CRT), have been administered to improve the poor outcomes of PC[4].

A growing body of evidence establishes a central role for systemic CT in the treatment of PC. Appropriate CT might result in decreased recurrence and metastasis rates to improve the survival rate of patients[5]. Formerly, 5-fluorouracil (5-FU) was considered an effective CT agent for PC[6]. However, gemcitabine (GEM) has gained increasing acceptance since it was introduced to treat PC in 1997[7]. Numerous clinical trials and meta-analyses have demonstrated that GEM, compared with 5-FU, increases survival and clinical benefits in locally advanced or surgically resected PC[8,9]. Currently, GEM-based CT is the standard of care for PC.

In addition to CT, RT and CRT are regarded as acceptable treatment options. RT could palliate common symptoms through the intensification of local control and thus prolong survival for patients with locally advanced PC[10]. However, this conclusion was significantly challenged by studies showing that favorable outcomes could be achieved without radiation[11]. Considering the conflicting opinions, we conducted a meta-analysis to compare the efficacy and safety of RT in the management of PC, to provide objective information that might help guide clinicians who treat PC.

MATERIALS AND METHODS

Trial selection

Published and unpublished trials fulfilling the following selection criteria were included in the present meta-analysis: (1) study design - randomized controlled trials (RCTs) or other comparative studies; (2) population - patients with PC, at the resectable or locally advanced stage; and (3) intervention - comparing GEM-based chemotherapy with GEM-based chemotherapy plus radiotherapy. To minimize publication bias, we did not limit the publication language. The primary outcome measure of the study was overall survival (OS), which should include clear survival data.

Literature search

Databases, *i.e.*, MEDLINE, EMBASE and the Cochrane Library, were searched to identify pertinent citations published since January 1997. The following searching strategy was employed: [radiotherapy (Text Word) OR chemoradiotherapy (Text Word)] AND [pancreatic cancer (Title) OR pancreatic neoplasm (Title) OR pancreatic carcinoma (Title) OR pancreatic adenocarcinoma (Title) and gemcitabine (Text Word)]. For unpublished data, trial registries, including clinicaltrial.gov, the national research register, and current controlled trials, were searched. Additionally, a manual search was performed for potential related articles. The manufacturers of relevant pharmaceutical agents were contacted for additional information.

Data extraction

The data extraction and analysis were conducted independently by two reviewers (Zhang X and Huang H) using a pre-designed form. If results from more than one follow-up analysis were published in one study, only those with the longest follow-up were included. For results not clearly described in the paper, the author was contacted for the necessary data. Disagreements were resolved by discussion.

Quality assessment

Two reviewers (Zhang X and Huang H) used standard criteria (*e.g.*, allocation concealment, blinding, intention-to-treat analysis, and withdrawals) to assess the methodological quality of RCTs, in addition to the quantitative quality assessment using the scoring system developed by Jadad[12]. The quality scoring system was as follows: (1) allocation concealment, coded as adequate (1 score), or inadequate or unclear (0 score); (2) blinding, coded as double blind (2 scores), single blind (1 score), or open label (0 score); (3) intention-to-treat analysis, coded as used (1 score), or not used or unable to assess (0 score); and (4) withdrawals, coded as given (1 score) and not given (0 score).

Statistical analysis

The log hazard ratios (HR) and their variances for the time-to-event data were estimated using published methods, and when appropriate, summary statistics or Kaplan-Meier curves were reported[13]. An estimate of the relative risk (RR) was used for the dichotomous outcomes. The results were reported with 95% confidence interval (CI) on the test for overall effect, and heterogeneity was quantified using a χ^2 test with a P value < 0.1 considered statistically significant. For outcomes without heterogeneity, the pooled effects were calculated through the fixed effect model; the randomized effect model was employed if heterogeneity was detected among the studies. The funnel plot was applied to estimate the potential publication bias, with an asymmetric plot indicating a possible publication bias. Review Manager (Version 5.0. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration) was used for the statistical analyses mentioned above, whereas Stata Statistical Software (Release 10, StataCorp LP, College Station, TX, United States) was used to perform the publication bias test as described previously[14].

