



REVIEW ARTICLE

High-intensity focused ultrasound for treatment of pancreatic cancer: a systematic review

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Efficacy; high-intensity focused ultrasound; pancreatic cancer; safety; systematic review.

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Abstract**Objective:** To explore the efficacy and safety of high-intensity focused ultrasound combined with other physical therapies for the treatment of pancreatic cancer, so as to provide reference for clinical application.**Methods:** The PubMed, EMBASE, The Cochrane Library (Issue 11, 2013), CBM, CNKI, and WanFang databases were systematically searched up to November 2013. The randomized controlled trials and clinical controlled trials about the treatment of high-intensity focused ultrasound were included. According to the inclusion and exclusion criteria, two reviewers independently screened the studies, extracted the data, and assessed the quality. The meta-analysis was performed by using the RevMan 5.0 software.**Results:** A total of 23 studies including 19 randomized controlled trials and four clinical controlled trials were included. Of which 14 studies reported the safety. The results of meta-analyses showed that: the survival rate at 6 months and 12 months, overall efficacy, and clinical benefit rate in high-intensity focused ultrasound plus radiation and chemotherapy group were significantly higher than those in groups treated with three-dimensional conformal radiation therapy ($P < 0.05$), gemcitabine ($P < 0.05$), gemcitabine plus cisplatin ($P < 0.05$), and gemcitabine plus 5-fluorouracil ($P < 0.05$). The adverse effect caused by high-intensity focused ultrasound plus other therapy was equal to those in the control group. The major high-intensity focused ultrasound-related adverse effect was skin damage and fever.**Conclusion:** The current evidence suggested that the efficacy of HIFU for pancreatic cancer was superior to other therapies, but with poor quality. Therefore, a standard and unified criterion for the diagnosis and outcome measures of pancreatic cancer is needed, and the quality of study design and implementation should be bettered, so as to improve the high quality of evidence for its clinical application.**Introduction**

Pancreatic cancer is a common and highly malignant disease. Globally, there are approximately 185,000 new individuals who are diagnosed with pancreatic cancer each year (1, 2). Surgical resection is the only potentially curative therapy for its treatment. Unfortunately, only 10% to 15% of patients are resectable at the time of diagnosis (3). Radiotherapy and chemotherapy are the primary treatment methods for

unresectable pancreatic cancer, but these treatments are limited to relieving symptoms, improving quality of life, and prolonging survival. High-intensity focused ultrasound (HIFU) has been shown to produce a well-demarcated area of coagulation necrosis by generating regions of high intensity, raising tissue temperatures to 65°C. Any tissue at the focal point is destroyed through thermal coagulative necrosis, while tissues outside the focal point remain unharmed (4). HIFU is increasingly being promoted as a noninvasive

therapy for malignant and benign solid tumors of tissues and organs, including tumors of the lung, stomach, liver, pancreas, kidney, prostate, breast, and bone. HIFU has been applied extensively for pancreatic cancer, combined with radiotherapy or chemotherapy, but no meta-analytic study has been performed for its efficacy and safety. This study evaluates the safety and efficacy of HIFU for the treatment of pancreatic cancer and provides a comprehensive evidence for the government decision, professional use, and patient selection.

Material and Methods

Inclusion criteria

- Study designs: Either randomized controlled trials (RCTs) or NRCTs were included.
- Population: Patients with pancreatic cancer diagnosed by classical histological characteristics together with radiological findings (ie, ultrasound and/or computed tomography, magnetic resonance imaging).
- Intervention: HIFU alone or HIFU combined with other therapies (ie, chemotherapy or radiotherapy).
- Comparison: Chemotherapy or radiotherapy alone, or chemotherapy combined with radiotherapy.
- Outcome: O₁: Overall survival rate at 6 months and 12 months; O₂: total effective rate (TER); O₃: clinical benefit rate (CBR); and O₄: adverse event (ie, leukopenia, thrombocytopenia, decreased haemoglobin, liver and kidney function damage, gastrointestinal reaction, and nausea and vomiting). According to the WHO criteria (5), acute and subacute toxicity of anticancer drugs was divided into 0 to IV levels, and the III to IV levels were considered as the most serious adverse effect. Complete response (CR) is defined as disappearance of target lesion for at least one month, and partial response (PR) is considered as a decline of at least 50% in maximum tumor diameter. Stable disease (SD) is defined as a decline of at most 50% and an increase of at most 25% in maximum tumor diameter for at least one month. Progressive disease (PD) is defined as an increase of at least 25% in maximum tumor diameter.
- $TER = \frac{CR+PR}{Totalcases(CR+PR+SD+PD)} \times 100 \times 100\%$. CBR (7) is defined as the pain decreased more than 50% and lasted more than four weeks, and the Karnofsky scores (physical condition improvement) increased more than 20% and lasted more than four weeks, and the weight increase over 7%.

Exclusion criteria

Studies that were unable to obtain full texts or those with baseline data not available were excluded. Studies that the

HIFU was regarded as basic treatment to compare the efficacy and safety of other intervention were also excluded.

