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A meta-analysis evaluating the role of high-intensity focused ultrasound (HIFU) as a fourth treatment modality for patients with locally advanced pancreatic cancer

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Abstract

Background This study aimed to evaluate the outcomes of high-intensity focused ultrasound (HIFU) on patients with advanced pancreatic cancer.

Methods A literature search was performed in PubMed, Scopus and Cochrane databases, in accordance with the PRISMA guidelines. The Odds Ratio, Weighted Mean Difference, and 95% Confidence Interval were evaluated by means of the Random-Effects model.

Results Nineteen articles met the inclusion criteria, incorporating 939 patients. This study reveals that patients in the HIFU group presented increased median overall survival (OS), along with higher OS at 6 and 12 months after treatment compared with the control group ($p < 0.05$). Furthermore, patients treated with HIFU in conjunction with chemotherapy presented reduced levels of pain ($p < 0.05$) compared to the traditional treatment group. In addition, HIFU contributed to significant tumor responsiveness, in terms of CA19-9 reduction ($p < 0.05$). Finally, HIFU was a considerably safe treatment modality with a low incidence of complications.

Conclusion These outcomes suggest that HIFU is a feasible and safe treatment modality for patients with advanced pancreatic cancer and provides enhanced outcomes regarding survival and quality of life. Given the lack of a significant number of randomized clinical trials, this meta-analysis represents the best currently available evidence. New randomized trials assessing HIFU are necessary to further evaluate their outcomes.

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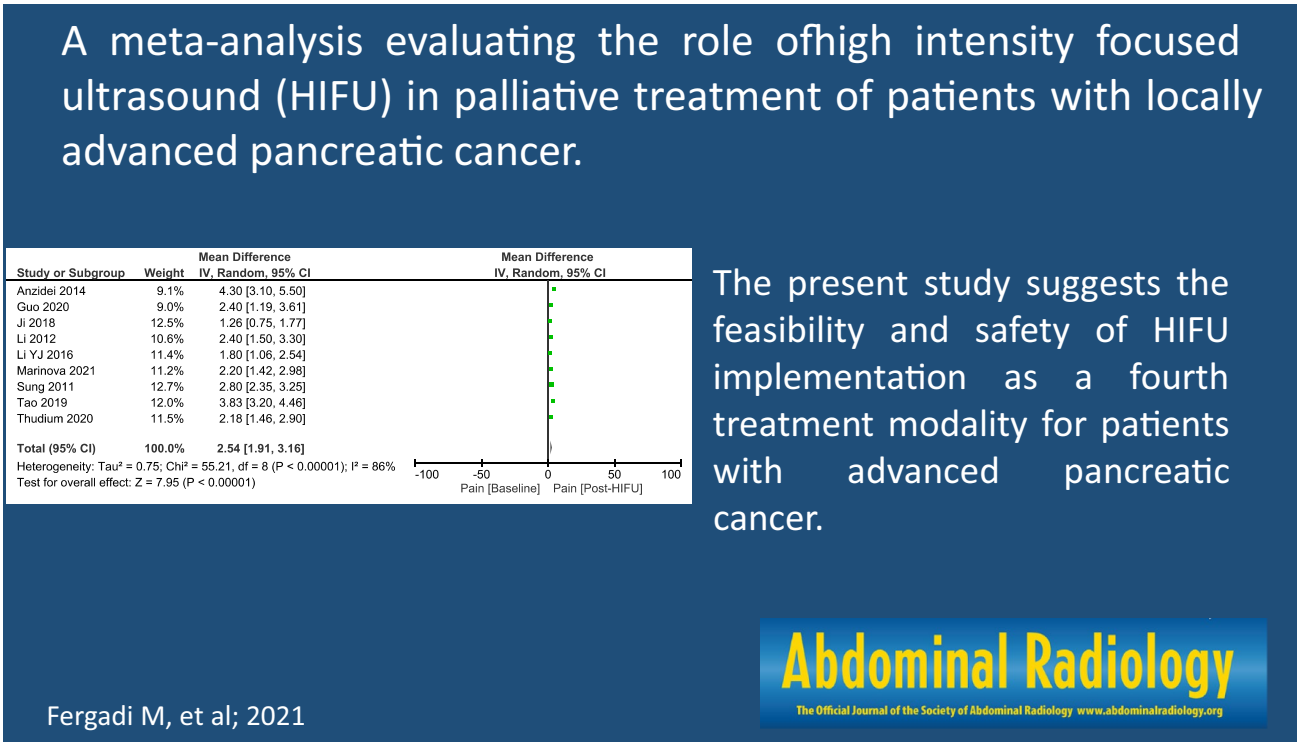
Graphic abstract



Keywords High-intensity focused ultrasound · HIFU · Pancreatic cancer · Meta-analysis

Introduction

Pancreatic cancer represents one of the leading causes of cancer-related death and the fourth cause of cancer mortality in the USA [1, 2]. The majority of the cases diagnosed with pancreatic cancer are ductal adenocarcinomas (PDAC), commonly located in the head of the pancreas [3, 4]. The disease is generally advanced at the time of diagnosis, is associated with poor prognosis, and a significant number of patients present with a non-resectable tumor [5]. In fact, the 5-year survival rate of pancreatic cancer is approximately 6% [5]. Depending on the degree of differentiation and the tumor microenvironment, the malignancy may present poorly to well-formed glands or infiltrating cells forming sheets [3, 4]. Despite the significant progress in research, the mortality rate regarding pancreatic cancer continues to increase and it is projected that by 2030 pancreatic cancer will be the second cancer-related cause of mortality [6].

