A Retrospective Case Series Of High-Intensity Focused Ultrasound (HIFU) In Combination With Gemcitabine And Oxaliplatin (Gemox) On Treating Elderly Middle And Advanced Pancreatic Cancer

**Purpose:** This retrospective study was conducted to evaluate the safety and efficacy of high-intensity focused ultrasound (HIFU) ablation combined with Gemcitabine and Oxaliplatin (Gemox) for the treatment of middle and advanced pancreatic cancer in elderly patients.

**Methods:** Forty-seven patients with pancreatic cancer treated with HIFU and Gemox were evaluated for inclusion, and 38 cases were finally included. The primary endpoint was safety. Secondary endpoints included the response rate, the clinical benefit response (CBR), overall survival (OS), progression-free survival (PFS).

**Results:** After combination therapy of HIFU and Gemox, severe complications were rarely reported, and no treatment-related death occurred. The rate of three or four-degree myelosuppression was low, and no obvious impairment of hepatorenal function was observed. Pancreatitis and gastrointestinal injury did not occur. The disease control rate (DCR) was estimated to be 76.3%, including complete remission (CR), partial remission (PR), stable disease (SD) in 1, 6, 22 cases, respectively. And the objective response rate (ORR) was 18.4%. The clinical benefit rate (CBR) was 68.4%, with the pain significantly relieved (P<0.01). The serum level of CA19-9 showed significant changes after HIFU treatment. The median overall survival (OS) was 12.5 months, with a 6-month and 12-month OS rate of 82.13% and 59.34%, respectively. Stratified analyses did not reveal any significant difference between patients in different stages.

**Conclusion:** Elderly patients (≥ 60 years old) with pancreatic cancer would experience tolerable toxicity and obtain good clinical benefits from the combination therapy of HIFU ablation and Gemox.

**Keywords:** high intensity focused ultrasound, Gemox, advanced pancreatic cancer, overall survival, elderly

**Introduction**
Pancreatic cancer is one of the highly prevalent malignant tumors with poor long-term prognosis. It is predicted that the new cases would be 56,770 in the United States in the year 2019. Moreover, the number of cancer-related deaths will be as high as 45,750. More than 80% of patients with pancreatic cancer die within a few months after the initial diagnosis, while less than 10% of patients are expected to
Most patients with pancreatic cancer are often in the advanced stage and unresectable at the time of diagnosis, and this would mainly contribute to the decreased survival. In recent years, the incidence rate in China, especially in the urban areas, has shown an upward trend, of which 2/3 patients are >65 years old. The median survival of untreated pancreatic cancer is only 3 to 4 months.

Systemic chemotherapy (FOLFIRINOX) is the treatment of choice for patients with unresectable advanced pancreatic cancer as a potential role for consolidative radiation, yet overall survival remains low compared with those who are eligible for upfront surgical resection, notwithstanding recent advances in chemotherapy and radiation therapy. FOLFIRINOX is seldom used in China, as few patients could tolerate this regimen. The safety and efficacy of the Gemox regimen (gemcitabine and oxaliplatin) have been evaluated by numbers of studies as first-line therapy in patients with metastatic or unresectable locally advanced pancreatic cancer. The objective response rate was 10–30%, and the median overall survival was lower than one year. Gemox in combination with other therapies, such as erlotinib, bevacizumab, were also be evaluated.

High-intensity focused ultrasound (HIFU) is a non-invasive, conformal ablation technique developed in the past two decades and rapidly popularized in China. It can focus ultrasound energy on the target lesions and induces tumor coagulation necrosis by thermal effect. HIFU also have non-thermal effects including cavitation through the generation and collapse of gas-filled bubbles in an ultrasound field and mechanical tissue disruption by generating boiling bubbles. Besides, the immunomodulatory function of HIFU has also been reported. In the pancreas, the local treatment of cancer shows a unique advantage. Several clinical trials of HIFU palliative therapy for pancreatic carcinoma cases have provided promising results. HIFU monotherapy or in combination with systemic chemotherapy have been proved to be able to relieve pain and might bring an additional survival benefit with rare severe adverse events.

HIFU ablation combined with Gemox for pancreatic cancer has not been investigated by previous study. This retrospective case series analysis was conducted to evaluate the safety and feasibility of combination therapy of HIFU ablation and Gemox for the treatment of elderly patients with unresectable middle and advanced pancreatic cancer.

