

Clinical Effectiveness and Potential Survival Benefit of US-Guided High-Intensity Focused Ultrasound Therapy in Patients with Advanced-Stage Pancreatic Cancer

Klinische Wirksamkeit und potenzielle Überlebensvorteile der Therapie mit US-gesteuertem hoch-intensivem fokussiertem Ultraschall bei Patienten mit fortgeschrittenem Pankreaskarzinom

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ABSTRACT

Purpose Pancreatic cancer (PaC) is a life-limiting tumor with a wide range of incapacitating symptoms such as cancer pain in more than 80 % of patients. This prospective interventional study addresses the clinical effectiveness of ultrasound-guided high-intensity focused ultrasound (HIFU) treatment for patients with advanced-stage PaC, including pain perception, tumor size and survival benefit.

Materials and Methods 50 patients with late-stage PaC underwent HIFU. Clinical assessment included evaluation of tumor volume by imaging and pain burden (pain severity, pain sensation, interference with daily activities) using the Brief Pain Inventory at baseline and follow-up. Median overall survival, progression-free survival and time to local progression were estimated using Kaplan-Meier analysis.

Results In 84 % of patients, significant early relief of cancer-induced abdominal pain was achieved by HIFU independent of metastatic status; it persisted during follow-up. Tumor volume reduction was 37.8 ± 18.1 % after 6 weeks and 57.9 ± 25.9 % after 6 months. 21 % of HIFU-treated patients had local tumor progression with a median time of 14.4 months from intervention. The median overall survival and progression-free survival were 16.2 and 16.9 months from diagnosis and 8.3 and 6.8 months from intervention.

Conclusion In patients with advanced pancreatic cancer and otherwise limited treatment options, HIFU resulted in significant early and long-lasting pain relief and tumor size reduction over time independent of metastatic status. Clinical data suggest an additional potential survival benefit.

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ZUSAMMENFASSUNG

Ziel Das Pankreaskarzinom ist ein lebenslimitierender Tumor mit einer Vielzahl von tumorbedingten Beschwerden wie Tumorschmerzen bei mehr als 80 % der Patienten. Ziel dieser prospektiven Studie ist, die klinische Wirksamkeit des Ultraschall-gesteuerten hoch-intensiven fokussierten Ultraschalls (HIFU) in Bezug auf die Schmerzintensität und -empfindung, die Tumorgroße und das Überleben zu evaluieren.

Material und Methode Fünfzig Patienten mit fortgeschrittenem Pankreaskarzinom wurden mit HIFU behandelt. Die klinische Evaluation umfasste die Beurteilung des Tumorumfanges durch bildgebende Verfahren sowie der Schmerzbelastung (Schmerzintensität, Schmerzempfindung, Beeinträchtigung der täglichen Aktivitäten) anhand des Brief-pain-inventory-Fragebogens initial und im Verlauf. Das mediane Gesamtüberleben, das progressionsfreie Überleben und die Zeit bis zum lokalen Progress wurden mit der Kaplan-Meier-Analyse evaluiert.

Ergebnisse Nach HIFU wurde bei 84 % der Patienten eine signifikante frühzeitige Reduktion von tumorinduzierten Bauchschmerzen unabhängig vom Metastasierungsstatus erreicht; dieser Effekt blieb im Verlauf erhalten. Die Tumorumfangsreduktion betrug $37,8 \pm 18,1\%$ nach 6 Wochen und $57,9 \pm 25,9\%$ nach 6 Monaten. 21 % der HIFU-behandelten Patienten hatten einen lokalen Tumorprogress mit einer medianen Zeit von 14,4 Monaten nach Intervention. Das mittlere Gesamtüberleben und das progressionsfreie Überleben waren jeweils 16,2 und 16,9 Monate ab Erstdiagnose und 8,3 und 6,8 Monate ab HIFU-Intervention.

Schlussfolgerung Bei Patienten mit fortgeschrittenem Pankreaskarzinom führte HIFU zu einer signifikanten und anhaltenden Schmerzlinderung und Tumorumfangsreduktion im zeitlichen Verlauf unabhängig vom Metastasierungsstatus. Die Auswertung der Überlebensdaten gibt zusätzlich Hinweise auf einen potenziellen Vorteil.

Introduction

With a 5-year survival rate of 8 %, pancreatic cancer (PaC) has a dismal prognosis [1]. Worldwide PaC is the eighth leading cause of death from cancer in men and the ninth leading cause of death from cancer in women [2]. 85–90 % of patients present with advanced disease and are considered unresectable due to locally advanced tumor or presence of metastases. Symptoms often include severe pain in the back or stomach area, unexpected weight loss, jaundice, malaise, diarrhea, loss of appetite, thus severely reducing patients' quality of life (QoL) [3]. The median survival time is 6 to 10 months and in the case of metastatic disease 3 to 6 months [1, 2]. Current standard therapy in advanced PaC using chemotherapy or radiochemotherapy has only limited antitumoral effects and survival advantage. Despite a few established chemotherapy regimens, such as FOLFIRINOX, and the addition of nab-paclitaxel to gemcitabine, the 1-year survival rate of patients with inoperable PaC is only about 18–20 % and the 5-year survival rate is less than 1 % [1, 4]. Nearly 75 % of patients with locally advanced disease suffer from serious cancer-related abdominal or back pain substantially reducing their health-related QoL. Cancer pain often requires opioid analgesics which may be associated with difficult side effects. Percutaneous celiac plexus blocks, external radiation therapy and chemotherapy showed only limited duration of pain control. Other invasive/minimally invasive thermal and laser-based ablative techniques or irreversible electroporation (IRE) are often associated with a negative benefit-risk assessment or significant morbidity and mortality [5]. Therefore, high-intensity focused ultrasound (HIFU) could be of particular value in this patient population with otherwise limited treatment options [6, 7]. Ultrasound (US)-guided HIFU is based on the delivery of focused energy to the target tissue mainly causing coagulation necrosis by thermal effects and acoustic cavitation without damaging the adjacent structures at risk [8]. This prospective observational study includes the largest number of Caucasian

patients to date and evaluates for the first time the clinical effectiveness regarding pain burden including both pain severity and pain sensation in patients with advanced PaC with and without metastatic disease. Local tumor control and possible survival benefits were additionally investigated.

Materials and Methods

Patient selection

50 patients with histologically proven, locally advanced and/or metastatic PaC (48 patients with pancreatic ductal adenocarcinoma, 2 patients with recurrence after Whipple surgery) undergoing standard palliative therapy received additional US-guided HIFU. All patients provided written informed consent. This prospective study was approved by the institutional review board (302/12, 307/15) prior to trial initiation and registered at the German Clinical Trials Register (DRKS).

