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To cite this article: Kun Zhou, Holger Strunk, Dobromir Dimitrov, Joan Vidal-Jove, Maria A. Gonzalez-Carmona, Markus Essler, Chengbin Jin, Zhechuan Mei, Hui Zhu & Milka Marinova (2024) US-guided high-intensity focused ultrasound in pancreatic cancer treatment: a consensus initiative between Chinese and European HIFU centers, International Journal of Hyperthermia, 41:1, 2295812, DOI: [10.1080/02656736.2023.2295812](https://doi.org/10.1080/02656736.2023.2295812)

To link to this article: <https://doi.org/10.1080/02656736.2023.2295812>



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Published online: 30 Dec 2023.



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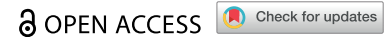


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BRIEF REPORT



US-guided high-intensity focused ultrasound in pancreatic cancer treatment: a consensus initiative between Chinese and European HIFU centers

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ABSTRACT

Purpose: Ultrasound-guided high-intensity focused ultrasound (USgHIFU) represents a safe and effective non-invasive thermoablative technique for managing inoperable pancreatic cancer. This treatment method significantly alleviates disease-related symptoms and reduces pancreatic tumor volume. However, the current body of evidence is constrained by a lack of randomized controlled trials. The utilization of USgHIFU is primarily indicated for patients with unresectable, locally advanced, or metastatic pancreatic cancer, particularly those experiencing symptoms due to a locally advanced primary tumor.

Methods: This collaborative consensus paper, involving European and Chinese HIFU centers treating pancreatic cancer, delineates criteria for patient selection, focusing on those most likely to benefit from USgHIFU treatment. Consideration is given to endpoints encompassing symptom alleviation, local response rates, other oncological outcomes, as well as overall and progression-free survival. Additionally, this paper defines relevant contraindications, side effects, and complications associated with USgHIFU. The publication also explores the feasibility and role of USgHIFU within the context of palliative care, including standard systemic chemotherapy.

Results: The non-invasive local treatment of advanced pancreatic cancer using HIFU should be regarded as an adjunctive option alongside systemic chemotherapy or best supportive care for managing this aggressive disease. Based on the ability of USgHIFU therapy to mitigate pain and reduce primary tumor volume, it should be considered as a complementary therapy for symptomatic patients with inoperable pancreatic cancer and as a potential means of tumor debulking. The underutilized yet promising USgHIFU exhibits the potential to enhance patients' quality of life by alleviating cancer-related pain. Experts in the field should evaluate this treatment option be evaluated by experts in this field, with this consensus paper potentially serving as a guiding resource for the medical community.

Conclusions: US-guided HIFU for advanced pancreatic cancer addresses treatment goals, available options, success rates, and limitations. As a non-invasive, effective local therapy, complementary to chemotherapy and best supportive care, it plays a pivotal role in pain relief, reducing of tumor volume, and potentially improving survival rates.

ARTICLE HISTORY

Received 1 November 2023
Revised 5 December 2023
Accepted 12 December 2023



KEYWORDS

US-guided HIFU; pancreatic cancer; expert consensus

Prembel/Introduction

Worldwide, pancreatic cancer is the 8th leading cause of cancer deaths in men and the 9th leading cause of cancer deaths in women according to data from the World Health Organization (WHO). The disease incidence rises sharply after the age of 45 years and is greater in males than in females (male-to-female ratio 1.3:1). Over the last 10 years, the age-adjusted incidence rate and mortality have increased by 2.1% [1–3]. With an overall 5-year survival rate of 8%

pancreatic cancer has still a dismal prognosis. Already at the time of diagnosis, more than 85–90% of patients with pancreatic cancer are no longer curatively operable due to locally advanced tumor or the presence of metastases; the median survival time in these patients is only 4–6 months and the 5-year survival is less than 5% [3–5]. 85–90% of the newly diagnosed patients are considered unresectable. Late diagnosis, early metastasis, and the resulting low number of curative surgical procedures contribute to the high mortality of this disease.