Materials And Methods

Patients

From March 2012 to March 2016, newly diagnosed unresectable middle and advanced pancreatic cancer patients were eligible for treatment in our center. The diagnostic criteria should meet at least one of the following conditions: (1) biopsy of pancreatic tumor during surgical exploration, pathological confirmation; (2) percutaneous puncture under ultrasound guidance, pancreatic occupying tissue, pathological confirmation; (3) patients who cannot obtain pathological evidence must have typical Imaging findings, or evidence of liver or retroperitoneal lymph node metastasis, accompanied by increased peripheral blood CA19-9.

The inclusion criteria were as follows: (1) patients aged ≥ 60 years old; (2) patients with adequate liver, kidney, and bone marrow function (white blood cell ≥ 3.9×10⁹/L, absolute neutrophil count ≥ 1.5×10⁹/L, platelets ≥ 100×10⁹/L, hemoglobin ≥ 10g/dL, and serum creatinine ≤ 150mmol/L); (3) patients with Karnofsky Performance Status (KPS) of ≥ 60 points and expected survival of > 3 months. All patients had no possibility of radical resection (tumor could not be removed; patients could not tolerate radical surgery or patients refused surgery). Some cases should be excluded, including poorly controlled diabetes, prior cerebrovascular event, active second malignancy, and uncontrolled intermittent illness. Besides, patients with tumor size > 10 cm were also excluded as they were not suitable for HIFU treatment.

The research obtained the approval of the ethics committee of Xinhua Hospital affiliated to Shanghai Jiaotong University and was done according to the Declaration of Helsinki.

Procedure

Patients with jaundice should receive percutaneous transhepatic cholangiography/gallbladder drainage (PTCD/PTGD) or endoscopic retrograde cholangiopancreatography (ERCP) prior to HIFU.

HIFU treatments were performed using the instrument of HIFUNIT-9000 (Shanghai Aishen Sci-Tec Co., Ltd.). The equipment parameters: sound intensity (I) = 3000 ~ 8000W/cm², focal spot = 3mm × 3mm × 8mm; power: 60%~100%; unit launch time: 0.15 ~ 0.2s, interval time (t2): 0.3 ~ 0.4s, t1: t2 = 1: 2; single point of treatment (n): 8 ~ 14 times; number of transducers (T): 3 to 6. Before treatment, according to the location, size, shape of the lesion, and the relationship with adjacent organs,
combined with the general situation of the patient to develop a preliminary treatment plan. The patient was fasted to gas-producing food three days before treatment and fasted and banned water in the morning of treatment. During treatment, the patient should be placed in the supine position without anesthesia (Figure 1A). The position of the lesions was firstly determined by b-mode sonography, CT, MRI, or PET/CT. Then the re-localization of the therapy area was completed through the built-in detecting head of the instrument. The US monitoring system was started, and the treatment range was defined according to the real-time image, by ascertaining the treatment levels and power. After setting up the treatment parameters, the treatment focus was moved following the X, Y and Z axes in terms of the planned procedure to cover the entire predetermined target regions. Each treatment time is 30 to 40 mins, once a day, five times in a row. If the tumor is difficult to cover the scan within five sessions, the number of treatments was added until the predetermined target area was completely covered.

**Figure 1** Treatment process and CT imaging of a 65-year-old male patient with pancreatic cancer who received HIFU treatment.

**Notes:** (A) This patient was receiving HIFU ablation in a supine position. (B) Before treatment, a space-occupying lesion with a diameter of about 2 cm could be seen in the pancreatic uncinate process, without pancreatic duct dilated. The CA 19–9 level was tested to be 4370 U/mL. (C) Six months after HIFU treatment, the size and morphology of the pancreas returned to normal, and no visible space-occupying lesions were found in the uncinate process. The CA 19–9 level reduced to 362 U/mL.

**Abbreviations:** CT, computed tomography; HIFU, high-intensity focused ultrasound.
One cycle of chemotherapy was given on the first day after HIFU ablation. The chemotherapy regimen was Gemox: gemcitabine 1000 mg/m², day 1 and day 8; oxaliplatin 135 mg/m², day 1; 21 days for a chemotherapy cycle. Changes in peripheral blood, liver and kidney function, and electrocardiogram were measured during chemotherapy. Each patient completed at least 3 cycles of chemotherapy.

