

High-intensity focused ultrasound (HIFU) therapy for pain palliation in advanced stage pancreatic carcinoma: A Meta-Analysis with recent studies

^{1,2*}Yadav Ajay Kumar, ²Gnawali Suman, ²Mandal Sandip Kumar, ²Shrestha Gyan Bahadur, ²Adhikari Ganga Dutta, ²Shah Bhanu Pratap, ¹Yuan Gengbiao

¹Department of Nuclear Medicine, The Second Affiliated Hospital of Chongqing Medical University, PR China. ²Department of Radio-diagnosis, Imaging and Nuclear Medicine, BP Koirala Memorial Cancer Hospital, Bharatpur, Nepal,

Abstract

Background: Day by day, High-intensity focused ultrasound (HIFU) therapy is becoming more familiar in medical field because it is non-invasive technique with fewer side effects and provides promising therapeutic results. Several HIFU therapy applications have approved by many approval authorities of deferent countries since last decade. It is a novel, emerging, therapeutic modality that uses ultrasound waves, propagated through tissue media, as carriers of energy. HIFU has great potential for tumor ablation and the main mechanisms of HIFU ablation involve mechanical and thermal effects. Pancreatic adenocarcinoma is currently the fourth-leading cause of cancer-related death. Up to 60–90% of patients with advanced disease suffer cancer-related pain, severely impacting their quality of life. Current management involves primarily pharmacotherapy with opioid narcotics and celiac plexus neurolysis; unfortunately, both approaches offer transient relief and cause undesired side-effects. High intensity focused ultrasound (HIFU) is a non-invasive thermal ablation technique that has been used to treat pancreatic cancer. This meta-analysis aims to evaluate the role of HIFU in pain palliation of advanced unresectable pancreatic adenocarcinoma.

Methods: Paper selection was performed electronically in PubMed up to the end of March 2021, for pain palliation treatment of advanced staged pancreatic cancer with HIFU. Relevant papers were identified through the PubMed search engine using these keywords: HIFU, pancreas, pancreatic cancer, pain and palliation. Additional studies were also done included after manual search of the selected bibliographies. Palliation results reported in studies were analyzed using a logit-transformed random-effects model using the inverse variance method, with the DerSimonian-Laird estimator for t^2 , and Cochran's Q test for heterogeneity among studies. The I^2 was also calculated to assess the percentage of the total variability in the different effect size estimates that can be attributed to heterogeneity among the true effects and rank correlation test of funnel plot asymmetry was done to assess possible publication bias.

Results: In this meta-analysis, we includes only recent 10 year studies i.e. total number of 16 studies with 687total patients with pancreatic cancer. The total patients enrolled ranges from 7

Corresponding Author:

Yuan Gengbiao, Department of Nuclear Medicine, The Second Affiliated Hospital of Chongqing Medical University, PR China, (Email Id yuan_gb@126.com)

patients in the smallest series, up to 120 in the largest study. The calculated τ^2 was 0.187, and I^2 was 41%, the Q test p-value was 0.026, indicating significant heterogeneity among studies. The random effects estimate of the proportion of patients with pain reduction was 0.89.08.

Conclusions: We concluded that HIFU performs to be an effective tool for pain palliation in advanced staged pancreatic cancer. Prospective randomized and standardized studies are necessary to confirm the effectiveness of HIFU in relieving pain, and to evaluate for any potential impact on tumor control and patient survival.

Key words: HIFU, MRI guided HIFU, USG guided HIFU, ablation

Introduction

With references with new data, pancreatic carcinoma is increasing in the world and now it's become the fourth leading cause of cancer related death.^{1,2} In the western countries, it may be due to worse environmental condition, pancreatic cancer more frequently affects male between 65 to 68 years of ages.³ Among all categories of pancreatic carcinomas, ductal pancreatic adenocarcinoma is the most common histology that is 85 to 90 % of all these cancers.⁴

There is huge development in medical diagnostic field as well as there are a lots of new approaches in medical therapeutic field, despite of that the development; there is still lack in prognosis in pancreatic carcinomas over last 40 years.⁴ According to recent available studies, Overall survival rate of pancreatic carcinomas is about 5 year in less than 8% whereas median survival rate is approximately 6 to 10 months for unresectable pancreatic carcinomas i.e. locally advanced carcinoma and for the patients with distance metastases, survival rate is only 3 to 6 months.⁵

As we know, the best option of radical treatment for pancreatic carcinomas is surgery but due to the late occurrence of

symptoms in patients with pancreatic carcinomas, only less than 20 % of patients are eligible for surgery at the time of diagnosis.⁶ In spite of even after early detection and early surgery, mortality rate remains still high even after surgery due to the high loco-regional recurrence rate and propensity of early distance metastatic spread.⁷ Bearing in mind the poor prognosis in patients with pancreatic cancer patients, the main objectives of pancreatic carcinoma treatment in late staged disease are palliative treatment, improve the overall life quality and increase the overall survival rate. All the way through the illness and during hospice life care, there is need of comprehensive symptoms control. Among all the symptoms, pain is the major problem in patients with pancreatic carcinomas and it is reported by 60 to 90% of patients with late staged carcinoma.⁸ The main reported symptoms with the patients with pancreatic carcinoma are dull pain, colicky spasms, and pain referred to the mid back or epigastric region.⁹ According to the recent research studies, GEM chemotherapy combination with tele-radiotherapy provides a limited improvement in survival rate, but it is still not such effective in pain palliation and it generates high toxicity.¹⁰