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To date, the most accepted frontline palliative treatment regimens for advanced pancreatic cancer are FOLFIRINOX (5-FU/LV, irinotecan, and oxaliplatin) and the combination of gemcitabine and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) [6,7]. The FOLFIRINOX regimen demonstrated a significant survival benefit of 11.1 months compared to 6.8 months for gemcitabine alone in a randomized phase III trial conducted by Conroy et al. The second established frontline regimen of palliative systemic chemotherapy, the combination of gemcitabine and nab-paclitaxel, provided a survival benefit of almost two months compared to gemcitabine alone (8.5 months vs. 6.7 months). In second-line treatment, the combination of 5-FU/LV with nanoliposomal irinotecan (nal-IRI) has been shown to be effective following gemcitabine-based therapy [8].

Despite new chemotherapy regimens, the 1-year survival rate continues to be only approximately 18–20%. Moreover, chemotherapy has limited efficacy in local tumor control and the reduction of pain and symptoms [9]. In more than 80% of cases, the quality of life of affected patients is significantly impacted by cancer pain, the primary clinical symptom. Other symptoms associated with advanced primary tumors include pancreatic exocrine and endocrine insufficiency, as well as biliary congestion and duodenal stenosis. In addition, there are other psychosocial stress factors such as fatigue, sleep disturbances and disturbed emotional and cognitive function [10]. Chemotherapy and radiotherapy are palliative treatment approaches for advanced pancreatic cancer, but their efficacy in terms of local tumor control and pain or symptom relief remains limited. Therefore, there is an urgent need for new alternative and adjunctive forms of therapy, especially also in palliative intent. The primary goals of local therapies in pancreatic cancer are to inhibit tumor growth, prevent tumor-related complications, and alleviate symptoms. While radiotherapy is currently the most established local treatment method, additional local ablation methods have been utilized with varying degrees of success in recent years. These local treatment options include radiofrequency ablation, microwave ablation, irreversible electroporation, and high-intensity focused ultrasound (HIFU) [11–13]. However, comparative studies are currently still lacking, and the outcomes largely depend on the expertise of the specific interventionalist.

Local treatment of pancreatic cancer with ultrasound (US)-guided HIFU offers an innovative treatment option that enables targeted, noninvasive thermal ablation of tumor tissue [12,14–16]. In contrast to other methods of local ablation, it does not involve the use of needles, probes, or electrodes to unfold its effects. During ablation, ultrasound waves are focused by special transducers and directed to a target point within the human body, causing heat generation and coagulative necrosis in the target tissue [17].

In a few centers worldwide in Asia (China, Japan, South Korea), Europe (Bulgaria, Germany, Spain), and North Africa (Egypt), USgHIFU currently represents a treatment option for patients with pancreatic cancer. Although the procedure has not been standardized yet among treating HIFU centers, HIFU represents an effective and safe treatment option for advanced pancreatic cancer in a palliative setting,

substantially reducing cancer pain and tumor mass, thus improving quality of life and physical discomfort with a low rate of side effects [18–26]. In addition to stereotactic radiation, HIFU is currently the only local ablation method among those mentioned above that does not require the use of needles, electrodes, or probes [26,27]. This characteristic allows HIFU treatment to be performed even in patients with tumors located in close proximity to blood vessels, the bowel, or a biliary stent. Furthermore, potential complications caused by a puncture, particularly bleeding (e.g., in cases with extensive collateral blood vessels in tumors obstructing the mesenteric veins) or seeding metastases along the puncture channel, are not an issue when using HIFU. With its noninvasiveness as a unique feature and key advantage, HIFU may become a worthwhile co-player besides supportive care in a multidisciplinary approach toward the management of this devastating disease.

Aim of consensus initiative

The intention of this consensus initiative was to evaluate and categorize USgHIFU in the treatment spectrum in particular of non-operable, symptomatic pancreatic cancer. For this purpose, a literature search was carried out by the participants of the expert meeting in both the Chinese-language and the English-language literature.

