INTERVENTIONAL

High-intensity focused ultrasound (HIFU) for pancreatic carcinoma: evaluation of feasibility, reduction of tumour volume and pain intensity

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Abstract

Objectives Prognosis of patients with locally advanced pancreatic adenocarcinoma is extremely poor. They often suffer from cancer-related pain reducing their quality of life. This prospective observational study aimed to evaluate feasibility, local tumour response, and changes in quality of life and symptoms in Caucasian patients with locally advanced pancreatic cancer treated by ultrasound-guided high-intensity focused ultrasound (HIFU).

Methods Thirteen patients underwent HIFU, five with stage III, eight with stage IV UICC disease. Ten patients received simultaneous palliative chemotherapy. Postinterventional clinical assessment included evaluation of quality of life and symptom changes using standardized questionnaires. CT and MRI follow-up evaluated the local tumour response.

Results HIFU was successfully performed in all patients. Average tumour reduction was 34.2 % at 6 weeks and 63.9 % at 3 months. Complete or partial relief of cancer-related pain was achieved in 10 patients (77 %), five of whom required less analgesics for pain control. Quality of life was improved revealing increased global health status and alleviated symptoms. HIFU treatment was well tolerated. Eight patients experienced transient abdominal pain directly after HIFU.

Conclusions HIFU ablation of pancreatic carcinoma is a feasible, safe and effective treatment with a crucial benefit in terms of reduction of tumour volume and pain intensity.

Key Points
- *US-guided HIFU is feasible and safe for patients with unresectable pancreatic cancer.*
- *HIFU can considerably reduce tumour volume and cancer-related pain.*
- *Patients treated with HIFU experienced significant and lasting reduction of pain intensity.*
- *HIFU has a crucial clinical benefit for patients with pancreatic cancer.*

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Introduction

The majority of patients with pancreatic adenocarcinoma present at an advanced disease, as symptoms are non-specific in early stages. Although surgical resection gives the best chances for possible cure, 85–90 % of newly diagnosed

patients are considered unresectable because of locally advanced tumour or presence of metastasis. Median survival time is only 6–10 months, but even shorter in the case of metastatic disease (3–6 months) [1]. Current standard therapy is limited to chemotherapy or radiochemotherapy in a palliative setting showing very limited antitumoral effects and survival advantage [2, 3]. Despite the fact that some newer chemotherapy regimens like nab-paclitaxel plus gemcitabine, FOLFOX-6 or FOLFIRINOX have shown a substantial survival advantage in patients with pancreatic adenocarcinoma [4–8], the 1-year survival rate is only about 18–20 % and 5-year survival is less than 10 % [9]. Although different chemotherapy regimens as well as standard palliative therapy are used, nearly 75 % of patients with locally advanced disease suffer from serious cancer-related abdominal or back pain substantially reducing their quality of life. Therefore, improvement of quality of life and alleviation of symptoms are of particular importance for these patients.

Ablation with high-intensity focused ultrasound (HIFU) is a non-invasive procedure [10, 11] based on the principle that focused ultrasound (US) beams cause coagulation necrosis in the target. Multiple retrospective non-randomized studies and case series on US-guided HIFU for pancreatic cancer have been reported to date, nearly all coming from Asia [12–17]. To our knowledge, there is only one retrospective study on US-guided HIFU treatment of six patients with pancreatic cancer in Europe [10]. Even though all these data are promising, they still suffer from the retrospective design of the studies.

We designed a prospective observational study, including the largest number of Caucasian patients with unresectable locally advanced pancreatic cancer to date. The aim of this study was to evaluate the feasibility, efficacy and clinical benefits of US-guided HIFU treatment on local tumour response, quality of life and symptom intensity, in particular on relief of cancer-related pain.

Methods

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. Eligibility for HIFU was confirmed in a multidisciplinary tumour conference including surgeons, oncologists, gastroenterologists, radiotherapists and interventional radiologists.

Patient selection

Patients had to fulfil the following inclusion criteria: (1) 18 years or older; (2) histological/cytological diagnosis of pancreatic adenocarcinoma; (3) locally advanced tumour with a diameter ≥2 cm verified either by computed tomography (CT) or magnetic resonance imaging (MRI) within 8 weeks prior to treatment; (4) tumour sufficiently visible on ultrasound; (5) estimated life expectancy of more than 3 months; (6) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (7) adequate coagulation, renal and hepatic function (neutrophil count $\geq 1.5 \times 10^9$/L; platelets $\geq 75 \times 10^9$/L; haemoglobin ≥8 g/dL; normal liver enzymes AST/ALT, serum creatinine, creatinine clearance ≥50 mL/min).

Main exclusion criteria were (1) eligibility for surgical resection; (2) non-eligibility for general anaesthesia; (3) tumour not sufficiently visible on ultrasound; (4) extensive scarring along the acoustic path.

All patients exhibited cancer-related pain and/or local tumour growth leading to disease-associated findings such as mesenteric or splenic vein occlusion, cholestasis, duodenal stenosis etc. The presence of metastasis or biliary drainage was not taken as an exclusion criterion.