The recent pain palliation management of the patients with pancreatic carcinoma primarily involves pharmacotherapy with celiac plexus neurolysis and opioid narcotics. Even though, this pharmacotherapy causes many undesirable side effects ranging from mild constipation to altered mental status. It is also reported that some of the opioids may produce dysphoric effect symptom which can expressively impact life quality of the patients with pancreatic cancer.¹¹ On the other hand, celiac plexus neurolysis is accomplished in pancreatic carcinoma patients who have sever obstinate pain that is not properly controlled on other pharmacotherapy but this procedure is invasive and it required any of medical imaging guidance like ultrasound, CT scan or endoscopy. It is suggested by retrospective case series that early uncontrolled pain can be achieved complete pain relief up to 70 to 90% in patients by using technique Neurolytic celiac plexus blockade (NCPB).¹² However a meta-analysis of randomized controlled trials of NCPB study reported that the overall advantage was lesser and there is only 6% pain reduction in the mean visual analogue pain score compared with baseline pain score.¹³ So it is clear that its time evaluate new techniques for treatment, pain palliation and to improve life quality of patients with advanced staged pancreatic carcinoma.

High intensity focused ultrasound (HIFU) is a noninvasive technique which is guided by medical imaging like Ultrasonography (USG) or magnetic resonance imaging (MRI) is thermal ablation method that uses an extracorporeal transducer to deliver high intensity ultrasound energy to induce an

increase of temperature in a abruptly delineated region. In this HIFU technique, Ultrasonography (USG) or magnetic resonance imaging (MRI) is used to guide anatomically to the targeted region of carcinoma and to provide real time feedback during ablation.¹⁴ HIFU provides two types of effects on target tissue, first one is thermal damage as well as mechanical damage to cancer cells. During the HIFU ablation therapy, the targeted cancer cells are heated up to 60 to 80 degree centigrade range within certain time duration, inducing liquefaction and coagulation necrosis in the cancer tissue, with the principle of thermal ablation of cancer tissue without affecting the neighboring healthy cells.^{14,15} In this technique, the temperature is controlled between certain degree centigrade so it should not cause an immediate necrosis of the cancer cells, but firstly it causes intracellular denaturation of protein, and thus of the stored pancreatic enzymes, followed by cellular degeneration and necrosis. In HIFU technique, thermal fixation phenomenon efficiently reduces the risk of pancreatitis as a complication of the procedure.¹⁵ Besides the thermal effects of HIFU, there are also mechanical effects generated by high intensity acoustic energy that cause cavitation, micro-streaming and radiation force. Cavitation effects is generated from the oscillating motion of gas-filled bubbles (stable cavitation); these bubbles coalesce and collapse under higher ultrasound field energy, causing a shock wave confined to the microenvironment (inertial cavitation).^{16, 17} Micro-streaming is a phenomenon which produces consequence of stable cavitation occurring close to fluids,

producing shear stress that transiently damages the cell membrane.¹⁸ The last one is radiation force which results from the absorption or reflection of the acoustic waves by the encountered medium and can result in cellular apoptosis.^{16, 17}

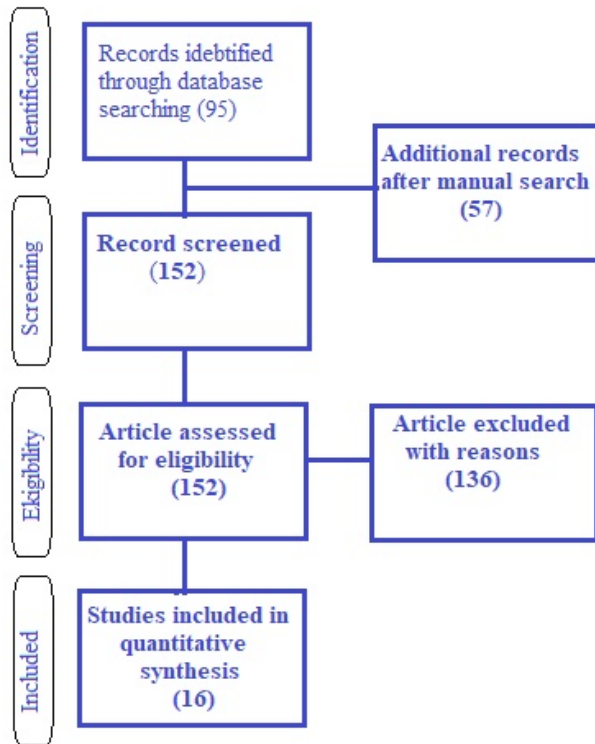


Figure 1: PRISMA Diagram

Although there are several narrative reviews, systematic meta-analysis reviews and literature reviews done in past. Day by day, there are several developments are done in HIFU technique to improve accuracy in treatment and other regarding approaches to obtain best therapeutic effect. Our aim of this meta-analysis review to evaluate most recent which are only last 10 year literatures on the role of HIFU in pain palliation in advanced staged pancreatic cancer and to compare their methodologies used for treatment procedure, with the goal of providing a comprehensive resource of comparable data for the design of future studies.

Materials and Methods

Article search: In this meta-analysis literature review, we performed systematic electronic search on the PubMed Medline database through March 2021 for most recent literature since last 10 years. That electronic search was performed with these following keywords: HIFU, Pancreatic cancer and Pain. These words are used on search portal on different ways of format so there is no chance of missing single literature. All the similar words like pancreatic and pancreas were searched in the search engine. The literatures which are not in English are converted to English by electronically available language converter. Manual search was also performed in the references of selected studies because some of the research published in this area was not written in English which does not appear in PubMed and reviews were completed to supplement the electronic search.