Eligibility for HIFU was confirmed in a multidisciplinary tumor conference in consensus with oncologists, gastroenterologists and surgeons. The key inclusion and exclusion criteria are summarized in ► Table 1. At presentation, all patients showed incapacitating symptoms such as cancer pain and/or local findings (tumor-related cholestasis, infiltration of adjacent organs and vessels with mesenteric or splenic vein occlusion, etc.). 84 % of patients (42/50) were receiving chemotherapy at the time of presentation at our hospital. Because HIFU ablation was considered as an addition to standard systemic therapy, patients continued chemotherapy after HIFU treatment without changing the standard chemotherapy regimens. Eight patients did not undergo chemotherapy either before or after HIFU ablation and the main reason for this was intolerance.

► **Table 1** Inclusion and exclusion criteria for HIFU treatment.

inclusion criteria	exclusion criteria
<ol style="list-style-type: none"> 1. age ≥ 18 years 2. ECOG functional status 0 – 2 3. histologically/clinically diagnosed inoperable pancreatic carcinoma 4. tumor diameter ≥ 2 cm verified by imaging (CT, MRI) within the last 8 weeks 5. cancer pain and local tumor growth 6. written informed consent 7. sufficiently visible tumor on ultrasound 8. distance between skin surface and deepest tumor regions of maximum 11 cm 9. eligibility for general anesthesia 	<ol style="list-style-type: none"> 1. age < 18 years 2. ECOG functional status > 2 3. eligibility for surgical resection 4. tumor not sufficiently visible on ultrasound 5. non-eligibility for general anesthesia

Pre-treatment procedures and HIFU intervention

Pre-treatment evaluation included medical history, physical examination and laboratory tests, as well as an abdominal ultrasound examination. Due to the lesion proximity to the gastrointestinal tract, a specific bowel preparation similar to colonoscopy preparation is required to avoid possible complications. The bowel preparation starts one day before the procedure and consists of liquid food, no milk or other gas producing products, fasting for 12 hours, and use of laxatives. On the treatment day, a naso-gastric tube is placed for intragastric gas reduction. The skin of the patient's upper abdominal wall is shaved, degreased and degassed. Degassing is performed using a special device to remove even the smallest residual air bubbles from the skin pores in order to prevent skin burning.

US-guided HIFU ablation was performed using the Focused Ultrasound Tumor Therapeutic System (JC HIFU, Chongqing HAIFU Technology, China) equipped with a 1 – 8 MHz ultrasound imaging device (MyLab 70, Esaote, Italy) for real-time guidance of the treatment. The therapeutic ultrasound beam was transmitted by a ceramic transducer with a diameter of 20 cm and a focal length of 15 cm, operated at a frequency of 0.8 MHz. The design of the HIFU system with the water basin and transducer below the table requires treatment in the prone position. Water is used as a coupling medium between the ultrasound device and the patient's skin. For planning and ablation, a sagittal scanning mode was used. US energy was delivered to a circumscribed focal area using a dot mode. Ablation of larger volumes was obtained by sonication of multiple foci. The final sonication power (200 – 400 W) was determined exclusively for each tumor depending on adjacent structures at risk, e. g. stents or bowel loops. A power of 300 W was generally applied in the tumor center in tumors up to 4 cm in size, and a power of 400 W in tumors larger than 4 cm. For ablation of the tumor periphery, a power of 200 W was applied with a margin of 1 cm with respect to the border of the mass. A

safety margin of 1 cm with respect to biliary stents and other structures at risk (bowel, stomach) was maintained to prevent potential damage by local temperature increase. To avoid injury of gastrointestinal structures at risk in the acoustic pathway, a water-filled balloon was placed between the patient's upper abdominal wall and the transducer. The balloon served to compress the stomach, push the bowel away and maintain an optimum acoustic window. To avoid skin burning and prevent cutaneous edema, the skin was cooled by water in the water basin during treatment, and repeatedly checked by palpation after each 150 s of sonication time.

During the HIFU procedure, the extracorporeal therapeutic transducer generates an ultrasound beam forming an oval-shaped focus with a width of 1 – 3 mm and a length of 8 – 15 mm (► **Fig. 1**, **Supplementary Fig. 1, 2**). In this way a lesion of coagulation necrosis can be induced in the target area. In the case of visible grayscale changes in the target area suggesting effective ablation or after 150 s sonication time in the center and 50 s at each other focal point, the transducer was moved to the next focus. Multiple juxtaposed lesions generate linear and discoidal necrosis areas and ultimately allow ablation of the whole tumor area.

Follow-up

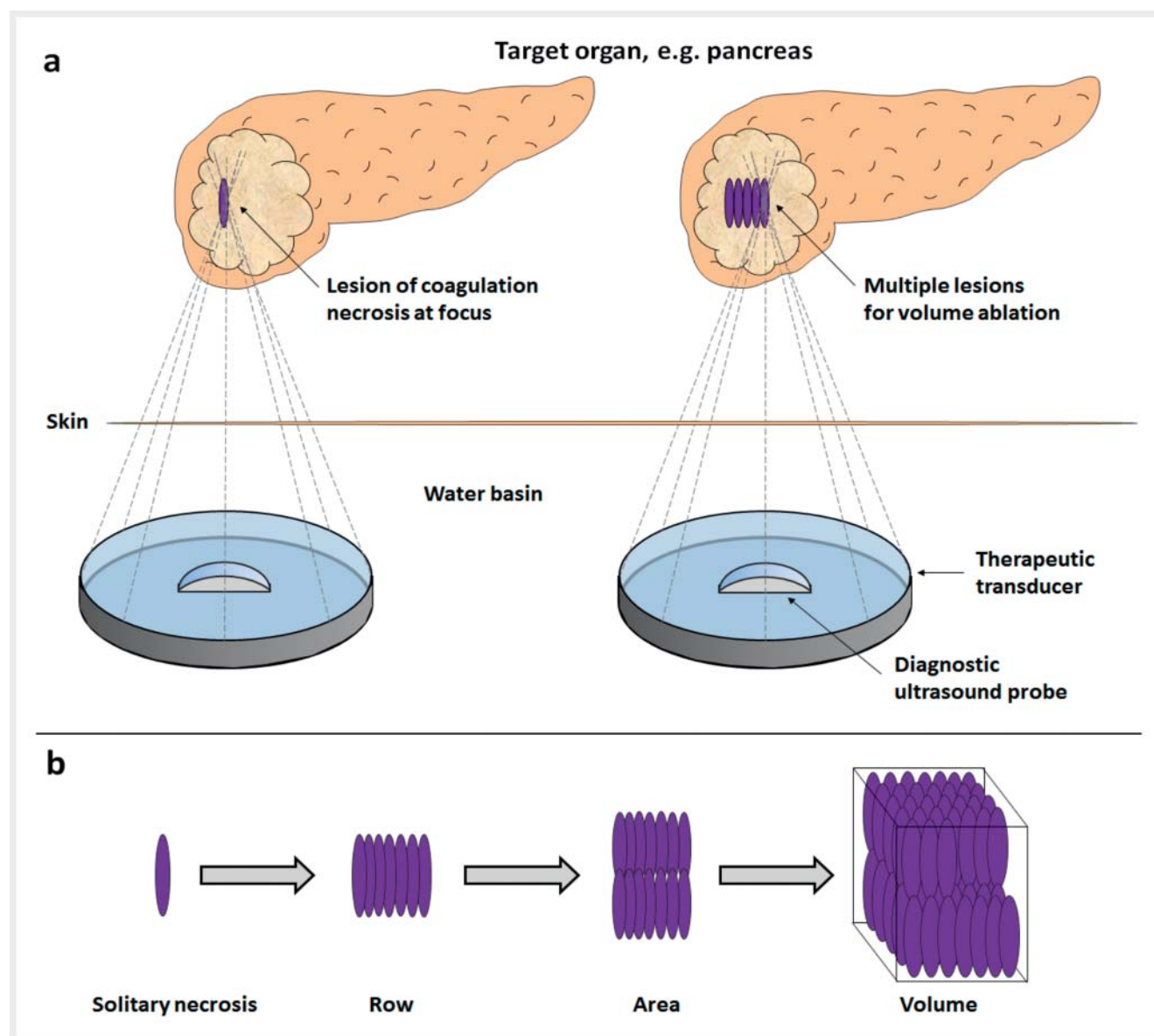
Imaging included contrast-enhanced CT and MRI examinations (64-slice CT Brilliance, 1.5-Ingenia MRI, Philips, the Netherlands) and US (Logiq E9, GE, USA). Within the first 24 hours after HIFU procedure, CT and CEUS were performed to exclude early treatment-related complications and evaluate initial treatment effectiveness. MRI of the pancreas within one week post-procedure was used for precise evaluation of treatment efficacy. Long-term follow-up included CT (for staging) and MRI at 6 weeks and 3 months after HIFU, then every 3 months until death, if patients were not lost to follow-up.