Baseline imaging

Baseline imaging was performed within 2 weeks before HIFU using CT and MRI (Brilliance 64, Ingenia 1.5-T, Philips Healthcare, Amsterdam, the Netherlands). Baseline tumour volumes were calculated [18]. Contrast-enhanced US (CEUS) with Sonovue® (Bracco, Italy) was also performed prior to HIFU treatment.

Pretreatment procedures

Pretreatment evaluation included medical history, physical examination, biochemical laboratory tests (liver and pancreas enzymes, prothrombin time, complete blood cell counts, C-reactive protein (CRP), serum carbohydrate antigen (CA19-9). Standardized questionnaires were used to determine the baseline status of quality of life and tumour-associated symptoms. For the treatment of lesions adjacent to the gastrointestinal tract, a specific bowel preparation is required. The bowel preparation consists of liquid food, no milk or other gas-producing food, fasting for 12 h and use of laxatives. Prior to therapy, a stomach tube is placed to apply antifoaming agents and bind air bubbles, which reduces risk of injury of stomach and duodenum.

High-intensity focused ultrasound therapeutic procedure

HIFU was performed using a US-guided device (JC, Haifu Technology, Chongqing, China) equipped with a 3.6-MHz ultrasound imaging device (MyLab 70, Esaote, Genova, Italy) for real-time guidance. The therapeutic ultrasound beam was transmitted by a 20-cm-diameter ceramic transducer with a focal length of 15 cm, operating at 0.8 MHz.

A specific skin preparation is a crucial step for successful HIFU treatment. Skin preparation includes shaving of the anterior abdominal wall, degreasing and degassing the skin in

order to avoid deflection of ultrasonic beams which might result in accidental skin burn. Patients were positioned prone on the treatment table. To compress the stomach and dislocate the bowel away from the acoustic path, a balloon filled with degassed water was positioned between the transducer and the upper abdominal wall. HIFU was performed under general anaesthesia and patients' vital signs were monitored with special attention to body temperature.

Pretreatment planning and therapy were performed in sagittal scanning mode. Ultrasound energy was delivered using a dot mode. Sonication power was adjusted for each patient depending on adjacent risk structures and ranged from 200 to 400 W. For volume ablation, a number of sequential single lesions were induced within tumours. After HIFU treatment, the patients remained hospitalized for 1–3 days.

Treatment evaluation

To exclude major complications and evaluate treatment efficacy, contrast-enhanced CT and US were performed within 24 h after HIFU and an MRI examination within 3 days after HIFU. Long-term follow-up included contrast-enhanced MRI or CT 6 weeks and 3 months after HIFU therapy and every 3 months thereafter. Tumour ablation ratio (%) was estimated as a ratio of non-contrast-enhancing area to the complete target area. Volume reduction (%) was calculated at 6 weeks and 3 months after HIFU as a ratio of tumour volume at follow-up and respective tumour volume at baseline. Adverse events and complications were according to the Society of Interventional Radiology classification system by outcome [19].

Evaluation of pain relief and quality of life

Pain response, including changes in pain medication over time, and quality of life were assessed during follow-up by EORTC QLQ-C30 questionnaire (European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire [4, 20]), a numerical rating score (NRS; 0–10; 0 "no pain at all", 10 "most intense pain imaginable"). Fifteen common EORTC scales were calculated [20]: global health status, five functional scales and nine symptom scales. Complete pain relief was defined as an NRS of one or less and no need for opioid analgesics after HIFU. Partial pain relief was defined as an NRS decrease of two or more [16, 17, 21].

Statistical analysis

Data were analysed using Stata (Version 13.1, Stata Corp, Lakeway Drive College Station, US) and SPSS (Version 22 for Windows, SPSS Inc, Chicago). Mean, median, standard deviation (SD), range and exact 95 % confidence intervals (CI) were estimated. The primary statistical evaluation of quality-of-life scales, pain scores and tumour volumes was performed using the mixed longitudinal (panel) model [22] with scales, scores and tumour volumes at each post-baseline follow-up and baseline values as dependent variable. A mixed panel model allows for missing data (unbalanced panel). Results were presented as contrasts (differences) and verified for susceptibility of model dependency using a non-parametric Skilling–Mack test for unbalanced panel data. Analysis of variance (ANOVA) for repeated measurements was performed considering the data at baseline and at 1- and 6-week follow-up, as there were no missing data for these time points. A p value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 13 patients with unresectable pancreatic cancer (seven men, six women, aged 66.2 ± 10.8 years) were treated with US-guided HIFU (Table 1): 12 had locally advanced disease at time of diagnosis, one a local tumour recurrence following surgery and radiotherapy. Initial tumour volumes ranged from 12.6 to 61.8 mL (34.3 ± 17.9 mL).

Five patients presented with UICC stage III, eight with stage IV disease. Nine patients had no or only slightly impaired performance status (ECOG 0 or 1). Seven patients presented with hepatic metastasis, one with pulmonary metastasis. Initial symptoms and tumour characteristics are summarized in Table 2. All treated lesions were in close proximity to stomach, bowel and/or main blood vessels in the upper abdomen (celiac axis, splenic artery, common hepatic artery, superior mesenteric artery). As a result of cholestasis, a plastic or metal stent was placed in two patients; a percutaneous biliary drainage was performed in one patient. Ten patients underwent simultaneous standard chemotherapy. All patients had cancer-related abdominal and/or back pain at presentation (NRS "mild pain" in three patients with pain medication on demand, "moderate pain" in five patients necessitated ibuprofen or novaminsulfone analgesia, "severe pain" in five patients necessitated opiate analgesia; Table 2).