RESULTS

Descriptions of studies

After an initial search in the databases, a total of 1062 potential studies were identified; 186 papers were re-

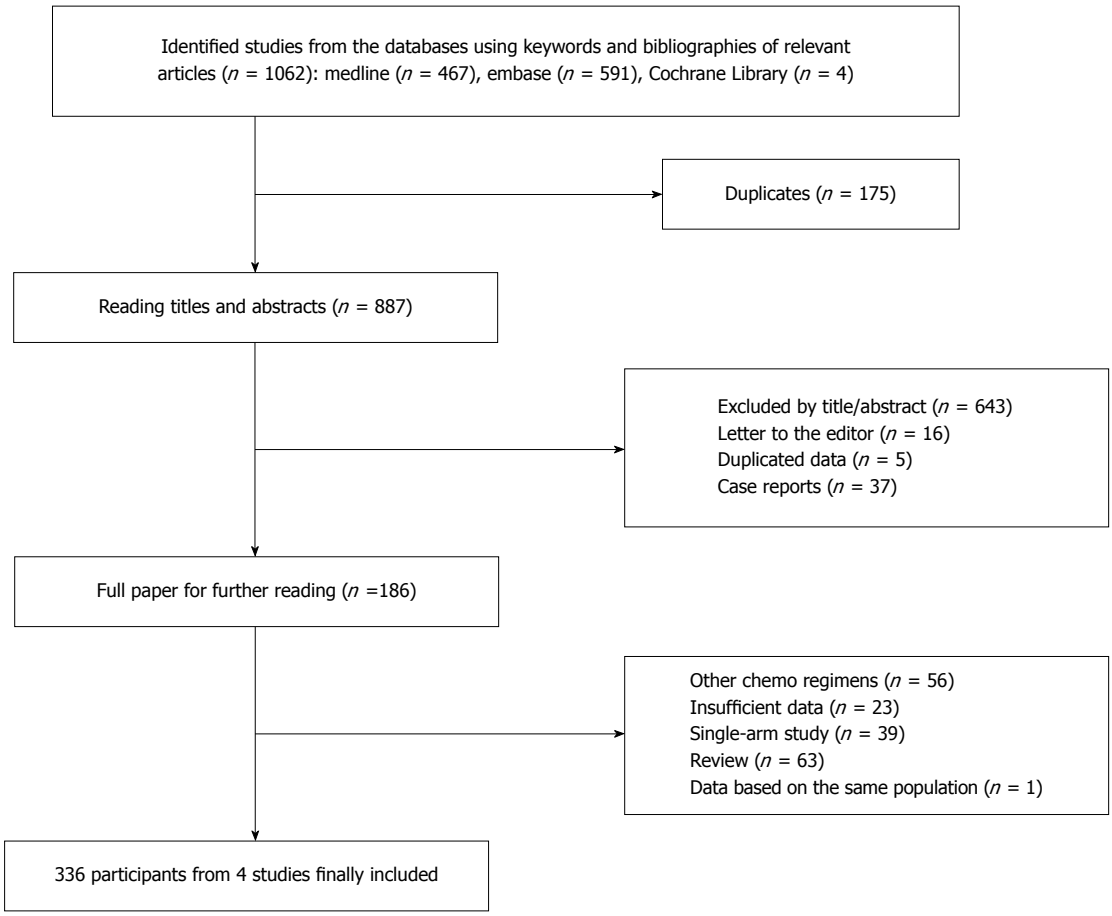

Figure 1 Flow of studies through the review process.

trieved for full-text review after excluding 887 articles on the basis of titles and abstracts. The data from one trial were published twice in different languages[15,16], and only the English version was included, which was labeled as Chauffert 2008[16]. In total, four studies including 336 participants were included in the meta-analysis[16-19], of which three were RCTs[16,18,19] and one was a retrospective follow-up study[17]. The specific flowchart identifying the qualified studies is shown in Figure 1. The demographics of the studies are shown in Table 1. The quality assessments of the studies are shown in Table 2.

Meta-analysis

OS was reported in the four studies. The pooled analysis revealed that there was no statistically significant difference in OS between treatment with GEM plus RT and GEM alone (four studies, 336 participants, HR = 0.84, 95%CI: 0.53-1.34, P = 0.48, Figure 2). However, high heterogeneity was detected (I^2 = 78%).

Information on progress free survival (PFS) or disease free survival was available in three publications. Because the definitions of the terms are similar[20], the results were summarized as PFS. Additionally, concurrent RT did not show obvious superiority to GEM alone in improving PFS (three studies, 280 participants, HR = 0.99, 95%CI: 0.97-1.01, P = 0.36, Figure 3) under homogeneity conditions.

The data regarding treatment-related toxicity were available in three RCTs. For the subsequent analysis, only severe (grade 3 or greater) toxicity (National Cancer Institute Common Toxicity Criteria; ctep.cancer.gov) was considered. The meta-analysis demonstrates that concomitant RT was associated with a significantly higher incidence of adverse events. Particularly, the incidence of anemia, leukocytopenia, thrombocytopenia, anorexia, nausea/vomiting, and asthenia/fatigue occurred more frequently in GEM plus radiation treatment than that in GEM treatment alone (Table 3). The heterogeneity for the evaluation of all toxicity variables was absent or acceptable except for neutropenia.