Local recurrence was defined as a focal or diffuse growing mass ($> 20\%$ of solid lesion increase in longest diameter on the axial plane) within 1 cm of the ablated region. In such cases, retreatment was considered if recurring tumor-associated pain was present.

Pain perception including pain severity and pain sensation as well as pain interference with daily activities was assessed using the Brief Pain Inventory (BPI, German version) (► **Table 5**).

Statistical analysis

Data were analyzed using Stata version 13.1 (Stata Corp, Lakeway Drive College Station, US). Primary statistical evaluation of BPI scales and tumor volumes were performed at baseline and follow-up using a mixed panel data model. Overall survival (OS), progression-free survival (PFS) and time to local progression (defined as local tumor growth by $\geq 20\%$ compared to baseline) were estimated from time of diagnosis and time of HIFU intervention using non-parametric analysis (Kaplan-Meier methods). Progression in PFS was defined as local or distant progression (progression of existing metastases by $\geq 20\%$ of the largest diameter of target lesions or detection of new metastases). In case of death without local progression or progression of metastases, patients were censored. Log-rank tests and Wilcoxon tests were



► **Fig. 1** Schematic illustration of HIFU ablation. **a** An extracorporeal therapeutic transducer generates an ultrasound beam forming an oval-shaped focus (1–3 mm wide, 8–15 mm long) with a lesion of coagulation necrosis in the target. The diagnostic ultrasound probe and therapeutic transducer are located in a water basin underneath the patient lying in a prone position. Multiple lesions at the focus allow volume ablation of the tumor. **b** The application of sequential single lesions generates linear and discoidal necrosis areas to achieve volume ablation.

performed for testing equality of survivor functions between groups. To evaluate the effect of distant metastases (UICC stage III vs. IV) and ECOG performance status at baseline, semiparametric analysis and generalized linear models (Cox regression, Poisson) were used.

Results

Between May 2014 and October 2016, 96 patients with locally advanced PaC were evaluated for inclusion by the multidisciplinary tumor board. Selection exclusion criteria are listed in ► **Table 1**. Patients with very extensive liver metastases or widespread peri-

toneal carcinosis and considerable cancer-induced abdominal pain were treated outside this study for compassionate reasons.

50 patients with locally advanced PaC undergoing US-guided HIFU were included in the study. Baseline information (demographic characteristics, stage of disease, previous treatment etc.) is presented in ► **Table 2**. All treated lesions were in close proximity to the stomach, bowel and/or main blood vessels in the upper abdomen. The median hospital stay was 4 days, including the treatment day (range: 3–7 days).

US-guided HIFU was successfully performed in all patients, even in the presence of biliary stents and tumor vessel encasement. Within the study, HIFU treatment was performed under general anesthesia, especially to avoid uncontrolled movements

► **Table 2** Demographic and clinical characteristics of HIFU-treated patients with non-resectable pancreatic cancer (n = 50).

parameter	all patients	patients without distant metastases ¹	patients with distant metastases ²
Study group	50	21	29
gender			
▪ male	26 (52%) ³	11	15
▪ female	24 (48%)	10	14
age	65.0 ± 9.7 (41 – 82) ⁴	62.4 ± 10.5 (47 – 81)	64.7 ± 9.4 (41 – 82)
ECOG			
▪ 0	16 (32%)	5	11
▪ 1	26 (52%)	15	11
▪ 2	8 (16%)	1	7
site of pancreatic disease			
▪ head	27 (34%)	10	17
▪ body and/or tail	10 (20%)	3	7
▪ head and body	13 (26%)	8	5
UICC stage of disease			
▪ stage III	19 (38%)	19	0
▪ stage IV	29 (58%)	0	29
▪ recurrence after Whipple procedure	2 (4%)	2	0
metastases			
▪ hepatic	23 (46%)	0	23
▪ pulmonary	8 (16%)	0	8
▪ peritoneal/lymph nodes	28 (56%)	11	17
CA 19 – 9			
▪ positive	37 (74%)	17	20
▪ negative	10 (20%)	4	6
▪ no laboratory data	3 (6%)	0	3
biliary drainage			
▪ metal stent ⁵	9 (18%)	4	5
▪ plastic stent ⁵	7 (14%)	3	4
▪ PTCD	1 (2%)	0	1
previous treatment			
▪ chemotherapy	42 (84%)	20	22
▪ radiotherapy	5 (10%)	2	3
▪ surgery (Whipple)	2 (4%)	2	0

CA 19 – 9: Carbohydrate antigen 19 – 9 (tumor marker); ECOG: Eastern Cooperative Oncology Group performance status (0 – 5); HIFU: High-intensity focused ultrasound. PTCD: Percutaneous transhepatic cholangiography drainage. UICC: Tumor classification of the Union for International Cancer Control

¹ Including patients with UICC stage III (n = 19) and tumor recurrence after Whipple (n = 2).

² Including patients with UICC stage IV.