Exclusion and inclusion criteria were fixed before selecting the literature. The exclusion criteria are as follows

- 1) Reviews literatures
- 2) Studies which were not included pancreatic carcinoma
- 3) Preclinical literatures
- 4) Literatures without pain assessment
- 5) Literatures other than primary pancreatic carcinoma
- 6) Literatures with less than 3 patients
- 7) Literatures in which pancreatic carcinoma related pain assessment was not reported

Full-text articles were screened. Translation of articles written in Chinese was done by Baidu language translator website. Selection of literatures was done according to PRISMA (model 19) {Fig. 1}.

Statistical analysis

Among all searched literatures, we selected 16 studies last 10 year (most recent) which met our aim of literature review analysis. A meta-analysis of all selected papers on “HIFU therapy for pain palliation in advanced stage pancreatic carcinoma: A Meta-Analysis with recent studies” defined as evaluation of pain intensity of patients with pancreatic carcinoma either change or no change after treated with High Intensity Focused Ultrasound (HIFU), was carried out. We carried out different statistical analysis methods like a random effect model with inverse variance technique was used for t^2 and Q test for heterogeneity among the research papers. The other statistical factor I^2 was also calculated to evaluate percentages of the total variability in the different effect size estimates that can be attributed to heterogeneity among the true effects. Statistical tool Rev-Man 5.4 software was used to evaluate and complete this meta-analysis.

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) model

Results

Search results and characteristics of the included studies

More than one hundred fifties literatures were found in primary electronic search in PubMed website and manually as we mentioned previously in the methodology. All these literatures were printed and identified manually. According to exclusion criteria, only 16 papers were selected which are published in last 10 year. Some of our papers are available in other language than English which were translated in English

with the help of recently available language translator website. Selected literatures are published between from 2014 to 2021. All selected literatures were included in the statistical analysis. Most of the studies are from china and other from Italy, Germany, Bulgaria, and Japan.

The demographic and clinical characteristic data are included in Table 1. Total 687 patients of all selected studies are pancreatic carcinoma. One of the studies which are listed 15th number in table included 55 patients. In this study, patients were divided in two group that were L group and H group. In L group, 23 patients were included which were underwent Low power cumulative HIFU treatment. In H group, 32 patients were included which were underwent general HIFU treatment. Except that remaining all patient were received HIFU treatments. So in total 687 patients, 664 patients were received HIFU treatment with different pre decided treatment like chemotherapy, radiotherapy, surgery and others and 23 patients were received low power cumulative HIFU treatment. The largest population included in one series was 120 whereas the lowest population included in one series was 7 patients. All total 687 patients with patients included were supposed to unrespectable. All the 16 studies underwent HIFU with different pre-defined supportive treatment methods i.e. chemotherapy, radiation therapy and surgery. Pre-treatment and post-treatment diseases staging and recovery evaluation was done by Ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Histology report. Among the all listed studies in table 1, Number 14

literature (Study) included 2 patients with first stage and 28 patients with second stage of pancreatic carcinoma. One more study which is listed in number 13 in table 1 included 4 patients with second stage pancreatic carcinoma. Except these two remaining all studies only included third and fourth stage pancreatic carcinoma patients. Other information like staging of the patients, site of the carcinoma, different treatment modalities received by patients and size of tumor are listed in detail in table 1.

Clinical outcome

Among all patients 687 patients treated with HIFU, 612 patients observed reduction in pain relief either complete or partial. Based on this result, 89.08% patients experienced pain relief after receiving HIFU treatment which is listed in detail in table 2. The random effect calculated of proportion of patients with pain reduction was 0.89 (95% CI: 0.76-86) which is shown in fig 2. Probably the lower boundary of 76% is little bit conservative but it gives more accurate and true result.

The I² of the all included studies was calculated 40%. This result shows that multiple effect sizes are feasibly present; this may be due to different in more variability in patient patients, treatments, and other parameters in the literatures.

In our study, the Q test p-value was calculated 0.026, confirmed that important sign of heterogeneity among all studies.

Pain evaluations listed in all selected 16 literatures are not similar and also follow up periods are not consistent, with different or not certain assessment intervals. Among all studies, most of the studies adopt NRS (Numerical Range Scale) for pain relief

evaluation whereas small number of studies are adopted VAS (Visual Analog Scale) ranging from 0 to 10. In both of above pain relief evaluation methodology, 10 indicate maximum and intolerable pain whereas 0 indicate no pain at all. There is also another difficulty with these literatures that is use of painkillers which patients used to take before and after treatment but it should be mandatory to discontinue the analgesic medicine. Most of the literatures reported clearly about this but small number of literatures are not reported that. Due to this heterogeneous reporting in detail about analgesic in these literatures, it is not possible to quantify these pain evaluation modalities. The details about all clinical outcomes are listed in table 2.

There are not such well-defined criteria for tumor response previously so there is also heterogeneity in tumor response in different studies. This literatures review was also not aimed to include tumor response evaluation so our paper selection was not affected by either tumor response is reported or not reported. Most of the literatures reported tumor response evaluation but there are not similarities in all literatures. The modalities of assessment for tumor response evaluation, its results after HIFU ablation are briefly summarized in table number 3 (Table 3). Tumor response evaluation criteria are also depending upon different medical diagnostic imaging system. For example, if Ultrasonography is used, the tumor response evaluation criteria is change in grey scale on the other hand if Magnetic Resonance Imaging is used the tumor response evaluation criteria depend on contrast enhancement reduction, tumor size reduction

(tumor volume). Tumor response evaluation results are categorized in for terms that are CR (Complete Response), PR (Partial Response), SD (Stable Disease), and PD (Progressive Disease).