Outcomes And Measurements
The primary endpoint was the safety of HIFU and Gemox. Chemotoxic side effects were evaluated according to the NCI Common Toxicity Grading Standard Version 3.0.³³

The secondary endpoints included best overall response, clinical benefit rate (CBR), overall survival (OS), progression-free survival (PFS). The response rate was evaluated by self-determination criteria, which was combination of the response evaluation criteria in solid tumor (RESIST 1.1) established by the American Cancer Institute (NCI)³⁴ and the specificity of pathological changes after HIFU ablation. Complete response (CR): the lesion completely disappears and remains more than 4 weeks; partial response (PR): the sum of the maximum diameter of the lesion is reduced by ≥30% and maintained for more than 4 weeks; progression disease (PD): The sum of the maximum diameters of the lesions increased by ≥20% or new lesions appeared; stable disease (SD): the lesion shrinks less than PR or increases to PD. Patients achieved CR, PR, and SD were both considered as effective. Because the tumor tissue is mostly coagulative necrosis after HIFU ablation, the tumor is reduced by <30%, and the tumor in a stable state was also regarded as therapeutically effective. CBR was assessed based on the following criteria: (1) pain is reduced by ≥50% for more than 4 weeks, (2) the amount of analgesic medication is reduced by ≥50% for more than 4 weeks, (3) the improvement of KPS score is ≥20 points for more than 4 weeks, (4) and the weight gain is ≥7%. At least one of these items exceeds the above criteria with the others stable was consider as valid. Otherwise, it was invalid.³⁵

As to the heterogeneity between the patients in different stages, subgroup analyses were also conducted by us to describe the results in more detail.

Patients’ Follow-Up
The OS and PFS were defined as the duration between the date of all-cause death and disease progression or death, respectively, from the end of HIFU intervention. Censoring occurred if patients were still survival at the last follow-up. Peripheral blood CA19-9 was examined every four weeks during the first year after HIFU combined with chemotherapy. The pain was evaluated by using the visual analogue scale (VAS) method at 1 month after HIFU ablation and then 3-month intervals during the follow-up.³⁶ Tumor size was measured by computed tomography (CT) or magnetic resonance (MRI) methods. Response evaluation was performed at 1 month and 3 months after HIFU and then 3-month intervals during the first year and 6-month intervals during the remainder of the follow-up phase. The best overall response was reported.

Statistical Methods
Data analyses were performed using STATA 12.0 statistical software (Stata Crop, Lakeway Drive College Station, USA). Normally distributed data were presented as mean ± standard deviation. Non-normally distributed data were expressed with a median (range). The independent Student’s t-tests or Wilcoxon tests were used to compare data between each time point after treatment and baseline, as appropriate. Median OS and PFS with 6 and 12-month survival rates were calculated by the Kaplan-Meier method. Chi-square tests were conducted to compare results between different clinical stages in the subgroup analyses. The P<0.05 indicates that the difference was statistically significant.

Results
Characteristics Of Patients
Forty-seven patients were retrospectively evaluated for inclusion. Thirty-eight patients of them were included finally, with a median age of 69 years (range: 60–78), including 21 males and 17 females. Twenty-eight cases were confirmed by surgical or biopsy histopathology, and 10 cases were diagnosed with pancreatic cancer based on clinical signs, imaging, and serum radioimmunoassay. The tumors were located in the head, body, and tail of the pancreas in 16, 13, and 9 cases, respectively. KPS score ≥ 80 was seen in 17 patients. According to the Union for International Cancer Control (UICC) clinical stage:³⁷ stage II, stage III, and stage IV pancreatic cancer were confirmed in 4, 15, and 19 cases, respectively. All the cases with occupying diameter were larger than 1cm (the built-in probe with a diameter of less than 1cm is difficult to detect), and the largest tumor was 8.4×6.0cm (Table 1).
All patients received at least five HIFU sessions, with median HIFU sessions of 8 (range: 5–16) times.

Safety Of HIFU And Gemox Treatment

All these 38 patients were included in the safety evaluation. During HIFU treatment, upper abdominal discomfort was complained by 4 cases (10.5%), which was disappeared after an adjusted dose or stopping treatment. After HIFU ablation, three patients (7.9%) reported the tolerable liver area pain or low back pain, and two (5.2%) patients with moderate to severe pain required non-steroidal or morphine analgesics for analgesia. Two cases (5.2%) complained fever of <38.5 °C and returned to normal at 1 to 3 days after symptomatic treatment. Two patients (5.2%) with pancreatic head cancer developed obstructive jaundice after treatment. Combined with clinical sign and CT imaging, it was speculated that the necrotic tumor tissue fibrosis was compressed by the common bile duct after treatment. All patients had no complications such as gastrointestinal bleeding, intestinal perforation, pancreatic fistula, pancreatitis, mesenteric artery rupture, skin burning, or embolism.