³ Number (%).

⁴ Mean ± standard deviation (range).

⁵ Including one patient with both a metal and a plastic stent.

of the patient under conscious sedation resulting in displacement of ventrally located structures (e. g. stomach, bowel loops). These would increase the risk of injury and lead to treatment interruptions with consecutively longer treatment times.

Most patients (45/50) underwent a single HIFU session. HIFU treatment was performed for a second time in 5 patients with local tumor recurrence in the periphery of previously treated regions and recurring tumor-associated symptoms. Intervention data are summarized in ► **Table 3**. 31 of 50 treated tumors showed grayscale changes during treatment. Immediate post-procedural CEUS showed no contrast enhancement in treated tumor areas indicative of devascularization. Treated regions without visible grayscale changes (19 from 50 tumors) also showed absent

contrast enhancement on CEUS. None of the 16 stents was affected or damaged by the HIFU procedure. Postinterventional CT imaging excluded major treatment-related complications like bowel perforation or vessel occlusion. Determination of tumor volume and ablation ratios on post-interventional MRI (n = 46) or CT (n = 4) (► **Fig. 2, 3**) revealed no change in tumor size within the first week with volumes averaging 25.6 ± 14.9 ml vs. 25.9 ± 15.9 ml at baseline ($p = 0.926$) (► **Table 4**, ► **Fig. 2**). The tumor ablation ratio (non-perfused to total tumor volume) was 59.3 ± 15.6 %. A tumor volume reduction was seen during follow-up in 97.2 % at 6 weeks, 91.7 % at 3 months and 85.7 % at 6 months after treatment; it averaged 37.8 ± 18.1 %, 51.8 ± 19.5 % and 57.9 ± 25.9 % of initial volumes, respectively.

During the observational period of 3 years, 28 patients died. The leading cause of death (n = 23, 82 %) was progressive disease (e. g. progressive liver metastases, diffuse peritoneal tumor growth). Non-cancer-related causes of death were myocardial infarction, pulmonary embolism, and stroke, each in one patient, and critical illness due to cancer-related immunosuppression in two patients. No procedure-related deaths were observed.

Post-procedural pain perception

Up to 24 hours after HIFU intervention, 58 % (29/50) of patients experienced transient abdominal pain, which was considered mild by 18 and severe by 11 patients. **Within the first week post-procedure, 84 % (42/50) of patients reported considerable reduction of averaged pain severity compared to baseline** ($p < 0.001$)

► **Table 3** Therapeutic parameters of US-guided HIFU (n = 50).

treatment time ¹ [min]	117 ± 33 (60 – 231) ²
sonication time [s]	899 ± 356 (314 – 2452)
total energy [J]	$330\,433 \pm 138\,954$ (93\,600 – 851\,200)
average power [W]	359 ± 54 (200 – 400)
energy/volume [J/ml]	$16\,750 \pm 12\,132$ (2772 – 76\,734)

¹ time from positioning on therapeutic table to last sonication.

² mean $\pm$ standard deviation (range).

► **Table 4** Tumor volume of HIFU-treated patients with advanced pancreatic cancer including patients without and with distant metastases at baseline and follow-up (1 and 6 weeks, 3 and 6 months after HIFU) and corresponding tumor volume reduction.

	baseline	FU1 1 week after HIFU	FU2 6 weeks after HIFU	FU3 3 months after HIFU	FU4 6 months after HIFU
all patients	26.0 ± 15.9 ml (4.5 – 83.6 ml) ¹	25.6 ± 14.9 ml (3.5 – 80.2 ml)	17.1 ± 11.3 ml (3.0 – 46.7 ml)	12.1 ± 7.6 ml (2.9 – 27.4 ml)	10.6 ± 7.0 ml (2.8 – 25.3 ml)
		NPV 59.3 ± 15.6 % (32.9 – 100 %)	VR 37.8 ± 18.1 % (6.2 – 65.3 %)	VR 51.8 ± 19.5 % (21.1 – 90.1 %)	VR 57.9 ± 26.0 % (13.4 – 95.5 %)
patients without distant metastases ²	23.4 ± 13.4 ml (8.0 – 61.8 ml)	22.8 ± 13.8 ml (8.0 – 68.0 ml)	15.6 ± 9.8 ml (5.9 – 38.9 ml)	9.7 ± 5.6 ml (5.3 – 22.1 ml)	8.9 ± 5.5 ml (2.8 – 18.2 ml)
		NPV 55.3 ± 14.1 % (32.9 – 79.9 %)	VR 37.6 ± 21.2 % (5.0 – 62.6 %)	VR 54.2 ± 20.4 % (25.0 – 90.1 %)	VR 60.0 ± 28.3 % (23.8 – 95.5 %)
Patients with distant metastases ³	27.7 ± 17.4 ml (4.5 – 83.6 ml)	27.5 ± 15.6 ml (3.5 – 80.2 ml)	18.2 ± 12.4 ml (3.0 – 46.7 ml)	14.7 ± 9.0 ml (2.9 – 27.4 ml)	12.6 ± 8.7 ml (4.8 – 25.3 ml)
		NPV 62.6 ± 17.9 % (33.3 – 114.9 %)	VR 36.1 ± 17.5 % (11.3 – 65.3 %)	VR 46.5 ± 19.6 % (21.1 – 83.2 %)	VR 48.5 ± 26.2 % (13.4 – 80.9 %)

HIFU: High-intensity focused ultrasound; NPV: Non-perfused volume (%); VR: Volume reduction (%); UICC: Tumor classification of the Union for International Cancer Control.

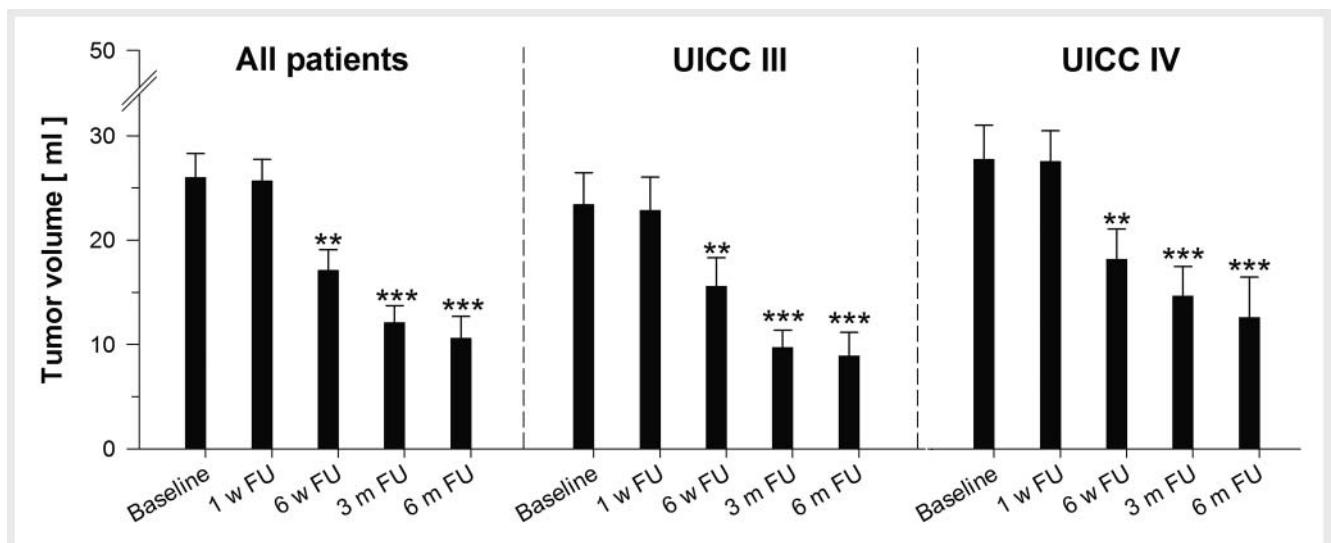
¹ mean $\pm$ standard deviation (range).