Search strategy

PubMed, EMBase, The Cochrane library (Issue 11, 2013), CNKI, CBM, VIP, and WanFang Database were systematically searched through November 2013 for the RCTs and clinical controlled trials (CCTs) about the treatment of HIFU. The reference citations in retrieved articles were also scrutinized. The Medical Subject Headings (MeSH) was as follow: 'pancreatic cancer', 'pancreatic tumor', 'ultrasound therapy', 'HIFU' or 'high-intensity focused ultrasound'. Take PubMed for example, the detail search strategy was stated in Box 1.

Box 1: Search strategy in PubMed database

#1 (((((((("pancreatic adenocarcinoma"[Text Word]) OR "pancreatic cancer"[Text Word]) OR "pancreatic cancer"[Title/Abstract]) OR "pancreatic tumor"[Text Word]) OR "pancreatic tumor"[Title/Abstract]) OR "pancreatic neoplasms"[Text Word]) OR "pancreatic neoplasms"[Title/Abstract])

#2 (((((((("high intensity focused ultrasound ablation"[MeSH Terms]) OR "high intensity focused ultrasound"[Text Word]) OR "high intensity focused ultrasound"[Title/Abstract]) OR "focused ultrasound"[Text Word]) OR "focused ultrasound"[Title/Abstract]) OR "haifu"[Text Word]) OR "hifu"[Text Word]) OR "ultrasound therapy"[Title/Abstract]) OR "ultrasound therapy"[Text Word])

#3 #1 AND #2

Study selection, data extraction, and quality assessment

Two reviewers independently screened the literature by browsing title and abstract according to predefined inclusion and exclusion criteria. Primary screening of lectures was undertaken by two reviewers who carefully read the full text to determine their eligibility for inclusion. Any disagreement was resolved by discussion or with a third person. The absent data were supplemented by contacting the author as soon as possible. Data were extracted based on the predefined data extraction form, and the extracted contents including: first author, publication year, study design, the key element of quality assessment, the characteristic data of patients (ie, gender, age), number of patients included in experiment group and control group, and the relevant outcome indicators.

The criteria of Cochrane Handbook 5.0 for Systematic Reviews of Interventions were applied to evaluate the methodological quality of RCTs by two appraisers (8). Although there are number of tools that can be used to evaluate the quality of RCTs and observational studies, a unified tool (Cochrane risk of bias tool) was applied to assess the quality of RCTs and CCTs. The six appraisal items in this tool may not apply to evaluate the quality of CCTs, however, it can also actually reflect the quality difference between RCTs and CCTs.

Statistical analysis

The RevMan 5.0 software was used to perform the meta-analysis. The GRADEpro 3.2.2 was applied to evaluate the quality of outcome (9). For dichotomous variables, the relative risk (RR) with 95% confidence intervals (CIs) was applied. Chi-square was used to examine the heterogeneity of outcomes. When $P \geq 0.10$, and $I^2 \leq 50\%$, the fixed-effect model was used, otherwise the random-effect model was applied. If there is apparently clinical and statistical heterogeneity among outcomes, the description analysis was only used.

Results

Search results

A bibliographic search yielded 812 references (Fig 1). Twenty-three studies with a total of 1157 participants ultimately met the inclusion criteria. The studies included 14 RCTs (10–28) covering 893 cases and 9 CCTs (29–32) covering 264 cases. All studies reported effectiveness indicators, and 14 reported safety indicators.

Baseline characteristics of included studies

The interventions that combined with HIFU can be classified in 10 groups (Table 1): HIFU plus three-dimensional conformal radiation therapy (3D-CRT; five studies, 71.9%), HIFU plus gemcitabine (GEM; five studies, 9.4%), HIFU plus GEM plus cisplatin (DDP; four studies, 9.4%), HIFU plus GEM plus 5-fluorouracil (5-FU; three studies, 6.3%), HIFU versus GEM, HIFU versus Gama knife, HIFU plus GEM plus DDP plus interferon, HIFU plus carboplatin plus 5-FU, HIFU plus support care, and HIFU plus flurocitabine. In this study, we only include studies with the number of interventions more than three and the sample size of 100 or more. For the other studies, a description analysis was only applied.

The 23 indicators in the 23 studies contained objective and subjective indicators of patients (Table 2). The objective indicators included nine items of seven category: age (two

items: ≥ 10 year old and 45 to 59 years old), gender ratio (one item: male to female > 1), clinical stage (three items: II, III, and IV), tumor location (five items: head, body and tail, body, tail, and whole), tumor diameter (two items: 4–10 cm and 3–10 cm), complications (two items: hepatic metastases and jaundice), and pathological types (four items: cystadenocarcinoma, duct cell carcinoma, acimic cell carcinoma, adenosquamous carcinoma).

The subjective indicators included four items of two categories: KFS scale (2 items: scored ≥ 60 and scored 50 to 59) and estimated survival (2 items: > 3 months and 1 to 2 months) (Table 2).

Quality assessment

Only three studies (13.0%) mentioned the randomized methods, and the rest did not state the method of randomization, allocation concealment, and blinding in detail. None of the studies reported outcome assessors, and the intentional analysis was not performed. All studies did not state that the outcome indicators were predefined. Four CCTs did not use the randomized or blinding methods, and a high risk of bias may exist (Table 3).