Given the poor prognosis of patients with locally advanced pancreatic cancer, it is crucial to develop novel treatment modalities that enhance survival and quality of life. High-intensity focused ultrasound (HIFU) has emerged as a promising non-invasive imaging-guided thermal ablation technique inducing thermal and mechanical energy to the targeted tumor tissue, without affecting the surrounding healthy tissue [7, 8]. HIFU is guided by other imaging modalities such as CT (Computed Tomography guided Focused Ultrasound—CTgFUS) or MRI (Magnetic Resonance guided Focused Ultrasound—MRgFUS) to enable guidance of the treatment and monitoring. Although HIFU delivers thermal ablation, the temperature reached is not high enough to cause immediate cell necrosis [7]. In fact, HIFU induces the intracellular denaturation of proteins and stored pancreatic enzymes, followed by cellular degeneration and necrosis [7]. Except for thermal effects, HIFU also induces mechanical effects associated with high-intensity acoustic energy [7]. Through these effects HIFU in conjunction to systemic chemotherapy is expected to provide pain relief, quality of life enhancement, along with increased survival in patients with locally advanced pancreatic cancer. According to a previous meta-analysis [9], HIFU appears to be an effective tool for pain palliation in this patient group. However, it failed to analyze survival endpoints and its outcomes were associated with high heterogeneity [9]. As the number of studies assessing the feasibility of HIFU for patients with advanced pancreatic cancer increases, it is necessary to conduct a meta-analysis to provide the best level of evidence on the topic. The purpose of this study is to

summarize the existing evidence assessing the survival and pain-relief outcomes of HIFU in conjunction with systemic chemotherapy.

Materials and methods

Search strategy and articles selection

The current study was designed and performed according to the protocol agreed by all participating authors and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. A thorough literature search was performed in three databases—Scopus (ELSEVIER), Pubmed (Medline), and Cochrane Central Register of Controlled Studies (CENTRAL) (last search: June 30, 2021) using the following keywords: "high intensity focused ultrasound" or "hifu"; "pancreatic cancer" or "pancreatic adenocarcinoma" or "pdac"; "advanced" or "locally advanced"; "treatment" or "palliation" or "palliative" or "pain" or "survival". The inclusion criteria of the present meta-analysis were as follows: (1) original articles with > 5 patients, (2) written in the English language, (3) published from 1990 to 2021, (4) conducted on human subjects (5) reporting outcomes (median overall survival (OS), OS at 6 and 12 months, pain relief, CA19-9 reduction, and complications) evaluating the implementation of HIFU in the treatment of patients with locally advanced pancreatic cancer, and (6) in cases of multiple studies reporting on the same population, only the largest study or the one with the longest follow-up was included.

Two investigators (MPF, DEM) independently extracted data from the included studies. Any discrepancies between the two authors regarding the inclusion or exclusion of studies were discussed with the senior author (DZ) so as to include only the articles that best matched the protocol until a consensus was reached. Besides, the reference lists of the included articles were further evaluated for additional potentially eligible articles.

Data extraction

For each study that was included, data were extracted relative to demographics (sample size regarding each group, age, sex, site/size/stage of the tumor, type of image guidance, treatment modality, type of HIFU device), along with the primary endpoints (median overall survival (OS), OS at 6 and 12 months) and secondary endpoints (pain relief, CA19-9 reduction, and complications). Two authors (MPF, DEM) performed the data extraction and compared the validity of the data until a consensus was reached. Additionally, the kappa coefficient test was applied in order to assess the level of agreement between the two investigators.

Statistical analysis

Regarding the categorical outcomes, the Odds Ratio (ORs) and 95% confidence interval (95% CI) were estimated, by means of the Random-Effects model (Mantel–Haenszel statistical method). OR < 1 denoted an outcome that was more frequent in either the post-HIFU treatment evaluation, when compared with the baseline status, or in the control group, when compared with the HIFU group. Continuous outcomes were evaluated by means of weighted mean difference (WMD) with its 95% CI, using Random-Effects (Inverse Variance statistical method) models. In cases where WMD < 0, values in either the post-HIFU treatment evaluation or the control, respectively, were increased. The Random-Effects model was chosen, given that it was not expected that all included studies would share a common effect size. Inter-study heterogeneity was assessed through Cochran Q statistic and by estimating I^2 [11]. Forest plots were produced regarding the variables that were analyzed. Data analysis was performed using the Cochrane Collaboration RevMan version 5.4.1.

Quality and publication bias evaluation

The Newcastle–Ottawa Quality Assessment Scale (NOS) [12] was facilitated to evaluate all non-Randomized Controlled Trials (non-RCTs). The scale ranges from zero to nine stars. Studies that were graded with a score equal to or higher than five stars were considered to have adequate methodological quality and were incorporated. The RCTs were assessed for their methodological quality with the tools used to evaluate the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions [11]. Two authors (MPF, DEM) rated the included studies independently and the final decision was reached by consensus.

The risk of publication bias was evaluated by the visual inspection of the funnel plots. Publication bias could not be further evaluated using Egger's formal statistical test [13] due to the inadequate number of the study arms that were included in the analyses, thus substantially compromising the power of the test.

Results

Article selection and patient demographics

The flow diagram of the systematic literature search is shown in Fig. 1. Among the 257 articles that were originally retrieved, nineteen articles were included in the qualitative and eleven in the quantitative synthesis. The level of agreement between the two reviewers regarding data extraction was "almost perfect" (kappa = 0.920; 95% CI 0.831, 1.000).