² Including patients with UICC stage III (n = 19) and tumor recurrence after Whipple procedure (n = 2).

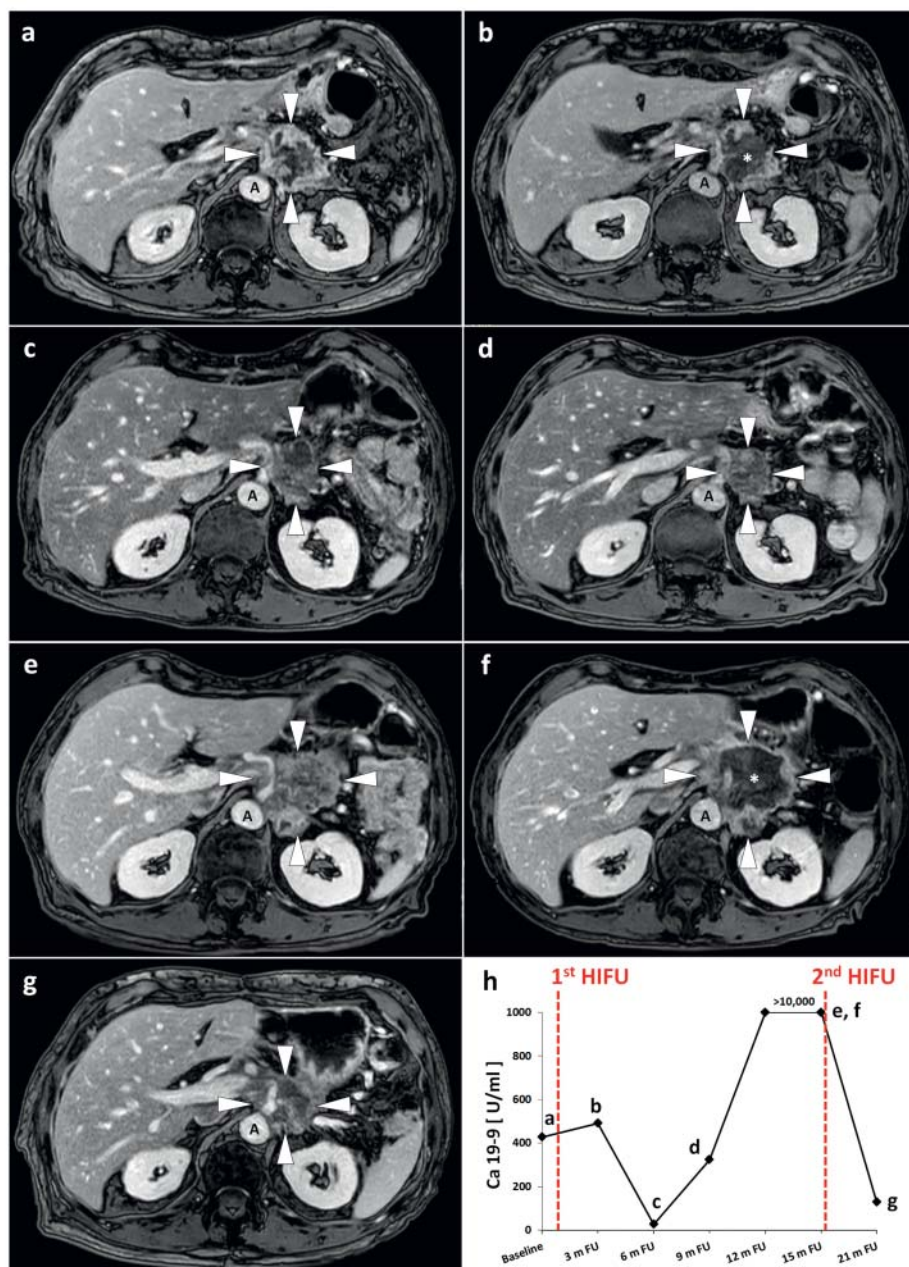
³ Including patients with UICC stage IV (n = 29).

► **Table 5** Overview of BPI (brief pain inventory) questionnaire used for evaluation of pain perception at baseline and follow-up.

scale	range		measure and items
pain severity	0 – 10	0 “no pain” 10 “pain as bad as you can imagine”	arithmetic mean of four pain severity items: 1. worst pain 2. least pain 3. average pain 4. pain right now
pain sensation	0 – 3	0 “does not apply” 3 “fully applies”	arithmetic mean of fifteen adjectives applying to the pain perceived: 1. aching 2. throbbing 3. shooting 4. stabbing 5. gnawing 6. sharp 7. tender 8. burning 9. exhausting 10. tiring 11. penetrating 12. nagging 13. numb 14. miserable 15. unbearable
interference with daily activities	0 – 10	0 “does not interfere” 10 “completely interferes”	arithmetic mean of seven interference items: 1. general activity 2. mood 3. walking activity 4. normal work 5. relations with other people 6. sleep 7. enjoyment of life