Result of efficacy outcome

Of the 23 studies, 6 (26.1%) reported 6-month survival rates, 7 (30.4%) reported 12-month survival rates, 21 (91.3%) reported TER, and 17 (73.9%) reported the CBR. The reported rate of HIFU plus GEM versus GEM alone in intervention group 2 was good (Table 4). Table 5 comprehensively illustrates the detailed result of efficacy outcome.

- HIFU plus 3D-CRT versus 3D-CRT: Five trials reported the efficacy of HIFU plus 3D-CRT compared with 3D-CRT alone for the treatment of pancreatic cancer. One study reported the survival rates at 6 months and 12 months. Five studies reported the total effective rate, and four studies stated CBR. The pooled results of meta-analysis indicated that the TER and CBR in HIFU plus 3D-CRT group were significantly higher than 3D-CRT group ($P < 0.05$). The number needed to treat to harm (NNTH) for survival rate at six months is more than 6, which indicated a poor effect, however, it cannot rule out bias due to small sample size.
- HIFU plus GEM versus GEM alone: Five trials reported survival rate at 6 months and 12 months, TER, and CBR. Compared to the GEM alone, the pooled results showed that the survival rate at 6 months and 12 months, TER, and CBR were significantly improved in HIFU plus GEM group ($P < 0.05$).
- HIFU plus GEM plus DDP versus GEM plus DDP: Four trials only reported TER and CBR. The pooled results of

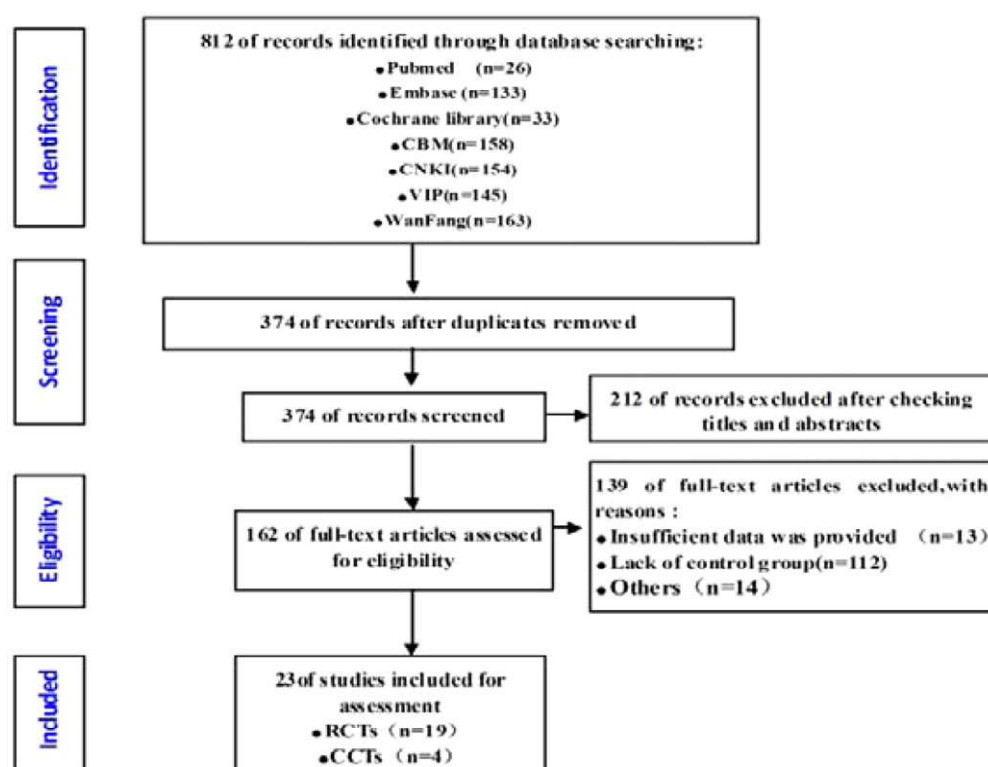


Figure 1 Flow diagram according to PRISMA statement.

Table 1 Categories of interventions

No.	Interventions	No. of studies	Number of cases
①	HIFU plus 3D-CRT vs. 3D-CRT	5	244
②	HIFU plus GEM vs. GEM	5	262
③	HIFU plus GEM plus DDP vs. GEM plus DDP (GP)	4	200
④	HIFU plus GEM plus 5FU vs. GEM plus 5FU (GF)	3	115
⑤	HIFU vs. GEM	1	91
⑥	HIFU vs. GN	1	80
⑦	HIFU plus GEM plus DDP plus IFN vs. GEM plus DDP plus IFN	1	64
⑧	HIFU plus CBP plus 5FU vs. CBP plus 5FU	1	36
⑨	HIFU plus BSM vs. BSM	1	36
⑩	HIFU plus FEM vs. FEM	1	29
Total		23	1157

3D-CRT: three-dimensional conformal radiation therapy; GEM: gemcitabine; DDP: cisplatin; 5FU: 5-fluorouracil; FEM: flurocitabine; GN: gamma knife; IFN: interferon; CBP: carboplatin.

meta-analysis showed that the two indicators were significantly improved in HIFU plus GEM plus DDP group when compared to GEM plus DDP group ($P < 0.005$).

