July 2021, Volume 5, Issue 3

The Efficacy and Safety of Iodine-125 Implantation Combined with Gemcitabine in the Treatment of Advanced Pancreatic Cancer: A Systematic Review and Meta-analysis

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DOI: 10.30699/mci.5.3.500-2

Submitted: 28 February 2021
Revised: 23 May 2021
Accepted: 15 June 2021
e-Published: 27 July 2021

Keywords:
Iodine-125
Pancreatic Neoplasms
Meta-Analysis
Gemcitabine

Introduction: A systematic review and meta-analysis was conducted to assess the efficacy and safety of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer.

Methods: PubMed, Chinese National Knowledge Infrastructure database (CNKI), Cochrane Library, Embase, and Wanfang database through Oct 2020 were searched for randomized controlled trials (RCTs) and retrospective studies assessing the efficacy and safety of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer. The main outcome measures included the overall remission [complete response (CR)+partial response (PR)] rate, overall survival (OS), hypofunction of the liver, clinical benefit response (CBR) rate, survival rate, and adverse events.

Results: Totally, 19 studies involving 1496 patients were included in the current systematic review and meta-analysis. The pooled results showed that efficacy and safety of patients treated with Iodine-125 combined with gemcitabine were superior to those undergoing gemcitabine alone: overall remission (CR+PR) rate [odds ratio (OR)=3.10, 95% confidence interval (CI): 2.40, 4.00; P<0.00001], OS [hazard ratio (HR)=0.56, 95% CI: 0.47, 0.68; P<0.00001], hypofunction of liver (OR=1.08, 95% CI: 0.67, 1.74; P=0.75), CBR rate (OR=3.85, 95% CI: 2.83, 5.22; P<0.00001), survival rate of six months (OR=3.44 95% CI: 1.83, 6.46) and survival rate of 12 months (OR=2.67, 95% CI: 1.68, 4.26). And there was no statistical association in adverse events between the groups.

Conclusions: The combination of iodine-125 seed implantation and gemcitabine significantly prolonged the survival of patients with pancreatic cancer, compared with the gemcitabine alone, indicating a better prognosis.

INTRODUCTION

Pancreatic cancer is one of the most common malignant tumors, and its mortality closely parallels its incidence [1]; with an estimated rate of more than 55,000 new cases and 44,000 deaths in 2018 in the United States [2]. The poor prognosis is attributed to late detection, early metastasis, and rapid progression. The worldwide five-year survival rate for patients with pancreatic cancer is around 6% but ranges from 2% to 9% in published studies [3-5]. Radical resection is the first choice for patients with pancreatic cancer, but only 10%-20% of patients are eligible for initial resection because most cases are locally advanced at the time of diagnosis [6]. For the ones who were good candidates for the surgery, the five-year survival rate is only about 20% [7, 8]. Gemcitabine is considered the first-line drug for locally advanced and metastatic pancreatic cancer over years. As several clinical trials showed, some novel regimens, erlotinib plus gemcitabine [9] and gemcitabine plus nab-paclitaxel [10], are the treatments of choice for patients who could tolerate. However, although gemcitabine and other therapeutic drugs are effective in the treatment of patients with advanced pancreatic cancer, the development of chemo-resistance to gemcitabine severely limits the utilization of this chemotherapy [11]. There is no established evidence regarding the regimen of second-line chemotherapy [1]. Undoubtedly, the patients' therapeutic option is rather limited, and novel effective treatment modalities need to be explored. Radioactive seed implantation is widely used in a variety of solid tumor, including hepatocellular carcinoma [12], lung cancer [13], and brain tumor [14]. Local adaptation and low-dose continuous therapy are the main and superior characteristics of iodine-125 seeds in the treatment of pancreatic cancer, which could kill the tumor tissue with minimal damage to normal tissue [15]. Several studies reported that gemcitabine in combination with iodine-125 seed implantation was a feasible and effective treatment for patients with pancreatic cancer. These studies prompted us to conceive a safe and effective therapy that could improve the prognosis of patients with pancreatic cancer. Although some conclusions are made, safety and effect of gemcitabine in combination with iodine-125 seed implantation are not systematically reviewed. Therefore, the current meta-analysis was performed to assess the existing evidence for the prognosis of gemcitabine in combination with iodine-125 seed implantation in the treatment of patients with pancreatic cancer.

METHODS

Search Strategy and Trial Selection

The current systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [16]. Two researchers (JY and TL) independently searched the Pubmed, Embase, Cochrane library, CNKI, and Wanfang databases up to Oct 2020. The mesh and keywords used for the searches included: "brachytherapy" OR "iodine-125" OR "I125" AND "pancreatic cancer" AND "chemotherapy" AND "gemsitabine" AND "prognosis".