The adverse are generally categorized in three terms i.e. mild, moderate and sever but sometimes these are also categorized as minor adverse effects and major adverse effects. In this review, the adverse effects are categorized as minor and major. The summarized details about adverse effects are listed in table number 2.

The most common mild adverse effect in the patients receiving after HIFU were mild to severe abdominal pain, cutaneous or muscular edema, and first and second degree skin burns. Most of the patients reported only minor adverse effect after receiving HIFU treatment and smaller size of patients reported major complication which is summarized in Table 2.

High Intensity Focused Ultrasound (HIFU) Technique

The patient preparations of patients are reported differently in different literatures but the common preparations are similar to pre-operative checkup and preparations before HIFU performance. Almost in all literatures, it is reported that medical history, physical examination and biochemical laboratory blood tests are collected. Bowel preparations of patients are also reported differently, NPO (Nothing by mouth “NIL PER OS”) is reported from 12 to 24 Hours prior to the HIFU performed. Shaving and cleaning of abdominal area prior to HIFU ablation was reported in all most all literatures to avoid skin burns due to abdominal skin hair. A special pad was used

in between the ultrasound transducer and abdominal skin to dislocate gastro-intestinal bowel loops from the ultrasound beam pathway. In some of Chinese literatures reported additional procedures which were using laxatives, having liquid diet, some traditional Chinese medication,^(21,22) and in one literature, it was reported about stomach tube to inject antifoaming agents and blind air bubbles.²³ The patients with obstructive jaundice went through chole-cysto-jejunosotomy or biliary stenting for temporary relief.

Although, now a day's MRI-guided HIFU devices are becoming more familiar in medical field because of its better accuracy in treatment procedure but it is highly expensive. In spite of accuracy of MRI-guided HIFU device, Most of the researches were performed by using US-guided HIFU equipment. Chongqing Haifu equipment (JC Model) and Yuande Biomedical Beijing HIFU equipment (FEP-BY) are mostly reported in the literatures. Both of the equipment (Chongqing Haifu and Beijing HIFU) are mostly similar like both used Ultrasonography for guidance for treatment (tumor ablation) but the principle difference is in the pattern of delivery and intensity of ultrasound waves.

Chongqing Haifu equipment system perform continuous high intensity focused ultrasound wave in the range of five to twenty kW/cm² which allow single session treatment. In this type of equipment, Patients requires sedation or general anesthesia and hospitalization of patient. On the other hand, Beijing HIFU (FEB-BY) system produce pulsed-wave low intensity focused ultrasound i.e. three kW/cm². Due to the pulse wave, the patients must

require underwent for multiple session treatment i.e. from four to seven times. But there is no need of sedation and general anesthesia for the procedures. One of study was performed on an MRgFUS system model Exblate 2100 sub model company inSightec, Haifa, Israel. The model was equipped with MRI of 3.0 Tesla. The ultrasound frequency used in this model range from 0.95 to 1.35 MHz and energy from one hundred to seven thousand two hundreds Joule (J). This type equipment setting, patients' needs anesthetized to avoid overcome motion artifacts.²⁴

Summarized regarding features of different HIFU systems used in all selected studies for this review are listed I table number 4 (Table 4).

According to the equipment available in their department, sedation, general anesthesia, local anesthesia and epidural anesthesia were performed as we mentioned above paragraphs. Chongqing USgFUS and MRgFUS performed single session HIFU ablation whereas Beijing USgFUS performed multiple session HIFU ablations. Post-operative cares were performed according to adverse effects developed and post diagnostic test results like USG, CT, MRI, Biochemical blood tests. The tumor ablation and tumor response are also evaluated after HIFU procedures.

Discussion

The principle phenomenon of pain mechanism is somehow similar in human body except some exceptional cases. In the case of pancreatic carcinoma, the pain origin is generated by different factors. First factor is infiltration of tumor up to nerves, second factor is compression of tumor mass and

third or final factor is inflammatory reaction in human body excited by the distance metastasis (25, 26). The principle and mechanism regarding pain palliation by HIFU treatment are not significantly described. There are 3 possibilities may be assumed and have been proposed. These possibilities are as follows; i) damaging of those nerves which are intervening tumor by thermal energy of ultrasound, ii) reduction in tumor size or tumor volume after HIFU treatment which effect in reduction mass effect, and iii) thermal energy of ultrasound deactivate the fibers of celiac plexus which transmit the pain sensation to brain.¹⁰

Our literature review advices that High Intensity Focused Ultrasound (HIFU) is really very effectual for pain palliation in patients with pancreatic cancer. There are lots of heterogeneity in all selected studies in our review, despite of that 89.08% patients achieved relief from pain either complete or partial after HIFU treatment and in follow up study most of the patients achieve better quality life. Some case reports were also reported promising result in pain palliation in the patients with pancreatic carcinoma but these literatures are not included in our review due to smaller sample sizes but very consistent with our outcome on the safety and efficacy of High Intensity Focused Ultrasound (HIFU) for pain relief.⁽²⁷⁻³¹⁾ There are lots of literatures which reported long follow up for both pain palliation and quality life survival rate. One of the longest follow up period was reported by Wu et al. They reported that there is no pain seen up to 17 months after HIFU ablation (24).

