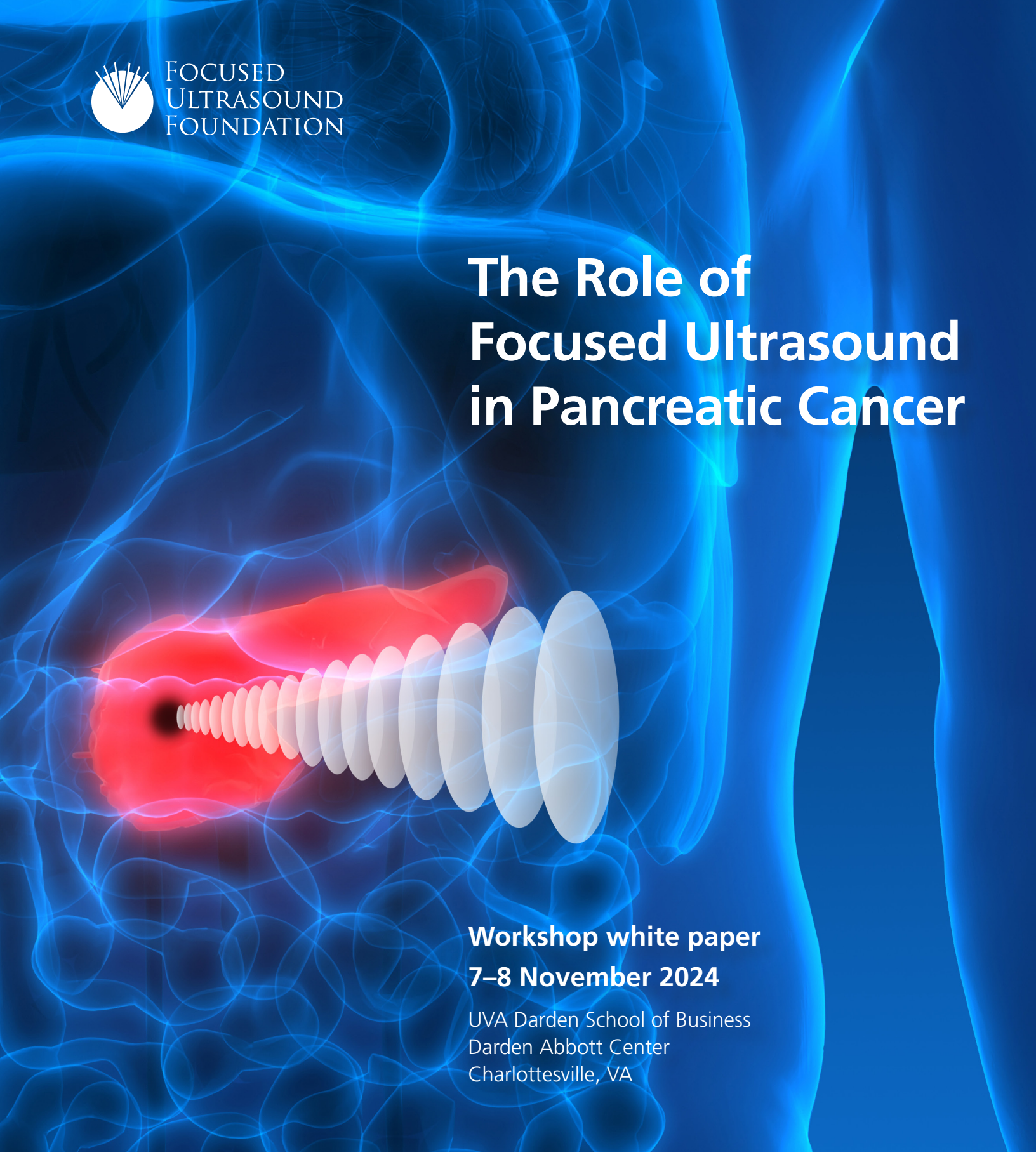
Focused Ultrasound Foundation

The Role of Focused Ultrasound in Pancreatic Cancer



Workshop white paper

7–8 November 2024

UVA Darden School of Business
Darden Abbott Center
Charlottesville, VA

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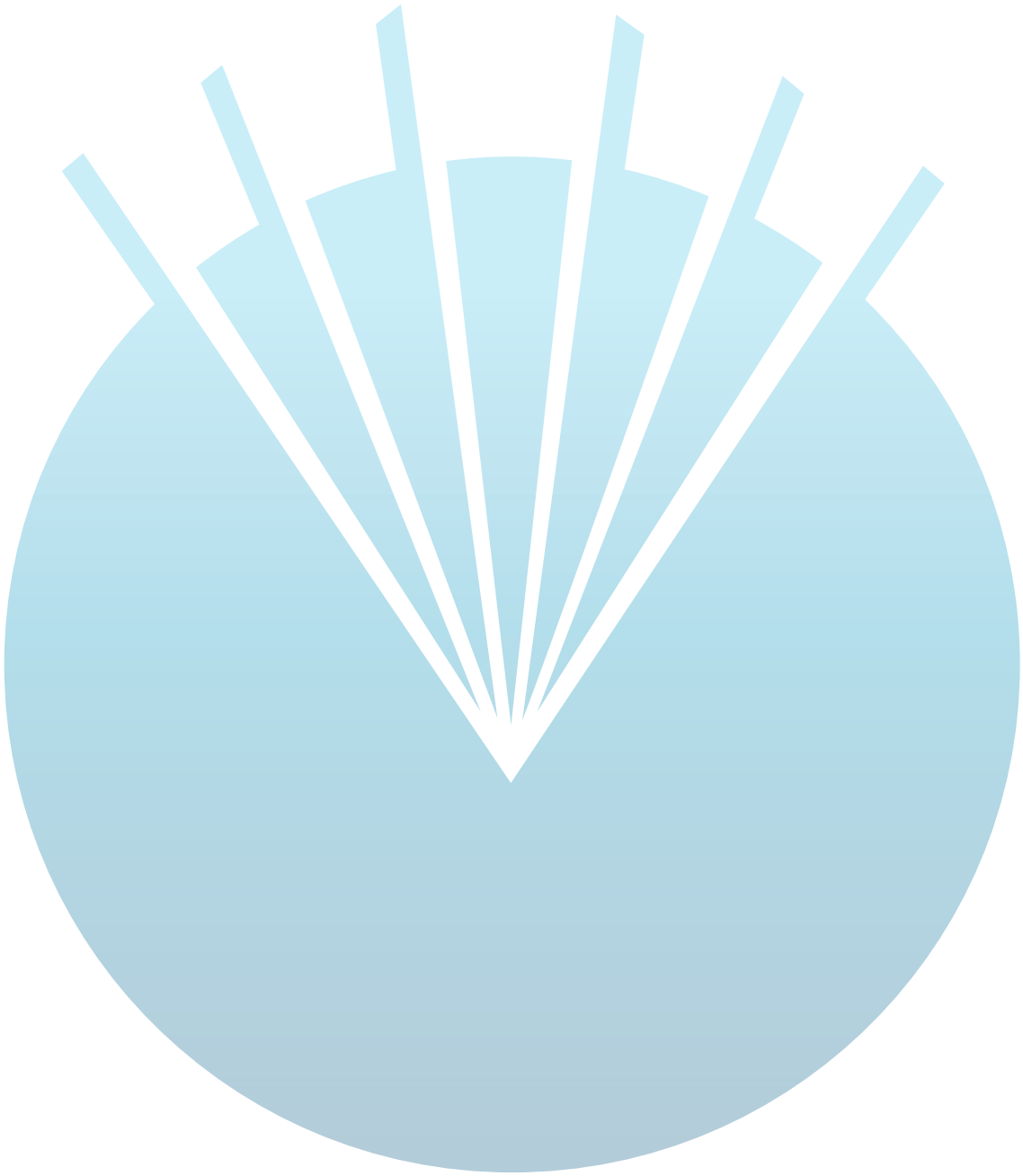

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Executive Summary

The Focused Ultrasound Foundation (FUSF), along with the meeting sponsors, Haifu Medical, HistoSonics, IMGT, Profound Medical, and SONIRE Therapeutics, hosted the workshop on the role of focused ultrasound (FUS) in pancreatic cancer on November 7–8, 2024, in Charlottesville, VA, at the UVA Darden School of Business. This invitational workshop brought critical stakeholders together to share information and ideas freely.

