The Role of Focused Ultrasound in Pancreatic Cancer

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The Role of Focused Ultrasound in Pancreatic Cancer
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Executive Summary

The Foundation is thankful for the work of Joo Ha Hwang, who organized and led the workshop, held on February 28 – March 1, 2019, to identify novel preclinical, translational, and clinical research projects that would enable additional treatment options and further develop the potential for focused ultrasound (FUS) to help patients with pancreatic cancer. FUS is an early-stage, disruptive, noninvasive therapeutic technology that has the potential to improve the lives of millions of patients with a variety of medical disorders by providing an alternative, or complement to, existing techniques.

Workshop attendees included a multidisciplinary group of experts in pancreatic cancer, representing the fields of oncology, surgery, cancer immunotherapy, and focused ultrasound. These physicians and scientists were joined by leaders from the US Food and Drug Administration (FDA) and industry and scientific staff from the Cancer Research Institute (CRI) and the Focused Ultrasound Foundation. The workshop’s overarching goal was to share experiences, candidly challenge the status quo, and then outline and prioritize the most promising pathways for using FUS to treat pancreatic cancer. Current FUS treatment for pancreatic cancer, which is aimed at pain control and reduction in tumor size, is approved in Europe, Korea, Russia, and China. This use is still in its early days, and considerable variability exists in the details of the treatment – notably dosing, frequency, and timing with respect to other treatments. Clinical applications are underway in some centers, and the FUS Foundation will soon be tracking them in a new registry: the Pancreatic Cancer International Registry (ARRAY). ARRAY was designed to capture treatment parameters, better understand best practices, and compare outcomes. Principle investigators from many of the sites interested in participating in the ARRAY registry attended the workshop.

The workshop began with presentations that provided background information on the state-of-the-art standard for treating patients with pancreatic cancer, how FUS is currently being used to treat patients with pancreatic cancer, how FUS could be further developed to provide more solutions in treating this devastating disease, and the current limitations of the technology. On the second day, the group discussion was led by an expert panel to generate ideas, answer burning questions, and formulate three possible pathways for future research. The workshop attendees recommended a roadmap that focused on three specific areas of research: to advance the field of FUS for the treatment of pancreatic cancer, including ablation, targeted drug delivery, and immunotherapy. Specifically, the workshop attendees recommend the following:

1. For FUS ablation, conduct a clinical trial wherein patients with stage 3 or 4 pancreatic cancer would receive FUS ablation plus chemotherapy versus chemotherapy alone using current state-of-the-art chemotherapy regimens.

2. For FUS-enhanced drug delivery, (a) determine how much of an increase in drug delivery would be clinically significant (preclinical study); (b) improve FUS technology to reliably achieve stable hyperthermia to pancreatic tumors;
and (c) treat patients with stage 3 or 4 pancreatic cancer using current chemotherapeutic agents.

For FUS-enhanced immunotherapy, initiate a collaborative, multicenter trial performing immune treatment on patients with pancreatic cancer in an effort to reliably produce an abscopal effect (i.e., disappearing metastases). This may include (a) performing additional preclinical studies in appropriate mouse models of pancreatic cancer to evaluate treatment regimens using immune agonist and checkpoint inhibitor prior to FUS ablation; and (b) obtaining biopsies before and after FUS ablation in treatment-naïve patients to evaluate the immune response resulting from ablation.

FUS Foundation staff asked attendees to continue thinking about and collaborating on these issues. The Foundation will be delighted to consider funding the resulting research proposals.
Workshop Presentations

Workshop presentations provided background information on the state-of-the-art standard for treating pancreatic cancer, how FUS is currently being used to treat patients with pancreatic cancer, how FUS could be further developed to provide more solutions to treating this devastating disease, and the current limitations of the technology.

Types of Pancreatic Cancer

The two main types of pancreatic cancer, exocrine tumors and neuroendocrine tumors, are classified by their cell types. Exocrine tumors comprise 96 percent of pancreatic cancers and start in the exocrine cells, where digestion enzymes are made. The most common type of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), is an exocrine tumor. Neuroendocrine tumors, or PancNETs, originate in the hormone-producing neuroendocrine cells. Pancreatic hormones help control normal body functions (e.g., insulin production).

Pancreatic cancer rapidly metastasizes to the abdomen and liver, and it also spreads to the lungs, bones, brain, and other organs. It is most often treated as a systemic disease rather than being focused on a specific tumor. Patients commonly succumb to the disease as a result of complications from the metastases. The American Cancer Society website provides a comprehensive overview of the current treatment of pancreatic cancer.