All patients were treated with US-guided HIFU in a single session under general anaesthesia. Treatment data are summarized in Table 3.

Short-term imaging follow-up

Immediately after HIFU, all treated tumour areas showed no contrast enhancement on CEUS indicative of devascularized tissue. Massive and moderate greyscale changes were observed on B-mode scan in treated areas

Table 1 Demographic and clinical characteristics of HIFU-treated patients with non-resectable pancreatic cancer

Parameter	Value
Study group	$n = 13$
Gender	
Male	7 (53.8)[a]
Female	6 (46.2)
Age (years)	66.2 ± 10.8 (45–82)[b]
ECOG performance status	
0	4 (30.8)
1	5 (38.5)
2	4 (30.8)
Site of pancreatic disease	
Head	4 (30.8)
Body and/or tail	4 (30.8)
Head and body	5 (38.5)
UICC stage of disease	
III	5 (38.5)
IV	8 (61.5)
Metastases ($n = 8$)	
Hepatic	7 (53.8)
Pulmonary	1 (7.7)
CA19-9	
Positive	12 (92.3)
Negative	1 (7.7)
Vascular encasement	12 (92.3)
Biliary drainage	
Metal stent	2 (15.4)
Plastic stent	1 (7.7)
PTCD	1 (7.7)
Previous treatment	
Chemotherapy	10 (76.9)
Radiotherapy	1 (7.7)
Surgery	1 (7.7)
Nontherapeutic laparotomy	5 (38.5)

HIFU high-intensity focused ultrasound, *ECOG* Easter Cooperative Oncology Group, *UICC* Union internationale contre le cancer, *CA19-9* carbohydrate antigen 19–9, *PTCD* percutaneous transhepatic cholangiography drainage

[a] Number (%)

[b] Mean±standard deviation (range)

in five and four of 13 tumours, respectively. On CT images major complications were excluded. Tumour volume and ablation ratios were evaluated on postinterventional CT ($n = 4$) or MRI images ($n = 9$). Tumour volume did not change substantially within the first week and ranged from 12.4 to 68.0 mL (mean 33.0 mL), compared to 12.6–61.8 mL (mean 34.3 mL) at baseline (Table 2). The tumour ablation ratio averaged 33.7–72.3 % (50.7 ± 12.4 %).

Long-term imaging follow-up

During follow-up (Table 4, Figs. 1, 2 and 3), tumour volume regressed considerably over time in 11 of 13 patients with an average tumour volume reduction of 34.2 %±17.6 % at 6 weeks and 63.9 %±21.9 % at 3-month follow-up. Two patients showed tumour growth outside the treated tumour regions 3 months after HIFU therapy (one had no simultaneous chemotherapy because of intolerance, the other underwent radiotherapy but no simultaneous chemotherapy).

Pain relief and quality of life

After a single HIFU session, cancer-associated pain was reduced within 24–48 h in 10 of 13 (77 %) patients; five of them experienced complete and five partial pain relief. Five of 10 patients required postinterventionally less analgesic drugs. One week after HIFU three patients showed no changes in NRS; two of these had progressive liver/peritoneal metastases. Pain relief persisted during follow-up ($n = 11$ at 6 weeks and $n = 8$ at 3-month follow-up; Figs. 4, S1). Evaluation of EORTC scales (Figs. 5, S2) revealed considerable improvement of functional and symptom status over time. These were statistically significant with regard to global health status, physical functioning, emotional functioning, fatigue and pain.

Adverse events

Eight of 13 patients experienced mild to severe transient abdominal pain for up to 24 h immediately after HIFU. This required prolonged hospitalization of 7 days in one patient (tumour recurrence after radiation) and was therefore defined as a major complication. One patient showed a minor superficial umbilical second-degree burn 2 days after HIFU healing within 3 weeks without specific treatment. In one patient an induration of subcutaneous fat tissue within the upper anterior abdominal wall was observed, resolving spontaneously within 6 weeks. Local short-lasting oedema of the upper anterior abdominal wall was detected in six patients. Increase of pancreatic lipase was observed in three patients; however, this was without clinical pancreatitis-related symptoms.