The meeting brought together critical stakeholders, including researchers, clinicians, industry, government, and others, to share and combine knowledge to advance the field. FUS is an early-stage, non-invasive 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 treatment approaches.

The ultimate goal is to improve outcomes and reduce barriers (poor drug penetration, immunologically a "cold" tumor, difficult physical access, surgical intervention limited at the typical stage of diagnosis) for patients with pancreatic cancer. Key topics for discussion included clinical translation approaches for pancreatic cancer therapy that may reduce the time it takes for FUS and cancer immunotherapy combination treatment(s) to reach clinical adoption. This workshop was another step towards accomplishing this goal by critically evaluating the current body of evidence, assessing the value of ongoing work, and creating a roadmap of projects that will address any remaining gaps and "burning questions." The workshop included several presentations designed to orient participants to the current state of the field and to provide moderated open discussion sessions to address gaps and "burning questions."

The primary objectives of the workshop were to:

1. Assess the state of the field concerning the "burning questions."
2. Develop a roadmap for a two-year action plan that provides the best pathway forward, with tentative suggestions as follows.
   - **a.** Consider a follow-up IMGT HIFU with short-duration (non-thermal) treatment of the entire tumor to see if the enhanced penetration by FOLFIRINOX can be verified.
   - **b.** Consider combination studies, e.g., neo-adjuvant approaches to lower the interstitial pressure followed by checkpoint inhibition or CAR-T cell approaches.
   - **c.** Consider doing tissue culture studies to determine the impact of FUS-treated tumor lysates on dendritic cell activation.

d. Consider a "window-of-opportunity" study for Whipple surgical patients in the 6 to 8 week delay prior to surgery (for UK patients) or for patients with underlying conditions that make surgery not an option. (e.g.>80), for treatment with either ablation or histotripsy.

e. Be certain to include pain control in studies. Consider a "pain management" indication, as this may be the quickest way to gain access to patients.

f. Consider a study on the abscopal effect following histotripsy (as opposed to noticing that it is present as an incidental finding), including regular blood samples.

3 Create a collaborative environment to achieve our goals as rapidly as possible by standardizing reporting on methodology, biomarkers, and sharing of results.

Experts highlighted that pancreatic cancer presents unique challenges due to its location, dense stromal tissue, and typically late diagnosis, with only 15% of patients being candidates for surgical resection at diagnosis. Multiple FUS approaches were discussed, including thermal ablation, histotripsy, and low-intensity FUS for drug delivery enhancement. The potential of FUS to stimulate immune responses and enhance immunotherapy effectiveness was a significant focus of discussion.

The workshop identified several priority areas for future research, including the need for well-designed clinical trials to demonstrate efficacy, particularly in combination with current standard-of-care treatments. Participants emphasized the importance of careful patient selection and the potential role of FUS in pain management for palliative care.

Introduction

Focused Ultrasound Foundation

Tim Meakem, MD, and **Chrit Moonen**, PhD, welcomed participants and thanked the meeting sponsors, Haifu Medical, HistoSonics, IMGT, Profound Medical, and SONIRE Therapeutics. The workshop covered the current standards of care for pancreatic cancer, technical aspects of FUS, preclinical work, and the potential for combining FUS with immunotherapy.

Throughout the workshop, attendees were encouraged to consider the six burning questions posed by FUSF:

1. What is the role of focused ultrasound in treating pancreatic cancer (e.g., pain palliation, drug delivery, immunomodulation, conversion of inoperable to operable lesions, increase in life expectancy, biomarker enhancement)?
2. What focused ultrasound modality is most promising (e.g., thermal ablation, moderate hyperthermia, histotripsy, mechanical stimulation)?
3. What devices are most suitable with respect to the treatment envelope, treatment time, and an optimal beam path?
4. What endpoints in clinical trials should we aim for with respect to immuno-monitoring, biomarkers, clinical outcomes, and imaging?
5. What therapeutics can be combined with the different focused ultrasound modalities (e.g., chemotherapy, radiotherapy, immuno-therapeutics, immuno-modulation)?
6. What immunotherapy options exist for focused ultrasound in pancreatic cancer treatment to consistently convert a “cold” into a “hot” tumor or modify the tumor microenvironment, and what biomarkers are suitable?