Sensitivity analysis

To explain the heterogeneity among the included studies, a sensitivity analysis was performed first by excluding the non-RCTs. Notably, similar OS results were observed (three studies, 280 participants, HR = 1.06, 95%CI: 0.78-1.43, P = 0.72, Figure 4), and a marked reduction in heterogeneity was observed (I^2 = 33%), suggesting that the publication type contributes to the heterogeneity.

Another sensitivity analysis was conducted by including only the participants with locally advanced PC. Consistently, no significant difference in OS was observed

Table 1 Patient demographics and characteristics of the included studies

Study	Groups	Chemo regimens	RT regimens	No. of patients	Male	Age (yr)	MS (M)	Follow-up (M)	Clinical stage
Chauffert *et al*[16]	GEM-CRT	5-FU infusion, 300 mg /m^2 per day, days 1-5 for 6 wk; cisplatin, 20 mg /m^2 per day, days 1-5 during wk 1 and 5. Then, GEM 1000 mg/m^2 weekly, 3/4 wk	Induction: 60 Gy, 2 Gy/fraction	59	31	60 (41-79)	8.6	31	Locally advanced unresectable PC
	GEM alone	GEM 1000 mg/m^2 weekly for 7 wk. Then, GEM 1000 mg/m^2 weekly, 3/4 wk	None	60	34	62 (38-80)	13	33	Locally advanced PC
Loehrer *et al*[18]	GEM+RT	600 mg/m^2 per week for wk 1 to 5, then 4 wk later, 1000 mg/m^2 for 3 of 4 wk	Starting on day 1, 1.8 Gy/Fx for a total of 50.4 Gy	34	19	66 (46.9-83.5)	11.1	NG	
	GEM alone	1000 mg/m^2 per week for wk 1 to 6, followed by 1 wk rest, then for 3 of 4 wk	None	37	18	69 (49.7-83.7)	9.2	NG	
Van Laethem *et al*[19]	GEM-CRT	2 cycles of GEM (1000 mg/m^2 on days 1, 8, 15, followed by 1 wk rest-a cycle), then GEM 300 mg/m^2 once per wk for 5 to 6 wk	50.4 Gy in 28 fractions, 1.8 Gy per fraction for 5 to 6 wk	45	24	61 (44-75)	24.3	30.7	Curatively resected PC
	GEM alone	4 cycles of GEM (1000 mg/m^2 on days 1, 8, 15, followed by 1 wk rest-a cycle)	None	45	27	58 (32-77)	24.4	33.3	
Wang *et al*[17]	GEM-RT	2 cycles of GEM (1000 mg/m^2 on radiation 1, 8, 15, 21-d a cycle)	50.4 Gy in 28 fractions on Monday through Friday over 5.5 wk	35	17	61 (44-71)	13	8-24	Locally advanced PC
	GEM alone	4-6 cycles of GEM (1000 mg/m^2 on days 1, 8, and 15, 28 d a cycle)	None	21	13	61 (39-71)	8	8-24	

GEM: Gemcitabine; RT: Radiotherapy; CRT: Chemoradiotherapy; PC: Pancreatic cancer; MS: Median survival; NG: Not given.

Table 2 Quality assessment of the studies included

Study	AC	Blinding	ITT	Withdrawals	Score
Chauffert *et al*[16]	Unclear	Open-label	No	4.0%	1
Loehrer *et al*[18]	Unclear	Open-label	Yes	21.0%	2
Van Laethem *et al*[19]	Adequate	Open-label	Yes	0.8%	4
Wang *et al*[17]	Unclear	Open-label	No	NG	0

AC: Allocation concealment; ITT: Intention-to-treat; NG: Not given.

between the GEM plus RT group and the GEM alone group (three studies, 246 participants, HR = 0.76, 95%CI: 0.41-1.40, P = 0.38, Figure 5), with high heterogeneity remaining (I^2 = 83%). These results indicate that although data derived from patients at different clinical stages were pooled, this type of data management might not be a definite cause of heterogeneity in this meta-analysis.

Publication bias

The funnel plot of the included studies for the OS analysis was largely symmetric (Figure 6; Begg's test: P = 0.308, Egger's test: P = 0.328), indicating the absence of publication bias. Because there were less than three studies included in the analysis of other variables, a test for publication bias was not performed.

DISCUSSION

This systematic review provides a comprehensive overview of current evidence on the efficacy and safety of RT in combination with GEM-based CT for PC, showing that additional RT does not provide a significant increase in survival but rather results in an increased incidence of adverse events. Therefore, the use of RT is not recommended in PC patients in the setting of GEM-based CT.