Discussion

In patients with unresectable locally advanced pancreatic cancer, there is still an urgent need for effective therapies. Besides achieving sufficient local tumour control, these therapies should also improve symptoms, such as pain, and quality of life. In this regard, HIFU seems to be a promising option for patients with pancreatic cancer. During HIFU ablation, focused energy is delivered to the target tissue, causing coagulation necrosis by thermal

Table 2 Summary of initial symptoms and tumour characteristics

Patient no./ age (years)/ sex	ECOG	Pain[a]	Weight lost	Cholestasis	Biliary stent	Duodenal stenosis	Local growth[b]	Pre-HIFU tumour extension				Imaging technique	UICC disease stage	Metastatic status
								r.l. (cm)	a.p. (cm)	s.i. (cm)	Volume (mL)			
1/55/M	0	●●●	●				●	5.3	4.3	5.2	61.8	MRI	III	None
2/63/F	2	●●	●				●	5.1	4.9	4.4	57.7	MRI	IV	Hepatic, peritoneal
3/43/M	0	●●						3.5	3.6	3.0	19.6	MRI	IV	Hepatic
4/74/M	2	●	●	●	●	●	●	3.1	3.5	4.0	22.9	CT	IV	Pulmonary
5/70/M	1	●	●				●	5.1	4.9	4.1	53.0	MRI	III	None
6/56/F	1	●●●	●				●	4.8	4.1	5.7	58.6	MRI	IV	Hepatic, peritoneal
7/71/M	0	●	●					3.0	3.6	3.2	18.0	MRI	IV	Hepatic
8/74/F	1	●●	●	●	●	●		4.2	3.5	4.1	32.9	CT	III	None
9/70/F	2	●●●	●	●	●	●	●	2.8	2.9	3.0	12.6	CT	IV	Hepatic
10/74/F	0	●●	●				●	2.9	3.1	3.0	14.2	MRI	III	None
11/74/F	2	●●	●				●	4.4	3.8	4.0	36.5	MRI	IV	Hepatic
12/45/M	1	●●●	●			●		2.9	3.9	4.2	24.7	MRI	III	None
13/82/M	1	●●●	●	●	●		●	3.6	4.0	4.3	33.4	CT	IV	Hepatic

ECOG Easter Cooperative Oncology Group, *r.l.* right-left, *a.p.* anteroposterior, *s.p.* superoinferior diameter, *UICC* Union internationale contre le cancer

[a] ● mild pain, ●● moderate pain necessitated ibuprofen or novaminsulfone analgesia, ●●● severe pain necessitated opiate analgesia

[b] Local growth under therapy

effects and acoustic cavitation [23–25]. In addition, HIFU may also enhance cell-mediated immunity in the host [26–28].

As an emerging therapeutic option with encouraging clinical results, HIFU therapy can be used for patients with advanced pancreatic cancer. At present, there are two different HIFU methods available dependent on imaging guidance to treat patients with advanced solid tumours on different areas of the body: ultrasound-guided and MR-guided HIFU. Treatment of unresectable pancreatic tumours by HIFU has been performed under ultrasound guidance in the majority of reports. At present,

we are aware of early results of only one study performing MR-guided HIFU in six patients [29].

The vast majority of case series and predominantly retrospective reports on US-guided HIFU of pancreatic cancer come from Asia [10, 13–17, 21, 30–32]. More than 70 % of these publications are only available in Chinese, more than 90 % were exclusively performed in China, Korea and Japan, and more than 90 % have a retrospective study design. There are no data from the USA or Canada. To our knowledge, there is only one published European study reporting on six patients with pancreatic cancer [10]. Therefore, even though a large number of Asian patients have been treated with HIFU, there is still an urgent need for prospective controlled randomized studies in order to evaluate if Caucasian patients with pancreatic cancer in Western medical settings also benefit from this therapeutic modality.

To address some of these points, we performed a prospective observational longitudinal study in 13 Caucasian patients with unresectable late-stage pancreatic cancer. We used standardized postinterventional evaluation (US, CT, MRI imaging immediately and up to 9 months after HIFU). These patients are a highly selective subsample, i.e. about one third of the total number of patients referred to us for HIFU. Most of the referred patients were not eligible for HIFU therapy because of poor performance status, unsuitability for general anaesthesia or because tumours were not sufficiently visible on ultrasound.

Table 3 Therapeutic parameters

Treatment time (table to last sonication) (min)	114 ± 29 (77–190)
Sonication time	
(s)	1142 ± 446 (599–2452)
(min)	19 ± 7 (10–41)
Power range (W)	80–400
Average power (W)	344 ± 72 (200–400)
Greyscale changes	
Massive	5 (38.5 %)
Moderate	4 (30.8 %)
None	4 (30.8 %)

Table 4 Changes in tumour volume after HIFU therapy

Tumour volume (mL)				Tumour volume reduction (%)[b]		
pre-HIFU baseline	1 week post-HIFU	6 weeks post-HIFU	3 months post-HIFU	1 week post-HIFU	6 weeks post-HIFU	3 months post-HIFU
34.3 ± 17.9	33.0 ± 18.8	21.6 ± 10.9	13.2 ± 7.8	1.0 ± 8.6	34.2 ± 17.6	63.8 ± 21.9
(12.6–61.8)[a]	(12.4–68.0)	(11.1–41.8)	(3.3–22.1)	(−10.0 to 14.1)	(7.9–62.6)	(32.7–90.1)

[a] Mean±SD (range)

[b] Reduction of tumour volume after HIFU treatment (%)

In all HIFU-treated areas, postinterventional imaging demonstrated a lack of perfusion as direct treatment effect. In 11 of 13 patients significant tumour shrinkage was seen with an average reduction in tumour volume of 34.2 % after 6 weeks and 63.8 % after 3 months (Table 4, Figs. 1, 2 and 3). In one patient a volume reduction of even 90.1 % was seen at 3-month follow-up, and tumour remission is still observed at 12-month follow-up. Thus, sufficient control of local tumour growth can be accomplished by US-guided HIFU treatment alone or in combination with simultaneous chemotherapy. A combination of HIFU and chemotherapy with gemcitabine has been shown to be more effective in a mouse xenograft model of human pancreatic cancer [33].