The chemotherapy toxic side effects were mainly dose-limiting bone marrow suppression (Table 2). Severe digestive tract reaction (nausea and vomiting) is rare due to symptomatic treatment by antiemetic drugs. Hepatic and renal dysfunction were few and mostly mild, of which mainly manifested by elevated levels of alanine aminotransferase and urea nitrogen. No chemotherapy-related deaths occurred. No complications such as pancreatic fistula, gastrointestinal bleeding, pancreatitis, and gastrointestinal perforation occurred.

Clinical Response And CA 19-9 Response

All these patients received at least once CT or MRI scan for response evaluation, of which 23 patients were followed up by CT only, and the other 15 cases were followed up by both CT and MRI. Median follow-up scans were 3 times (range: 1–5). As presented in Table 3 and Figure 1, CR, PR, SD, and PD were observed in 1, 6, 22, and 9 cases, respectively, after HIFU treatment. Objective response rate (ORR, CR + PR) was 18.4% (7/38). Disease control rate (DCR, CR+PR+SD) was 76.3% (29/38). Mean serum CA19-9 level was 247.9±68.6 U/mL before treatment, and decrease to 193.5±59.4 U/mL (P<0.05) at six weeks after HIFU treatment. Subgroup analysis by UICC stage revealed no significant difference in the CBR (Chi-square test p=0.470 and 0.098 for clinical response evaluation and CA 19-9 response evaluation, respectively)

CBR Evaluation

Eight cases (21%) with the KPS score of greater than 80 points had no significant pain before treatment or no obvious weight loss. Therefore, the evaluation of pain relief, analgesic reduced, KPS improvement, and weight gain were conducted in 30 cases. As shown in Table 4, the pain relief rate was 90.0% (27/30), the analgesic medication was reduced by 76.6% (23/30), the KPS level was improved by 63.3% (19/30), and the weight gain was 56.6% (17/30), the clinical benefit rate was estimated to be 68.4% (26/38). Among them, the primary manifestation was the decrease in pain intensity. VAS level decreased from 5.86±2.13 before treatment to 2.03±0.51 after treatment significantly.
Subgroup analysis by UICC stage revealed no significant difference in the CBR (Chi-square test p=0.327).

**Survival**
Within a median follow-up of 15.5 (range: 3.4–24.0) months, the median OS was estimated to be 12.5 months, with 95% CI of 10.3–13.9 months. The 6-month and 12-month OS were 82.13% (95% CI=64.45–91.56%) and 59.34% (95% CI=38.93–47.92%), respectively. Median PFS was 6.7 (95% CI=5.1–9.7) months, and the 6-month and 12-month PFS were 53.91% (36.65–68.36%) and 16.39% (6.14–30.98%), respectively. (Table 5 and Figure 2)

**Discussion**
Pancreatic cancer is considered to be one of the worst prognostic evaluated, especially for unresectable cases.
Treatment options with significant efficacy and safety remain to be explored and evaluated, notwithstanding recent advances in chemotherapy and radiation therapy.

HIFU treatment is a newly developed non-invasive technique and applied in the treatment of various malignant tumors in recent years. In China, nearly 10,000 treatment experiences of HIFU ablation had been accumulated in clinical application for the past ten years. Pancreatic cancer, especially advanced pancreatic cancer, has gradually been considered as one of the best indications for HIFU treatment. The technical advantages of HIFU and the characteristics of pancreatic cancer are

| Survival | Overall (n=38) | Stage II (n=4) | Stage III (n=15) | Stage IV (n=19) | Log-rank p-values |
|----------|---------------|---------------|-----------------|----------------|-----------------|
| Median OS, months (95% CI) | 12.5 (10.3–13.9) | 11.5 (5.7-NE) | 12.5 (4.8-NE) | 12.2 (7.5–14.2) | 0.95 |
| 6-month OS rate, % (95% CI) | 82.13 (64.45–91.56) | 75.00 (12.79–96.05) | 76.92 (44.21–91.91) | 87.50 (58.60–96.72) | - |
| 1-year OS rate, % (95% CI) | 59.34 (38.93–47.92) | 37.50 (1.10–80.80) | 65.93 (31.54–86.04) | 59.58 (30.84–79.62) | - |
| Median PFS months (95% CI) | 6.7 (5.1–9.7) | 6.2 (4.8-NE) | 6.9 (1.7–10.8) | 5.7 (3.7–10.4) | 0.81 |
| 6-month PFS rate, % (95% CI) | 53.91 (36.65–68.36) | 75.00 (12.79–96.05) | 53.33 (26.32–74.38) | 48.63 (24.29–69.27) | - |
| 1-year PFS rate, % (95% CI) | 16.39 (6.14–30.98) | 0 (NE-NE) | 23.33 (5.92–47.27) | 14.19 (2.42–35.88) | - |