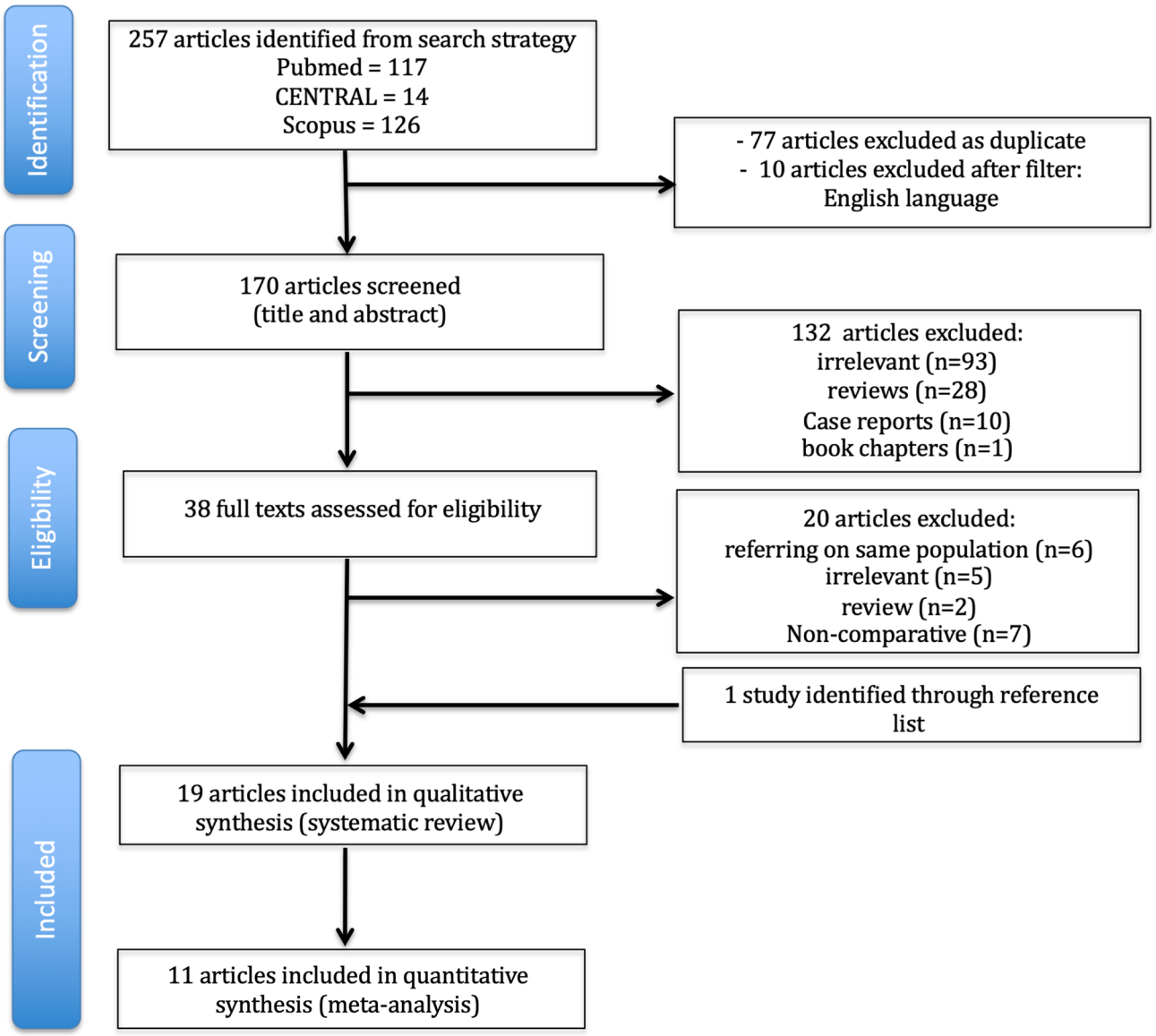


Fig. 1 Trial-flow of the systematic review and meta-analysis

The study design was retrospective in eight studies [15, 18, 20, 21, 24, 27, 28, 32], prospective in ten studies [14, 16, 17, 19, 23, 25, 26, 29–31], randomized controlled in one study [22], and were published between 2005 and 2021. The total study population was 939 patients. The image guidance was performed using CT/MRI modalities in eight studies [14–18, 24, 27, 28] and US in eleven studies [19–23, 25, 26, 29–32]. Baseline characteristics and information regarding tumor characteristics, along with the type of treatment, and HIFU characteristics are presented in Table 1. The pooled estimates of primary and secondary endpoints are reported in Table 2, and the reported complications in Table 3. The Newcastle–Ottawa Scale (NOS) assessment for all studies is shown in Table 1.

Primary endpoints: survival

All studies included in the analyses of the primary endpoints compared patients treated with either HIFU plus chemotherapy (gemcitabine) or chemotherapy (gemcitabine regimen) alone. The median OS was also higher in the HIFU group compared with the chemotherapy-alone group (WMD: 2.83 [95% CI 1.06, 4.59]; $p = 0.002$ (Fig. 2a, Table 2). The OS at 6, and 12 months was higher ($p < 0.05$) in patients treated with HIFU combined with chemotherapy compared with those receiving standard chemotherapy alone (Fig. 2b, c, Table 2). Although it would be of great interest to compare HIFU plus chemotherapy with HIFU alone treatment, no relative data were available to perform such a comparison.

Table 1 Baseline characteristics of the studies that were finally included in the meta-analysis

Author, Date	Design of study	No. of patients (M/F)	Age (mean)	Stage of tumor	Tumor location	Tumor size (mean)	Image guidance	Treatment	HIFU device	Other treatments	NOS
Anzidei et al., 2014 [14]	P	7 (5/2)	67	III (7)	Body (7)	2 mL	MRI	HIFU	ExAblate 2100; InSightec	Chemotherapy/ Radiotherapy	7
Ge et al., 2014 [15]	R	20 (12/8)	68.3	III/IV (6/14)	Body	3.5 × 4.5 cm	CT	HIFU	FEP-BY02 HIFU	None	6
Guo et al., 2019 [16]	P	15 (9/6)	62	II/IIII/IV (2/6/7)	Body/ Tail		CT /MRI	HIFU	Model-JC	None	7
Ji et al., 2018 [17]	P	87 (41/46)	68	N/A	Head/ Body/ Tail	3.6 cm	CT/MRI	HIFU	HIFUINT-9000	Chemo/ Radiotherapy/ Surgery	6
Jung et al., 2010 [18]	R	35(18/17)	62.6	IV (35)	Head/ Body	3.7 cm	CT/ MRI	HIFU	Model-JC	None	6
Li YJ et al., 2016 [19]	P	16(10/6)	62,3	N/A	Head (9) Body (7)	3.7 cm	US	HIFU + Radiotherapy	N/A	N/A	6
Li X et al., 2016 [20]	R	61(32/29)	50.13	N/A	Head (31) Other (30)	N/A	US	HIFU + Chemotherapy	Model-JC HIFU System	N/A	7
Li et al., 2012 [21]	R	25 (14/11)	60	III/ IV (12/23)	Head /Body	N/A	US	HIFU	Model-JC HIFU System	Chemotherapy + radiotherapy/ Alcohol ablation	8
Lv et al., 2016 [22]	RCT	24	59	III/ IV (29/16)	Head (22) Tail and Body (23)	8.1 × 7.5x5.8– 2.6 × 2.5x1.8 cm	US	HIFU + Chemotherapy	JC200 HIFU System	N/A	-
Marinova et al., 2021 [23]	P	13 (7/6)	66.2	III/IV (5/8)	Body (12) Tail and/ or Body (4)	12.6– 61.8 mL	US	HIFU	Model-JC HIFU System	Chemotherapy/Radiotherapy/Non therapeutic laparotomy	6
Ning et al., 2019 [24]	R	347 (229/118)	61	II/III/IV (26/75/246)	Head-Neck/ Body – Tail (73/274)	N/A	CT	HIFU + Chemotherapy	Chongqing Haifu	Chemo (GEM)	8
Orsi et al., 2010 [25]	P	31 (6 pancreatic cancers)	64	N/A	N/A	N/A	US	HIFU	Model-JC HIFU System	Chemotherapy/radiotherapy	7