Current Treatments for Pancreatic Cancer

Obstacles and Results

Eileen O’Reilly from Memorial Sloan Kettering Cancer Center described Current Treatments for Pancreatic Cancer: Obstacles and Results. In her review of the state-of-the-art standard for treating patients with pancreatic cancer, Dr. O’Reilly said that 56,770 US patients would be diagnosed with pancreatic cancer in 2019. It is currently the 9th or 10th most common cancer, and it is increasing at a rate of 1.2 percent per year.

Physicians who research and treat patients with PDAC face many challenges. The at-risk patient population is difficult to identify. There is a lack of strategies for early detection and prevention. Most diagnoses are made late in the disease course, so the best therapies are only modestly effective. There are limited biomarker-based strategies, and there is essentially no impact for adding novel therapies to the standard of care. There are tissue acquisition constraints, and less than 20 percent of pancreatic tumors are operable. Finally, patient advocacy is a challenge, because of the lack of survivors to act as advocates.
The standard of care for patients with PDAC is a cytotoxic combination of chemotherapy agents. The current front-line therapy is a regimen of modified FOLFIRINOX/gemcitabine/nab-paclitaxel. If patients experience disease progression after gemcitabine-based therapy, current second-line treatment combinations include oxaliplatin or irinotecan (Onivyde); however, the NAPOLI 1 clinical trial showed that irinotecan alone improved overall survival by two months. The National Comprehensive Cancer Network (NCCN) publishes treatment guidelines with evidence blocks, a framework for resource stratification, guidelines for patients, a list of educational resources and programs, and international adaptations for pancreatic cancer.

Genetic evaluations, now a part of routine clinical care, help determine therapy. Genetic evaluation of the pancreatic cancer genome shows two commonly affected genes (i.e., KRAS and tumor protein p53 or TP53) and a smattering of lower-frequency genetic events. Researchers at Memorial Sloan Kettering are studying pancreatic cancer genetics, and novel genetic-based drugs are in development.

With regard to immunotherapy, the tumor microenvironment in PDAC is hypovascular and hypoxic with a physical stromal barrier and excessive hyaluronan (HA) accumulation. A series of clinical trials, such as HALO 202, showed improvement in patients with an elevated level of HA, so a Phase II trial (HALO 301) is underway. However, the addition of PEGPH20 to gemcitabine/nab-paclitaxel causes thrombosis, so participating patients also need anticoagulation therapy. Pancreatic cancer has an immune suppressive environment, with a lack of effector T cells and a low mutational load. It is considered a cold tumor, and many approaches are trying to improve the environment. Research has been done with durvalumab (an anti-PD-L1 antibody), and the Parker Consortium is trying chemotherapy plus immunotherapy (i.e., FOLFOX plus Peg IL-10, FOLFOX plus immune therapy). Another curious investigational agent is eryaspase—a drug encapsulated within red blood cells. Researchers are seeking to understand how treatments affect the immune landscape, but sophisticated immune profiling is difficult in a disease that progresses so rapidly. Asking patients for additional biopsies during end-of-life care, although difficult, might help researchers understand why treatments are not working and elucidate the unique makeup of individual tumors.

In rare cases, a patient will have a nearly complete response to treatment and live for several years with advanced disease. Researchers are seeking to identify these patients, and those with germline mutations who also appear to do better.

In conclusion, cytotoxic therapy is the mainstay for treating patients with unresectable pancreatic cancer. Besides that, novel therapeutics are undergoing phase I/II trials, researchers are conducting intense biomarker evaluation and DNA-repair targeting, while others are studying stromal degradation, metabolism, and immunotherapy.
Summary of International Focused Ultrasound Experience

Joan Vidal-Jové from Hospital Universitari Mutua Terrassa provided a summary of the current international FUS experience for treating pancreatic cancer. He described the FUS bioeffects that are being explored, the commercially available FUS systems being used, and the clinical groups pursuing treatment for this disease.

Several bioeffects of FUS are under development for treating pancreatic cancer, including hyperthermia, ablation, cavitation, histotripsy, boiling histotripsy, immune regulation, drug activation, and drug delivery. Ultrasound-guided FUS devices are most often being used for these indications because of the positioning requirements for reaching the pancreas. Systems that are being used, or that could be used, include the Chongqing HAIFU JC200, Alpinion Alpius 900, Theraclion Echopulse, and Histosonics. Respiratory gating is an important consideration with the pancreas, because it is a moving organ.