Abbreviations: OS, overall survival; PFS, progression-free survival; HIFU, high-intensity focused ultrasound; CI, confidence interval; UICC, Union for International Cancer Control; NE, not evaluable.

Figure 2 Survival outcome of patients treated with HIFU and Gemox.
Notes: (A) OS of the overall cohort; (B) PFS of the overall cohort; (C) Subgroup analysis of OS by UICC Stage; No significant difference was detected between cases in different stages (Log-rank p = 0.95); (D) Subgroup analysis of PFS by UICC Stage; No significant difference was detected between cases in various stages (Log-rank p = 0.95).
Abbreviations: OS, overall survival; PFS, progression-free survival; HIFU, high-intensity focused ultrasound; CI, confidence interval; UICC, Union for International Cancer Control.
HIFU ablation does not damage the large blood vessels around the lesions, thus avoiding the bleeding events which might occur in surgical resection. The pancreas is located in the retroperitoneum and will not move with respiratory movement, which is beneficial to HIFU localization and real-time monitoring. Most of the pancreas tumors are lack of blood supply, which would attenuate the effect of chemotherapeutic drugs. Meanwhile, HIFU ablation in the tissue with low blood supply will avoid the loss of heat, which is conducive to rapidly reaching the lethal temperature of the tumor. Non-invasive characteristics of HIFU treatment ensures the sustainability and reproducibility of patients with pancreatic cancer. However, HIFU ablation is a topical treatment, which would rarely achieve a significant efficacy and long-term survival for cases with metastatic pancreatic cancer. Previous studies have shown that HIFU is synergistic with chemotherapy. Thus we adopt the combination therapy to achieve optimal efficacy.

In terms of the adverse events, the main toxic side effects of chemotherapy were myelosuppression and digestive tract reactions, but most of them were mild and tolerated. The complications of HIFU ablation were rare and usually healed themselves. The most common complications reported by patients are local pain and temporary fever. In all the subjects, local mild pain occurred in 3 cases and moderate to severe pain in 2 cases. The leading cause of pain is that when the mass is close to the ribs and the spine, the mechanical force of the ultrasound causes adjacent nerve damage. Skin burn is a complication of special interest as it was reported by numerous studies on HIFU. However, our results did not show any evidence of skin burn. This might be attributed to the differences in the type of HIFU equipment used for treatment. Our device (HIFUNIT-9000) adopts dual focus mode, and the energy upon the skin could be reduced effectively during operation compared with other equipment. Besides, we conducted the ablation of each patient in several days to avoid potential complications by energy accumulation, including skin burns. A case of skin blisters was observed, which might be caused by poor performance status and body weight loss. Therefore, performance status of patients during HIFU treatment should be considered to adjust the treatment parameters. Also, the treatment parameters should change with the location, size, blood supply of the tumor, and different combination treatment options, in order to avoid tissue damage caused by excessive power. No gastrointestinal bleeding, gastrointestinal perforation, pancreatic fistula, pancreatitis, peritonitis, mesenteric artery rupture or embolism, or nerve trunk injury were observed. High safety of HIFU provides more options for elderly, frail patients, cases with comorbidities, and patients who are intolerant to conventional treatment.