An up to date comprehensive search on Medline Web of science and WanFang database (search strategy is shown in Figure 1) was performed between 2012 and 2022 (without language restrictions). This search revealed 225 contributions about the topics in the Chinese language (WanFang database) and 224 contributions in the English language (Web of Science) (Figure 2). Apart from a few prospective data, most data on the feasibility and safety of HIFU therapy in patients with inoperable pancreatic carcinoma are retrospective observations. To the best of our knowledge, at present there is only one randomized controlled trial (RCT) (DRKS00012367) comparing standard chemotherapy alone with standard chemotherapy plus local HIFU ablation in patients with unresectable, pancreatic cancer. This RCT continues to be conducted at the HIFU center in Germany (University Hospital Bonn).

Based on these evaluations of the current literature, internationally published recommendations and their own experience and after detailed discussion the participating experts working in the field of gastroenterology, oncology, surgery, and radiology found the following consensus. The panel of experts was aware that this was an assessment of the possibilities and limitations of a treatment method held in conjunction with oncology specialists who do not perform the procedure themselves but have expertise and experience with the diagnosis and medication-based and surgical treatment of pancreatic cancer.

The expert group comprised of oncologists, oncological gastroenterologists, surgeons, and HIFU interventionalists from China and Europe (Bulgaria, Germany, Spain). The current paper reflects the recent state of knowledge. The authors are aware, the data regarding USgHIFU in pancreatic

cancer is limited due to a lack of results of randomized controlled studies and this treatment modality is provided by only a few specialized facilities worldwide.

A	Web of Science, Core Collection Database
# 1	TS=(Pancreatic Neoplasm OR Neoplasm, Pancreatic Neoplasm, Pancreatic OR Pancreatic Neoplasm OR Pancreas Neoplasms OR Neoplasm, Pancreas OR Neoplasms, Pancreas OR Pancreas Neoplasm OR Neoplasms, Pancreatic OR Cancer of Pancreas OR Pancreas Cancers OR Pancreas Cancer OR Cancer, Pancreas OR Cancers, Pancreas OR Pancreatic Cancer OR Cancer, Pancreatic OR Cancers, Pancreatic OR Pancreatic Cancers OR Cancer of the Pancreas)
# 2	TS=(High Intensity Focused Ultrasound OR High-Intensity Focused Ultrasound OR High Intensity Focused Ultrasound Ablation OR High-Intensity Focused Ultrasound Ablation OR Focused ultrasound surgery OR Focused ultrasound surgery Ablation)
# 3	#1 AND #2
Publication time	2012-01-01/2022-12-31

B	WanFang Database
# 1	高强度聚焦超声 OR 高强度聚焦超声(HIFU) OR 高强度聚焦超声热疗 OR 高强度聚焦超声消融 OR 高强度聚焦超声波 OR 高强度聚焦超声刀OR 高强度聚焦超声消融术 OR 高强度聚焦超声技术 OR 高强度聚焦超声治疗 OR 高强度聚焦超声疗法 OR 高强度聚焦超声辐照OR聚焦超声消融OR聚焦超声手术OR超声消融手术
# 2	胰腺癌 OR 胰腺恶性肿瘤 OR 癌, 胰腺
# 3	#1 AND #2
Publication time	2012-01-01/2022-12-31

Figure 1. Search strategy. (A) Web of Science database. (B) Wan Fang database.

Methodology of USgHIFU in pancreatic cancer: structural requirements and quality assurance

US-guided HIFU treatment in pancreatic cancer should only be performed at medical facilities with the necessary technical equipment as well as obligatory expertise and experience regarding USgHIFU for malignancies. This also includes non-surgical and surgical management of side effects and complications. Moreover, there should be options for initiating and performing adequate and structured pre-, inter- and post-procedural pain management.

Before introducing USgHIFU treatment, theoretical and practical instruction at a center with extensive experience in performing USgHIFU treatment is recommended. In addition to the documentation required by law, the key points determined for the treatment (e.g., treatment time, sonication time, total energy, power range, mean power, visible grey-scale changes) should also be documented and optimized if necessary for quality assurance purposes. If available, participation in a suitable quality assurance programme of the professional associations is recommended.