A further positive effect of HIFU was improvement in cancer-related pain, which occurs in up to 80 % of patients with pancreatic cancer. Pain can be both neuropathic and nociceptive (inflammatory) resulting from tumour expansion and tumour invasion of the celiac and mesenteric plexus [34–36] and often requires opioid analgesics with disease progression. However, analgesics may have incapacitating side

Fig. 1 A 56-year-old male patient with non-resectable locally advanced adenocarcinoma in the pancreatic head and corpus and significant cancer-related pain symptoms was treated by HIFU in our hospital after the first cycle of FOLFIRINOX. Two days after HIFU pain was completely relieved. Contrast-enhanced MR images of treated tumour (transverse plane): **a** Tumour (*arrowheads*) before HIFU treatment. CA19-9, 648.8 U/mL. **b** 1 day after HIFU-treated tumour region shows no contrast enhancement indicative of effective ablation (*). **c** Considerable regression of tumour volume of 62.6 % 6 weeks after HIFU treatment. CA19-9, 336.3 U/mL. **d** Further tumour shrinkage with a volume reduction of 90.1 % 3 months after HIFU. CA19-9, 205.6 U/mL. **e** Tumour remission 12 months after HIFU. CA19-9, 15.8 U/mL. **f** Course of the tumour marker CA19-9 during 1 year-follow-up (normal range 2–37 U/mL; *horizontal grey line* indicates upper value of normal)
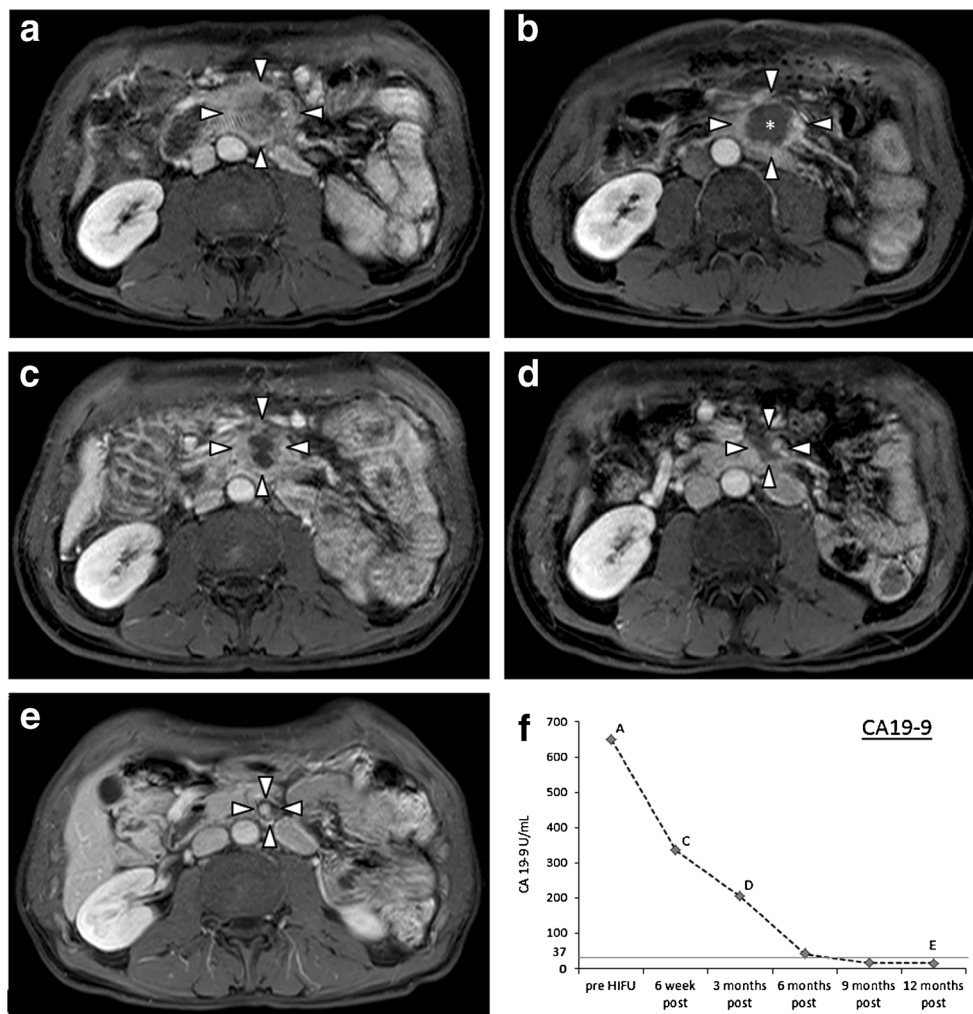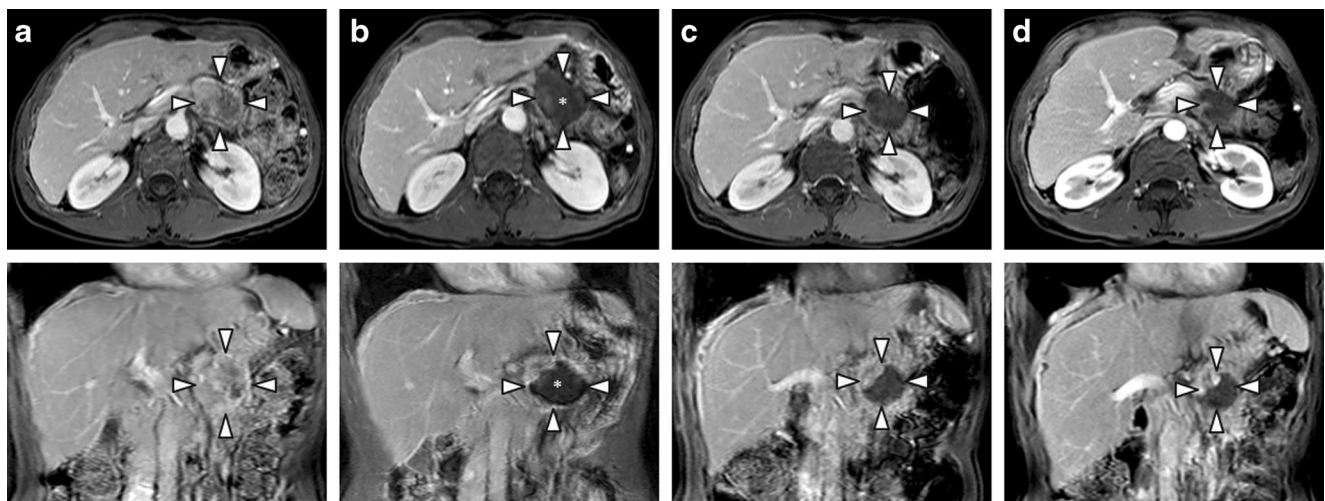
Fig. 2 A 54-year-old female patient with non-resectable locally advanced adenocarcinoma in the pancreatic corpus and tail and significant cancer-related pain necessitating opiate analgesics was treated by HIFU in our hospital additionally to gemcitabine chemotherapy. Six weeks after HIFU there was no need for any pain medication and pain was completely relieved. Contrast-enhanced MR images of treated tumour (*top row* transverse plane and *bottom row* coronal plane): **a** Tumour (*arrowheads*) before HIFU treatment. **b** 3 days after HIFU-treated tumour region shows no contrast enhancement indicative of effective ablation (*). **c** Considerable regression of tumour volume of 28.7 % 6 weeks after HIFU treatment. **d** Further tumour shrinkage with a volume reduction of 66.0 % 3 months after HIFU