- HIFU plus GEM plus 5FU versus GEM plus 5FU: Three trials reported TER (three studies) and CBR (two studies). The results of meta-analysis showed that the TER and CBR were both significantly higher in HIFU plus

GEM plus 5FU group compared to GEM plus 5FU group ($P < 0.05$).

The No. 5 to 6 interventions in Table 1 included only one study. The efficacy rate in HIFU group was lower than GEM group by 2.6%, and other studies showed that the survival rate at 6 months (23.8%) and 12 months (5.7% to 44.7%),

Table 2 The baseline characteristics of included studies

Indicator	Author, year	Age		Gender		Stage				Tumor location				Diameter		Complication		Pathological types				KFS scale		Estimated survival		
		≥60 y	45–59 y	M	F	IV	III	II	I	Head	Body and tail	Body	Tail	Whole	4–10 cm	3–10cm	HM	Jaundice	CA-CA	DC-CA	AC-CA	AS-CA	≥S-	50–59	>3mo.	1–2 mo.
①	Chen 2011 (11)	•		•	•	•	•	•		•	•	•				•							•		•	
	Chen 2010 (12)		•	•	•					•		•	•										•		•	
	Sun 2008 (13)		•	•	•																		•		•	
	Xu 2012 (10)		•	•	•																		•			
	Du 2012 (29)	•		•	•																					
②	Wang 2011 (15)	•		•	•	•	•	•		•			•										•			
	Zhao 2008 (30)	•		•	•	•	•	•		•	•	•														
	Shi 2011 (14)	•		•	•	•	•	•																		
	Zeng 2006 (17)	•		•	•					•															•	
	Yu 2009 (16)	•		•	•	•	•	•																		
③	Gao 2006 (21)		•	•	•	•	•	•		•	•												•		•	
	Bian 2009 (19)		•	•	•	•	•	•		•	•												•		•	
	Chen 2008 (20)		•	•	•	•	•	•		•													•		•	
	Gao 2010 (18)		•	•	•	•	•	•		•	•		•										•		•	
	Wang 2003 (24)		•	•	•	•	•	•		•	•						•						•		•	
④	Mao 2009 (23)		•	•	•	•	•	•		•	•												•		•	
	Wu 2009 (22)		•	•	•	•	•	•		•	•												•		•	
	Zhang 2009 (25)	•		•	•	•	•	•		•							•						•		•	
	Xu 2010 (31)		•	•	•					•	•															
	Zhang 2011 (26)	•		•	•	•	•	•																		
⑤	Yin 2009 (27)	•		•	•	•	•	•		•																
	Qin 2010 (28)	•		•	•	•	•	•		•																
	Xie 2001 (32)		•	•	•	•	•	•		•																

HM: hepatic metastases; CA-CA: cystadenocarcinoma; DC-CA: duct cell carcinoma; AC-CA: acinic cell carcinoma; AS-CA: adenosquamous carcinoma.

Table 3 Risk of bias in included studies

					Incomplete outcome data			Selective reporting	Other risk	Risk of bias
Included study, year		Random	Allocation concealment	Blinding	Lost (T/C)	ITT	Comprehensive			
RCT	Xu 2012 (10)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Chen 2011 (11)	Yes	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Chen 2010 (12)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Sun 2008 (13)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Shi 2011 (14)	Yes	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Wang 2011 (15)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Xu 2009 (16)	Yes	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Zeng 2006 (17)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Gao 2010 (18)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Bian 2009 (19)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Chen 2008 (20)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Gao 2006 (21)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Wu 2009 (22)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Mao 2009 (23)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Wang 2003 (24)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Zhang 2009 (25)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Zhang 2011 (26)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Yin 2009 (27)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
	Qin 2010 (28)	Unclear	Unclear	Unclear	Nothing	–	Yes	Unclear	Unclear	High
CCT	Du 2012 (29)	Unclear	Unclear	Unclear	Nothing	–	Yes	No	Unclear	High
	Zhao 2008 (30)	Unclear	Unclear	Unclear	Nothing	–	Yes	No	Unclear	High
	Xu 2010 (31)	Unclear	Unclear	Unclear	Nothing	–	Yes	No	Unclear	High
	Xie 2001 (32)	Unclear	Unclear	Unclear	Nothing	–	Yes	No	Unclear	High