Although surgery is central in a potentially curable case, a multidisciplinary team is typically required to guarantee the most coordinated treatment for PC[21]. Compared with other malignancies, the metastasis of PC occurs at a very early stage. Even in patients with

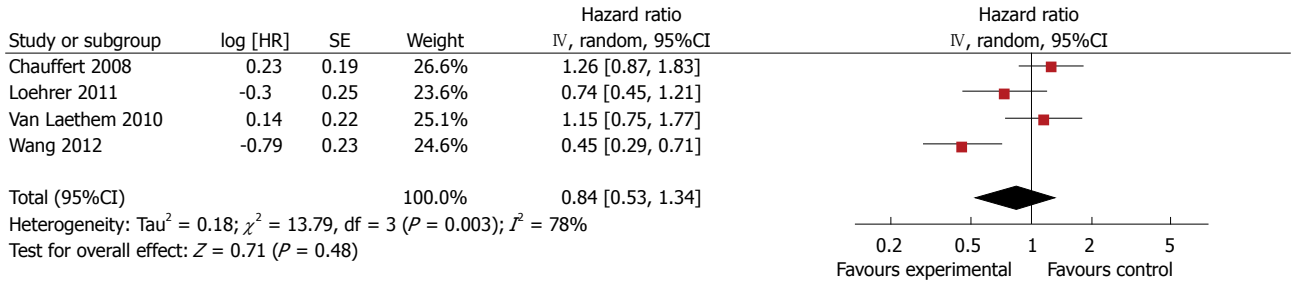

Figure 2 Forest plot to show the pooled estimates of overall survival.

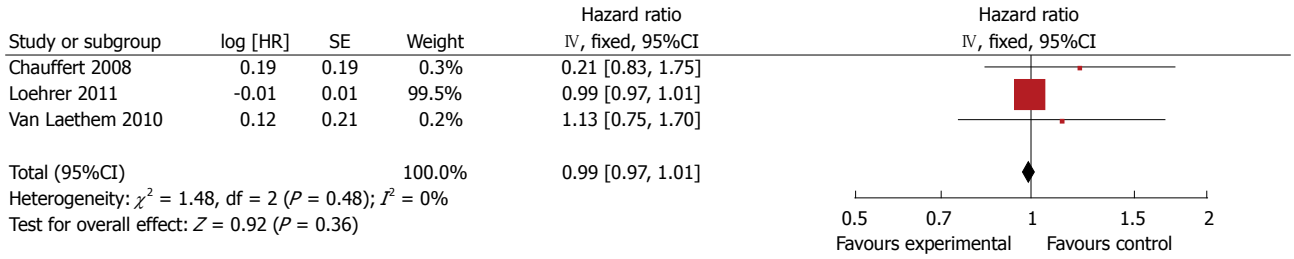

Figure 3 Forest plot to show the pooled estimates of progression free survival.

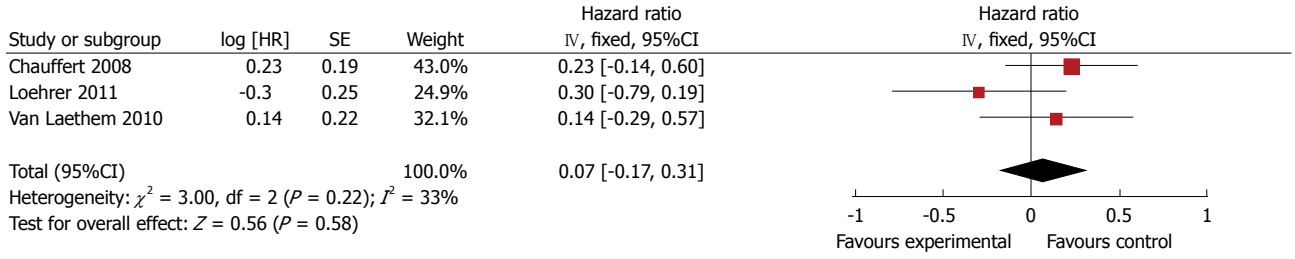

Figure 4 Similar overall survival results.

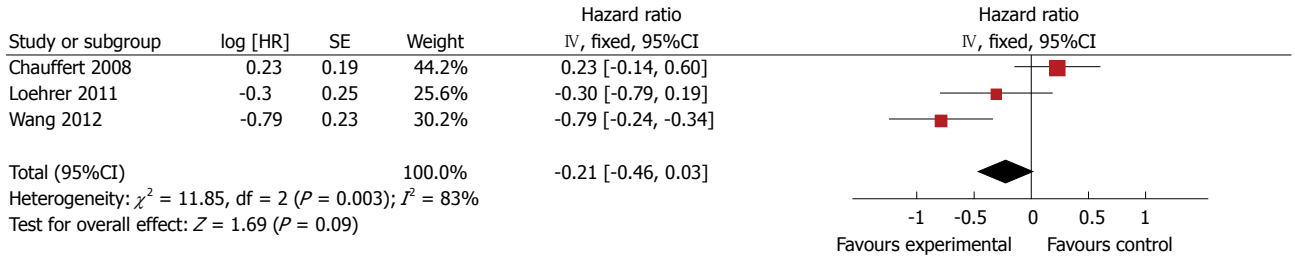

Figure 5 No significant difference in overall survival between the gemcitabine plus radiotherapy group and the gemcitabine alone group.