Table 1 (continued)

Author, Date	Design of study	No. of patients (M/F)	Age (mean)	Stage of tumor	Tumor location	Tumor size (mean)	Image guidance	Treatment	HIFU device	Other treatments	NOS
Sung et al., 2011 [26]	P	46(25/21)	61	III (18)/IV (28)	Head (17) Tail and/ or Body (25) Tail (4)	4.2 cm	US	HIFU	Model-JC HIFU System	Pre HIFU Chemoth/ Chemo-radiation therapy (10)/ Radiation therapy (3)/ After HIFU Chemo-therapy (29)/ Chemoradiation (1)	7
Tao et al., 2019 [27]	R	38 (21/17)	69	II/III/IV (4/15/19)	Head/ Body/Tail (16/13/9)	4.2 cm	CT/MRI/PET CT	HIFU + chemotherapy	HIFUNIT-9000	Chemo (GEM)	6
Thundium et al., 2020 [28]	R	71 (30/41)	62.8	I/II/IIII/IV (2/28/29/4)		27.3 mL	CT/MRI	HIFU	JC HIFU	None	6
Wang et al., 2011 [29]	P	40(24/16)	57	III (13)/IV (27)	Head (9) Tail and/ or Body (31)	2–10 cm	US	HIFU	Model-JC HIFU System	Chemo-therapy (28) Chemotherapy + radiotherapy	7
Wu et al., 2005 [30]	P	8(6/2)	62	III (3) /IV (5)	Body (2)/ Head and Body (2)/ Tail and Body (4)	5.89×5.40 cm	US	HIFU	Model-JC HIFU System	Chemotherapy (2)/Local radiation therapy	6
Xie et al., 2008 [31]	P	16(10/6)	50	N/A	N/A	N/A	US	HIFU	HIFUNIT-9000 HIFU System	Chemotherapy (7)	6
Zhao et al., 2010 [32]	R	39	55	IIa (3) /IIb (5)/ III (31)	Body (12) Head (27)	3.4 cm (range 1.7–8.5 cm)	US	HIFU + Chemotherapy	HIFUNIT-9000 HIFU System	Endoscopic biliary drainage with plastic stent (9) Percutaneous biliary drainage (4)	6

The study design (Prospective, Retrospective) is presented, along with the number of female patients, the mean age, the stage, size, and site of primary tumor, the type of guidance, the type of HIFU device, other treatments, and the number of stars according to the Newcastle–Ottawa Quality Assessment Scale (NOS)

R Retrospective, *P* Prospective, *RCT* Randomized Controlled Trial, *N/A* Not available, *HIFU* High-intensity Focused Ultrasound, *n* number, *SD* Standard Deviation, *NOS* = Newcastle–Ottawa Scale

Table 2 Summary of the pooled estimates regarding the outcomes of the included patients

Categorical Outcomes	*n*	Number of patients	OR [95% CI]	*p*	Heterogeneity	
					I^2	*p*
OS at 6 months	2	371	2.31 [1.62, 3.30]	< 0.01	0%	0.36
OS at 12 months	2	371	1.76 [1.08, 2.88]	0.02	0%	0.62
Continuous outcomes	*n*	Number of patients	WMD (95% CI)		I^2	*P*
Median OS	3	432	2.83 [1.06, 4.59]	< 0.01	100%	< 0.01
Pain levels	9	378	2.54 [1.91, 3.16]	< 0.01	86%	< 0.01
CA19-9	4	170	49.81 [8.53, 91.09]	0.02	53%	0.09

OR < 1 or WMD < 0 denoted outcome that was more frequent in the LFS group

n number of patients eligible for inclusion studies, *MOT* Mean Operative Time, *OR* Odds Ratio, *WMD* Weighted Mean Difference, *CI* Confidence Intervals, *LOS* Length of Stay, *OS* Overall Survival, *DFS* Disease-free survival

Table 3 Summary of the main complications of HIFU treatment

Complications	*N* = 939 (%)
Skin burns	31 (3.3)
Abdominal pain	55 (5.9)
Fever	15 (1.6)
Peripancreatic effusion/pancreatic fistula	8 (0.9)
Jaundice	4 (0.4)
GI bleeding	3 (0.3)
Thrombosis or embolism	1 (0.1)

Secondary endpoints: pain relief and tumor responsiveness

The reported pain was assessed using the numerical rating score (NRS). The reported level of pain was significantly lower after HIFU treatment (WMD: 2.54 [95% CI 1.91, 3.16]; $p < 0.001$) (Fig. 3a, Table 2). CA19-9 was significantly reduced following HIFU treatment (WMD: 49.81 [95% CI 8.53, 91.09]; $p = 0.02$) (Fig. 3b, Table 2).

Secondary endpoints: complications

Complications are presented in Table 3. Complications were reported in all the included studies. The most common reported complication was skin burn. Other minor complications included abdominal pain, vomiting, fever, and local edema. These side-effects were treated conservatively and were resolved in a period of 6 weeks. Major adverse events were rare and included portal vein thrombosis (one case [25]), severe abdominal pain requiring hospitalization, pancreatic fistula (two cases [26]), and jaundice aggravation (four cases). No death was reported.