Examinations required prior to USgHIFU

Treatment decisions are based on examinations incl. ultrasound performed by a specialist. At presentation, a medical history is obtained, a physical examination performed and laboratory parameters are collected. A state-of-the art CT (computed tomography) scan with a contrast medium is required for planning purposes. In case of contraindications to CT, a contrast-enhanced MRI can be performed. The contrast-enhanced images are used to assess the exact location of the tumor, the distance to adjacent structures at risk (e.g., stomach, duodenum, bile drainage), the vessel involvement and the degree of tumor perfusion (low, medium, high).

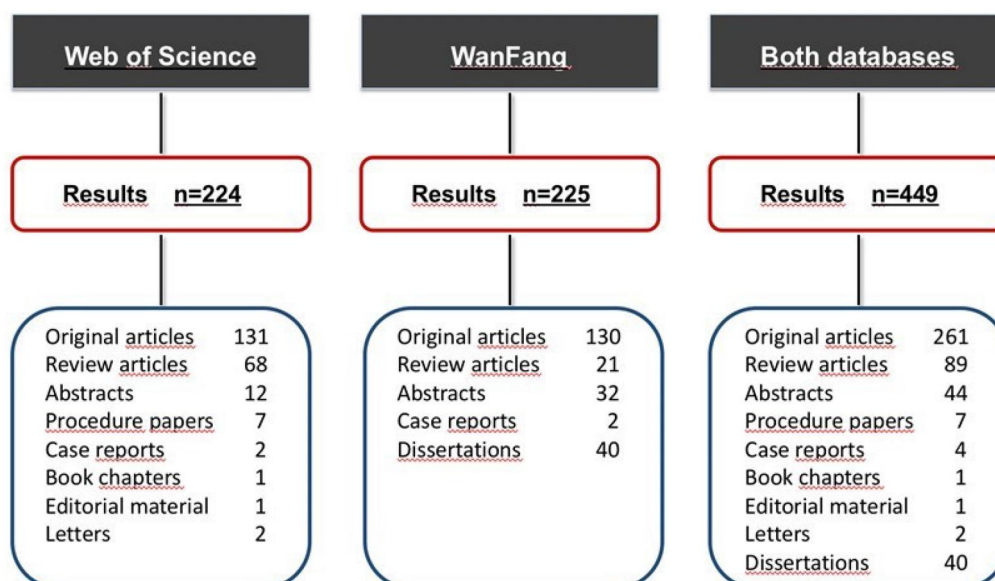


Figure 2. Search outcome in Web of science and Wan Fang database.

Indications for USgHIFU in pancreatic cancer

The aim of US-guided HIFU (USgHIFU) treatment in inoperable pancreatic cancer is to reduce the tumor-associated symptom burden as well as the tumor mass of the advanced primary tumor, and to prolong progression-free survival by allowing affected patients to increase or maintain a good quality of life. Thus, a comprehensive and complete consultation about treatment options for patients with pancreatic cancer includes also innovative local treatment with HIFU in addition to systemic therapies, surgical treatment options and radiation. This particularly applies to patients in advanced stages of the disease. HIFU is a worthwhile additional treatment besides systemic palliative chemotherapy or the best supportive care in the management of this aggressive disease.