Study Inclusion and Exclusion Criteria

The trails included in the study had to meet the following criteria: 1) original research reported the prognosis or related data of patients with pancreatic cancer treated with iodine-125 seed implantation combined with gemcitabine; 2) a retrospective study design or RCT; 3) availability of the full-text article. Exclusion criteria were as follows: 1) unavailable, incomplete, or inaccurate data so that the study could not be analyzed; 2) lack of reporting relevant outcome indexes; 3) case reports, comments, meta-analyses, systematic reviews, reviews, abstracts, editorials, and theses; and 4) duplicate publications.

Data Extraction and Quality Assessment

The following data from the included studies were extracted by two researchers (JY and TL): for each study, author, year of publication, sample size, mean age, intervention measure, type of procedure, and any outcome that met the inclusion criteria. The quality of the included trials was assessed and scored by two researchers (YG and YW) and checked by a third researcher (JY) using the Newcastle–Ottawa scale (NOS) [17].

Statistical Analysis

ORs with 95% CI were calculated for dichotomous

outcomes, and the mean difference (MD) was reported for continuous data. Time-to-event data from each study were summarized using the HR with 95% CI. When HR was not reported by the trials, Tierney's method [18] was followed to extract HR from studies that reported Kaplan-Meier curves. Kaplan-Meier curves were interpreted with the Engauge Digitizer software 4.1. Cochran's Q-statistic test and I^2 test were applied to access heterogeneity among studies (I^2 statistic above 50% and $P<0.05$ were considered significant heterogeneity). A fixed-effect meta-analysis was performed when no significant heterogeneity was present. In case of substantial heterogeneity ($I^2 \geq 50\%$), a different effect model was selected to explore the source of the heterogeneity, and sensitivity analysis was performed by eliminating one study at checking for resolution of heterogeneity or carrying out subgroup analysis [19, 20]. Publication bias was assessed by the visual funnel plot. All analyses were performed using comprehensive meta-analysis statistical software (RevMan version 5.3; Cochrane Collaboration).

RESULTS

Study Inclusion

The initial search yielded 1113 records, of which 263 were removed due to duplicate records, and 783 were excluded after a review of titles/abstracts. Then, 67 studies were potentially appropriate for further analysis. However, 48 articles were excluded for the following reasons: 16 did not have enough original data, one was withdrawn, one was unable to extract data, and 20 were not relevant to the current systematic review and meta-analysis. Finally, 17 studies [21-37] published in Chinese and two [38, 39] in English languages, involving 1496 patients, were included in the current systematic review and meta-analysis. The details of the included studies are shown in Table 1. Among the included studies, eleven were RCTs and eight were retrospective researches. A diagram summarizing the process of study selection is shown in Figure 1.

Study Quality

All of the 11 included RCTs stated that participants were selected randomly; three [23, 24, 38] described the method of random sequence generation (table of random numbers). Double-blind and double-dummy techniques were discarded since the nature of the treatment and the associated outcomes were not feasible. Reporting bias was unclear in all studies since the full and detailed protocols were not available. The details are shown in Table 2.

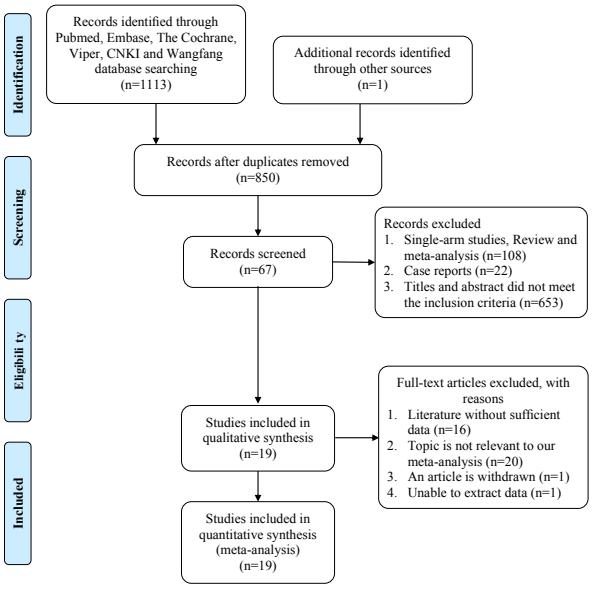

Figure 1: The Flowchart of the Study

The NOS were also utilized to assess the retrospective studies. The included retrospective studies met most of the quality assessment criteria, and all of the studies were scaled as a total score of ≥5, indicating a low risk of bias. The details are shown in Table 3.