Publication bias

The evaluation of median OS and pain levels were associated with increased heterogeneity (Table 2). Furthermore, the heterogeneity of tumor responsiveness in terms of Ca19-9 levels, along with OS at 6 and 12 months post-intervention was generally low. Funnel plots (Fig. S1) seemed asymmetrical, with studies being absent from either top or bottom of the graph, thus suggesting certain publication bias. The small number of the included studies was the main reason for the reported asymmetry.

Discussion

Despite the progress in cancer research, survival and quality of life of patients with pancreatic cancer remain poor [5]. In fact, locally advanced pancreatic cancer is associated with reduced median OS, while the quality of life is affected by pain [5]. In fact, the pain with pancreatic cancer origin is multifactorial, and is mainly attributed to tumor infiltration of nerves, along with compression and inflammatory reaction elicited by the malignancy [33]. In this context, the exact physiologic mechanisms by which HIFU reduced the reported pain are not clear, yet. There have been proposed three potential mechanisms of action: (1) thermal collateral damage to the nerves adjacent to the tumor, (2) the reduced post-ablation size of the tumor resulting in reduced mass effect, and (3) the ablation of celiac plexus fibers [34]. Compared with a previous meta-analysis [9], the present study is the first to analyze survival endpoints, thus providing the best level of evidence on the topic.

According to our meta-analysis, HIFU is associated with an increased survival when combined with chemotherapy. In fact, our outcomes indicate enhanced mean OS, along with survival at 6 and 12 months post-HIFU treatment in patients receiving combined therapy compared with those receiving only systemic chemotherapy. The physiologic

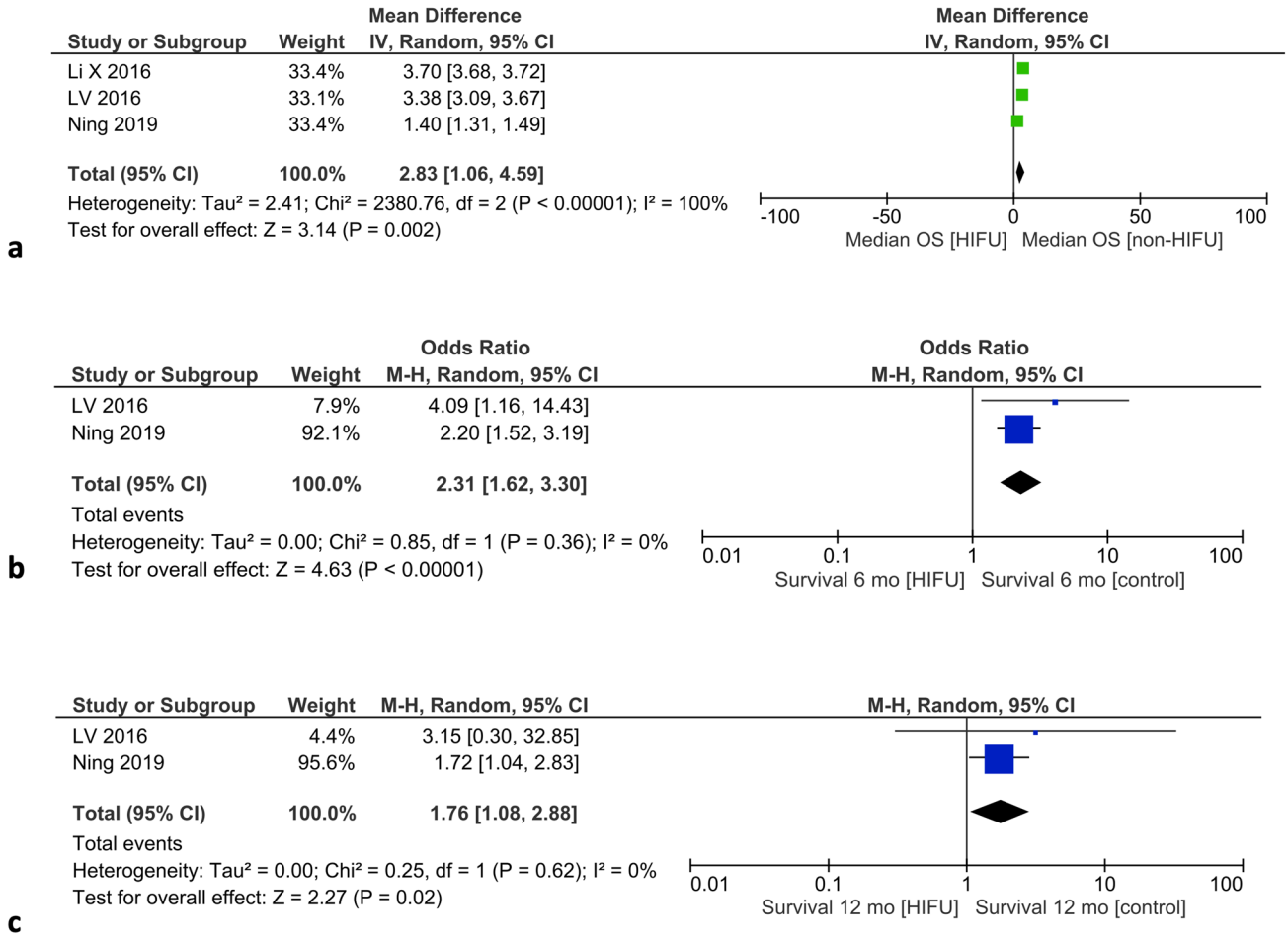


Fig. 2 Forest plot describing the differences in **a** median overall survival (OS), **b** OS at 6 months, and **c** OS at 12 months

background that explains these findings is that PDAC is a relatively hypovascular tumor, enclosed by a fibrous ring that limits the penetration and diffusion of chemotherapeutic agents. In this context, HIFU might provide a synergistic effect with chemotherapy, through increased vascular permeability, thus boosting the drug concentration in the tumor microenvironment [8]. Furthermore, our study indicated that HIFU inhibits tumor progression, as evaluated by CA19-9 levels and tumor volume. In fact, the present meta-analysis represents the first evidence synthesis indicating the value of HIFU combined with chemotherapy in raising OS of patients with advanced pancreatic cancer.