apparently localized tumors, distant micrometastases most likely already exist[22,23]. Therefore, systemic CT has always been recognized as an essential therapeutic option to maximize survival[24]. In the last decade, there has been great progress in the treatment of PC following the advent of GEM, which is used as the first-line CT agent[4].

Advances in the field of radiation oncology, particularly those in radiation treatment delivery techniques, have led to improvements in local tumor control and a reduction in radiation toxicity[25,26]. Some clinicians hypothesize that although PC is dominated by distant metastatic spread, the importance of local progression should not be completely ignored because local recurrence in PC is very common, frequently with potential obstructions[27]. Controlling local progression in PC could decrease symptoms, whereas failure to control the primary tumor is associated with symptoms such as pain, gastric outlet and duodenal obstruction[28]. Therefore, RT to the postoperative bed and draining lymph nodes is frequently employed to ensure better locoregional control, and the data from clinical studies supporting the use of RT for

Table 3 Meta-analysis of adverse events

Outcome	Studies	Participants	Statistical method	Effect size	95%CI	*P*	I^2 (%)
Anemia	3	240	RR, Fixed	5.32	(2.23-12.66)	0.0002	0
Leukocytopenia	3	240	RR, Random	2.31	(1.08-4.97)	0.03	49
Neutropenia	3	240	RR, Random	1.37	(0.60-3.16)	0.46	78
Thrombocytopenia	3	240	RR, Fixed	2.34	(1.04-5.29)	0.04	0
Anorexia	2	154	RR, Fixed	5.74	(1.05-31.39)	0.04	0
Diarrhea	3	240	RR, Fixed	2.58	(0.51-13.01)	0.25	0
Nausea/ vomiting	3	240	RR, Fixed	3.58	(1.32-9.69)	0.01	0
SGPT abnormality	2	154	RR, Fixed	0.99	(0.34-2.88)	0.98	0
Asthenia/ Fatigue	2	154	RR, Fixed	3.54	(1.23-10.18)	0.02	29
Weight Loss	2	154	RR, Fixed	4.02	(0.46-35.04)	0.21	0

RR: Relative risk.

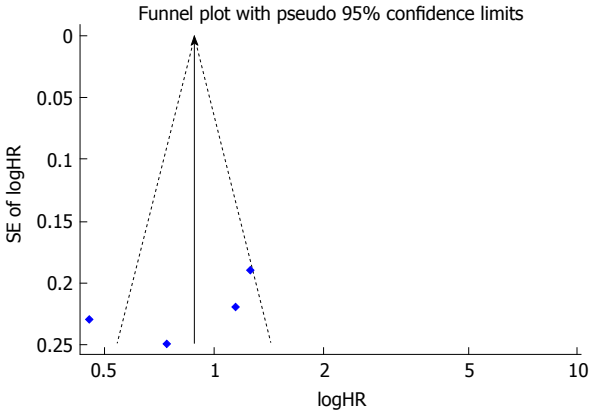

Figure 6 Funnel plot of the included studies for the overall survival analysis is largely symmetric.

PC were documented[29,30].

There have been several opposite opinions with regard to the contribution of RT to the improvement of survival. In a retrospective study, locally advanced PC patients receiving 5-FU-based CRT showed similar OS compared with those receiving GEM-based CT alone[31]. In a group of surgically resected PC patients, adjuvant 5-FU-based CT resulted in a significant survival benefit, whereas additional RT appeared to have a deleterious effect on survival[32]. In a previous meta-analysis by Ren *et al*[33], they concluded that RT appeared to provide benefits in terms of locoregional control; however, RT may not improve the OS for patients with resectable PC. In this meta-analysis, a benefit of RT for OS or PFS was not observed from the pooled results, which was consistent with the results from two sensitivity analyses, indicating that our primary findings were reliable and stable.