Researchers in China were the first clinical groups to use high intensity focused ultrasound (HIFU) to treat pancreatic cancer, and they treated thousands of patients with excellent local results but minimal follow-up data. Ning et al. retrospectively compared outcomes in 689 patients (436 HIFU, 253 other treatments) and determined that a multimodal treatment approach (the combined therapy of HIFU, regional intra-arterial chemotherapy, and chemotherapy with or without radiotherapy) could improve survival of patients with unresectable pancreatic cancer; repeated HIFU presented a survival benefit and did not increase risk. It is difficult to determine which element of the treatment was responsible for the results, but repeated HIFU and multimodality treatments did improve survival.

At the University of Bonn Department of Radiology, in Germany, Holger Strunk and Milka Marinova treated 35 patients with pancreatic cancer for pain control, and some cases showed improved survival. In addition to pain control, this research group has published recent articles on tumor reduction, clinical effectiveness, and potential survival benefit.

At Pleven University Department of Surgical Oncology in Bulgaria, Dobromir Dimitrov published a safety study using FUS to treat 47 patients with advanced (stage 3 or 4) pancreatic cancer. The group found FUS to be safe with a complication rate of 10.6 percent and no severe complications.

In Milan, Italy, at the European Institute of Oncology’s Department of Interventional Oncology, Franco Orsi, has treated at least 80 patients with pancreatic cancer and has observed an abscopal effect that he attributes to the tumor ablation process.

In Barcelona, Joan Vidal-Jové has completed 80 cases since 2010. He compared these patients to a control group comprising a similar cohort of patients undergoing only chemotherapy using a seven-year observational retrospective comparative cohorts study, and his team found a statistically significant difference in survival in the FUS treated patients.
At Stanford University Medical Center’s Department of Radiology and Department of Gastroenterology, Pejman Ghanouni and Joo Ha Hwang collaborated with Alessandro Napoli’s group at La Sapienza University in Rome to conduct a meta-analysis evaluating pain palliation, tumor control, and immune activation for patients with PDAC. The analysis included 23 studies and 639 patients treated with FUS, 459 of whom experienced partial or complete relief. The group concluded that FUS provides good pain control in patients with PDAC. The La Sapienza group believes that FUS represents a multimodality approach to treating patients with all types of malignant diseases because it affects pain palliation through multiple pain pathways, including tissue denervation, tumor-mass reduction, and neuromodulation.

In summary, more than 1,000 patient treatments have been reported in the literature, with a focus on pain control, tumor reduction, and survival. Most reports describe single-center experience and possibly contain patient selection bias. A patient registry will allow the technology to move toward a randomized multicenter study. Collaboration with interventional oncologists is needed to select the best treatment or combination of treatments. Future projects should investigate immunological activation, enhanced chemotherapy delivery into the tumor, tumor burden reduction, immunotherapy combination therapies, activated liposomes, and the use of microbubbles. Clinical trials should replicate current clinical realities.

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How Can the Immune Response Improve Results in Pancreatic Cancer?

Petros Mouratidis from the Institute of Cancer Research (ICR) described how a specific immune response—the abscopal effect—might improve treatment results for patients with pancreatic cancer.

The goal of cancer immunotherapy is to initiate a self-sustaining cycle of cancer immunity. Checkpoint inhibitors, oncolytic viruses, cancer vaccines, bispecific antibodies, and CAR-T cells can contribute to enabling, amplifying, and propagating the cancer immunity cycle without generating unrestrained autoimmune inflammatory responses. Scientists have manipulated various stages of the cancer immunity cycle and the interventions have been effective in some, but not all patients with various types of cancers. Essentially, not every patient treated with immunotherapy receives the same benefit.

The abscopal effect is defined as the destruction of tumors at anatomical locations far outside of the treated tumor, probably owing to activation of systemic antitumor immunity. First described in 1953, the treatment schedule has been identified as a factor in creating an abscopal effect, which improves patient survival. More than 45 cases were reported prior to 2014. The biological mechanism underlying the abscopal effect is not yet fully understood, but the following parameters are likely to be involved: optimal dose range, single or multiple fractions, the sequence of combination treatments, the number...
of sites treated, the relevance of preclinical models, and tumor heterogeneity and evolution (i.e., the communication between the tumor microenvironment and the tumor).

In recent preclinical studies, the abscopal effect has been demonstrated with both FUS ablation and cavitation. In a preclinical in vivo study of metastatic mammary carcinoma, Silvestrini et al. found priming with immunotherapeutic agents to be the key to effective incorporation of image-guided thermal ablation into an immunotherapy protocol. Silvestrini’s results also showed that 80 percent of the nonirradiated tumors were eliminated by day six and that survival was improved to 100 days for those treated with combination therapies. Although the FUS model may or may not have been relevant, the critical finding was that immunotherapy must be given before the immune system is activated. A preclinical in vivo colorectal cancer study designed to use microbubbles and cavitation to improve checkpoint inhibitor therapy found an abscopal effect following FUS cavitation with 50 pulses, 0.1 ms long, 1 ms apart, repeated at 20 sec intervals for a total exposure duration of 2 minutes, with peak negative pressures of 1.65MPa. This study provides an example of an adaptive immune response after treatment with an FUS protocol. Clinically, FUS ablation has been associated with an abscopal effect in patients with pancreatic cancer. A 2016 case report of a 74-year-old patient with anaplastic pancreatic carcinoma showed a reduction in tumor size after 6 weeks and further reduction 16 weeks after FUS treatment.