RESULTS

Overall Remission (CR+PR) Rate

Nineteen studies reported the overall remission of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer. There was no significant heterogeneity ($I^2=20\%$, $P=0.21$); therefore, a fixed model was performed. A pooled OR of 3.10 (95% CI: 2.40, 4.00; $P<0.00001$, Figure 2), implying that iodine-125 implantation combined with gemcitabine was superior to gemcitabine alone. A subgroup analysis was also conducted, but no differences were found between intervention measures and the type of procedures.

Table 1: Characteristics of the Included Literature [a]

	Design	Number of Persons (I/ C)	Intervention	Control	Year (I/ C)
Chen, S. (2016) [24]	Single-center, RCT	32/ 29	Iodine-125 implantation combined with gemcitabine	Gemcitabine	50.20 ± 11.20/ 45.20 ± 10.20
Chen, X.G. (2019) [27]	Single-center, RCT	106/ 106	Iodine-125 implantation combined with gemcitabine	Tegafur and gemcitabine	60.30±5.20/ 60.50±5.00
Du, J.D. (2011) [34]	Single-center, retrospective	16/ 18	Iodine-125 implantation combined with gemcitabine and cisplatin	Gemcitabine and cisplatin	NA
He, A.L. (2018) [33]	Single-center, retrospective	36/ 47	Iodine-125 implantation combined with gemcitabine	Gemcitabine	59.68±7.35/ 60.38±8.42
Hu, Z.Q. (2007) [22]	Multi-center, RCT	32/ 32	Iodine-125 implantation combined with gemcitabine	Gemcitabine	62.00±10.64 62±8.27
Jiang, Y.P. (2008) [26]	Single-center, RCT	21/ 20	Iodine-125 implantation combined with gemcitabine	Gemcitabine	NA
Li, K. (2007) [25]	Single-center, retrospective	12/ 42	Palliative operation, Iodine-125 implantation combined with gemcitabine	Palliative operation and gemcitabine	NA
Li, Y.F. (2016) [39]	Single-center, retrospective	137/ 87	Iodine-125 implantation combined with gemcitabine	Gemcitabine	58.50±11.70/ 60.10±10.90
Li, Y.L. (2007) [31]	Multi-center, retrospective	18/ 25	Iodine-125 implantation combined with gemcitabine	Gemcitabine	NA
Lun, J.J. (2015) [29]	Single-center, RCT	38/ 30	Iodine-125 implantation combined with gemcitabine	Gemcitabine	NA
Shen, J.J. (2010) [30]	Single-center, RCT	30/ 27	Iodine-125 implantation combined with gemcitabine	Gemcitabine	NA
Shi, G.Y. (2017) [23]	Single-center, RCT	41/ 41	Iodine-125 implantation combined with gemcitabine	Gemcitabine	39.00-73.00/ 72.00
Sun, Y. (2009) [32]	Single-center, RCT	25/ 22	Iodine-125 implantation combined with gemcitabine	Gemcitabine	NA
Wei, M. (2016) [35]	Single-center, RCT	15/ 15	Iodine-125 implantation combined with gemcitabine	Gemcitabine	45.21±2.76/ 45.12±1.37
Wu, H,Q. (2009) [36]	Single-center, retrospective	62/ 82	Palliative operation, Iodine-125 implantation combined with gemcitabine	Palliative operation and gemcitabine	NA
Wu, X. (2018) [28]	Single-center, RCT	25/ 25	Iodine-125 implantation combined with gemcitabine	Gemcitabine	60.40±7.60/ 61.50±6.90
Yan, B.J. (2019) [21]	Single-center, retrospective	49/ 49	Iodine-125 implantation combined with gemcitabine	Gemcitabine	48.25±5.32/ 48.94±5.41
Yang, W.K. (2014) [37]	Single-center, retrospective	45/ 43	Iodine-125 implantation combined with gemcitabine and cisplatin	Gemcitabine and Cisplatin	NA
Yu, Y.P. (2014) [38]	Single-center, RCT	15/ 15	Iodine-125 implantation combined with gemcitabine chemo-radiotherapy	gemcitabine chemo-radiotherapy	61.20±12.50/ 59.47±10.62

[a] Abbreviations: C, control; I, intervention; NA, not available; RCT, randomized controlled trails

Table 2: Results of Quality Assessment Using JADA's Score for RCTs [a]

	Randomization	Double-Blinded	Withdrawal and Dropouts	Quality Score
Chen, S. [24]	2	0	1	3
Chen, X.G. [27]	1	0	1	2
Hu, Z.Q. [22]	1	0	1	2
Jiang, Y.P. [26]	1	0	1	3
Lun, J.J. [29]	1	0	1	2
Shen, J.J. [30]	1	0	1	2
Shi, G.Y. [23]	2	0	1	3
Sun, Y. [32]	1	0	1	2
Wei, M. [35]	1	0	1	2
Wu, X. [28]	2	0	1	3
Yu, Y.P. [38]	1	0	1	2

[a] Double-blind and double-dummy techniques were discarded because the nature of the treatment and associated outcomes were not feasible.