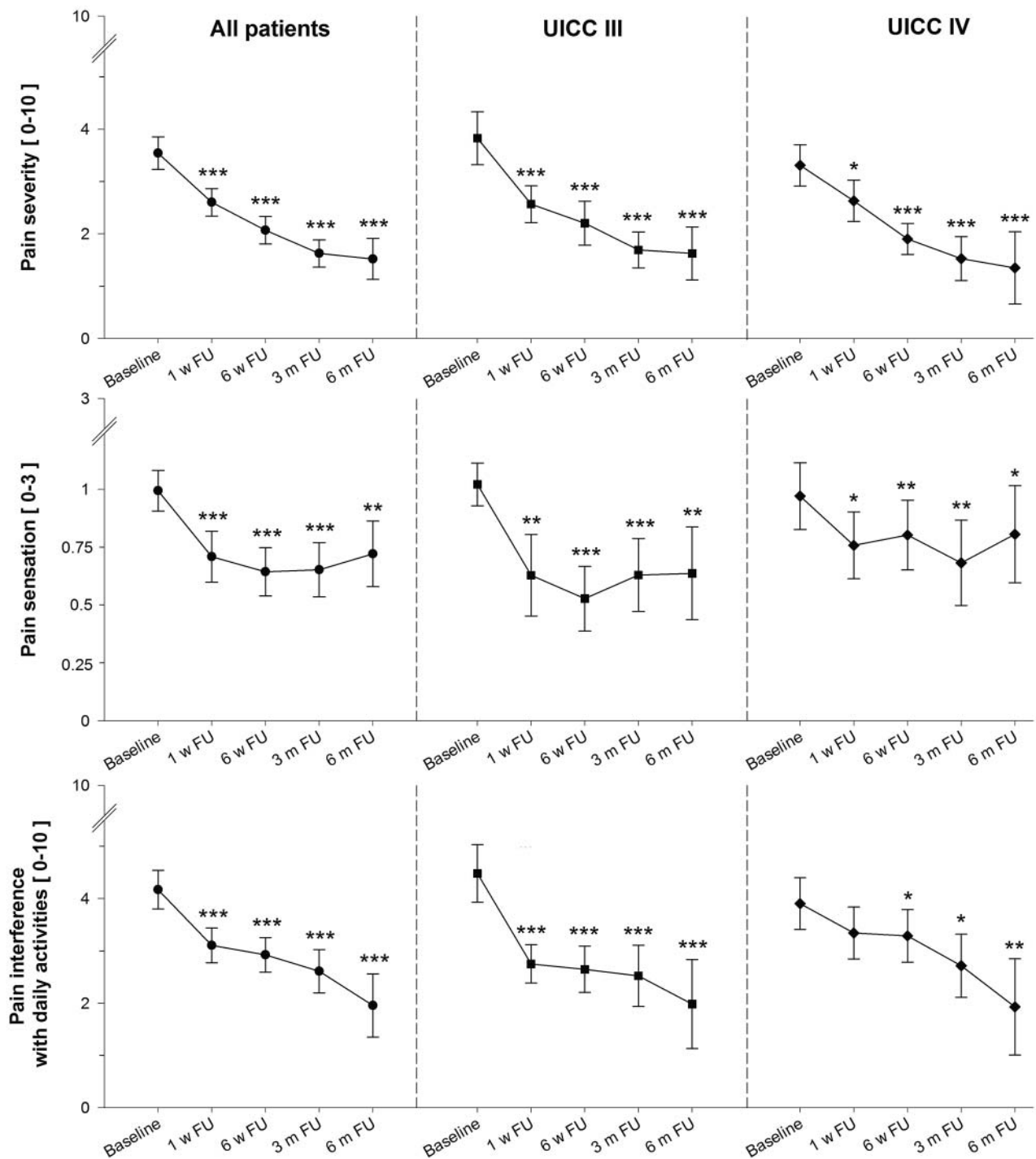
► **Fig. 2** Tumor volume regression over time following US-guided HIFU for advanced pancreatic cancer. Considerable tumor volume reduction 6 weeks, 3 and 6 months after HIFU treatment compared to baseline was achieved in non-metastatic and metastatic patients with advanced pancreatic cancer. Tumor volumes (ml) are presented as means and standard error of the mean. FU: follow-up; m: month; w: week; UICC: tumor classification of the Union for International Cancer Control.



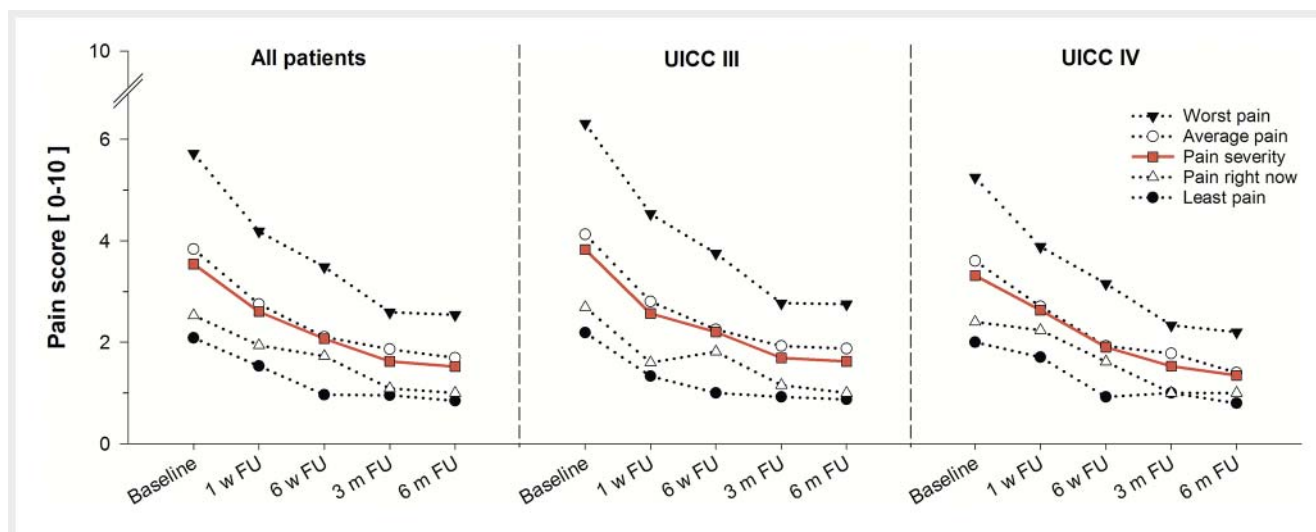
► **Fig. 3** A 70-year-old male patient with non-resectable locally advanced adenocarcinoma of the pancreatic body and tail (UICC stage III) was treated by HIFU in our hospital. No simultaneous chemotherapy was given to the patient because of intolerance. Contrast-enhanced MR images (T1w FFE, transverse plane) are shown as follows: **a** Tumor (arrowheads) before HIFU treatment with an initial tumor volume of 53.0 ml. Baseline CA19-9: 426.5 U/ml. **b** One day after HIFU, treated tumor regions showed no contrast enhancement indicative of effective ablation (*). CA19-9 one week after HIFU: 491.4 U/ml. **c, d** Considerable regression of tumor volume of 64.4% and 79.9% at 3- and 6-month follow-up after HIFU treatment without simultaneous chemotherapy; corresponding CA19-9 values of 26.9 and 324.0 U/ml at 3- and 6-month follow-up, respectively. **e, f** Local tumor progression at 15-month follow-up **e** by 81% compared to baseline (95.9 ml vs. 53.0 ml; CA19-9 52,984.3 U/ml), then consecutive 2nd HIFU, one day thereafter **f** treated tumor regions show no contrast enhancement again indicative of effective ablation (*). **g** Significant tumor shrinkage 6 months after 2nd HIFU procedure with a volume reduction of 79.5% (19.7 ml). **h** Course of the tumor marker CA19-9 during 21-month follow-up (normal range 2–37 U/ml). A: Aorta; CA19-9: Carbohydrate antigen 19-9 (tumor marker); UICC: Tumor classification of the Union for International Cancer Control.