Table 4 Efficacy indicators of included studies

Group	Author, year	Number (T/C)	Survival rate		TER (T:C)	CBR (T:C)
			6 month	12 month		
①	Du 2012 (29)	22/29	95.5% vs. 93.1%	59.1% vs. 41.4%	63.6% vs. 44.8%	95.5% vs. 86.2%
	Xu 2012 (10)	16/17			43.7% vs. 35.3%	81.3% vs. 64.7%
	Chen 2011 (11)	25/25			48.0% vs. 24.0%	
	Chen 2010 (12)	24/24			37.5% vs. 20.8%	52.2% vs. 21.7%
	Sun 2008 (13)	20/20			35.0% vs. 20.0%	70.5% vs. 31.3%
②	Shi 2011 (14)	25/22	73.8% vs. 52.3%	35.2% vs. 17.3%	64.0% vs. 31.8%	72.0% vs. 40.9%
	Wang 2011 (15)	28/20			50.0% vs. 15.0%	83.3% vs. 30.0%
	Xu 2009 (16)	26/13			23.1% vs. 15.4%	61.5% vs. 15.4%
	Zhao 2008 (30)	65/17				
	Zeng 2006 (17)	24/22				87.5% vs. 36.4%
③	Gao 2010 (18)	17/13	76.9% vs. 38.5%	30.9% vs. 13.0%	47.1% vs. 15.4%	82.4% vs. 46.2%
	Bian 2009 (19)	30/26			36.7% vs. 34.6%	66.7% vs. 38.5%
	Chen 2008 (20)	22/22			40.9% vs. 36.3%	90.9% vs. 63.6%
	Gao 2006 (21)	29/25			62.1% vs. 32.0%	
④	Wu 2009 (22)	17/15	75.0% vs. 36.4%	30.9% vs. 13.0%	70.6% vs. 40.0%	70.5% vs. 33.3%
	Mao 2009 (23)	23/20			60.9% vs. 35.0%	
	Wang 2003 (24)	20/20			50.0% vs. 40.0%	64.7% vs. 31.3%
⑤	Zhang 2009 (25)	46/45	90.5% vs. 66.7%	71.4% vs. 26.7%	41.3% vs. 35.6%	17.4% vs. 20.0%
⑥	Xu 2010 (31)	26/54			26.9% vs. 24.1%	84.6% vs. 57.4%
⑦	Zhang 2011 (26)	32/32			68.8% vs. 43.8%	55.6% vs. 28.6%
⑧	Yin 2009 (27)	19/17			68.4% vs. 35.2%	
⑨	Qin 2010 (28)	21/15			38.1% vs. 20%	76.2% vs. 33.3%
⑩	Xie 2001 (32)	15/14			33.3% vs. 14.3%	80.0% vs. 28.6%

T: treatment; C: control; TER: total effective rate; CBR: clinical benefit rate.

TER (2.8% to 33.2%), and CBR (4.2% to 51.4%) were all higher than the control group.

Result of safety outcome

Fourteen studies (60.9%) reported adverse reactions including blood system, digestive system, skin and subcutaneous

tissue, symptoms and signs, circulatory system, and nervous system. More than five studies reported leukopenia, thrombocytopenia, haemoglobin reduction, gastrointestinal tract reaction, liver and kidney function damage, and nausea and vomiting. According to the WHO criteria for adverse effect, these six adverse reactions reported can all be classified as

Table 5 Efficacy evaluation of included studies

Group	Effectiveness		Studies	Patients	RR (95% CI)	NNTH	GRADE
①	Total effective rate		5	222	1.60 (1.13, 2.25)	6	⊕⊕⊕⊖
	Survival rate	6 m	1	51	1.03 (0.90, 1.17)	43	⊕⊖⊖⊖
		12 m	1	51	1.43 (0.82, 2.49)	6	⊕⊖⊖⊖
	Clinical benefit rate		4	163	1.44 (1.15, 1.79)	5	⊕⊕⊕⊖
②	Total effective rate		3	134	2.25 (1.31, 3.88)	4	⊕⊕⊕⊖
	Survival rate	6 m	4	215	1.69 (1.29, 2.22)	3	⊕⊕⊕⊖
		12 m	3	176	2.81 (1.46, 5.44)	3	⊕⊕⊕⊖
	Clinical benefit rate		4	180	2.42 (1.72, 3.41)	2	⊕⊕⊕⊖
③	Total effective rate		4	184	1.50 (1.03, 2.20)	6	⊕⊕⊕⊖
	Clinical benefit rate		3	130	1.61 (1.22, 2.13)	3	⊕⊕⊕⊖
④	Total effective rate		3	115	1.57 (1.05, 2.33)	5	⊕⊕⊕⊖
	Clinical benefit rate		2	65	2.09 (1.20, 3.67)	3	⊕⊕⊕⊖

m: month.

blood and digestive system (Table 6). The detailed appraisal results of safety are described in Table 7.

- HIFU plus 3D-CRT versus 3D-CRT alone: Of five trials included, two reported five types of adverse reactions: leukopenia, thrombocytopenia, haemoglobin reduction, gastrointestinal tract reaction, and liver and kidney function damage. The pooled result of meta-analysis showed that there were no significant differences between HIFU plus 3D-CRT and 3D-CRT alone at adverse effect rate ($P > 0.05$; GRADE: very low to moderate quality).
- HIFU plus GEM versus GEM alone: Only one trial reported three types of adverse reactions: leukopenia, gastrointestinal tract reaction, and liver and kidney functional damage. There was no statistically significant difference at adverse effect rate among groups due to limited sample size (GRADE: very low).
- HIFU plus GEM plus DDP versus GEM plus DDP: Two trials reported four types of adverse reactions: leukopenia, thrombocytopenia, haemoglobin reduction, and nausea and vomiting. The pooled result of meta-analysis of adverse reactions showed no significant difference between HIFU plus GEM plus DDP and GEM plus DDP groups ($P > 0.05$; GRADE: very low to moderate quality).