To answer the question, “How can the immune response improve results in pancreatic cancer and induce an abscopal effect?”, Mouratidis and his group at the ICR are testing whether FUS-induced thermal ablation and cavitation can augment the anticancer effects of immunotherapy, induce the abscopal effect, and protect against rechallenge (publication in progress). The group observed that pulsed FUS plus anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and anti-programmed cell death protein 1 (PD1) immune checkpoint inhibitors decreased the relative volumes of orthotopic pancreatic tumors. The low number of abscopal effect case reports suggests a high threshold for the potency of immune activation to translate into a clinically relevant response. Therefore, there is an urgent need to design, test, and compare treatment regimens (dose, number of fractions, sequencing) of FUS-based combination treatments for cancers with different physical (stiffness, water content, extracellular matrix [ECM] density) and biological (mutation burden immunogenicity) characteristics. In pancreatic cancer, there is a need to understand whether mechanical changes in the tumor microenvironment or inflammatory-mediated changes in the immune phenotype are the predominant cause of the effect observed after FUS treatment. Additional FUS studies on pancreatic cancer and immunotherapy have been published.

The abscopal effect has also been found in other types of cancer with the application of energy from radiofrequency ablation, magnet-mediated hyperthermia and magnetic nanoparticles, electro-hyperthermia, and cryoablation. A 2017 case report showed an abscopal effect in a patient with metastatic pancreatic cancer (lung and liver metastases) following local radiotherapy.
Are There Preclinical Immune Therapies Using Focused Ultrasound that Are Ready for Clinical Application?

Katherine Ferrara from Stanford University presented data for attendees to help determine whether preclinical FUS immune therapies were ready for translation to clinical applications.

Dr. Ferrara’s work centers on combining activatable chemotherapy or ablation with innate immune stimulants (agonists) to achieve an in-situ vaccination against cancer. Agonists currently in clinical trials include toll-like receptor agonists, CD40, adenosine A2aR, and stimulator of interferon genes (STING) protein. Agonists can be injected locally or systemically to enhance the innate immune response and synergize with focal therapy. Clinical trials combining radiation therapy and immunotherapy are ahead of those using FUS. Multiple clinical trials are currently underway combining agonist therapies with checkpoint inhibitors and radiotherapy. Dr. Ferrara said that these are examples of the types of studies that could be considered for the incorporation of FUS.

Her laboratory uses preclinical models to study both treated and distant tumors. She showed that there are four important mechanisms by which focal ablation synergizes with immunotherapy: 1) tumor cells within a defined region of interest can be killed (thermal ablation can eliminate all cells); 2) therapeutic penetration of the tumor and accumulation at the boundary is enhanced due to leaky blood vessels and loss of cell-cell integrity; 3) tumor-specific antigen is presented on macrophages and dendritic cells (DCs) in tumor and lymph nodes at higher levels than achievable by either treatment alone; and 4) dying tumor cells release cytokines, inducing a viral-like antitumor response. The group sought to incorporate agonists and checkpoint inhibitors into a priming protocol and found that adding immunotherapy before ablation enhanced antigen levels in the lymph nodes, blood, and spleen. When starting with immunotherapy, the effects build. A locally injected CpG plus an anti-PD1 antibody activated innate immune sensors, altered the extracellular matrix, and enhanced chemokines, inflammatory cytokines and T cell costimulatory factors. Finally, adding ablation amplifies these effects and enhances the “hot tumor.” Researchers are currently trying to understand the mechanisms, because combining ablation and immunotherapy alters the expression of 10,000 genes, which is greater than when applying immunotherapy alone. There is a much greater effect magnitude with the combined treatment; in fact, the effect size is up to four standard deviations from the mean with changes in expression of some important genes exceeding 80-fold. Antitumor gene expression is thus enhanced, as is anti-tumor efficacy. Ablation alone induces fewer immune effects and fewer innate immune sensors. The group also combined agonists with mechanical FUS protocols and observed a smaller infiltration of CD8+ T cells as a result of this combination as compared with agonists combined with ablation.