Table 1 Characteristics of the included studies on HIFU therapy in Pancreatic Cancer

SN	Author, Date	Type of Study	Number of Total Patients	Age (mean)	Tumor Characteristics (#pt)			Image guidance	Treatment	HIFU Device	Other Treatments
					Stage	Location	Size(Mean)				
1	Anzidei2014	Pros	7	67	Stage III(7)	Head	Tumor Volume 20±5.6ml	MRI	HIFU	ExAblate 2100; InSightec	CT/RT before HIFU(7) Previous failed celiac Plexus alcoholization(7) Continuous CT after HIFU
2	Sofuni2014	Pros	30	64	Stage III (16) Stage IV(14)	Head(13) Uncinate4 Body(9) Tail(1) Other (3)	Tumor Size 31.7±1.7	US	HIFU	Pulsed wave HIFU, FEB-BY01	Pre HIFU Operation(3) Chemotherapy(28) Radiation Therapy(4) Interventional Radiology5 After HIFU Chemotherapy(24) Operation(2) Interventional Radiology5
3	Marinova 2016a	Pros	13	66.2	Stage III(5) Stage IV(8)	Head(12) Body/Tail(4) Head and Body(5)	Tumor size 31.7±1.7	US	HIFU	Continuous wave HIFU, Model-JC HIFU	Chemotherapy previous and concurrent with HIFU(10) RT + Surgery(1) Non-Therapeutic laparotomy(5) Plastic or metal stents for cholestasis(2) P/C Biliary Drainage
4	Li YJ, 2016	Pros	16	62.3	N/A	Head(9) Body(7)	Max Diameter 3.7cm	US	HIFU + Radiotherapy	N/A	N/A
5	Li X 2016	Retro	120	50.13	N/A	Head(31) Other(30)	N/A	US	HIFU + Chemotherapy	Continuous wave HIFU, Model-JC HIFU	N/A
6	Strunk, 2016	Pros	15	66.9	Stage III(6) Stage IV(9)	Head / Body(3) Body(5) Head(7)	N/A	US	HIFU	Continuous wave HIFU, Model-JC HIFU System	Pre HIFU Chemotherapy(13) Non-Therapeutic laparotomies(5) Surgery/Radiotherapy(1) Radiotherapy(2) Concurrent chemotherapy(13) Biliary drainage
7	Lv, 2016	Pros	45	59	Stage III(29) Stage IV(16)	Head(22) Tail and Body(23)	Tumor Size range 8.1x7.5x5.8-2.6x2.6x1.8cm	US	HIFU + Chemotherapy	Continuous wave HIFU, Model-JC200 HIFU	N/A
8	Marinova, 2016b	Pros	20	68	Stage III(6) Stage IV(12)	N/A	Tumor Volume 35.2±18.6ml	US	US	Continuous wave HIFU, Model-JC HIFU	Concurrent chemotherapy-16 Chemotherapy after HIFU(2) Metal or plastic bile duct stent-6
9	Shi Y-2017	Pros	71	<55-13 >55-58	Stage-III	Head (35) Body/Tail (37)	NA	US	HIFU	FEB-BY02 Yuande Biomedical	Chemotherapy Radiotherapy
110	Marinova M 2018	Pros	50	65±9.7	Stage-III-19 IV-29 Recurrence-2	Head - 27 Tail+Body - 10 Head+Body -13	26±15.9	US	HIFU	Chongqing HAIFU	Chemotherapy – 42 Radiotherapy – 5 Both - 2
11	JiYongshuo, 2018	Pros	87	68	N/A	Head (52) Body (29) Tail (6)	Median (3.7)	US	HIFU	HIFU INT-9000 System	Before HIFU Chemotherapy (26) Radiotherapy (6) Surgery (12) None (31)
12	Zhu B. 2019	Retro	86	60 (26-83)	Stage-III (23), IV (63)	Head (57) Body (23) Tail (6)	22.9.7 (4.5)cm	US	HIFU	Chongqing HAIFU	Combined with HIFU Chemotherapy (38) Radiotherapy (1) Both (17) None (30)
13	Tao S-2019	Retro	38	69	Stage II-4 III-15 IV-19	Head - 16 Body - 13 Tail - 9	4.2±1.6	US	HIFU	HIFU INT-9000 System	Chemotherapy

14	Thudium M 2020	Pros	71	62.8±9.9	Stage I – 2 II – 28 III – 29 IV – 4	NA	27.3±20.4 (Volume ml)	US	HIFU	Chongqing HAIFU	Chemotherapy Radiotherapy Both
15	Zhao J-2021	Retro	55	60.9±10.5 64.8±12.9	Stage-III	Head – 14+17 Body – 5+4 Tail – 4+11		US	HIFU	FEPBY02 Yuande Biomedical	Chemotherapy
16	Marinova M 2021	Pros	80 (50+30)	62±8.8	Stage III – 30 IV – 46 Rec – 4	Head – 39 Body – 21 Tail – 20		US	HIFU	Chongqing Haifu	Chemotherapy Radiotherapy Both

Table 2 Summary of the results of the included studies on HIFU therapy in pancreatic cancer

S N	Author, Date	P a i n Evaluation	Number of patients with pain at baseline	Number of patients with pain relief	% of patients with pain reduction	Pain scale 0-10		HIFU related adverse effects	
						Before HIFU	After HIFU	Minor	Major
1	Anzidei, 2014	P a i n Scale	6	6	1.00	7±1	3±1	None	None
2	Sofuni, 2014	P a i n Scale	21	16	0.76	N/A	N/A	Mild pancreatitis (1) Pseudocyst formation (2)	None
3	Marinova, 2016a	P a i n scale	13	10	0.77	N/A	N/A	Mild to severe abdominal pain (7), Skin Burn II (1), Increase in pancreatic lipase(3)	S e v e r e abdominal pain required hospitalization
4	Li YJ, 2016	P a i n scale	16	15	0.94	5.1±2.2	3.3	None	None
5	Li X, 2016	P a i n scale	61	35	0.57	6	N/A	Slight skin burn	None
6	Strunk, 2016	Pain Scale + use of opioids	15	12	0.80	N/A	N/A	Transient S/C edema (9), Skin Burn II (1), S/C Sclerosis (1). Lipase Increase (3)	None
7	Lv, 2016	Memorial P a i n , Assessment Card	23	15	0.65	N/A	N/A	None	None
8	Marinova, 2016b	P a i n Scale	20	15	0.75	3.75±2.07	1.60±1.35	Mild severe abdominal pain (13), C u t a n e o u s / subcutaneous edema (11), Subcutaneous tissue indurations (1), Skin burn IIa (1), Increase in lipase (3)	None