Besides the six indicators above, the included studies also stated the other nine adverse reactions: (see Table 8 for detail) anemia (6.2%), abdominal reactions (1.6%), elevated aminotransferase (12.0%), skin lesions (1.6%), mucositis (7.8%), fever (6.2%), phlebitis (9.9%), orthostatic hypotension (7.8%), and peripheral neuropathy (9.9%). Fever (6.2%) and skin lesions (1.6%) were the most commonly reported adverse events in the HIFU groups. The major HIFU-related adverse reactions were skin damage (1.6%) and fever (6.2%). The adverse effects of chemotherapy, radiation therapy, gamma knife, and supportive therapy were marrow suppression, gastrointestinal reaction, and liver function

damage. There was no significant difference between treatment and control groups, indicating that the HIFU combined with other interventions did not increase adverse reactions.

Discussion

The rationality of clinical studies into the efficacy and safety

The efficacy indicators included survival rates, TER, and CBR. The sample size of all studies was small and the follow-up period varied. Only five studies reported follow-up period without long-term follow-up results. The reporting rate of survival was the lowest, while that of the total effective rate, which was applied with unified and standard efficacy criteria, was the best. Only eight studies (8/17, 47.1%) reported the CBR based on evaluation standards. Most physicians in China currently do not have the methodological conditions to design and perform high-quality RCTs. An op-design, comprehensive planning, and unified training are needed to conduct multicenter, large-scale, and high-quality RCTs with sufficient long-term follow-up outcomes which should be evaluated with strictly efficacy criteria.

The reporting rate (14/23, 60.9%) of safety was poorly reported compared to efficacy indicators. Only three studies reported adverse effect based on WHO criteria for adverse reactions grading. The adverse reactions included leukopenia, thrombocytopenia, haemoglobin reduction, gastrointestinal tract reaction, liver and kidney functional damage, and nausea and vomiting. Studies evidence indicated that these adverse reactions were mainly due to radiotherapy or chemotherapy. HIFU can produce high temperatures to cause coagulation necrosis and damage the local tumor blood vessels; so as to inhibit sublethal radiotherapy damage to normal tissues and reduce radiation damage (7). This may be the reason that

Table 6 The adverse reaction of included studies

No.	Author, year	Blood system				Digestive system				Skin			Symptom		Circulatorysystem		Nervous system
		Leukopenia	Thrombocytopenia	Haemoglobin reduction	Anemia	Gastrointestinal tract reaction	Liver, kidney function damage	Nausea and vomit	Other reactions of abdominal	Transaminase	Skin damage	Mucositis	Fever	Phlebitis	Orthostatic hypotension	Peripheral neuropathy	
①	Du 2012 (29)																
	Xu 2012 (10)	•						•			•		•				
	Chen 2010 (12)	*	*	*		*	*										
	Sun 2008 (13)	*	*			*	*										
②	Shi 2011 (14)					•	•										
	Wang 2011 (15)	•			•			•	•	•	•		•				
	Yu 2009 (16)	*				*	*										
	Zhao 2008 (30)								•				•				
③	Gao 2010 (18)	•	•											•			•
	Bian 2009 (19)	*	*	*		*	*	*									
	Chen 2008 (20)	*	*	*		*		*		•		•			•		
	Wu 2009 (22)	•	•					•									
④	Xu 2010 (31)	•	•	•		•	•				•						
	Qin 2010 (28)					•							•				

•pooled data; *description only; ① HIFU plus 3D-CRT vs. 3D-CRT; ② HIFU plus GEM vs. GEM; ③ HIFU plus GEM plus DDP vs. GEM plus DDP; ④ HIFU plus GEM plus 5-FU vs. GEM plus 5-FU; ⑤ HIFU vs. gamma knife; ⑥ HIFU plus support care vs. support care.