Table 3: Results of Quality Assessment Using Newcastle–Ottawa Scale for Cohort Studies

	Representativeness of the Exposed Cohort	Selection of the Non-exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Long Enough Follow-ups to Occur Outcomes	Adequacy of Follow-ups in Cohorts	Quality Score
Du, J. D. [34]	0	0	1	1	0	1	1	1	5
He, A. L. [33]	1	1	1	1	2	1	1	1	9
Li, K. [25]	1	1	1	1	2	1	1	1	9
Li, Y. F. [39]	1	1	1	1	1	0	1	0	6
Li, Y. L. [31]	1	1	1	1	1	0	1	1	7
Wu, H. Q. [36]	1	1	0	1	1	0	1	1	6
Yan, B. J. [21]	1	1	0	1	1	0	1	1	6
Yang, W. K. [37]	1	1	1	1	1	0	1	1	7

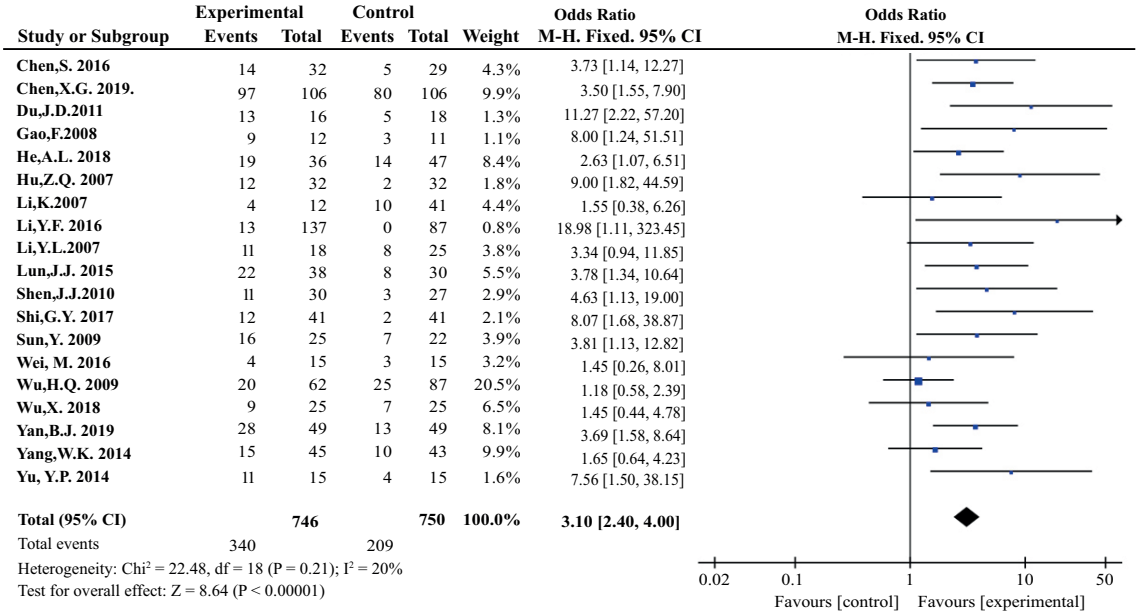

Figure 2: Forest Plot Showing Overall Remission (CR+PR) Rate Under the Fixed-Effects Model

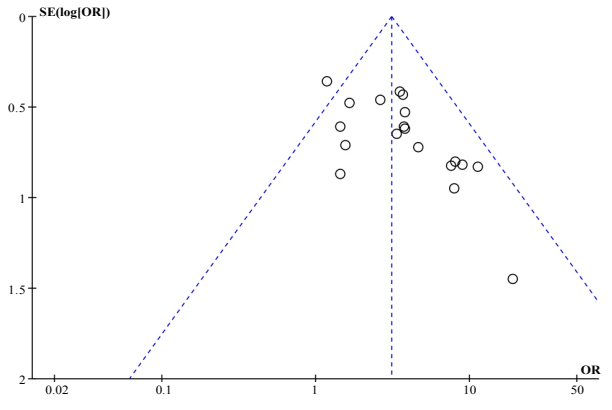

Figure 3: Funnel Plot Showing Publication Bias

The funnel plot showed asymmetry. The proportion of positive or negative trials implied no publication bias (Figure 3).