The related toxicities of therapeutic strategies in clinical practice are markedly important. The data from this meta-analysis indicate that concurrent RT resulted in a significant increase in toxic events compared to those associated with GEM-based CT alone. This finding could be attributed to the low sensitivity of PC cells to radiation and the narrow therapeutic window with GEM-based RT[34,35]. In a retrospective study in Japan, GEM-based CT showed comparable survival to CRT, with significantly less toxicity[36]. Recently, Takatori *et al*[37] published their results from an observational study in which it was shown that 49.4% of PC patients treated with GEM-concurrent proton RT developed radiation-induced ulcers in the stomach and duodenum that were detected by endoscopic examination. Moreover, given that endoscopic examination was only performed when indicated, the incidence of gastroduodenal ulcers caused by radiation might have been greatly underestimated in many clinical studies. Therefore, an unsatisfactory toxic profile might serve as the dominant barrier to the successful use of RT for PC.

Given the systemic nature of PC at diagnosis, the marked effect of radiation on quality of life (QOL) and the relatively low possibility of long-term survival, the decisions concerning therapeutic options should be entirely balanced. Simply highlighting small differences in survival without adjusting for QOL effects might lead to inappropriate therapeutic recommendations[38]. Among the four included original studies, QOL data are available in one study[18] in which the authors showed that no significant differences were observed between GEM alone and GEM plus RT treatment. However, considering that a small number of patients were included, future studies with larger samples of patients are needed to further confirm these results.

Another consideration of selecting a treatment option pertains to the medical cost, and the technology innovations in radiation oncology naturally lead to the question of cost-effectiveness[39]. Particularly when considering comparable efficacy, medical expense might be a deciding factor in the selection of a therapeutic regimen[40]. Murphy *et al*[41] evaluated the cost-effectiveness of modern RT techniques using a Markov decision-analytic model. The results demonstrated that RT had an incremental cost-effectiveness ratio of $126800 per quality-adjusted life years (QALY) compared to that of GEM alone, and the probability of cost-effectiveness at a willingness to pay of $50000 per QALY was much higher for GEM alone than that for any form of RT. Therefore, it is unlikely that RT would be cost-effective in diseases, such as PC, that have

markedly limited survival, and this cost analysis might be an additional argument for not using RT.

Some limitations remain in this meta-analysis. First, the sample size of the included studies was fairly small, which impairs the interpretative power of the results. Second, this meta-analysis was performed independently of surgical considerations of resectability, and the conclusions might be further limited because surgery had a major effect on PC complications and survival. Third, the RT techniques used in the included trials might be outdated, and new radiation modalities, such as particle therapy, are likely to be safer and more effective than older radiation techniques. Thus, the results from this study should not be considered a total negation of RT for PC. Finally, the issue of therapy for PC is too complicated to be addressed merely by a meta-analysis; therefore, individualized treatment should not be ignored. These conclusions should be adopted with caution.

The findings from this meta-analysis indicate that the application of RT is not beneficial with GEM-based CT for PC. Further exploration for better RT approaches and therapeutic regimens for the treatment of PC is warranted.

COMMENTS

Background

Pancreatic cancer (PC) is a highly malignant disease and the fourth cause of cancer-related death worldwide. Radical surgery is regarded as the only possible cure.

Innovations and breakthroughs

The authors conducted a meta-analysis to compare the efficacy and safety of gemcitabine (GEM) plus radiotherapy compared with GEM alone in the management of PC, to provide objective information that might help guide clinicians who treat PC.

Peer review

This meta-analysis addresses the clinically important issue, whether treatment of advanced PC by gemcitabine chemotherapy alone or in combination with radiotherapy results in different outcomes, especially overall survival, progression free survival, treatment related toxicity and quality of life.

REFERENCES

1 **Siegel R**, DeSantis C, Virgo K, Stein K, Mariotto A, Smith T, Cooper D, Gansler T, Lerro C, Fedewa S, Lin C, Leach C, Cannady RS, Cho H, Scoppa S, Hachey M, Kirch R, Jemal A, Ward E. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin* 2012; **62**: 220-241 [PMID: 22700443 DOI: 10.3322/caac.21149]

2 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

3 **Reni M**. Evidences and opinions for adjuvant therapy in pancreatic cancer. *Curr Drug Targets* 2012; **13**: 789-794 [PMID: 22458525]

4 **Wolfgang CL**, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, Hruban RH. Recent progress in pancreatic cancer. *CA Cancer J Clin* 2013; **63**: 318-348 [PMID: 23856911 DOI: 10.1002/caac.21190]

5 **Paulson AS**, Tran Cao HS, Tempero MA, Lowy AM. Therapeutic advances in pancreatic cancer. *Gastroenterology* 2013; **144**: 1316-1326 [PMID: 23622141]

6 **Moertel CG**, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981; **48**: 1705-1710 [PMID: 7284971]

7 **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 [PMID: 9196156]

8 **Yu Z**, Zhong W, Tan ZM, Wang LY, Yuan YH. Gemcitabine Adjuvant Therapy for Resected Pancreatic Cancer: A Meta-analysis. *Am J Clin Oncol* 2013; Epub ahead of print [PMID: 23934134 DOI: 10.1097/COC.0b013e3182a46782]