Originally, HIFU was presented as a palliative treatment for pain relief in patients with advanced pancreatic cancer. In the present meta-analysis, pain relief was evaluated as a secondary endpoint. According to our outcomes, HIFU is a very effective mean of relieving pain in patients with advanced pancreatic cancer. Differences regarding the treatment protocol among different centers contributed to high heterogeneity. Nonetheless, to limit the potential publication bias we excluded studies with a small number of patients, along with studies incorporating the same population. Finally, the evidence provided by case reports that were excluded from the present meta-analysis are consistent with our findings in terms of efficacy and safety of HIFU for pain palliation [35, 36]. The duration of pain relief has been validated for distant follow-up periods up to 17 months [30].

Complications represent a major endpoint when evaluating a potential treatment intervention in patients with advanced cancer, given that it is crucial to preserve the adequate quality of life standards. Herein, we demonstrated that HIFU is not associated with significant morbidity. In fact, the main alternate proposed treatment when opioids fail is neurolytic celiac plexus blockade (NCPB) [33]. However, NCPB is an invasive procedure, with only short-term efficacy (up to 3 months) and is associated with significant adverse events, such as local pain, diarrhea, hypotension, pneumothorax, and neurological side-effects [37].

The majority of the studies included in the present systematic review used US-guided HIFU technique, while eight studies implemented a CT/MRI-guided HIFU approach. The US-guided approach implements the ultrasound for both

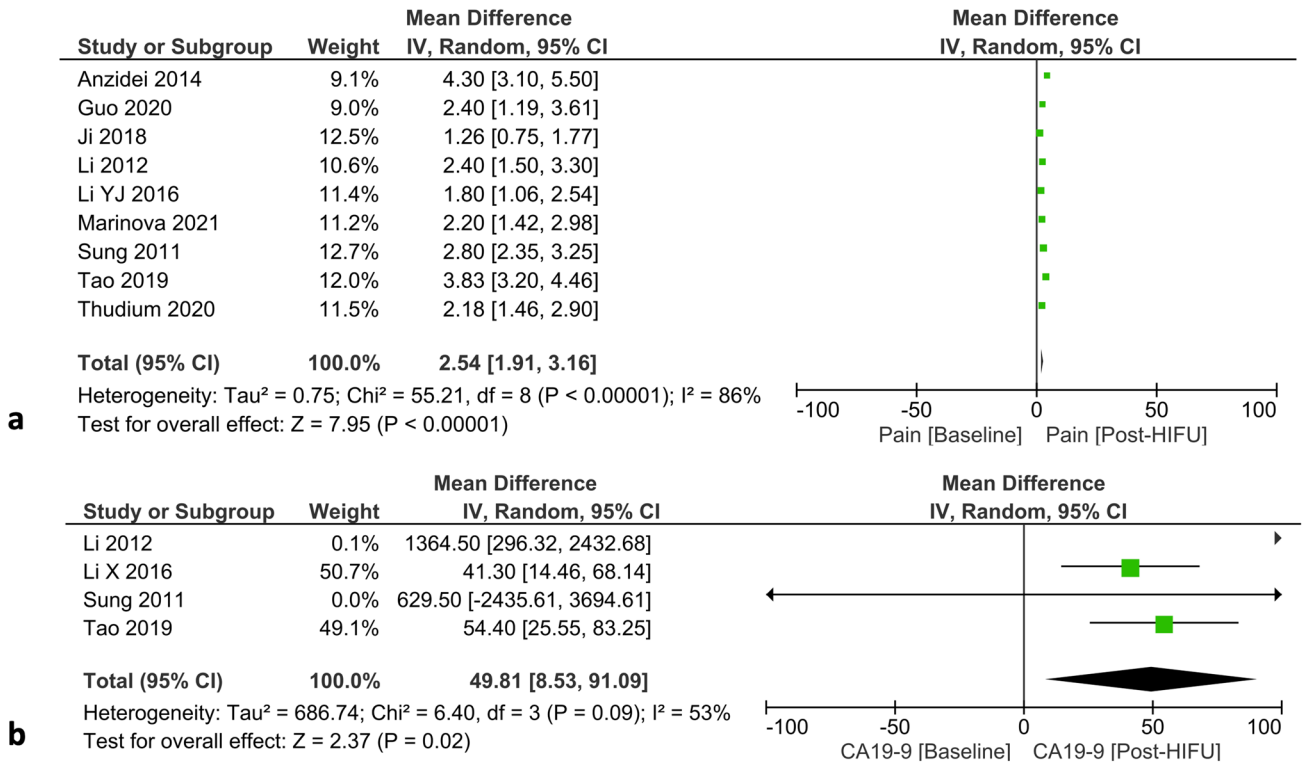


Fig. 3 Forest plot describing the effect of HIFU on **a** pain relief and **b** CA19-9 levels

detecting and ablation of the lesions, allowing identification of potential obstructions in the US beam pathway. Nonetheless, it is associated with certain limitations regarding the quality of depiction of tumor and its borders, the lack of temperature monitoring, along with its operator-dependent attributes. In this context, the contrast-enhanced US could provide enhanced capabilities of tumor imaging, thus raising the feasibility and efficacy of HIFU. MRI-guided HIFU has been proposed as an enhanced approach in terms of efficacy. However, there is a lack of real-world evidence on its superiority, cost-effectiveness, and availability compared with US-guided method.