Overall Survival

Eight studies reported the OS of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer. There was no significant heterogeneity (I^2=28%, P=0.20), therefore, a fixed-effect model was performed. A pooled analysis suggested the evident superiority of OS among the groups of patients undergoing gemcitabine (HR=0.56, 95% CI: 0.47, 0.68;

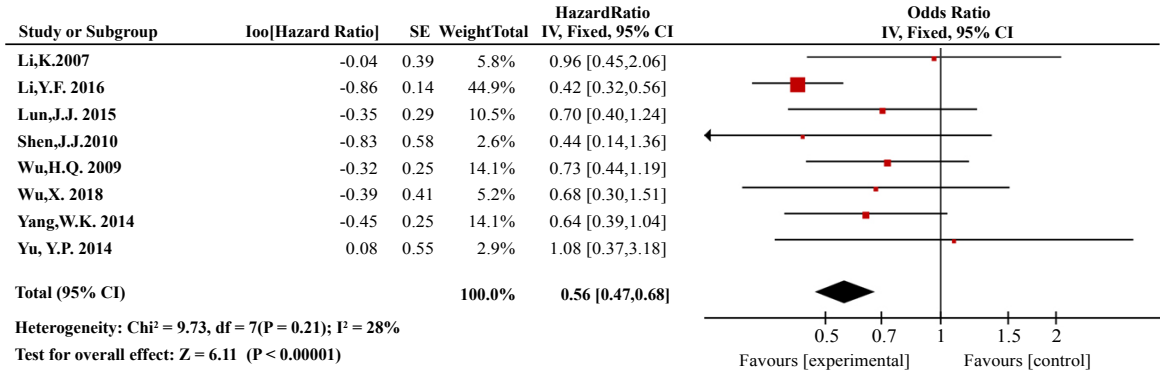

Figure 4: Forest Plot Showing OS Under the Fixed-Effects Model

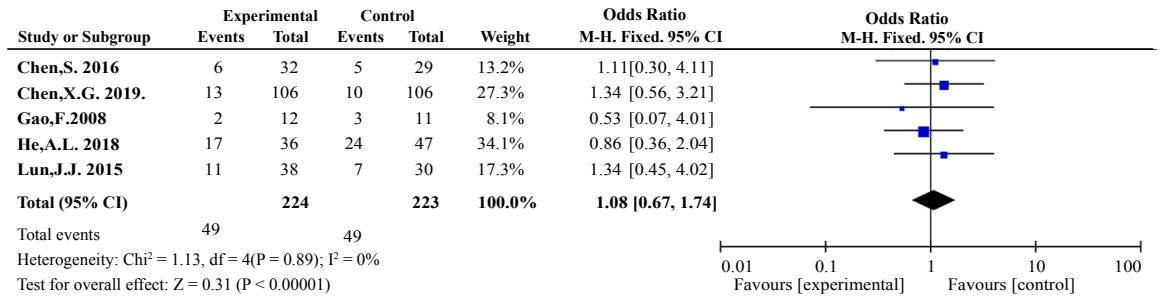

Figure 5: Forest Plot Showing Hypofunction of Liver Under the Fixed-Effects Model