In summary, FUS ablation releases antigen and cytokines, enhances therapeutic accumulation, destroys viable tumor, and synergizes with agonists. FUS creates a significantly greater immune response and affects ECM modulation, innate immune sensors, and chemokines.
Are There Focused Ultrasound-based Preclinical Drug Delivery Options that are Close to Being Used for Clinical Treatment?

Holger Grüll from Uniklinik Köln discussed FUS-based preclinical drug delivery options that are in development for clinical treatment.

To demonstrate how FUS works to deliver drugs to pancreatic cancer, Dr. Grüll showed a video of drug delivery to the pancreas from temperature sensitive liposomes (TSLs). This hyperthermia-induced drug delivery model uses FUS for local heating to 42°C prior to the injection of the TSL delivery systems. The increased temperature at the tumor triggers the release of the TSL’s payload.\(^34\)

Historically the melting transition process in lipids affected their ability to deliver drugs, because the melting temperature depended on whether the lipid was saturated, whether it was mixed with other lipids, and the length of the lipid chain. Lipids begin to turn to gel at physiological temperatures, or approximately 41°C, where they undergo a gel-to-liquid crystalline transition, increased membrane permeability, and the formation of transient grain boundaries in the lipid layer.\(^35, 36, 37, 38\) Modern lyso-lipid-based TSLs, such as ThermoDox, now have stabilized pores, and the composition for most TSLs are now similar.\(^34, 37, 39, 40, 41, 42\)

Are there FUS-based preclinical drug delivery options that are close to being used for clinical treatment? Several TSLs are available or in development. A CE-certified system is needed for magnetic resonance (MR)-guided HIFU hyperthermia (and ablation) of PDAC; Profound Medical’s Sonalleve platform has been in development for this application for 2 to 3 years.

To provide pancreatic cancer therapy using MR-HIFU, access to the pancreas is needed. The typical depth of pancreatic tumors is 7–16 cm, and critical structures (e.g., nerves and blood vessels) surround the pancreas. Other challenges are beam path obstruction by bowel and stomach tissue and motion from breathing and peristalsis.\(^43, 44\)

Preclinical MR-HIFU treatment protocols have been developed and published.\(^42\) Imaging and the predicted response from image-guided drug delivery have been described.\(^45\) HIFU heating strategies can target the tumor border zones or the tumor core, but combination protocols may be the most optimal, including the combination of ablation plus TSL drug delivery. In this case, the hyperthermia and TSL delivery precede the ablation of whatever tissue is left that can be ablated safely. During TSL delivery, doxorubicin accumulates on the outside of the tumor. There is also a danger zone near the ablation area: viable tissue that later recovers and creates a recurrence of the tumor. Possible treatment protocols include ablation alone, ablation plus TSL delivery, and hyperthermia plus TSL delivery, but hyperthermia plus TSL delivery followed by ablation produced the best survival advantage.\(^46\) Various quantities of doxorubicin have been used in preclinical rat studies in two models. MR-HIFU has been tested in a PDAC mouse model;\(^47\) i.e. in that study, hyperthermia increased the delivery and the uptake of doxorubicin by the tumor.
Several factors need to be addressed for clinical translation, including the following:

- Clinical MR-HIFU-induced hyperthermia
- Patient preparation protocol with a spacer to compress bowel
- Pancreas ablation using MR-HIFU
- Preclinical hyperthermia in a porcine model
- TSLs for clinical use
- Drug delivery protocols in large animals mimicking the clinical protocol

Although not in pancreatic cancer, clinical hyperthermia treatments have begun at University Hospital Cologne. A patient with sarcoma was treated with an infusion of olaratumab followed by an infusion of doxorubicin plus MR-HIFU induced hyperthermia every three weeks. Olaratumab is a human antiplatelet-derived growth factor receptor \( \alpha \) (PDGFR\( \alpha \)) monoclonal antibody that has antitumor activity in human sarcoma xenografts. Although the patient experienced bladder pain, the team developed a protocol for staging, treatment, volumetric heating, manual control of the hyperthermia application, and novel ideas for patient positioning and the use of a transparent acoustics spacer.

To prepare for human clinical trials, the team performed a pancreas ablation in a porcine model with the Sonalleve v2 system. Five reproducible ablations were applied during a one-minute phase of apnea with success at multiple ablation spots and no side effects after proper patient preparation. For future approaches, the team is developing a predictive control model to replace the currently used model of binary control (data to be published), and they are currently testing the custom software.

### Technical Considerations for Using Focused Ultrasound

**Chrit Moonen**

Chrit Moonen from Universitair Medisch Centrum Utrecht discussed technical considerations for using FUS to treat pancreatic cancer.