9	S h i Y-2017	NRS Pain Score	71	66	92.96	M a l e 0.54 F e m a l e 1.24	0.20 0.08	Only minor	None
10	Marinov a M 2018	P a i n Score	42	50	84	3.5	1Week - 2.6 6Week – 2.1 3Month – 1.6 6Month – 1.5	M o d e r a t e cutaneous & muscular edema, Pancreatic lipase increase	None
11	J i Y 2018	VAS Pain Score	87	87	1.0	4.62(±SD 2.07)	3.2(±SD 1.21)	Abdominal pain(7), fever(7), nausea(5), rash(4), elevated C R P (2) , Leucopenia(2), Subcutaneous nodule (2)	None
12	Zhu B. 2019	NRS Pain Score	76	74	0.97	6.20±1.5	2.20±1.9	Transient fever(3), Abdominal Pain(13), Skin burn(6), Amylase Elevation(2)	None
13	T a o S-2019	VAS Pain Score	30	27	90	5.86±2.13	2.03±0.51	L e u k o p e n i a , Thrombocytopenia, H e m o g l o b i n reduction H e p a t i c dysfunction Renal dysfunction N a u s e a a n d vomiting P e r i p h e r a l n e r v e toxicity	
14	Thudium M 2020	N R S P a i n Score	71	61	86	4.49±2.59	1day- 2.65 ± 2.22 (0-9) 6 w e e k s 2.32 ± 1.91 (0-7) 3 m o n t h s 2.31 ± 1.76 (0-6)		
15	Zhao J 2021	NRS Pain Score	55	50	91	(1-3)LIFU-7 HIFU-17 (4 - 6) L I F U - 6 HIFU-9	(0) L I F U - 10 HIFU-10 (1 - 3) L I F U - 2 HIFU-12 (4 - 6) L I F U - 1 HIFU-1	Fever, Abdominal pain, Skin burns	

16	Marinova M 2021	NRS Pain Score	80 (50 & 30)		Stro ng Pain Relief	4.39	1Month 3.3 3Month 2.82 6 Month 2.21		
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Table 3 Tumor response

SN	Author, Date	Tumor response			Complete response	Partial response	Stable disease	Progressive disease
		Imaging evaluation Method	Parameter evaluated	Result #pt				
1	Anzidei, 2014	CT and MRI	Changes in density and intensity, Contrast enhancement, non Perfused volume (at least 6%)	6				
2	Sofuni, 2014	CT	WHO Criteria	26	0	4	22	4
3	Marinova, 2016a	US	Lack of contrast enhancement	13				
4	Li YJ, 2016	CT,MRI, US	RECIST	11	0	7	4	5
5	Li X, 2016	CT	RECIST	16	1	15	N/A	N/A
6	Strunk, 2016	CT,MRI, US	Tumor ablation rate (NPV/total volume)	8				
7	Lv, 2016	CT	RECIST	18	0	10	8	0
8	Marinova, 2016a	MRI, CT	Tumor volume reduction	N/A				
9	Shi Y-2017	NA	NA	NA	NA	NA	NA	NA
10	Marinova M 2018	MRI, CT	Tumor volume reduction	46				22
11	J Yongshuo, 2018	CT, MRI	RECIST	87	7	25	36	19
12	Zhu B. 2019	CT, MRI	RECIST (83.1%)	83	3	66	11	3
13	Tao S-2019	CT MRI	Tumor size	38	1	6	22	9
14	T h u d i u m M-2020	MRI, CT	Tumor volume reduction	71				
15	Zhao J-2021	US,CT	Tumor size	54	0	1 & 0	26 & 25	2 & 6
16	Marinova M 2021	CT MRI	Tumor volume reduction	80				

RECIST – response evaluation criteria in solid tumors

Table 4 HIFU Technical Parameters

SN	Author, date	HIFU Device	HIFU Transducer features	I n t e n s i t y / frequency	Acoustic output power	Continuous or pulsed-wave	Number of sessions
1	Anzidei, 2014	ExAblade 2100; InSightec	Diameter 12cm; radius of curvature 16cm; focal distance 6-20cm	0.95-1.35 MHz	N/A		Single session
2	S o f u n i , 2014	F E B - B Y 0 2 HIFU System	Aperture of the ultrasound array 37cm; radius of curvature 25.5cm	1.1 MHz	Input electric power:0.5 – 2KW	pulsed	2.7±0.1SD
3	Marinova, 2016a	Model JC-HIFU System	20cm diameter; focal length 15cm	0.8 MHz	R a n g e : 8 0 - 4 0 0 W average 344±72 W (200-400)	continuous	Single session
4	Li YJ, 2016	N/A	N/A	0.8 MHz	300W	N/A	N/A
5	Li X, 2016	Model-JC HIFU	N/A	N/A	N/A	N/A	Single session
6	S t r u n k , 2016	Model-JC HIFU	Diameter 20cm; focal length 15cm	0.8MHz	200-400W	continuous	Single treatment expected, but additional treatments can be added when necessary
7	Lv, 2016						
8	Marinova, 2016b	Model JC-HIFU System	20cm diameter; focal length 15cm	0.8MHz	N/A	Continuous	Single session