In the studies of Gemox treatment for pancreatic cancer, the ORR and DCR varied from 10% to 30%, and from 80% to 85%, respectively, and the median OS and PFS were 3.2–15 months, and 2.5–7 months, respectively. HIFU monotherapy provided ORR of 14.6% to 77.5% and median OS of 5.4 to 16.2 months. Zhou et al overviewed 241 articles with a total of 653 cases on the HIFU monotherapy for locally advanced pancreatic cancer and revealed that the median OS is 10 months, and the pooled pain remission rate was 71.3%. In theory, HIFU monotherapy and Gemox combination therapy should be superior to the single treatment. However, in our subjects, the ORR and DCR were estimated to be 18.4% and 76.3%, respectively, which were comparable with previous studies. A monocentric retrospective study by Ning et al had evaluated the safety and effectiveness of HIFU combined with gemcitabine (GEM) in 347 pancreatic cancer patients. The median OS was reported to be 7.4 months, with 6-month and 1-year survival rate of 66.3% and 21.32%. As a comparison, the median OS and PFS in present analysis were observed to be 12.5 months and 6.7 months, which seems to be better than prior evidence. Similar superiority of the 6-month and 12-month OS rate were also obtained to be 82.13% and 59.34% in our study. What should be noted is that the patients included in previous studies mentioned above were both local advanced pancreatic cancer, without limit of age. Meanwhile, our study included only elderly cases (>60 years) and some metastatic cases, which might affect the response rate and survival time. Another meta-analysis by Dababou et al in 729 pancreatic cancer patients who treated by HIFU revealed a pain relief rate of 80.95% (459/567). The rate by us was observed as 90%, which might numerically superior to previous result. Therefore, the combination treatment of HIFU and Gemox should be considered to be one of the effective options for elderly patients. It is widely acknowledged that clinical-stage would affect the prognosis of pancreatic cancer patients. Regrettfully, subgroup analyses by clinical stage did not revealing any significant difference. It may be caused by low statistical power with small-size of samples, especially only four cases in the stage II.

Some limitations should be acknowledged: (1) This retrospective case series study with a small number of...
cases would not provide strong evidence to guide the clinical practice. Our report aims to share the experience of our center in elderly cases. (2) Potential selection bias would exist in our study, which would be one of the intrinsic characteristics of the retrospective study and hard to avoid. (3) Due to the limited number of cases included in this study, some factors which might affect the efficacy of HIFU were not analyzed, including gastrointestinal gas, therapeutic output, and patient tolerance. Therefore, top-level designed trails with a larger sample size are needed. Nevertheless, our investigation has provided a piece of reliable clinical evidence for the new direction of ablation treatment for advanced pancreatic cancer, especially in elderly patients.

In conclusion, elderly patients (≥60 years old) with pancreatic cancer would experience tolerable toxicity and obtain good clinical benefit from the combination therapy of HIFU ablation and Gemox. However, more well-designed randomized controlled trials are needed to confirm the efficacy of HIFU-based combination therapy.

**Ethical Statement**
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Xinhua Hospital Affiliated To Shanghai Jiaotong University School of Medicine (number: 2017-43).

**Acknowledgments**
The authors are grateful to all the staff at the study center who contributed to this study.

**Author contributions**
All authors made substantial contributions to the design and conception of the study, and acquisition, analysis and interpretation of data, and took part in either drafting or revising the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Disclosure**
All the authors declare that there are no conflicts of interest.