effects such as nausea and vomiting, constipation, sedation, concentration difficulties or even respiratory depression with impact on the patients' quality of life. To reduce and avoid these effects, various therapeutic attempts have been implemented, e.g. percutaneous blocks of the celiac plexus [37, 38], external radiation therapy [39, 40] and chemotherapy [5–8]. However, the duration of pain control is limited, and side effects of external radiation and chemotherapy may also be

pronounced. Ablative therapies for unresectable pancreatic cancer such as radiofrequency ablation, microwave ablation, cryoablation, laser-based ablative therapies or other methods
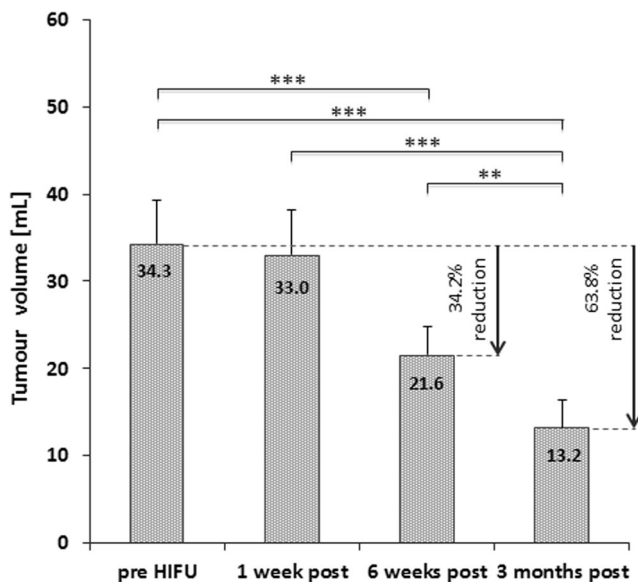