9	Shi Y-2017	F E B - B Y 0 2 HIFU System	Aperture of the ultrasound array 37cm; radius of curvature 25.5cm	1.1 MHz	Input electric power:0.5 – 2KW	pulsed	2.7±0.1SD
10	Marinova M 2018	C h o n g q i n g Haifu	20cm diameter; focal length 15cm	0.8 MHz	R a n g e : 8 0 - 4 0 0 W a v e r a g e 3 4 4 ± 7 2 W (200-400)	continuous	Single session
11	J i Yongshuo, 2018	HIFUINT-9000 system	practice-focused sphere, 3 X 3 X 8 mm ³		5–10 kW/cm ²	HIFU times at each lesion, 8– 10 times	
12	Zhu B. 2019	Model JC-HIFU System					
13	Tao S-2019	HIFUINT-9000 system	practice-focused sphere, 3 X 3 X 8 mm ³		5–10 kW/cm ²	HIFU times at each lesion, 8– 10 times	
14	Thudium M 2020	C h o n g q i n g Haifu	20cm diameter; focal length 15cm	0.8 MHz	R a n g e : 8 0 - 4 0 0 W a v e r a g e 3 4 4 ± 7 2 W (200-400)	continuous	Single session
15	Zhao J 2021	F E B - B Y 0 2 HIFU System	Aperture of the ultrasound array 37cm; radius of curvature 25.5cm	1.1 MHz	Input electric power:0.5 – 2KW	pulsed	2.7±0.1SD
16	Marinova M 2021	C h o n g q i n g Haifu	20cm diameter; focal length 15cm	0.8 MHz	R a n g e : 8 0 - 4 0 0 W a v e r a g e 3 4 4 ± 7 2 W (200-400)	continuous	Single session

Another author Anzidei et al also follow up for 6 months and they also reported that there is less inclination in pain for 6 months.³²

There is another two literatures reported by Wang et al. and Li YJ et al. that a median pain relief time of 10 weeks and 5.6 months, respectively.^{33,34} There are another three literature reported that confirm pain relief with 3 months follow up.^{23, 35, 36}

The reason behind proposing HIFU treatment is even opioids fail to control pain palliation after neurolytic celiac plexus blockade (NCPB). In NCPB procedure, anesthetics and neurolytic substances like ethanol or phenol are injected to block neurolytic celiac plexus.²⁵ There is another questionable thing is actual pain reduction is not consistent; it is reported in some studies.^{13, 37} Response rates were initially reported as high as 70-90%.¹² A meta-analysis review was reported on NCPB with 5 randomized control trials (RCT) and their result was just 6% pain palliation.¹³ There was also reported that NCPB can also reduce opioids use and related side effects.³⁷⁻³⁹ A double blinded RCT comparing NCPB to a placebo, by

Wong et al. and reported that there is no differences.⁴⁰

Regarding NCPB, Most of the literatures reported a short duration of pain palliation and follow up to three months.^{41, 42} One more thing was reported that if NCPB repeated then efficacy reduced up to almost fifty percent [repeated NCPB 29% Vs initial NCPB 67%].⁴² There are so many side effects of NCPB but most commons are local pain (96%), transient diarrhea⁴⁴, and hypotension (36%).^{12,41} It is reported that severe adverse effects are only occur in two percent of patients with NCPB but major severity are neurological and paraplegia this is really risky for all concern.

Due to non-invasive property of HIFU, it became a good alternative for quick pain palliation in pancreatic carcinoma with high safety profile.¹⁰ One study reported that HIFU was very good in pain relief after failure of NCPB.²⁴ It is proven that HIFU has capability to improve quality life by reducing pain score in pancreatic carcinoma and also good in controlling local tumor with extra advantages that enhances the effect of

chemotherapy to improve therapeutic approaches.¹⁵

In comparison with NCPB, HIFU has lower side effect, high safety approaches and only 0.9% severe adverse effect in our meta-analysis. Jung et al reported regarding adverse effects of HIFU ablation of pancreatic patients which were listed in their study. Minor complications among them were skin redness at the region of treatment and among the total patients population 35, one patient reported with third degree skin burn and three patients were reported with fistula formation which is very less as compare with other modalities.⁴³

In our literature review, the common adverse complications are reported is mild to severe abdominal pain which is followed by various degrees of skin burns. Except one patient need hospitalization, remaining were self-controlled. The worse complication reported in our review is bowel perforation. As seen in chemotherapy and radiation therapy, there are systemic side effects. But in HIFU, there are not such systemic side effects. Mild and transient pancreatitis classified as minor adverse effect and due to this there is elevation is noted increase of lipase on blood analysis and there are also pancreatitis noted without any signs and symptoms. Unlike chemotherapy or radiotherapy, there is no risk for poor wound healing or secondary malignancies in HIFU ablation.