**References**
1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;69(1):7–34. doi:10.3322/caac.21492
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7–34. doi:10.3322/caac.v69.1
3. Gemenetzis G, Groot VP, Blair AB, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. *Ann Surg*. 2018;270:340–347.
4. Goodman MD, Saif MW. Adjuvant therapy for pancreatic cancer. *JOP*. 2014;15(2):87–90. doi:10.1097/jop.0b013e3182d577f2
5. Lv W, Yan T, Wang G, et al. High-intensity focused ultrasound therapy in combination with gemcitabine for unresectable pancreatic carcinoma. *Ther Clin Risk Manag*. 2016;12:687–691. doi:10.2147/TCRM.S90567
6. Wolfgang CL, Herman JM, Laheru DA, et al. Recent progress in pancreatic cancer. *CA Cancer J Clin*. 2013;63(5):318–348. doi:10.3322/caac.v63.5
7. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115–132. doi:10.3322/caac.21338
8. Baize N, Abu Shalaa A, Berthier F, et al. Gemcitabine combined with oxaliplatin is safe and effective in patients with previously untreated advanced pancreatic adenocarcinoma. *Gastroenterol Clin Biol*. 2005;29(10):1006–1009. doi:10.1016/S0339-8320(05)88174-6
9. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23(15):3509–3516. doi:10.1200/JCO.2005.06.023
10. Demols A, Peeters M, Polus M, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer*. 2006;94(4):481–485. doi:10.1038/sj.bjc.6602966
11. Li J, Merl M, Lee MX, et al. Safety and efficacy of single-day GemOx regimen in patients with pancreaticobiliary cancer: a single institution experience. *Expert Opin Drug Saf*. 2010;9(2):207–213. doi:10.1517/14740330903555181
12. Tudini M, Palluzzi E, Cannita K, et al. Modulation of GemOx chemotherapy according to CIRS in elderly patients with advanced pancreatic cancer. *Oncol Rep*. 2012;27(2):423–432. doi:10.3892/or.2011.1517
13. Afchain P, Chibaudel B, Lledo G, et al. First-line simplified GEMOX (S-GemOx) versus classical GEMOX in metastatic pancreatic cancer (MPA): results of a GERCOR randomized phase II study. *Bull Cancer*. 2009;96(5):E18–E22. doi:10.1684/bdc.2009.0871
14. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30 min infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009;27(23):3778–3785. doi:10.1200/JCO.2008.20.9007
15. Fuereder T, Stift J, Kuehrer I, et al. Response to GEMOX plus erlotinib in pancreatic cancer is associated with ERCC1 overexpression. *Eur J Clin Invest*. 2014;44(10):958–964. doi:10.1111/eci.12329
16. Milandri C, Polico R, Garcea D, et al. GEMOX plus tomotherapy for unresectable locally advanced pancreatic cancer. *Hepatogastroenterology*. 2011;58(106):599–603.
17. Fogelman D, Jafari M, Varadhachary GR, et al. Bevacizumab plus gemcitabine and oxaliplatin as first-line therapy for metastatic or locally advanced pancreatic cancer: a phase II trial. *Cancer Chemother Pharmacol*. 2011;68(6):1431–1438. doi:10.1007/s00280-011-1601-4
18. Orsi F, Arnone P, Chen W, et al. High intensity focused ultrasound ablation: a new therapeutic option for solid tumors. *J Cancer Res Ther*. 2010;6(4):414–420. doi:10.4103/0973-1482.77064
19. Maloney E, Hwang JH. Emerging HIFU applications in cancer therapy. *Int J Hyperthermia*. 2015;31(3):302–309. doi:10.3109/0266734X.2014.969789
20. Unga J, Hashida M. Ultrasound induced cancer immunotherapy. *Adv Drug Deliv Rev*. 2014;72:144–153. doi:10.1016/j.addr.2014.03.004
21. van Den Biggaart RJ, Eikenboom DC, Hoogenboom M, et al. Thermal and mechanical high-intensity focused ultrasound: perspectives on tumor ablation, immune effects and combination strategies. *Cancer Immunol Immunother*. 2017;66(2):247–258. doi:10.1007/s00262-016-1891-9
22. Chang W, Lee JY, Lee JH, et al. A portable high-intensity focused ultrasound system for the pancreas with 3D electronic steering: a preclinical study in a swine model. Ultrasonography. 2017;37:298.

23. Zhou Y. High-intensity focused ultrasound treatment for advanced pancreatic cancer. Gastroenterol Res Pract. 2014;2014:205325. doi:10.1155/2014/205325

24. Wu F. High intensity focused ultrasound: a noninvasive therapy for locally advanced pancreatic cancer. World J Gastroenterol. 2014;20(44):16480–16488. doi:10.3748/wjg.v20.i44.16480

25. Orsi F, Zhang L, Amone P, et al. High-intensity focused ultrasound ablation: effective and safe therapy for solid tumors in difficult locations. AJR. Am J Roentgenol. 2010;195(3):W245–W252. doi:10.2214/AJR.09.3321

26. Wu F, Wang ZB, Zhu H, et al. Feasibility of US-guided high-intensity focused ultrasound treatment in patients with advanced pancreatic cancer: initial experience. Radiology. 2005;236(3):1034–1040. doi:10.1148/radiol.2362041105

27. Wang K, Chen Z, Meng Z, et al. Analgesic effect of high intensity focused ultrasound therapy for unresectable pancreatic cancer. Int J Hyperthermia. 2011;27(2):101–107. doi:10.3109/02656736.2010.525588

28. Sung HY, Jung SE, Cho SH, et al. Long-term outcome of high-intensity focused ultrasound in advanced pancreatic cancer. Pancreas. 2011;40(7):1080–1086. doi:10.1097/MPA.0b013e3181ef2d24

29. Wang K, Zhu H, Meng Z, et al. Safety evaluation of high intensity focused ultrasound in patients with pancreatic cancer. Onkologie. 2013;36(3):88–92. doi:10.1159/000348530

30. Gao HF, Wang K, Meng ZQ, et al. High intensity focused ultrasound treatment for patients with local advanced pancreatic cancer. Hepatogastroenterology. 2013;60(128):1906–1910. doi:10.5754/hge.13498