(► **Fig. 4, 5**). This effect was even more pronounced at the 6-week, 3- and 6-month follow-up (each $p < 0.001$) and was observed in patients with and without distant metastases. The

mean pain sensation across descriptors was also significantly alleviated (each $p < 0.001$) at the 1-/6-week, 3-/6-month follow-up (► **Fig. 4**). A considerable reduction of pain interference with



► **Fig. 4** Changes in pain perception in terms of pain severity and pain sensation as well as in pain interference with daily activities over time following US-guided HIFU for advanced pancreatic cancer. **Standardized BPI questionnaire was used for evaluation.** Significant reduction in pain perception and in pain interference with daily activities was observed over time for metastatic and non-metastatic locally advanced pancreatic cancer. The pain relief occurred directly to one week after HIFU. This effect persisted over time and even improved for pain severity at 3- and 6-month follow-up independent of metastatic status. BPI: brief pain inventory; FU: follow-up; m: month; w: week; UICC: tumor classification of Union for International Cancer Control.



► **Fig. 5** Changes in items of pain severity over time following US-guided HIFU for advanced pancreatic cancer. Significant reduction in all items of pain severity (Worst, Least, Average pain and Pain right now) was observed over time for metastatic and non-metastatic locally advanced pancreatic cancer. Pain relief occurred directly after HIFU (3.5 at baseline and 2.6 within first week post-procedure, $p < 0.001$) and persisted over time (2.1, 1.6, and 1.5 at 6-weeks, 3- and 6-months follow-up, respectively, each $p < 0.001$). FU: follow-up; m: month; w: week; UICC: tumor classification of Union for International Cancer Control.

daily activities was also shown over time (each $p < 0.001$). In 50 % of patients analgesic medication was no longer necessary at the 6-week follow-up.

Survival

The survival analysis (OS, PFS, time to local progression) was based on 48 patients (► Fig. 6); two HIFU-treated patients with local recurrence after surgery were excluded from this analysis. During the observational period, disease progression was observed in 22 patients: 10 patients showed local tumor progression only (median time to progression: 14.4 months from intervention); 12 patients developed progressive distant metastases. The median time between diagnosis and HIFU intervention was 6.8 months (95 % confidence interval (CI): 0.4 months, 34.7 months). The median OS was 16.2 months (95 % CI: 11.4 months, 26 months) from diagnosis and 8.3 months (95 % CI: 5.1 months, 21.9 months) from intervention. The median PFS was 16.9 months (95 % CI: 13.1 months, 23.4 months) from diagnosis and 6.8 months (95 % CI: 6.1 months, 14.4 months) from intervention. UICC III patients had a longer median PFS (31.7 months) compared to UICC IV patients (14.7 months, $p < 0.05$).

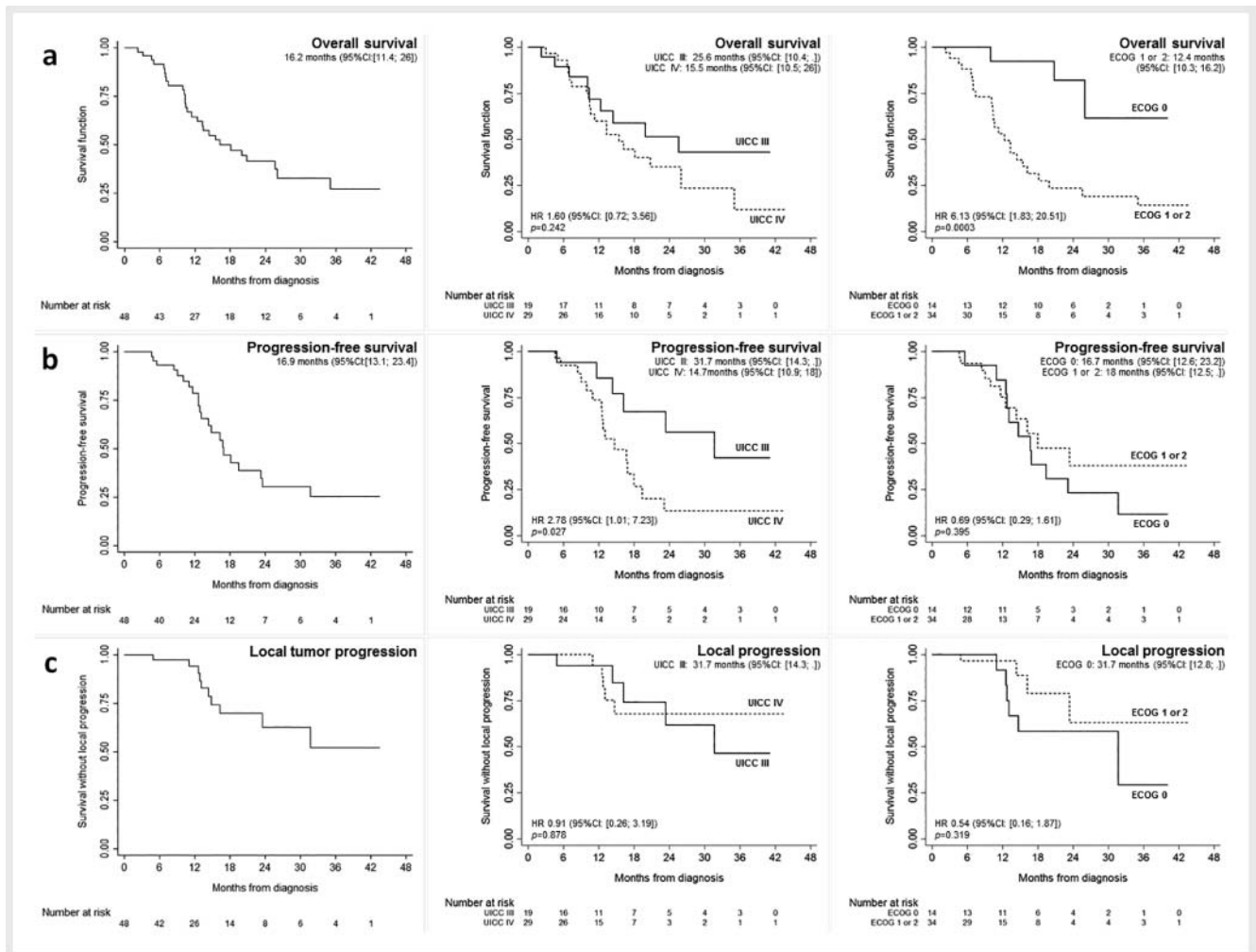
Adverse Events

Circumscribed slight to moderate (sub)cutaneous/muscular edema of the upper anterior abdominal wall in the acoustic pathway was detected in 32 of 50 patients as a local short-lasting procedural side effect. This spontaneously resolved in 23 affected patients within the following six weeks, and resulted in a not clinically relevant local induration of subcutaneous fat tissue (≤ 2 cm) in 9 patients. An increase in pancreatic lipase was observed in 4 patients without clinical pancreatitis-related symptoms. Major or long-lasting side effects and complications were not observed.