At present, the main indication for USgHIFU treatment is an inoperable, histologically or cytologically confirmed pancreatic carcinoma, either locally advanced pancreatic carcinoma, primary metastatic pancreatic carcinoma, or tumor recurrence following previous surgical resection (e.g., Whipple procedure, left pancreatic resection). These conditions result in pain or other local symptoms, leading to a deterioration in the patients' quality of life. As the HIFU procedure is performed transabdominally, the anatomical position of the tumor should allow safe access for USgHIFU. In this regards, certain criteria may generally favor safe access: (1) More superficially located tumors: Pancreatic tumors or recurrences located in the anterior regions of the pancreas are generally more accessible for USgHIFU. This enables better visualization and targeted treatment, reducing potential interference with major blood vessels or critical structures. (2) Distance to blood vessels: Tumors that are located at a safe distance (5–10 mm) from blood vessels (such as the superior mesenteric artery and the mesenteric vein) are less risky for USgHIFU treatment. Close proximity to these vessels may pose challenges due to the risk of heat dispersion or damage. (3) Distance to surrounding critical structures: Pancreatic tumors that are not in close proximity to critical structures such as the bile duct, stomach, or duodenum are preferred for USgHIFU treatment. Close proximity to these structures could increase the risk of complications or adverse effects. (4) Accessibility through ultrasound visualization: The tumor should be accessible and visible under ultrasound guidance to allow precise targeting during the HIFU procedure. Clear visualization ensures precise delivery of the focused ultrasound energy to the tumor site. (5) Size and depth: The size and depth of the tumor significantly influence its suitability for USgHIFU. For example, very large tumors often infiltrate the stomach or duodenum pose considerable risk. On the other side, deeply located tumors, e.g., of the pancreatic tail in the splenic hilus, are often obscured by gas and could become inaccessible due to limitations associated with the method.

The disciplines involved in pancreatic cancer treatment are in agreement that the indication for USgHIFU therapy is made in an interdisciplinary framework including a specialist examination and consultation by an oncologist and/or gastroenterologist working in oncology, abdominal surgeon

and the specialist carrying out the treatment. The decision for or against a therapy alternative or additive option should be made in consideration of the patient's wishes and in knowledge of all treatment alternatives, their prospects of success and limitations as well as typical side effects and possible complications (informed consent).

Key inclusion criteria for USgHIFU in pancreatic cancer

(1) Age \geq 18 years; (2) Functional status ECOG 0–2; (3) Histologically/cytologically diagnosed inoperable pancreatic adenocarcinoma with the indication for oncological treatment (recurrence after previous Whipple surgery or UICC stage III-IV; UICC stage II only in exceptional circumstances, e.g., non-eligibility for surgical resection; explicit wish of the patient, old age); (4) Locally advanced tumor with a diameter \geq 2 cm; (5) Symptoms of local disease, e.g., cancer pain; (6) Tumor is sufficiently visible on ultrasound; (7) Maximal distance between the skin surface and deepest tumor part of 11 cm in a prone position; (8) Ability to understand and respond to corresponding language and give informed consent; (9) Eligibility for general anesthesia (or sedation); (10) Eligibility for prone positioning.

Key exclusion criteria for USgHIFU in pancreatic cancer

(1) Eligibility for surgical resection (UICC stage I–II); (2) Extensive scarring along the acoustic pathway; (3) Open wounds or unhealed scars after previous surgery of the anterior wall in the acoustic pathway; (4) Acute serious infection (e.g., cholangitis); (5) Multiple metal clip materials after surgery (which may reflect the ultrasound waves uncontrollably and cause damage to surrounding structures at risk); (6) Large amounts of ascites; (7) Bowel infiltration with bleeding.

Timing of USgHIFU

To date, no studies have investigated the best timing of local HIFU ablation to realize the full analgesic potential of the treatment. Therefore, in the absence of studies in this regard, it is suggested that newly diagnosed inoperable pancreatic cancer should start with systemic therapy as soon as possible as oncologically indicated (if considered) and USgHIFU therapy can be given between the 1st and 3rd cycle of standard chemotherapy. If no systemic therapy is planned, HIFU treatment should be performed as soon as possible.

A potential useful application of HIFU could be a neoadjuvant approach for borderline resectable pancreatic cancer prior to surgical resection. These patients are considered inoperable due to vessel encasement mainly based on CT imaging. First clinical results (with 30 patients) suggest that presurgical USgHIFU can contribute to significant tumor shrinkage and downsizing before surgery and make these tumors potentially resectable, improve the resection rate, and reduce the difficulty and risk of surgery [26,28,29]. One of the aims of a clinical trial in Japan is to downstage locally advanced pancreatic tumors making them resectable after the combination of HIFU plus chemotherapy. However, in

patients with borderline or locally advanced pancreatic cancer who have indications for neoadjuvant therapy and secondary operability, HIFU therapy should currently be used primarily in the context of clinical trials to generate valid data on the topic.