31. Zhao H, Yang G, Wang D, et al. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. Anticancer Drugs. 2010;21(4):447–452. doi:10.1097/CAD.0b013e3283641a7

32. Li YJ, Huang GL, Sun XL, et al. The combination therapy of high-intensity focused ultrasound with radiotherapy in locally advanced pancreatic carcinoma. World J Surg Oncol. 2016;14:60. doi:10.1186/s12957-016-0809-5

33. Liu YJ, Zhu GP, Guan XY. Comparison of the NCI-CTCAE version 4.0 and version 3.0 in assessing chemoradiation-induced oral mucositis for locally advanced nasopharyngeal carcinoma. Oral Oncol. 2012;48(6):554–559. doi:10.1016/j.oraloncology.2012.01.004

34. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205–216. doi:10.1093/jnci/92.3.205

35. Bernhard J, Dietrich D, Scheithauer W, et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial–SAKK 44/00–CECOG/PAN.1.3.001. J Clin Oncol. 2008;26(22):3695–3701. doi:10.1200/JCO.2007.15.6240

36. Italiano A, Ciais C, Chamorey E, et al. Home infusions of biphosphonate in cancer patients: a prospective study. J Chemother. 2006;18(2):217–220. doi:10.1111/joc.2006.18.2.217

37. Minagawa M, Ikai I, Matsuyama Y, et al. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg. 2007;245(6):909–922. doi:10.1097/01.sla.0000254368.68787.d4

38. Bing F, Vappou J, de Mathelin M, et al. Targetability of osteoid osteomas and bone metastases by MR-guided high intensity focused ultrasound (MRgHIFU). Int J Hyperthermia. 2018;35:471–479.

39. Ferrer J, Molina V, Rull R, et al. Pancreas transplantation: advantages of a retropitoneal graft position. Cir Esp. 2017;95(9):513–520. doi:10.1016/j.ciresp.2017.05.004

40. Liszka L, Pajak J, Golka D. Serous neoplasms of the pancreas share many, but not all aspects of their microvascular and angiogenic profile with low-grade clear cell renal cell carcinomas. Pathol Res Pract. 2014;210(12):901–908. doi:10.1016/j.prp.2014.06.033

41. Ma M, Xu H, Chen H, et al. A drug-perfluorocarbon nanoemulsion with an ultrathin silica coating for the synergistic effect of chemotherapy and ablation by high-intensity focused ultrasound. Adv Mater. 2014;26(43):7378–7385. doi:10.1002/adma.v26.43

42. Tang H, Guo Y, Peng L, et al. In vivo targeted, responsive, and synergistic cancer nanotheranostics by magnetic resonance imaging-guided synergistic high-intensity focused ultrasound ablation and chemotherapy. ACS Appl Mater Interfaces. 2018;10(18):15428–15441. doi:10.1021/acsami.8b01967

43. Zhang N, Cai X, Gao W, et al. A multifunctional theranostic nanogent for dual-mode image-guided HIFU/chemo- synergistic cancer therapy. Theranostics. 2016;6(3):404–417. doi:10.7150/thno.13478

44. Zhao J, Zhao F, Shi Y, et al. The efficacy of a new high intensity focused ultrasound therapy for locally advanced pancreatic cancer. J Cancer Res Clin Oncol. 2017;143(10):2105–2111. doi:10.1007/s00432-017-2459-6

45. Marinova M, Huxold HC, Henseler J, et al. Clinical effectiveness and potential survival benefit of US-guided high-intensity focused ultrasound therapy in patients with advanced-stage pancreatic cancer. Ultraschall Med. 2018;40:625–637.

46. Li PZ, Zhu SH, He W, et al. High-intensity focused ultrasound treatment for patients with unresectable pancreatic cancer. Hepatobiliary Pancreat Dis Int. 2012;11(6):655–660. doi:10.1016/S1499-3872(12)60241-0

47. Ning Z, Xie J, Chen Q, et al. HIFU is safe, effective, and feasible in pancreatic cancer patients: a monocentric retrospective study among 523 patients. Onco Targets Ther. 2019;12:1021–1029. doi:10.2147/OTT.S185424

48. Dababou S, Marrocchio C, Rosenberg J, et al. A meta-analysis of palliative treatment of pancreatic cancer with high intensity focused ultrasound. J Ther Ultrasound. 2017;5:9. doi:10.1186/s40349-017-0080-4