Fig. 3 Changes in tumour volume after HIFU therapy. Tumour volumes (mL) are presented as means and standard error of the mean. Volume reduction 6 weeks and 3 months after HIFU treatment compared to baseline are shown in %
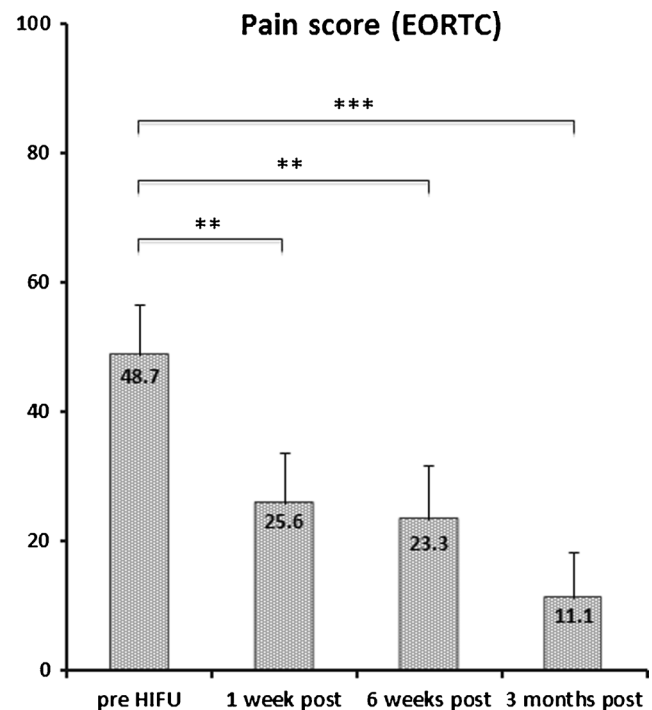

Fig. 4 Pain relief after HIFU treatment according to the pain score of EORTC QLQ-C30. Significant pain reduction was observed over time. The pain relief occurred directly to 1 week after HIFU therapy; this effect persisted over time and even improved at 3-month follow-up. *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
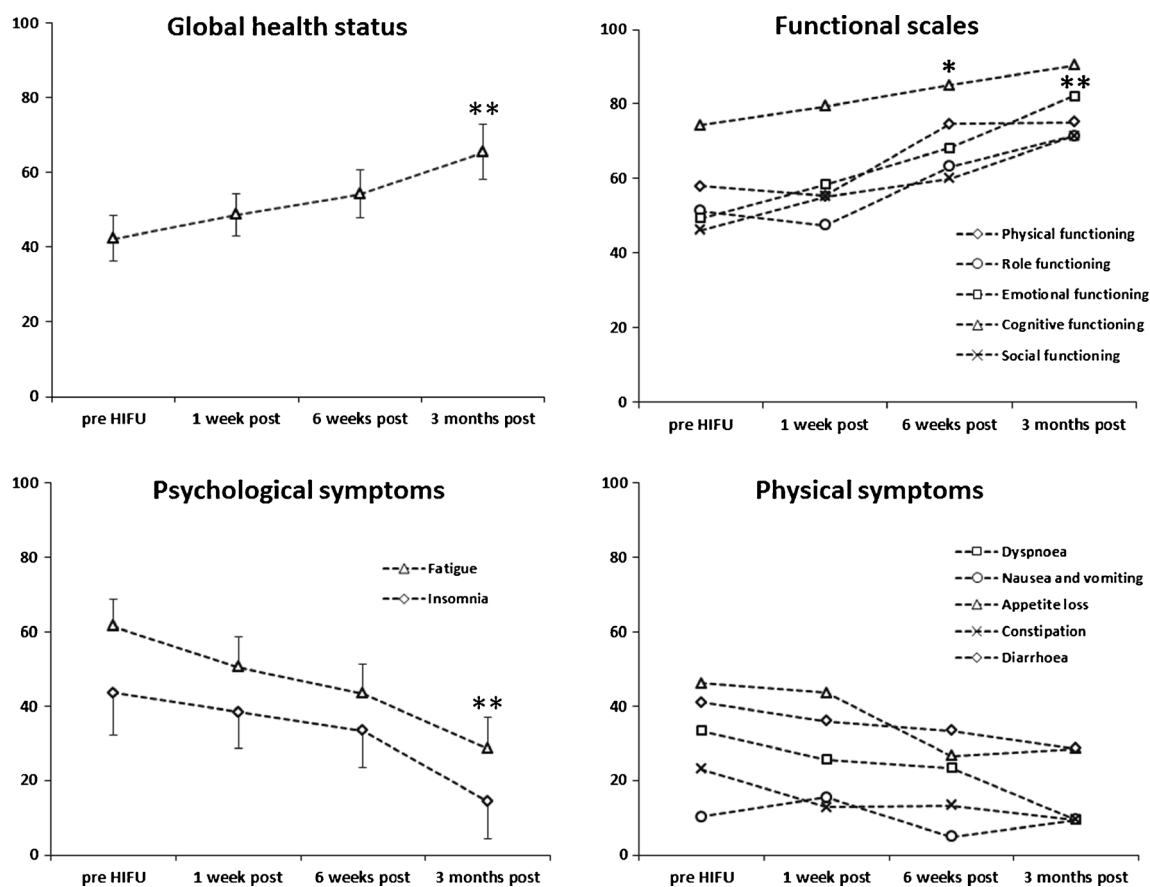
Fig. 5 Changes on the quality-of-life scales of the EORTC QLQ-C30 questionnaire over time (mean±standard error of the mean) in patients with locally advanced or metastatic pancreatic cancer who underwent at least one follow-up examination after HIFU treatment

such as irreversible electroporation have been demonstrated to be feasible and reproducible and improve quality of life [41–44]. However, these techniques necessitate needle or probe positioning within the tumour which is associated with increased risk of injury of adjacent critical structures such as stomach, bowel or vessels. Despite initial studies suggesting an additional survival benefit over best supportive care, prospective randomized studies are missing.