The limitations of the present meta-analysis reflect the limitations posed by the included studies. The majority of the studies were prospective, eight studies were retrospective, and only was RCT. The small number of arms in the meta-analyses poses also a certain publication bias, as it reflects the asymmetry of the funnel plots. The differences between the two groups and the high heterogeneity among studies regarding the baseline characteristics, the primary tumor location and biology, extend of the disease, the therapeutic protocols, along with the HIFU specifications should also be taken into consideration. Moreover, most of the included studies did not clearly state the dropout rate of patients during the protocol pathway, which is crucial in terms of evaluation of the success regarding each strategy. Furthermore, there was a lack of homogeneity among studies regarding the classification of complications, since classification scales such as Clavien–Dindo were not adopted. In addition, the available data were limited regarding the primary endpoints (median OS, OS at 6 and 12 months), thus posing a certain limitation in the present meta-analysis. Nonetheless, the limited available evidence highlights the value of the present meta-analysis as the best currently available level of evidence. Therefore, there is a need for well-designed RCTs with standardized reporting of staging, therapeutic protocols, HIFU specifications, and outcomes including dropout rate, pain relief, complications according to a classification scale, median and long-term OS and DFS.

On the contrary, the strengths of the present meta-analysis are as follows: (1) the clear study protocol, (2) the well-described inclusion criteria, (3) the systematic literature search in three different databases, (4) the quality assessment of the included studies (5) the detailed presentation of the outcomes, and (6) the low heterogeneity regarding the primary and secondary endpoints.

Conclusion

The present meta-analysis suggests that HIFU represents a safe and feasible fourth treatment modality for patients with advanced pancreatic cancer, in conjunction with surgery,

chemotherapy, and radiotherapy. In this context, the aim of oncologic care should be to evaluate each patient individually by the multi-disciplinary team and to select the appropriate strategy for each case. Patients with a higher burden of pancreatic disease, presenting with severe pain, might possibly be candidates for a HIFU approach, whereas the classical strategy may be more suitable for patients with a stable disease and with low levels of pain. Nonetheless, new RCTs with reduced selection bias and increased clarity of significant outcomes are required.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00261-021-03334-y.

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Author contributions MPF contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. DEM contributed to the design of the work, the interpretation of data for the work, the revising of the work critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. CR contributed to the acquisition and analysis of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. MV contributed to the acquisition and analysis of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. TA contributed to the design of the work, the acquisition and analysis of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. DS contributed to the acquisition and analysis of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. PAP contributed to the acquisition and analysis of data for the work, the drafting the work and revising it critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work. DZ contributed to the conception and design of the work, the interpretation of data for the work, the revising of the work critically for important intellectual content, the final approval of the version to be published and is accountable for all aspects of the work.

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Availability of data and material Raw data and material are available upon request. Supplementary electronic material is provided.

Code availability Review Manager 5.4 was employed for the present study.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval Does not apply.

Consent to participate Does not apply.

Consent for publication Does not apply.

Informed consent Does not apply.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer 2013; Available from: http://globocan.iarc.fr, accessed on 05/06/ 2019.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2015;65:5–29. DOI: https://doi.org/10.3322/caac.21254
3. Wong HH, Chu P. Immunohistochemical features of the gastrointestinal tract tumors. J Gastrointest Oncol. 2012;3:262–284. doi: https://doi.org/10.3978/j.issn.2078-6891.2012.019
4. Neoptolemos JP, Urrutia R, Abbruzzese J, Büchler MW, eds. Pancreatic Cancer. New York: Springer-Verlag; 2010:LVIII, 1390.
5. Yeo TP. Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. Semin Oncol. 2015;42:8–18. DOI: https://doi.org/10.1053/j.seminoncol.2014.12.002
6. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74:2913–2921. DOI: https://doi.org/10.1158/0008-5472.CAN-14-0155
7. Tempany CM, Mcdannold NJ, Hynynen K, Jolesz FA. Focused ultrasound surgery in oncology: overview and principles. Radiology. 2011;259(1):39–56. doi:https://doi.org/10.1148/radiol.11100155.
8. Jang HJ, Lee JY, Lee DH, Kim WH, Hwang JH. Current and future clinical applications of high-intensity focused ultrasound (HIFU) for pancreatic cancer. Gut Liver. 2010;4 Suppl 1:S57–61. DOI: https://doi.org/10.5009/gnl.2010.4.S1.S57
9. Dababou S, Marrocchio C, Rosenberg J, Bitton R, Pauly KB, Napoli A, et al. A meta-analysis of palliative treatment of pancreatic cancer with high intensity focused ultrasound. J Ther Ultrasound. 2017 Apr 1;5:9. doi: https://doi.org/10.1186/s40349-017-0080-4.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (2009) e1000100. doi: https://doi.org/https://doi.org/10.1136/bmj.b2700
11. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011 Available from www.cochrane-handbook.org
12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol, 25 (2010), pp. 603–605 doi: https://doi.org/10.1007/s10654-010-9491-z.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629– 34. doi: https://doi.org/https://doi.org/10.1136/bmj.315.7109.629
14. Anzidei M, Marincola BC, Bezzi M, Brachetti G, Nudo F, Cortesi E, et al. Magnetic resonance-guided high-intensity focused ultrasound treatment of locally advanced pancreatic adenocarcinoma: preliminary experience for pain palliation and local tumor control.