There are several challenges for MR-HIFU of the pancreas: HIFU access to the pancreas must pass through the stomach, duodenum, and ribs; the pancreas is in motion; and near-field heating is a concern.

To address access to the pancreas, scientists at Utrecht designed and built a compression device constructed for improved acoustic access (in press as part of the image-guided pancreatic cancer therapy [iPaCT] project). To remove the air in the beam path and improve acoustic access and MR thermometry readings, Arthurs et al. proposed using pineapple juice for the fluid filling of the digestive track. The juice plus compression removes the air in the beam path. Respiratory-gated MR thermometry combined with 4 cm of compression could eliminate air and improved MR thermometry for MR-guided systems.

Real-time image processing of magnetic resonance imaging (MRI) images could address the challenge of physiological motion. This technique allows visualization of each voxel.
and the cyclic movement of the pancreas. Data is recorded to correct the beam for the motion. Several technical solutions have been proposed for beam steering and respiratory gating with FUS that may be applicable for pancreatic cancer.\textsuperscript{50, 51, 52, 53, 54, 55, 56}

To address the challenge of rib obstruction and near-field heating, another iPaCT project developed a novel, MR-compatible transducer with a spiral design.\textsuperscript{57} Similarly, Wijlemans et al. also designed a phased-array element configuration that reduces the bone heating of the ribs.\textsuperscript{58} Another transducer design is optimized for uterine fibroids to provide near-field energy density, and there are a multitude of possible transducer designs. Near-field heating can be quantified.\textsuperscript{59}

Chrit Moonen’s conclusions and take-home messages included the following points:

- HIFU access and MR thermometry of the pancreas region can be improved with adapted patient preparation, including filling the stomach and duodenum with fluid and use of a 2 to 4-cm spacer between the transducer and the skin.

- Real-time tracking of pancreas motion by MRI is possible. However, for now, respiratory gated HIFU, together with adapted sedation medication, is advisable.

- A new phased-array transducer has been designed and integrated in the Sonalleve platform. This Voronoi-Tiled-Fermat-Spiral (VTFS) has superior characteristics for HIFU heating, as demonstrated by simulations, hydrophone measurements, and phantoms.

- After applying a binary apodization law for intercostal sonication, VTFS-transducers maintain a greater active surface compared to clinically available transducers. With VTFS, the distribution of absorbed energy in the near-field is more favorable. VTFS-transducers maintain higher focal point intensity, reducing the overall sonication time for the desired energy deposition in the target volume.

- Shortening the total sonication time reduces the amount of energy that is absorbed in the near-field.

- Near-field heating remains a limitation for ablation of the pancreas, and even more so for hyperthermia of typical volumes for prolonged periods.

- Can we use nonlinear effects for ablation of pancreas cancer?
Discussion from Presentations

Participants discussed the subgroup of patients with pancreatic cancer who have a high response to treatment (e.g., a man in his 70s with localized pancreatic cancer that recurred a number of years later. He had Lynch Syndrome, was treated with checkpoint inhibitors, and lived 11 years. He also got stomach cancer and two other cancers). It is a unique subgroup of patients with a different natural history.

There was a question as to what extent pancreatic cancer metastases resemble the primary tumor. Eileen O’Reilly said that there is a notion that the metastases have a significant stromal component, but it is less than what is seen in the primary tumor.

A medical oncologist said that it was striking that FUS research in this area was highly limited, non-rigorous, and not institutional-based. He was convinced that FUS reduced pain, but saw no evidence for why it would work in metastatic disease, saying that the studies did not differentiate whether FUS alone or other, later interventions influenced survival. Regardless, the overall survival in the published studies was not better than that achieved with single-agent chemotherapy. Joan Vidal-Jové responded that patients have not typically tried FUS until after chemotherapy failed; therefore, designing clinical trials with controlled variables, perhaps between cycles of chemotherapy, might be a place to start.

A participant said that pancreatic cancer was a systemic disease and suggested evaluating the data more carefully to theorize where the improved benefit might be originating; eventual systemic control would be the goal when there are circulating tumor cells.

Regarding the abscopal effect, Joan Vidal-Jové said that it occurred in three out of 200 of his patients, when treatment included the primary tumor and the metastases, but noted that Alessandro Napoli has observed it in a greater percentage of patients. Joan Vidal-Jové uses FUS hyperthermic ablation. He said that others who are working with histotripsy may be achieving a better immune response. Joo Ha Hwang explained the FUS mechanisms for damaging tissues (hyperthermia, ablation, histotripsy) and noted that histotripsy has the ability to destroy cells without denaturing the proteins. Importantly, each FUS mechanism is completely noninvasive and non-ionizing.