Discussion

Patients with late-stage pancreatic cancer have only limited treatment options and may benefit from the introduction of HIFU. In this study, the effectiveness and potential clinical advantages of HIFU were prospectively evaluated in patients with advanced PaC.

Cancer pain is a common symptom in PaC and occurs in more than 80 % of patients [9]. Opioid analgesics are frequently necessary, often leading to severe side effects with a negative impact on patient QoL. Local therapies such as percutaneous celiac plexus blocks or radiotherapy [10, 11] have a limited long-term effect on pain control. In recent years other local approaches for pain treatment included procedures such as cryotherapy, RFA and microwave therapy [5, 12, 13]. However, these procedures require the insertion of needles or probes with an increased risk of injury to adjacent structures. In contrast, HIFU is an innovative procedure with superior benefit-risk assessment due to its noninvasiveness. It allows targeted noninvasive thermal ablation of all tissues accessible by US [8, 14, 15]. Using HIFU, a considerable positive effect on pain perception and pain interference with daily activities was achieved. Both average pain severity and pain sensation decreased significantly following HIFU treatment independent of tumor stage. Over time, the reduction of pain interference with daily activities was quite pronounced. Limitations regarding work, daily or leisure time activities decreased or remained stable. This is of particular relevance because cancer treatment often grossly interferes with a wide spectrum of patient activities and negatively impacts their feeling of self-efficacy. Our findings confirm the significant alleviation of pain burden by US-guided HIFU in patients with advanced PaC, thereby ensuring clinically meaningful improvement of health-related QoL. HIFU as a low-risk procedure resulted in no additional morbidity. 42 of 50 patients (84 %) experienced a significant reduction of both pain severity



► **Fig. 6** Kaplan-Meier plots displaying overall survival **a**, progression-free survival **b** and survival without local progression **c** considering UICC stage and ECOG status. ECOG: Eastern Cooperative Oncology Group performance status (0–5); HR: Hazard ratio; UICC: Tumor classification of Union for International Cancer Control

and pain sensation within the first week following HIFU in our group of Caucasian patients. In patients mainly from Eastern Asia, comparable rates of pain reduction (70–82% of patients) were reported [16–19]. These reports, however, did not further differentiate aspects of pain perception. Impressively, early pain reduction was observed within days following HIFU, at a time, when tumor shrinkage could not be detected yet. This functional response preceded structural changes on a macrolevel, and must be ascribed to microlevel effects. Cytokine expression and action may already be reduced in this early postinterventional phase resulting in a reduced inflammatory tumor environment [20]. In addition, US-related destruction of locally active nociceptive neural fibers in the direct vicinity of the celiac trunk also reduces algietic stimulation [21]. With reduced peripheral nociceptive input, central nociceptive sensitization of spinal dorsal horn neurons may also be decreased. With ongoing tumor shrinkage over time, further effects upon neural structures are possible. Impressively, the pain reduction by HIFU sustainably lasted for months and even years in patients with a long survival. Because chemotherapy regimens did not change due to HIFU (42 patients were continuously

receiving chemotherapy, 8 did not undergo chemotherapy either before or after HIFU), the improvement in pain perception and pain interference with daily activities as well as in average pain severity and pain sensation can be regarded as an effect of the HIFU therapy.

For each tumor, the largest possible ablation was attempted. Maintaining a safety margin of 0.5–1 cm with respect to adjacent high-risk structures (stomach, bowel, vessels, stents), some vital tumor tissue remained in the margin area. Postinterventionally absent contrast enhancement indicated therapy-associated devascularization and was seen on early post-interventional imaging directly after the procedure. At six weeks the tumor volume had decreased by 37.8%, and at 6 months tumors had only 42% of the initial volume. Similar tumor shrinkage over time was also observed in 2 of 6 patients without initial tumor devascularization. This finding in relation to tumor mass reduction was independent of tumor stage as we suspected earlier [21–23]. It is conceivable that tumor shrinkage was at least partly an effect of the HIFU treatment, especially as considerable local tumor reduction was

also achieved in patients without simultaneous chemotherapy and in patients with progressive distant metastases.

Local tumor progression was observed in 10 of 48 HIFU-treated patients (20.3 %) with a median time of 14.4 months from HIFU intervention. In recent reports on percutaneous IRE in PaC patients, the median time to local progression after percutaneous IRE was 12 months, with only 20 % of the patients showing no local progress at 15 months [24] vs. 79 % following HIFU. Compared to HIFU, IRE is more invasive with higher complication rates and inoculation metastases in the access route also constitute a drawback. In contrast, US-guided HIFU is considered a low-risk procedure [25]. Following US-guided HIFU, there was no significant difference regarding local tumor progression between UICC III and IV (n = 5 each) and ECOG 0 and 1 resp. 2 patients (n = 6 and n = 4).

Our results also may suggest a possible survival benefit from HIFU affecting median OS, PFS and time to local tumor progression in patients with advanced PaC. In this context, the median OS has to be addressed in particular. According to the literature, PaC patients on chemotherapy/radiochemotherapy have a median OS of 6.2–11 months (6.2–8.4 months for UICC IV patients [26–28]. Even though our observational study has no control group data, our median OS of 16.2 months from diagnosis is longer compared to these data. Regarding HIFU-treated PaC patients, our results are close to the reported data for Asian patients [6, 18, 29], so that the usually different Caucasian constitution does not negatively affect the outcome. This is also supported by a study from Spain which reported a median OS of 13 months for HIFU-treated PaC patients [30].

In conclusion, noninvasive US-guided HIFU for advanced pancreatic cancer is a well-tolerated, low-risk procedure with beneficial clinical effects and significant reduction of pain burden independent of metastatic status as well as consecutive improvement of patient quality of life. As HIFU also results in a significant reduction in tumor volume, the procedure may be considered when tumor bulk reduction is desirable, e. g. in the context of other therapies. Survival data suggest a possible survival benefit. HIFU can be of particular value in this patient population with otherwise limited treatment options. To validate our findings, we are currently performing a randomized controlled clinical trial comparing standard palliative therapy alone with standard therapy plus HIFU in late-stage pancreatic cancer.

Conflict of Interest

The authors declare that they have no conflict of interest.

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