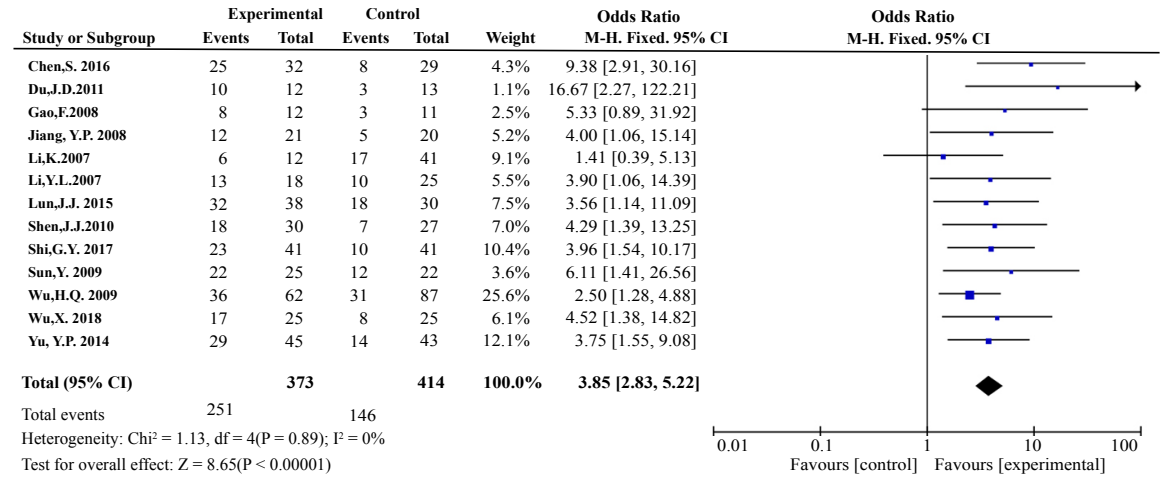

Figure 6: Forest Plot Showing CBR Rate Under the Fixed-Effects Model

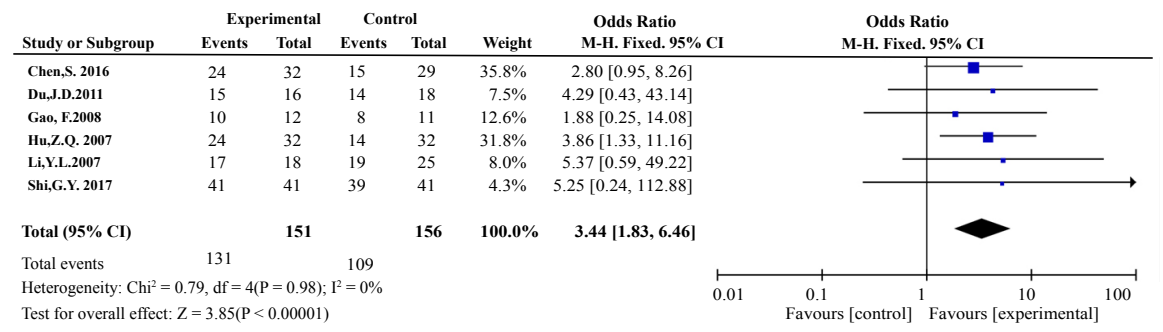

Figure 7: Forest Plot Showing 6-Month Survival Rate Under the Fixed-Effects Model

P<0.00001, Figure 4); implying that iodine-125 implantation combined with gemcitabine was superior to gemcitabine alone. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

Hypofunction of Liver

Five studies reported the hypofunction of the liver following iodine-125 implantation combined with gemcitabine to treat advanced pancreatic cancer. There was no significant heterogeneity (I^2=0%, P=0.89), therefore, a fixed-effect model was performed. A fixed-effect pooled OR=1.08 (95% CI: 0.67, 1.74; P=0.75, Figure 5) implied no difference between the two groups in the outcome. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

CBR Rate

Thirteen studies reported the CBR rate of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer. There was no significant heterogeneity (I^2=0%, P=0.71); therefore, a fixed-effect model was performed. A pooled OR=3.85 (95% CI: 2.83, 5.22; P<0.00001, Figure 6) implied that iodine-125 implantation combined with gemcitabine was superior to gemcitabine alone. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

The Six-Month Survival Rate

Six studies reported the survival rate of six months of iodine-125 implantation combined with gemcitabine in the treatment of advanced pancreatic cancer. There was no significant heterogeneity (I^2=0%, P=0.98), therefore, a fixed-effect model was performed. A pooled OR=3.44 (95% CI: 1.83, 6.46; P=0.98, Figure 7) implied that iodine-125 implantation combined with gemcitabine was superior to gemcitabine alone. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

The 12-Month Survival Rate

Seven studies reported the Survival rate of 12 months of iodine-125 implantation compared with gemcitabine alone in the treatment of advanced pancreatic cancer. There was no significant heterogeneity (I^2=36%, P=0.16), therefore, a fixed-effect model was performed. A pooled OR=2.67 (95% CI: 1.68, 4.26; P=0.16, Figure 8) implied that iodine-125 implantation combined with gemcitabine was superior to gemcitabine alone. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