Naren Sanghvi raised the question of the right instrument and the best approach for reaching the pancreas (e.g., approaching through the stomach instead of through the skin). A participant asked what proportion of locally advanced cases were amenable to FUS. Joan Vidal-Jové responded that 70–90 percent can be reached for partial treatment but that it was almost impossible to do 100 percent ablation.

The group discussed metrics for assessing the effectiveness of clinical trials. There was a question on performing core biopsies during oncology clinical trials, which would be needed to prove that an intervention was modulating the tumor microenvironment. Tim Bullock described a clinical trial at the University of Virginia that is looking at the tumor microenvironment, and another participant said that proteomics can be used to measure systemic responses to an intervention. Collecting and analyzing serum is used to determine cytokine responses.
In response to a question about the time points for measuring immune response changes, Kathy Ferrara said 24 hours to 7 days. She cautioned that it is dangerous to perform RNA sequencing too early and her laboratory is careful not to interpret the data too early. At the 7-day time point, the T-cell population in the tumor shows a robust distant response. Her group also evaluates the blood, spleen, and lymph nodes at each time point.

Participants also questioned whether the elevated immune effects were seen with ablation from any type of energy (e.g., radiation). It is difficult to conform a treatment region with radiofrequency ablation. Kathy Ferrara said that the FUS mechanical effect is likely creating the immune response and her group plans to study the degree to which it impacts survival. It is possible that the FUS is sparking a local fire that releases cytokines and educates cells and then that fire spreads systemically.

In response to a question about the optimal ablation temperature, Kathy Ferrara said that 60 degrees is high enough to see an effect, but the effect is lost if the entire tumor is ablated or heat-fixed.

In a discussion of heat effect versus mechanical effect versus other therapy parameters, Kathy Ferrara said that FUS changes start to heal at 48 hours, but mechanical FUS is even faster. With radiation therapy, the cells do not have time to create interferon, so that effect is lost. Kathy Ferrara said that thermal ablation is superior, and it is what is needed to create the immune response because the cell needs time as it dies to produce the type 1 IFN. Mechanical ablation, or mechanically changing the tissue, can cause cell death too quickly.

In response to a question about the types of cancer she has studied, Kathy Ferrara said breast cancer and pancreatic cancer cell lines. The group discussed the possibility of creating a pancreatic cancer model that is responsive to immunotherapy.

The group discussed novel TSLs that are in development and which therapeutic agents or drugs could be delivered by TSLs, including immune activating agents. Tatiana Khokhlova said that although hydrophobic drugs are difficult to encapsulate, there are some tricks to turning them into a hydrophilic prodrug.

Participants discussed beam steering versus gating, along with technical solutions for treating a conscious patient under free-breathing conditions. Anesthesiologists have tricks for sedation, breathing control, and displacement of the diaphragm. With regard to filling the stomach and duodenum with pineapple juice to reduce air, Pejman Ghanouni wondered whether anesthesiologists would allow this practice prior to a procedure that involves sedation.

A participant asked about using endoscopic ultrasound to approach the pancreas, which launched a discussion of whether endoscopic limitations could be addressed (e.g., the magnetic resonance environment).
Panel Discussion of Burning Questions

Moderator Joo Ha Hwang and panelists Joan Vidal-Jové, Alessandro Napoli, Gail ter Haar, and Gabriela Chiorean led attendees through a discussion of burning questions. Group discussion elicited the following responses:

What are the possible clinical indications for FUS regimens?
- pain palliation
- tumor ablation
- targeted drug delivery
- local tumor control
- immunotherapy
- preoperative tumor volume reduction

Which focused ultrasound mechanisms of action could be employed to treat pancreatic cancer?
- Tumor ablation via thermal ablation or mechanical ablation (i.e., histotripsy)
- Drug delivery via pulsed FUS plus a systemic drug
- Drug delivery via TSLs: what drugs should be loaded into the TSLs?
- Radiosensitization (i.e., hyperthermia)
- Timing considerations for FUS with other therapies

Are there animal models and tumor models that can be used for pancreatic cancer research?
- Subcutaneous
- Orthotopic
- Genetically engineered (i.e., KPC mouse model)

What technological advances are needed?
- Treatment planning that includes identification of critical structures around the tumor (e.g., vessels, nerves, lumen, ducts, and more)
- Image guidance and targeting
- Treatment monitoring
- Defining cavitation dosimetry for mechanical ablation trials
- Compensation for respiratory motion using gated respiration, breath holds, or high-frequency jet ventilation
- Patient positioning (prone vs. supine)
- Endoscopic transducer development
- Determining which medical specialists should be treating patients with FUS
What is needed to use immune therapy to treat pancreatic cancer?