HIFU therapy is a non-invasive method of ablation for the treatment of locally advanced, unresectable and metastatic pancreatic carcinoma and may be a potent treatment alternative for pain control in these patients: ultrasound-related destruction of pancreatic cancer cells reduces algesic stimulation, and neural fibres may also be destroyed accounting for further effects on pain. Ongoing tumour shrinkage may additionally reduce pressure upon neural structures.

In this study, cancer-related pain was the leading clinical symptom in all patients. Despite palliative chemotherapy, 10 of 13 patients required daily analgesics. Consistent with published reports [10, 13, 14, 17, 21, 30, 31], after a single HIFU session, pain was substantially reduced within 24–48 h in 10 of 13 patients (77 %) experiencing complete or partial pain relief. The early reduction of cancer-associated pain is not a

function of tumour shrinkage, since no tumour shrinkage was observed 1 week after HIFU. This functional response preceded the structural changes on a macrolevel. On a microlevel, changes of inflammatory processes such as cytokine expression and action may result in a reduced inflammatory tumour environment [26]. In addition, HIFU could have destroyed some locally active nociceptive nerve fibres. With reduced peripheral nociceptive input, central nociceptive sensitization of spinal dorsal horn neurons may be reduced. This combined peripheral and central reduction of previously increased neuronal excitability may account for prolonged and early decrease of ongoing pain intensity.

In contrast to experience with celiac or splanchnic blocks, in our patient cohort pain relief following HIFU persisted over time (Figs. 4 and S1 show follow-up up to 3 months) leading to markedly improved quality of life. At 6-week follow-up, functional status improved and symptoms were alleviated; this effect was even more pronounced 3 months after HIFU (Fig. 5). Most relevant were changes in pain intensity, global quality of health, physical functioning, emotional functioning and fatigue (Fig. 5, Table 5). Symptoms such as insomnia, appetite loss and dyspnoea were alleviated. Other symptoms such as diarrhoea did not change considerably after HIFU, as

most patients underwent simultaneous chemotherapy which together with tumour-associated diarrhoea is the leading cause for this symptom.

It has also been claimed in Asian studies that HIFU has an effect on overall survival. Reported median overall survival and median time to progression ranged from 6 to 11 months and from 5 to 8.4 months, respectively [16, 17, 21, 45]. One-year survival rates after HIFU reached 30.8 to 42 % [13, 17]. Moreover, Spanish results also suggest a survival advantage in stage III and IV pancreatic cancer (median survival of 13 months) [46].

Our study was not designed for evaluation of survival. During the time course of the study, four patients died as a result of progressive liver metastasis: two at 3 months, one at 4 months and one at 6 months after HIFU. Nonetheless, this study provides further evidence that HIFU offers a quick functional benefit and improvement of quality of life in Caucasian patients with advanced pancreatic cancer.

With technical improvements over time and increasing experience, the HIFU procedure has become rather safe [47]. Skin burns and subcutaneous tissue indurations have been reported in 3.1 % of 1717 Asian patients. Pancreatitis (1.9 %) and diabetes (1.3 %) were organ-specific problems. Other associated problems were jaundice aggravation (0.6 %), bleeding (0.1 %), occlusion of superior mesenteric artery (0.06 %), hepatic abscess (0.06 %), steatorrhoea (0.8 %), gastroenteric dysfunction (0.8 %) and vertebral damage (0.1 %). Further very rare adverse events following HIFU include peritonitis, formation of pancreatic pseudocysts, leakage of pancreatic and bile duct juice, or intestinal perforation.

In our small cohort of patients, there was one case of a minor superficial umbilical burn and one case of induration of subcutaneous fat tissue within the left upper anterior abdominal wall, both resolving spontaneously within 3 and 6 weeks, respectively. Local slight short-lasting subcutaneous oedema of the upper anterior abdominal wall was seen in about half our patients and resolved within 7–10 days without specific treatment. It is interesting that only three patients showed an elevated pancreatic lipase after HIFU, in no case accompanied by clinical signs of pancreatitis. Mild discomfort or local pain was observed rather often for up to 10 h after treatment, consistent with other studies [48–50]. Symptoms of venous intestinal congestion were seen in one patient after HIFU who had been repeatedly hospitalized because of this before undergoing HIFU treatment. We did not observe intestinal perforations or arterial obstructions. As HIFU does not interfere with chemotherapy, the latter does not have to be interrupted.

Collectively, our data indicate that HIFU can be safely and successfully applied toward tumour volume reduction and alleviation of cancer-related pain in pancreatic cancer. Patients treated with HIFU and simultaneous chemotherapy experienced significant and lasting reduction of pain intensity and tumour volume regression over time. Hence, quality of life was significantly improved. Nevertheless, large-scale prospective randomized clinical trials are necessary to evaluate the safety and long-term efficacy of HIFU treatment especially regarding overall survival with or without simultaneous chemotherapy and/or targeted drug therapy.

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