9 **Zhu CP**, Shi J, Chen YX, Xie WF, Lin Y. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis. *Radiother Oncol* 2011; **99**: 108-113 [PMID: 21571383]

10 **Ben-Josef E**, Lawrence TS. Radiotherapy: the importance of local control in pancreatic cancer. *Nat Rev Clin Oncol* 2012; **9**: 9-10 [PMID: 22124368]

11 **Isacoff WH**, Bendetti JK, Barstis JJ, Jazieh AR, Macdonald JS, Philip PA. Phase II trial of infusional fluorouracil, leucovorin, mitomycin, and dipyridamole in locally advanced unresectable pancreatic adenocarcinoma: SWOG S9700. *J Clin Oncol* 2007; **25**: 1665-1669 [PMID: 17470859 DOI: 10.1200/JCO.2006.06.7637]

12 **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 [PMID: 8721797]

13 **Tierney JF**, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**: 16 [PMID: 17555582 DOI: 10.1186/1745-6215-8-16]

14 **Zhang X**, Huang H, Han S, Fu S, Wang L. Is it safe to withdraw steroids within seven days of renal transplantation? *Clin Transplant* 2013; **27**: 1-8 [PMID: 23072524 DOI: 10.1111/ctr.12015]

15 **Barhoumi M**, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouché O, Bosset JF, Aparicio T, Mineur L, Azzedine A, Hammel P, Butel J, Stremsdoerfer N, Maingon P, Bedenne L, Chauffert B. [Locally advanced unresectable pancreatic cancer: Induction chemoradiotherapy followed by maintenance gemcitabine versus gemcitabine alone: Definitive results of the 2000-2001 FFCD/SFRO phase III trial]. *Cancer Radiother* 2011; **15**: 182-191 [PMID: 21315644]

16 **Chauffert B**, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouché O, Bosset JF, Aparicio T, Mineur L, Azzedine A, Hammel P, Butel J, Stremsdoerfer N, Maingon P, Bedenne L. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008; **19**: 1592-1599 [PMID: 18467316]

17 **Wang BH**, Cao WM, Yu J, Wang XL. Gemcitabine-based concurrent chemoradiotherapy versus chemotherapy alone in patients with locally advanced pancreatic cancer. *Asian Pac J Cancer Prev* 2012; **13**: 2129-2132 [PMID: 22901181]

18 **Loehrer PJ**, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011; **29**:

4105-4112 [PMID: 21969502]
19 **Van Laethem JL**, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010; **28**: 4450-4456 [PMID: 20837948]
20 **Faussner F**, Dempke WC. Multiple myeloma: myeloablative therapy with autologous stem cell support versus chemotherapy: a meta-analysis. *Anticancer Res* 2012; **32**: 2103-2109 [PMID: 22593496]
21 **Kumar R**, Herman JM, Wolfgang CL, Zheng L. Multidisciplinary management of pancreatic cancer. *Surg Oncol Clin N Am* 2013; **22**: 265-287 [PMID: 23453334 DOI: 10.1016/j.soc.2012.12.003]
22 **Kaťuchová J**, Bober J, Kaťuch V, Radoňak J. Significance of lymph node micrometastasis in pancreatic cancer patients. *Eur Surg Res* 2012; **48**: 10-15 [PMID: 22398863 DOI: 10.1159/000334171]
23 **Thorban S**, Roder JD, Siewert JR. Detection of micrometastasis in bone marrow of pancreatic cancer patients. *Ann Oncol* 1999; **10** Suppl 4: 111-113 [PMID: 10436799]
24 **Glimelius B**, Hoffman K, Sjödén PO, Jacobsson G, Sellström H, Enander LK, Linné T, Svensson C. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996; **7**: 593-600 [PMID: 8879373]
25 **Kooby DA**, Gillespie TW, Liu Y, Byrd-Sellers J, Landry J, Bian J, Lipscomb J. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. *Ann Surg Oncol* 2013; **20**: 3634-3642 [PMID: 23771249 DOI: 10.1245/s10434-013-3047-x]
26 **Berber B**, Sanabria JR, Braun K, Yao M, Ellis RJ, Kunos CA, Sohn J, Machtay M, Teh BS, Huang Z, Mayr NA, Lo SS. Emerging role of stereotactic body radiotherapy in the treatment of pancreatic cancer. *Expert Rev Anticancer Ther* 2013; **13**: 481-487 [PMID: 23560842 DOI: 10.1586/era.13.19]
27 **Terashima K**, Demizu Y, Hashimoto N, Jin D, Mima M, Fujii O, Niwa Y, Takatori K, Kitajima N, Sirakawa S, Yonson K, Hishikawa Y, Abe M, Sasaki R, Sugimura K, Murakami M. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiother Oncol* 2012; **103**: 25-31 [PMID: 22300608]
28 **Tonozuka R**, Itoi T, Sofuni A, Itokawa F, Moriyasu F. Endoscopic double stenting for the treatment of malignant biliary and duodenal obstruction due to pancreatic cancer. *Dig Endosc* 2013; **25** Suppl 2: 100-108 [PMID: 23617659 DOI: 10.1111/den.12063]
29 **Kooby DA**. Neuroendocrine tumors: a heterogeneous set of neoplasms. *Oncology* (Williston Park) 2011; **25**: 810, 812 [PMID: 21936441]
30 **Huguet F**, André T, Hammel P, Artru P, Balosso J, Selle F, Deniaud-Alexandre E, Ruszniewski P, Touboul E, Labianca R, de Gramont A, Louvet C. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007; **25**: 326-331 [PMID: 17235048 DOI: 10.1200/JCO.2006.07.5663]
31 **Park JK**, Ryu JK, Lee JK, Yoon WJ, Lee SH, Kim YT, Yoon YB. Gemcitabine chemotherapy versus 5-fluorouracil-based concurrent chemoradiotherapy in locally advanced unresectable pancreatic cancer. *Pancreas* 2006; **33**: 397-402 [PMID: 17079946 DOI: 10.1097/01.mpa.0000236725.26672.be]
32 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
33 **Ren F**, Xu YC, Wang HX, Tang L, Ma Y. Adjuvant chemotherapy, with or without postoperative radiotherapy, for resectable advanced pancreatic adenocarcinoma: continue or stop? *Pancreatology* 2012; **12**: 162-169 [PMID: 22487527]
34 **Crane CH**, Wolff RA, Abbruzzese JL, Evans DB, Milas L, Mason K, Charnsangavej C, Pisters PW, Lee JE, Lenzi R, Lahoti S, Vauthey JN, Janjan NA. Combining gemcitabine with radiation in pancreatic cancer: understanding important variables influencing the therapeutic index. *Semin Oncol* 2001; **28**: 25-33 [PMID: 11510031]
35 **Asanuma K**, Moriai R, Yajima T, Yagihashi A, Yamada M, Kobayashi D, Watanabe N. Survivin as a radioresistance factor in pancreatic cancer. *Jpn J Cancer Res* 2000; **91**: 1204-1209 [PMID: 11092988]
36 **Sawaki A**, Hoki N, Ito S, Matsumoto K, Mizuno N, Hara K, Takagi T, Kobayashi Y, Sawai Y, Kawai H, Tajika M, Nakamura T, Yamao K. Clinical impact of radiotherapy for locally advanced pancreatic cancer. *J Gastroenterol* 2009; **44**: 1209-1214 [PMID: 19705054 DOI: 10.1007/s00535-009-0116-9]
37 **Takatori K**, Terashima K, Yoshida R, Horai A, Satake S, Ose T, Kitajima N, Kinoshita Y, Demizu Y, Fuwa N. Upper gastrointestinal complications associated with gemcitabine-concurrent proton radiotherapy for inoperable pancreatic cancer. *J Gastroenterol* 2014; **49**: 1074-1080 [PMID: 23846547 DOI: 10.1007/s00535-013-0857-3]
38 **Short M**, Goldstein D, Halkett G, Reece W, Borg M, Zissiadis Y, Kneebone A, Spry N. Impact of gemcitabine chemotherapy and 3-dimensional conformal radiation therapy/5-fluorouracil on quality of life of patients managed for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2013; **85**: 157-162 [PMID: 22543205]
39 **Amin N**, Konski AA. Intensity-modulated radiation therapy for prostate cancer is cost effective and improves therapeutic ratio. *Expert Rev Pharmacoecon Outcomes Res* 2012; **12**: 447-450 [PMID: 22971031 DOI: 10.1586/erp.12.46]
40 **Hayman JA**, Hillner BE. Is the use of radiation therapy after mastectomy cost-effective? *Semin Radiat Oncol* 1999; **9**: 287-291 [PMID: 10378968 DOI: 10.1053/SRAO00900287]
41 **Murphy JD**, Chang DT, Abelson J, Daly ME, Yeung HN, Nelson LM, Koong AC. Cost-effectiveness of modern radiotherapy techniques in locally advanced pancreatic cancer. *Cancer* 2012; **118**: 1119-1129 [PMID: 21773972 DOI: 10.1002/cncr.26365]

P- Reviewer: Gangl O, Korkeila E **S- Editor**: Qi Y
L- Editor: Wang TQ **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327