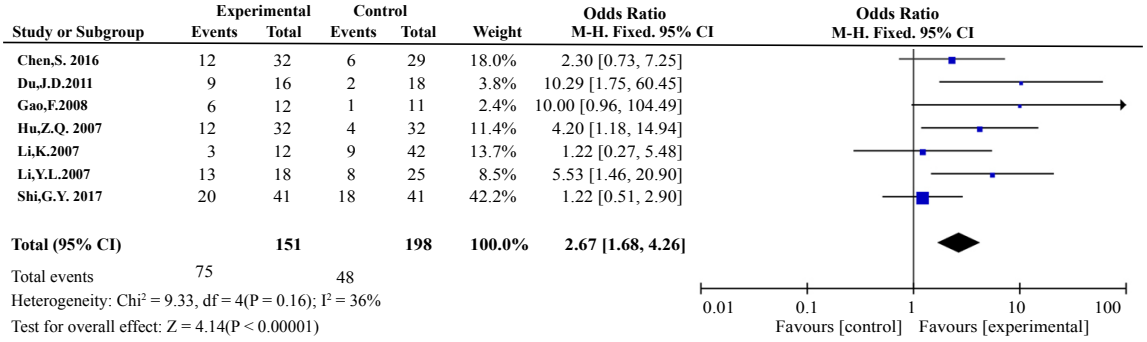

Figure 8: Forest Plot Showing 12-Month Survival Rate Under the Fixed-Effects Model

Table 4: Adverse Events [a]

	No. of Studies	No. of Patients	Pooled OR	95% CI of Pooled OR	P Value	Heterogeneity I^2 (%)
Leukocytosis	5	488	1.28	0.79-2.07	0.32	0
Hemoglobin Reduction	4	424	1.23	0.70-2.16	0.47	0
Nausea and/or Vomiting	6	511	1.28	0.79-2.09	0.32	0
Thrombocytopenia	5	488	1.55	0.97-2.47	0.04	0
Diarrhea	3	210	0.83	0.46-1.49	0.53	0

[a] Abbreviations: CI, confidence interval; NA, not acceptable; OR, odd ratio

Adverse Events

The most common adverse effects were observed in both groups. It was found that there was no significant difference between the two groups regarding the frequency of leucopenia, hemoglobin, thrombocytopenia, diarrhea, nausea, and vomiting (Table 4). Besides, after symptomatic treatment, most adverse events relieved completely. A subgroup analysis was also conducted, but no differences were observed between the intervention measures and the type of procedures.

DISCUSSION

In recent years, interstitial implantation of radioactive seeds into the site of pancreatic cancer therapy is developed. Several radioactive particles such as Phosphorus-32 [40] and yttrium-90 [41] are reported to be effective in different malignant tumors. Iodine-125 is another widely used particle in the treatment of malignant tumors, which extends the survival time for patients and creates a significant pain-relieving effect [42]. The present meta-analysis included 19 relevant studies involving 1496 patients with pancreatic cancer to ensure a sufficient sample. Pooled results demonstrated that the employment of iodine-125 in combination with gemcitabine was significantly superior to gemcitabine alone in overall remission, OS, hypofunction of the liver, CBR rate, and survival rate. Besides, in the included studies, most adverse events were mild to moderate and iodine-125 in combination with gemcitabine was generally safe. Among the included studies, the pooled results showed no significant heterogeneity; therefore, there was no need to carry out subgroup analysis or meta-regression. As a result, the conclusion may be much more convincing.

Mechanism and Feasibility

Some published trials demonstrated that pancreatic cancer cells were sensitive to continuous, low-energy iodine-125 seed irradiation [43, 44] and that the γ-rays released by iodine-125 seeds could lead to cell apoptosis and DNA hypermethylation [45], then reducing tumor volume. Besides, iodine-125 inhibits vascular endothelial hyperplasia and tumor cell growth, prolonging the OS of a patient with malignant tumors [46, 47]. Gemcitabine is a kind of pyrimidine analogue and the most important mechanism of action of gemcitabine is the inhibition of DNA synthesis and activity as a ribonucleoside reductase inhibitor, leading to interruption of DNA chains [48, 49]. Therefore, the double effect of gemcitabine and γ-rays on inhibiting the DNA of tumor cells might be more beneficial to patients. Similar to the included studies, previous studies demonstrated that iodine-125 seed implantation was utilized for malignant esophageal tumor obstructions [50] (median overall survival: 177 days vs 147 days) and non-small cell lung cancer [51] (two-year disease-free survival and OS estimates were 38.5% and 65.8%, respectively), with more beneficial prognosis compared with the non-brachytherapy group. Likewise, the current study pooled results also indicated that the iodine-125 brachytherapy could improve the OS and other prognostic parameters for advanced pancreatic patients. It was concluded that the ability of iodine-125 brachytherapy combined with chemotherapy to partly reduce the incidence of metastasis and cancer recurrence can be the reason for beneficial disease prognosis. Iodine-125 brachytherapy could avoid the limitation of traditional radiotherapy, while iodine-125 brachytherapy could release continuous radiation inside the tumor lesion without serious γ-ray-related toxic side effects. Liu et al., reported that the overall remission rate (65.38%), local control rate (88.46%), and median survival (15.3 months) showed that the iodine-125 seed implantation was a safe, effective, uncomplicated treatment for unrespectable pancreatic cancer [42]. Lu et al., reported that the ratio of patients with partial remission implanted iodine-125 was significantly higher than those receiving chemotherapy perfusion for advanced pancreatic cancer [52]. The aforementioned studies were consistent with the current study and suggested that iodine-125 seed implantation may be a more advantageous treatment for pancreatic cancer. The activities of gemcitabine include the inhibition of cytidine triphosphate synthesis, which is topoisomerase poison I, and breaking the formation of I-mediated DNA [53, 54]. There is significant evidence for nucleoside transport deficiency as an important predictive factor for gemcitabine response in the clinical setting [55]. Base on the evidence, the combination of gemcitabine and I125 seems feasible.