- Determining whether enough is known to pursue a clinical trial with FUS and immune therapy. (Some of the presented material in the Workshop is unpublished. It may be that following publication, the translation to clinical treatment can begin.)
- Establishing metrics for measuring effectiveness in immune treatment
  - Collecting and analyzing tissue specimens to evaluate for an immune response
  - Measuring a change in T-cell population
  - Measuring levels of PDL1, IDO, LAG
- Identification of a tumor marker

What are the priorities?

- Pain palliation
- Tumor ablation for local tumor control and/or preoperative tumor volume reduction
- Immunotherapy
- Drug delivery using pulsed FUS plus a systemic drug, or hyperthermia + TSL loaded with drug
- Device development, including better transducers, motion compensation, and endoscopic devices
Developing a Clinical Roadmap

To move forward with developing the use of FUS to treat patients with pancreatic cancer, workshop participants chose the following pathways.

**Route 1**
For FUS ablation, conduct a clinical trial wherein patients with stage 3 or 4 pancreatic cancer would receive FUS ablation plus chemotherapy versus chemotherapy alone using current state-of-the-art chemotherapy regimens.

**Route 2**
For FUS-enhanced drug delivery, (a) determine how much of an increase in drug delivery would be clinically significant (preclinical study); (b) improve FUS technology to reliably achieve stable hyperthermia to pancreatic tumors; and (c) treat patients with stage 3 or 4 pancreatic cancer using current chemotherapeutic agents.

**Route 3**
For FUS-enhanced immunotherapy, initiate a collaborative, multicenter trial performing immune treatment on patients with pancreatic cancer in an effort to reliably produce an abscopal effect (i.e., disappearing metastases). This may include (a) performing additional preclinical studies in appropriate mouse models of pancreatic cancer to evaluate treatment regimens using immune agonist and checkpoint inhibitor prior to FUS ablation; and (b) obtaining biopsies before and after FUS ablation in treatment-naïve patients to evaluate the immune response resulting from ablation.

A future protocol idea would be to start with a biopsy (the standard of care), and then apply HIFU one time. Another biopsy should be taken at least one week later to measure the effects of the HIFU, and serum markers should be checked to evaluate those patients as they progress through chemotherapy.

The group discussed clinical end points such as safety, the percentage of pain reduction (e.g., 90 percent), the percentage of tumor shrinkage, a length of time for progression-free survival, and a change in the immune response.

FDA representatives advocated for a step-wise approach to treating patients in clinical trials, meaning providing the FUS alone before adding drug delivery.

Next Steps

The FUS Foundation encouraged participants to submit research ideas and project proposals in this area. The Foundation will continue engagement with this community to move the research forward.
References


Focused Ultrasound Foundation


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
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<tr>
<td>ARRAY</td>
<td>Pancreatic Cancer International Registry</td>
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<tr>
<td>CAR-T</td>
<td>chimeric antigen receptor T</td>
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<td>CD40</td>
<td>Cluster of differentiation 40, a costimulatory protein found on antigen-presenting cells</td>
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<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
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<td>CRI</td>
<td>Cancer Research Institute</td>
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<tr>
<td>CTLA</td>
<td>cytotoxic T-lymphocyte-associated antigen 4</td>
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<td>DC</td>
<td>dendritic cells</td>
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<tr>
<td>ECM</td>
<td>extracellular matrix</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FUS</td>
<td>focused ultrasound</td>
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<tr>
<td>HA</td>
<td>hyaluranon</td>
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<tr>
<td>HIFU</td>
<td>high-intensity focused ultrasound</td>
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<tr>
<td>ICR</td>
<td>Institute of Cancer Research</td>
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<tr>
<td>IFN</td>
<td>interferon</td>
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<tr>
<td>iPACT</td>
<td>image-guided pancreatic cancer therapy program</td>
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<tr>
<td>LTSL</td>
<td>low temperature sensitive liposome</td>
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<tr>
<td>MR</td>
<td>magnetic resonance</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
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<tr>
<td>NIBIB</td>
<td>National Institute of Biomedical Imaging and Bioengineering</td>
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<tr>
<td>PancNETs</td>
<td>Pancreatic cancer neuroendocrine tumors</td>
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<tr>
<td>PD1</td>
<td>programmed cell death protein 1</td>
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<tr>
<td>PDAC</td>
<td>pancreatic ductal adenocarcinoma</td>
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<tr>
<td>STING</td>
<td>stimulator of interferon genes</td>
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<tr>
<td>TSL</td>
<td>temperature sensitive liposome</td>
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<tr>
<td>VTFS</td>
<td>Voronoi-tiled-Fermat-spiral</td>
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