Special issues

Using USgHIFU, precise tumor ablation is possible. Nevertheless, in the immediate vicinity of the focal zone, there can also be a temperature increase with potential damage to neighboring structures at risk. These include the gastrointestinal tract (typically the stomach and duodenum), hepatic and mesenteric vessels and the bile ducts. Especially the vessels and bile ducts are often encased or infiltrated in locally inoperable carcinomas of the pancreatic head and body. Thus, most patients with advanced pancreatic cancer present with involvement of the arterial vessels (e.g., superior mesenteric artery, hepatic artery, splenic artery), the venous vessels (e.g., portal vein, superior mesenteric vein, splenic vein) or both prior to HIFU therapy. The vessels are often thread-like constricted or even occluded by the tumor, which leads to the formation of multiple collaterals. Despite vessel narrowing or extensive collateral propagation, HIFU treatment can be safely applied to pancreatic tumors enveloping large mesenteric blood vessels [30]. Even if in some cases, increasing ablation-related narrowing of previously tumor involved vessels can occur, the majority of patients (>90%), some even with high-grade narrowing, experienced no adverse effects regarding vessel patency. However, for safety reasons, when patent vessels are enclosed by tumor tissue, an untreated margin should be maintained. Typically, a small safety distance of a few millimeters (approximately 5–10 mm) is considered adequate during treatment in color-coded Doppler sonography mode to mitigate potential damage to vessels involved by the tumor. This precision is crucial due to the risks involved in treating near vascular structures. The specific untreated margin required around vessels, however, can vary based on several factors. For example, the size and type of the vessel (artery or vein, major or minor) also impact the necessary safety margin. Major vessels like the superior mesenteric artery or vein might require a larger untreated margin due to their importance and susceptibility to damage. The treatment plan should ultimately be adjusted to the individual patient, considering their unique anatomy, tumor features, and the proficiency of the medical team conducting the procedure. This may involve detailed preoperative imaging to precisely evaluate the tumor's relationship with adjacent structures.

Overall, vessel involvement in pancreatic cancer does not pose an absolute contraindication to HIFU treatment. Even the presence of collateral circulations, usually due to splenic and/or superior mesenteric vein occlusion, did not hinder the implementation of HIFU therapy.

Although the tumor should be ablated as completely or as largely as possible in every patient, a sufficient safety distance should be maintained from adjacent high-risk structures, also with the knowledge that some vital tumor tissue

will remain in the margin area. As USgHIFU is a palliative treatment in most patients with pancreatic cancer, any serious harm to the patient should be avoided and a safety margin of 1 cm to critical structures should be maintained.

This also applies to bile duct stents in a similar way: plastic stents can get material damage from energy application; metal stents can deflect the ultrasound energy away from the focus in an unpredictable way and cause damage. If clinically feasible, metal stents should be preferred if HIFU treatment is planned. In some cases, e.g., with relatively small tumors, it may even be necessary to exchange a plastic stent for a metal stent before the procedure.

Due to safety concerns and the fact that HIFU is usually used as a palliative intervention in addition to standard chemotherapy or palliative care, the outermost edges of the tumor and cuff-like tumor strains around abdominal vessels can deliberately remain untreated.

In summary, HIFU is currently the only one of locally ablative procedures for pancreatic cancer that works without the insertion of needles, electrodes, or probes. Therefore, HIFU treatment can also be performed in patients with tumors in the direct vicinity of vessels, intestines or stents while maintaining the necessary safety distance from structures at risk. Potential complications caused by the puncture, especially bleeding (e.g., in the case of pronounced venous collateral vessels in carcinomas obstructing the mesenteric veins) or metastases in the puncture channel, do not play a significant role for HIFU with its noninvasive transabdominal approach.

Success criteria for USgHIFU in pancreatic cancer

According to current knowledge, the main goal of local USgHIFU treatment is to improve, alleviate or even eliminate tumor-related symptoms, e.g., the leading symptom of cancer pain, which consequently leads to an improvement in the disease-related quality of life of affected patients. Tumor mass reduction is also sought and desired, especially in terms of progression-free survival, but is still considered a secondary treatment goal.