In selected papers, tumor response evaluations were assessed by using different imaging methods. The most of the studies underwent tumor response evaluation whereas list of the studies not reported tumor response evaluation. From this analysis, we concluded that there is no correlation

between pain palliation and tumor response. These two variants are totally independent from each other but we cannot totally deny in practical outcome. Xiong et al reported that pain relief percentage is up to 88% after performing HIFU ablation on the patients with pancreatic carcinoma and only 76.2% patients reported tumor response.⁴⁴ Similarly, Zhao et al. reported pain palliation 88.2% after performing HIFU ablation on the patients with pancreatic carcinoma with tumor response too where as 35% patients' tumor response was stable diseases (SD) or progressive disease (PD).⁴⁵ The main reason behind showing poor tumor response evaluation after HIFU which is not real due to increased local edema but in real there were good tumor response but it seems that there is no change in tumor volume so it is bias to evaluate HIFU efficacy on the basis of either pain palliation effect or tumor response.^{46, 47}

Chemotherapy has poor therapeutic effect on pancreatic adenocarcinoma because pancreatic adenocarcinoma is comparatively poorly vascular and is completely enclosed with thick fibrous ring that restrict the infiltration and transmission.

Recent researches concluded that HIFU may have a harmonious effect with chemotherapy, enhance the therapeutic effect of chemotherapy to tumor and also reducing the systemic toxicity produced by chemotherapy. This effect was also reported by another study and they concluded that HIFU improve the therapeutic effect of chemotherapy in the patients with pancreatic carcinoma.¹⁵ Lv et al. compared the tumor response in two groups Chemotherapy alone Vs. Chemotherapy combination with HIFU in

one study and concluded that combination group evaluation was 65.2% in compare with only chemotherapy evaluation 31.8%. They also concluded that disease control rate was high too in HIFU group (78.2% vs. 59%), which was not statistically different. It is also reported that there were was improvement in survival rate in combination group.⁴⁸ Li Xiao et al concluded in one study that there were better overall survival rate, and better pain palliation rate.⁴⁹ It is observed that pain palliation has enhanced great impact on quality life of the patients but there are further researches should be performed to assess the significant about the survival rate. There are a lots of literatures reported about survival rate in the patients with pancreatic carcinoma after HIFU ablation. Vidal et al. reported that the HIFU and Chemotherapy combination treatment improve the survival rate up to 3.4 years in the patients with highly advanced stage (III and IV stage) pancreatic carcinoma. They also reported that there were significantly high survival rate in 33.5% the patients with pancreatic carcinoma still alive at 4.2 years.⁵⁰

Most of the literatures included in our review are not supposed to assess the survival rate in the patients with advanced staged pancreatic carcinoma. The studies which also concluded about survival rate response of HIFU in our study, after meta-analysis, it can be concluded that overall survival rate are excellent after getting treatment of HIFU in the patients with advanced staged pancreatic carcinoma.

Due to the heterogeneity in follow up periods regarding survival rate and there was neither definition of a starting point nor duration of follow up. After evaluating all papers, we

concluded that some literatures reported survival after only HIFU and some reported after HIFU combination with chemotherapy in the patients with advanced staged pancreatic carcinoma. So it is very clear, further studies are needed to evaluate survival rate in the patients with advanced staged pancreatic carcinoma.

There is principle limitation in our review is the lack of RCT and also considering the data are not similar even reported by single literatures, which sometimes create comparative results are not reasonable. There were was deference in pain palliation evaluation, tumor response evaluation and techniques used for HIFU ablation. Even it is also not possible to calculate quantitatively pain palliation due to heterogeneity in presentations and most of the studies did not use a numerical pain score to assess the difference at baseline and follow up studies. There was no consistency in duration of pain, interval of pain that one was easy to estimate and quantitatively calculate. There was considerable heterogeneity in use of analgesic drug use. A application of different analgesic drugs, some advices to continue analgesic after HIFU treatment, some advice to change the analgesic drugs. These are the main difficulties in our literature review. On the same way, there was similar heterogeneity in evaluation in tumor response evaluation criteria in difference literatures. On the other way, there should be update a fixed protocol for evaluate the survival rate evaluation that will be very beneficial for future studies. Homogeneity is required in the exclusion and inclusion criteria for treatment in in the patients with advanced staged pancreatic carcinoma. It

will improve to make data more homogeneous and compatible.

Most of the available studies results involve with USgFUS and only few studies results are available experience with MRgFUS. In the USgFUS, ultrasound is used for both guiding and treating the tumor and there is possibility to potential obstruction of ultrasound beam pathway from each other which may effect on accuracy in in the patients with advanced staged pancreatic carcinoma. There is lack of real time thermometry in USgFUS that also effect on accuracy. There were several literatures available which reported that there is massive improvement in newly developed HIFU system either USgFUS or MRgFUS. MRgFUS can provide real time thermometry which improves the treatment accuracy. MRgFUS is really promising because MRI guiding capacity is excellent due to better tissue contrast allowing definition of the tumor.^{51, 52}

Till now, most of the researches were experienced wit USgFUS, there are many improvement should be required like standardization in energy, power and other parameters to gain the better accuracy in treatment and lesser risk to patients. There are also difference in biological effect obtain from continuous ultrasound wave and pulsed ultrasound wave to the tumor and the therapeutic output became different in the patients. There should be further comparisons needs to evaluate the efficacy of HIFU alone and with combination with chemotherapy and radiotherapy in the patients with advanced staged pancreatic carcinoma.

At last, it is concluded that there is necessity

of uniformly arranged researches are required to perform to obtain accuracy and quantitative results. A clinical registry of treatment in the patients with both advanced stage and early stage pancreatic carcinoma is planned. It will provide analytical tool to evaluate pain palliation, accuracy, tumor response, and overall survival in the patients with pancreatic carcinoma, which still a poorly treated aggressive tumor bearing a poor prognosis.

Conclusions

Although the literature is heterogeneous, our study supports that High Intensity Focused Ultrasound is a potent tool for pain palliation in unresectable pancreatic cancer. The potential role of HIFU requires further well designed studies to confirm its efficacy, safety and advantages compared to other palliative techniques.

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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