Safety and Adverse Events

Most adverse events are mild to moderate. The postoperative side effects reported in the present

study in both the combination and gemcitabine groups primarily included leukocytosis, hemoglobin reduction, thrombocytopenia, diarrhea, hypofunction of liver, nausea, and/or vomiting. The complications were gradually relieved with symptomatic treatment in the follow-up period in reviewed studies. In our meta-analysis, there was no significant difference in adverse events between the combined therapy and gemcitabine groups, indicating that iodine-125 brachytherapy combined with gemcitabine does not intensify the incidence of common adverse reactions. Irradiation, particularly using high-dose regimens, comes with added concerns about toxicity. Iodine-125 can release γ-ray in a short radiation distance, meaning that the radiation damage to normal tissue can be minimized, and patients may receive chemotherapy tolerantly. Overall, the iodine-125 implantation procedure is considered safe. To summarize, we consider iodine-125 brachytherapy a safe, minimally invasive treatment. In literature searching, we used a strict exclusion criterion, inclusion criterion, and literature quality assessment to ensure the accuracy and quality of the pooled results. Iodine-125 seed implantation also has the following advantages: 1) γ-rays emitted by iodine-125 have a short radiation distance (within 1.7 cm), so high-dose irradiation can be kept within the tumor area with limited damage to the surrounding normal tissue; 2) Iodine-125 seeds have a long half-life (59.7 days), which can inhibit the replication of tumor cells and induce tumor cell apoptosis [56]; 3) Radiation emitted by iodine-125 seeds is not affected by patient respiration motion; 4) Ling et al., reported that low-dose radiations may decrease the incidence of metastasis by influencing the immunophenotype of tumor cells [57]; 5) Reduction of tumor volume may increase resection rate; 6) Furthermore, there is no need for additional uncertainty margins around the clinical target volume [58]. However, the long-term efficacy, adverse events, and survival rate of patients with pancreatic cancer need further research to verify.

Limitation

Similar to any meta-analyses, the present study had some limitations. First, both RCTs and retrospective studies were included in the study, the pooled results and final conclusions should be interpreted with caution. Second, all of the included researches were performed in Chinese populations, so the race or area may lead to some potential bias. Third, some patients undergoing first-line chemotherapy or other treatments were involved in our pooled results. Fourth, surgical experience and hospital costs should also be taken into account. Fifth, given that some of the included studies did not report the age range of the patients, and the remaining reported a wide range of age, the data cannot be pooled. Besides, the mortality rate of pancreatic cancer is correlated with age increase and slightly more common in males than females worldwide [59-61], so it is hypothesized that age may be a risk factor for pancreatic cancer. Lastly, since there were few reports on other risk factors affecting the prognosis of the disease, and there was no consensus on the risk factors for the prognosis of pancreatic cancer [62], it is suggested that future clinical studies focus on the risk factors. Because of these limitations, future trials to verify the obtained results are recommended to include a prospective, multi-center, randomized, double-blind design.

Compared with the gemcitabine alone, the combination therapy of iodine-125 seed implantation and gemcitabine significantly prolonged the survival time of patients with pancreatic cancer, indicating a better prognosis. However, the findings should be interpreted with caution because of potential biases.

ACKNOWLEDGMENTS

The authors would like to express their deepest gratitude to Kong Shunyu and Dai Rao, doctors at the Department of Interventional Radiology, Qinghai University, for their helpful suggestions and support.

CONFLICT OF INTEREST

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and publication of the article.

ETHICS APPROVAL

This is a meta-Analysis and doesn't not involve human subjects and doesn't not require IRB review.

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