Table 7 The comprehensive results of safety*

No.	Safety indicators	WHO grading	No. of studies	Patients	RR (95%CI)	NNH	GRADE quality
①	Leukopenia	0	2	88	1.23 (0.68, 2.22)	15	Moderate (⊕⊕⊕⊕)
		I	2	88	1.40 (0.70, 2.80)	11	Moderate (⊕⊕⊕⊕)
		II	2	88	0.73 (0.32, 1.63)	15	Moderate (⊕⊕⊕⊕)
		III	2	88	1.00 (0.15, 6.78)	—	Very low (⊕⊕⊕⊕)
	Thrombocytopenia	0	2	88	1.40 (0.71, 2.77)	11	Moderate (⊕⊕⊕⊕)
		I	2	88	0.86 (0.45, 1.64)	22	Moderate (⊕⊕⊕⊕)
		II	2	88	0.67 (0.20, 2.20)	22	Moderate (⊕⊕⊕⊕)
	Haemoglobin reduction	0	2	88	1.22 (0.77, 1.94)	11	Moderate (⊕⊕⊕⊕)
		I	2	88	1.11 (0.50, 2.46)	44	Moderate (⊕⊕⊕⊕)
		II	2	88	1.00 (0.27, 3.75)	—	Moderate (⊕⊕⊕⊕)
	Gastrointestinal tract reaction	III	2	88	0.33 (0.04, 3.09)	22	Moderate (⊕⊕⊕⊕)
		0	2	88	1.36 (0.79, 2.35)	9	Moderate (⊕⊕⊕⊕)
		I	2	88	1.25 (0.55, 2.87)	22	Moderate (⊕⊕⊕⊕)
		II	2	88	0.50 (0.10, 2.59)	22	Moderate (⊕⊕⊕⊕)
	Liver, kidney function damage	III	2	88	0.50 (0.10, 2.59)	22	Moderate (⊕⊕⊕⊕)
		IV	2	88	0.33 (0.04, 3.09)	22	Moderate (⊕⊕⊕⊕)
		0	2	88	1.15 (0.75, 1.76)	15	Moderate (⊕⊕⊕⊕)
		I	2	88	1.00 (0.46, 2.16)	—	Moderate (⊕⊕⊕⊕)
	Leukopenia	II	2	88	0.33 (0.04, 3.09)	22	Moderate (⊕⊕⊕⊕)
		0	1	39	0.83 (0.39, 1.79)	13	Very low (⊕⊕⊕⊕)
		I	1	39	1.25 (0.48, 3.23)	13	Very low (⊕⊕⊕⊕)
		II	1	39	1.25 (0.28, 5.59)	26	Very low (⊕⊕⊕⊕)
②	Gastrointestinal tract reaction	III	1	39	0.50 (0.03, 7.37)	26	Very low (⊕⊕⊕⊕)
		0	1	39	2.00 (0.84, 4.77)	3	Very low (⊕⊕⊕⊕)
		I	1	39	0.80 (0.33, 1.96)	13	Very low (⊕⊕⊕⊕)
		II	1	39	0.33 (0.06, 1.75)	7	Very low (⊕⊕⊕⊕)
	Liver, kidney function damage	III	1	39	0.17 (0.01, 3.97)	13	Very low (⊕⊕⊕⊕)
		0	1	39	0.92 (0.44, 1.92)	26	Very low (⊕⊕⊕⊕)
		I	1	39	1.25 (0.48, 3.23)	13	Very low (⊕⊕⊕⊕)
		II	1	39	0.83 (0.23, 2.96)	26	Very low (⊕⊕⊕⊕)
	Leukopenia	0	2	100	1.24 (0.68, 2.25)	18	Moderate (⊕⊕⊕⊕)
		I	2	100	1.07 (0.65, 1.76)	35	Moderate (⊕⊕⊕⊕)
		II	2	100	0.92 (0.38, 2.26)	78	Moderate (⊕⊕⊕⊕)
		III	2	100	0.52 (0.16, 1.67)	15	Moderate (⊕⊕⊕⊕)
③	Thrombocytopenia	IV	2	100	0.58 (0.10, 3.20)	42	Moderate (⊕⊕⊕⊕)
		0	2	100	1.13 (0.64, 1.97)	30	Moderate (⊕⊕⊕⊕)
		I	2	100	1.26 (0.71, 2.22)	14	Moderate (⊕⊕⊕⊕)
		II	2	100	0.59 (0.23, 1.48)	14	Moderate (⊕⊕⊕⊕)
	Haemoglobin reduction	III	2	100	0.87 (0.24, 3.13)	156	Moderate (⊕⊕⊕⊕)
		IV	2	100	0.87 (0.06, 13.18)	642	Very low (⊕⊕⊕⊕)
		0	2	100	1.21 (0.88, 1.66)	13	Moderate (⊕⊕⊕⊕)
		I	2	100	1.13 (0.59, 2.16)	25	Moderate (⊕⊕⊕⊕)
	Gastrointestinal tract reaction	II	2	100	0.56 (0.20, 1.57)	14	Moderate (⊕⊕⊕⊕)
		III	2	100	0.65 (0.16, 2.64)	39	Moderate (⊕⊕⊕⊕)
		IV	2	100	0.43 (0.04, 4.51)	45	Moderate (⊕⊕⊕⊕)
		0	1	44	1.06 (0.82, 1.37)	22	Very low (⊕⊕⊕⊕)
	Liver, kidney function damage	I	1	44	1.00 (0.15, 6.48)	—	Very low (⊕⊕⊕⊕)
		II	1	44	0.50 (0.05, 5.12)	22	Very low (⊕⊕⊕⊕)
		0	1	56	1.95 (1.02, 3.72)	3	Very low (⊕⊕⊕⊕)
		I	1	56	0.65 (0.26, 1.63)	9	Very low (⊕⊕⊕⊕)
	Nausea and vomit	II	1	56	0.50 (0.16, 1.50)	7	Very low (⊕⊕⊕⊕)
		III	1	56	0.58 (0.10, 3.20)	21	Very low (⊕⊕⊕⊕)
		0	2	100	1.23 (0.86, 1.76)	9	Moderate (⊕⊕⊕⊕)
		I	2	100	0.95 (0.44, 2.04)	62	Moderate (⊕⊕⊕⊕)
	Leukopenia	II	2	100	0.72 (0.29, 1.78)	19	Moderate (⊕⊕⊕⊕)
		III	2	100	0.65 (0.16, 2.64)	39	Moderate (⊕⊕⊕⊕)
		IV	2	100	0.29 (0.01, 6.83)	48	Very low (⊕⊕⊕⊕)
		0	2	100	1.23 (0.86, 1.76)	9	Moderate (⊕⊕⊕⊕)

*See the detailed comparison of interventions in Table 1.