Invest Radiol. 2014 Dec;49(12):759-65. doi: https://doi.org/10.1097/RLI.0000000000000080.
15. Ge HY, Miao LY, Xiong LL, Yan F, Zheng CS, Wang JR, et al. High-intensity focused ultrasound treatment of late-stage pancreatic body carcinoma: optimal tumor depth for safe ablation. Ultrasound Med Biol. 2014 May;40(5):947-55. doi: https://doi.org/10.1016/j.ultrasmedbio.2013.11.020.
16. Guo X, Zhu H, Zhou K, Jin C, Yang Y, Zhang J, et al. Effects of high-intensity focused ultrasound treatment on peripancreatic arterial and venous blood vessels in pancreatic cancer. Oncol Lett. 2020 Jun;19(6):3839-3850. doi: https://doi.org/10.3892/ol.2020.11511.
17. Ji Y, Zhang Y, Zhu J, Zhu L, Zhu Y, Hu K, et al. Response of patients with locally advanced pancreatic adenocarcinoma to high-intensity focused ultrasound treatment: a single-center, prospective, case series in China. Cancer Manag Res. 2018 Oct 9;10:4439-4446. doi: https://doi.org/10.2147/CMAR.S173740.
18. Jung SE, Cho SH, Jang JH, Han JY. High-intensity focused ultrasound ablation in hepatic and pancreatic cancer: complications. Abdom Imaging. 2011 Apr;36(2):185-95. doi: https://doi.org/10.1007/s00261-010-9628-2.
19. Li YJ, Huang GL, Sun XL, Zhao XC, Li ZG. The combination therapy of high-intensity focused ultrasound with radiotherapy in locally advanced pancreatic carcinoma. World J Surg Oncol. 2016 Feb 29;14:60. doi: https://doi.org/10.1186/s12957-016-0809-5.
20. Li X, Wang K, Zheng L, Meng Z. Retrospective analysis of high intensity focused ultrasound combined with S-1 in the treatment of metastatic pancreatic cancer after failure of gemcitabine. Am J Cancer Res. 2015 Dec 15;6(1):84-90.
21. Li PZ, Zhu SH, He W, Zhu LY, Liu SP, Liu Y, et al. High-intensity focused ultrasound treatment for patients with unresectable pancreatic cancer. Hepatobiliary Pancreat Dis Int. 2012 Dec 15;11(6):655-60. doi: https://doi.org/10.1016/s1499-3872(12)60241-0.
22. Lv W, Yan T, Wang G, Zhao W, Zhang T, Zhou D. High-intensity focused ultrasound therapy in combination with gemcitabine for unresectable pancreatic carcinoma. Ther Clin Risk Manag. 2016 May 2;12:687-91. doi: https://doi.org/10.2147/TCRM.S90567.
23. Marinova M, Feradova H, Gonzalez-Carmona MA, Conrad R, Tonguc T, Thudium M, et al. Improving quality of life in pancreatic cancer patients following high-intensity focused ultrasound (HIFU) in two European centers. Eur Radiol. 2021 Jan 23. doi: https://doi.org/10.1007/s00330-020-07682-z. Epub ahead of print.
24. Ning Z, Xie J, Chen Q, Zhang C, Xu L, Song L, et al. HIFU is safe, effective, and feasible in pancreatic cancer patients: a monocentric retrospective study among 523 patients. Onco Targets Ther. 2019 Feb 1;12:1021-1029. doi: https://doi.org/10.2147/OTT.S185424.
25. Orsi F, Zhang L, Arnone P, Orgera G, Bonomo G, Vigna PD, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. AJR Am J Roentgenol. 2010 Sep;195(3):W245-52. doi: https://doi.org/10.2214/AJR.09.3321.
26. Sung HY, Jung SE, Cho SH, Zhou K, Han JY, Han ST, et al. Long-term outcome of high-intensity focused ultrasound in advanced pancreatic cancer. Pancreas. 2011 Oct;40(7):1080-6. doi: https://doi.org/10.1097/MPA.0b013e31821fde24.
27. Tao SF, Gu WH, Gu JC, Zhu ML, Wang Q, Zheng LZ. A Retrospective Case Series Of High-Intensity Focused Ultrasound (HIFU) In Combination With Gemcitabine And Oxaliplatin (Gemox) On Treating Elderly Middle And Advanced Pancreatic Cancer. Onco Targets Ther. 2019 Nov 15;12:9735-9745. doi: https://doi.org/10.2147/OTT.S220299.
28. Thudium M, Bette B, Tonguc T, Ghaei S, Conrad R, Becher MU, et al. Multidisciplinary management and outcome in pancreatic cancer patients treated with high-intensity focused ultrasound. Int J Hyperthermia. 2020;37(1):456-462. doi: https://doi.org/10.1080/02656736.2020.1762006.
29. Wang K, Chen Z, Meng Z, Lin J, Zhou Z, Wang P, et al. Analgesic effect of high intensity focused ultrasound therapy for unresectable pancreatic cancer. Int J Hyperthermia. 2011;27(2):101-7. doi: https://doi.org/10.3109/02656736.2010.525588.
30. Wu F, Wang ZB, Zhu H, Chen WZ, Zou JZ, Bai J, et al. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. Radiology. 2005 Sep;236(3):1034-40. doi: https://doi.org/10.1148/radiol.2362041105.
31. Zhao J, Zhao F, Shi Y, Deng Y, Hu X, Shen H. The efficacy of high-intensity focused ultrasound (HIFU) in advanced pancreatic cancer. Chin. J. Clin. Oncol. 5, 183–186 (2008). https://doi.org/https://doi.org/10.1007/s11805-008-0183-3
32. Zhao H, Yang G, Wang D, Yu X, Zhang Y, Zhu J, et al. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. Anticancer Drugs. 2010 Apr;21(4):447-52. doi: https://doi.org/10.1097/CAD.0b013e32833641a7.
33. Sehgal S, Ghaleb A. Neurolytic celiac plexus block for pancreatic cancer pain: a review of literature. Indian J Pain. 2013;27(3):121. DOI: https://doi.org/10.4103/0970-5333.124584
34. Zhou Y. High-intensity focused ultrasound treatment for advanced pancreatic cancer. Gastroenterol Res Pract. 2014;2014:205325. doi:https://doi.org/10.1155/2014/205325.
35. Dimitrov D, Andreev T, Feradova H, Ignatov B, Zhou K, Johnson C, et al. Multimodality treatment by FOLFOX plus HIFU in a case of advanced pancreatic carcinoma. A case report. JOP. 2015;16(1):66–9. doi: https://doi.org/10.6092/1590-8577/2900.
36. Zhu X, Meng Z, Chen Z, Wang K, Yu B, Zhan H, et al. Metastatic adenocarcinoma of the epididymis from pancreatic cancer successfully treated by chemotherapy and high-intensity focused ultrasound therapy: a case report and review of the literature. Pancreas. 2011;40(7):116O–2. DOI: https://doi.org/10.1097/MPA.0b013e318221816d
37. Ischia S, et al. Three posterior percutaneous celiac plexus block techniques. A prospective, randomized study in 61 patients with pancreatic cancer pain. Anesthesiology. 1992;76(4):534–40.