As in other solid tumors, an NPVR (non-perfused volume rate, calculated as the ratio between the avascularized/ablated volume and the total volume) is positively associated with symptom control and considered a technical parameter for treatment success in focused ultrasound.

Side effects and complications of USgHIFU in pancreatic cancer

Since tumor ablation using HIFU is noninvasive and in compliance with the indications and contraindications usually a low-risk procedure, it is generally assumed that there are few and only in the rarest cases severe side effects [31]. Our experience and results to date confirm this and also show that ablation can even be performed on locally infiltrating tumors that encase and invade important vessels in the upper abdomen.

Relevant side effects and complications during and after USgHIFU therapy are rare and include:

- Discomfort and/or pain in the upper abdomen and/or skin overlying the treated tumor: this discomfort is usually of short duration (up to 1 day after intervention).
- Skin changes (in less than 5% of patients): slight redness, cutaneous edema, skin burn, hardening or inflammation of subcutaneous adipose tissue and the musculature of the abdominal wall
- Mild fever (in about 5–10% of cases) for up to 48 h after treatment
- Mild inflammatory reaction with blood count changes and CRP increase
- Injury to adjacent organs and vessels (very rare, in less than 1% of cases)
- Infection of the necrosis cavity with consecutive need for surgery or puncture
- Increase in pancreatic enzymes with or without clinical signs of pancreatitis (1.9%)
- Other possible risks: bleeding (0.1%); worsening of pre-existing jaundice (0.6%); occlusion of the superior mesenteric artery (0.06%); steatorrhea (0.8%); gastrointestinal dysfunction (0.8%); positional damage (0.1%); peritonitis, pancreatic pseudocyst formation, intestinal perforation (<0.01%)

Follow-up after USgHIFU in pancreatic cancer

Post-treatment examination by a specialist is recommended after USgHIFU. Imaging procedures are useful (e.g., CT, MRI, sonography in conjunction with contrast-enhanced sonography). Relying on imaging, the tumor ablation rate (% in terms of NPVR) as well as the tumor volume reduction (% compared to baseline values) can be calculated.

Follow-up studies are used on the one hand for staging and later re-staging of disease under continuous systemic therapy or best supportive care, on the other hand to evaluate the success of the local HIFU treatment. In most centers (Western setting), follow-up studies (usually contrast-enhanced CT scans) are therefore performed every 2–3 months.

If treatment is unsuccessful (no improvement in symptoms and/or increase in pancreatic cancer size) or in the case of abnormalities on imaging, a further diagnostic workup is required and a second HIFU treatment may be considered.

Summary

Ultrasound-guided high-intensity focused ultrasound is a safe and effective noninvasive palliative treatment option for patients with inoperable pancreatic carcinoma, that reduces effectively disease-related symptoms and pancreatic tumor volume. Thus, patients' quality of life is significantly improved in the majority of HIFU-treated patients. This is an innovative approach to the treatment of pancreatic cancer that could potentially be added to the relatively ineffective current therapy. In this context, the noninvasive aspects of the HIFU

approach are highly desirable for the treatment of these patients with limited life expectancy. HIFU can be performed additionally to standard oncological treatment. The procedure itself is associated with a comparatively very low rate of side effects and complications. In addition to the crucial symptomatic benefit for pancreatic cancer patients, there may also be potential prognostic advantages. The initial survival data emerging from current clinical evidence are encouraging and support the need for further randomized controlled trials.

Outlook

Based upon available data and experience, a revision and update of the recommendations for USgHIFU treatment of symptomatic patients with adenocarcinoma of the pancreas is planned in 2026. The participants of the consensus initiative recommend the preparation of an international interdisciplinary guideline on all aspects regarding USgHIFU treatment of pancreatic adenocarcinoma.

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For this expert consensus, there is no data to be shared.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Kuanren Talents Program of the 2nd Affiliated Hospital of Chongqing Medical University and the Future Medical Youth Innovation Team Support Program Project of Chongqing Medical University.

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