NNH: number need to harm.

Table 8 The adverse events in included studies (n (%))

No.	Author, year	Patient	Blood system			Digestive system			Skin			Circulatory system			Nervous system Peripheral neuropathy			
			Leukopenia	Thrombocytopenia	Haemoglobin reduction	Anemia	Gastrointestinal tract reaction	Liver, kidney function damage	Nausea and vomit of abdominal	Other reactions of abdominal	Transaminase	Skin damage	Mucositis	Symptom		Phlebitis	Orthostatic hypotension	
①	Du 2012 (29)	22																
		29																
	Xu 2012 (10)	16	11 (68.8)															
		17	11 (94.1)															
②	Shi 2011 (14)	25	10 (40.0)					11 (44.0)	2 (8.0)									
		22	10 (45.5)					11 (50.0)	2 (9.1)									
	Wang 2011 (15)	28	18 (64.3)				19 (68.2)											
		20	13 (65.0)				16 (80.0)											
	Zhao 2008 (30)	65																
		17																
③	Gao 2010 (18)	17	10 (59.9)															
		13	8 (59.3)															
	Bian 2009 (19)	30																
		26																
	Chen 2008 (20)	22																
		22																
④	Wu 2009 (22)	17																
		15																
⑤	Xu 2010 (31)	26	4 (15.3)					5 (19.2)										
		54	17 (31.5)					32 (59.3)	10 (18.5)									
⑥	Qin 2010 (28)	32																
		32																

few grade III or IV adverse events were reported in HIFU group.

The efficacy and safety of different interventions

The pooled results of meta-analysis revealed a superior effect in HIFU group compared to that in non-HIFU groups. In HIFU plus 3D-CRT versus 3D-CRT studies, they reported four efficacy indicators, and the quality evidence of TER and CBR was moderate, while the survival rate at 6 months and 12 months was very low. The HIFU plus GEM versus GEM alone studies reported four indicators in which the quality of evidence was moderate. The HIFU plus GEM plus DDP versus GEM plus DDP studies and HIFU plus GEM plus 5FU versus GEM plus 5FU studies both reported two outcomes in which the quality of evidence was moderate.

The reporting rate of adverse events from highest to lowest was No. 1 > No. 3 > No. 2 in Table 1. The number need to harm from highest to lowest was No. 1 > No. 3 > No. 2. The safety of included trials from serious to slight was No. 2 > No. 1 > No. 3. There were few studies that reported adverse events, and with limited sample size. Therefore, after integrating above criteria, we can conclude that the safety of interventions varies for pancreatic cancer from serious to slight as No. 2 > No. 1 > No. 3 or No. 1 > No. 3 > No. 2.

The impact of study design, implementation, report quality on outcomes

The design quality, implementation and report quality of the 23 included studies were low. Sixteen studies only mentioned 'randomly allocated participants', but did not describe the method of randomization in detail. None of the studies reported allocation concealment, blinded participants, blinded personnel, or outcome assessors. The random or blinding method was not applied in CCTs, which may lead to a high risk of selection. Therefore, a intensive training about study design and implementation was extremely needed in further studies, and pre-registration of trials should be encouraged. What's more, the ethics and methodology before implementation of researches must be fully controlled, so as to improve the quality of clinical research and power of test.

Limitations

We conducted comprehensive search strategies, however, the journal supplements and some gray lectures are not available, and so it cannot rule out the potential publication bias. The quality of evidence in China was low, especially lack of high-quality and standardized RCTs, which may impact the credibility to some extent. HIFU is large medical

equipment with fully intellectual property in China, so the most of included patients were Chinese, which may influence the extrapolation.

Conclusion

The pooled results of meta-analysis showed that the survival rate at 6 months and 12 months, TER, and CBR, all efficacy indicators in HIFU combined with radiotherapy or chemotherapy group, were higher than that in 3D-CRT group, GEM group, GEM plus DDP group, and GEM plus 5FU group. The adverse effect rate in HIFU group was similar to that in control group, however, the pooled effect of grade 0 to IV adverse effect tends to favor HIFU group indicating that HIFU may alleviate some adverse effects due to radiotherapy and chemotherapy. The quality evidence of included studies was very low, which may impact the reliability to some extent. Currently, the standard and unified criteria of diagnosis and measuring outcome for pancreatic cancer is needed so as to improve the quality of study design and implement, and provide a high quality of evidence for the application of HIFU.

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