State-of-the-Art in Pancreatic Cancer Therapy

Session chairs
Srikanth Reddy and **Keaton Jones**

Surgical Approaches in Pancreatic Cancer

Keaton Jones, MD, PhD, provided an overview of the current treatment landscape for pancreatic cancer and some new therapies on the horizon. Diagnosis and staging are based on imaging, and patients are categorized into three groups: resectable (tumor can be removed entirely), borderline resectable (tumor has some vessel involvement but might be operable), and unresectable. Only 15% of patients are classified as resectable at diagnosis, with 80% likely to have a recurrence within the first few years after surgery. Despite the lack of imaging findings, systemic disease is often present at the time of surgery. Unlike other cancers, progression is not sequential, with metastasis already occurring at diagnosis. This explains why surgery alone is often insufficient, and patients need both surgery and chemotherapy to have the best chance of survival. The location of the pancreas over critical blood vessels (superior mesenteric artery and vein) makes surgical resection particularly challenging, as achieving clear margins while preserving these vessels is crucial. The latest guidelines (2024 National Comprehensive Cancer Network (NCCN)) recommend different approaches based on categorization: resectable tumors can go straight to surgery followed by chemotherapy, while borderline resectable cases should receive neoadjuvant chemotherapy first to ensure disease stability before attempting surgery.[1] Unlike other cancers where neoadjuvant chemotherapy is expected to shrink tumors, in pancreatic cancer, the primary goal is to achieve disease stability and prevent progression before surgery, as tumor shrinkage is rare. This allows surgeons to proceed with necessary procedures like vein resection. The main surgical procedure for head of pancreas tumors is the Whipple procedure, which has not changed dramatically in decades. However, perioperative care has improved significantly, lowering mortality rates to about 3%. The artery must be maintained, meaning cancer cells are often left behind.

Srikanth Reddy, MD, PhD, emphasized the importance of neoadjuvant therapy in improving surgical outcomes and reducing complications. A high-quality contrast CT scan is required to determine resectability. For resectable tumors, surgery followed by chemotherapy has better outcomes.[2] However, for borderline resectable tumors, chemotherapy before surgery has better outcomes.[3] Standard-of-care for chemotherapy is FOLFIRINOX, which comprises four agents: 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin.[2] The alternative to FOLFORINOX is the Gemcitabine Abraxane combination. By treating with chemotherapy upfront, there is an opportunity to treat micrometastases that surgical interventions would not treat.[3] As portal vein involvement increases, surgical difficulty increases. The Da Vinci robotic-assisted pancreatic duodenectomy is being increasingly used by surgeons. Robotic/laparoscopic distal

pancreatectomy has become the standard-of-care. However, only 10% to 15% of patients undergo surgery for pancreatic cancer.

A phase I trial demonstrated that an individualized mRNA neoantigen vaccine, combined with immunotherapy (atezolizumab) and chemotherapy (mFOLFIRINOX), induced strong T-cell responses in half of patients and may lead to improved recurrence-free survival in patients that were responders.[4] Dr. Reddy emphasized that hospital centers that perform more pancreatic surgeries per year have lower mortality rates, and that the team effect is equally important as surgeon effect on outcomes because of the entirety of the team needed to care for these patients.[5]

Questions

Q. How often is MRI used to detect micrometastases?

- Dr. Reddy responded that contrast CT and PET scans are the standard/routine approach, particularly in the UK under NICE guidelines. There was a debate over whether using MRI to detect the presence of micrometastases that CT/PET missed can avoid surgery in a patient that has already progressed. MRI while more sensitive in picking up small metastases could also lead to false negative findings, potentially impacting decision making. The UK faces significant waiting list issues for imaging and a shortage of radiologists to report results; additional testing could delay treatment.

Q. Is there a role for surgical resection in patients with oligometastatic disease?

- Dr. Jones said that this is a tiny fraction of patients with pancreatic cancer, and certain cases could benefit from surgical resection combined with ablation or with radiotherapy. It could be considered for lung-only metastasis (shows better survival than liver or peritoneal metastases) and patients with BRCA mutations who respond well to systemic therapy.

Q. Is metastatic disease (rather than primary site recurrence) the main issue for susceptible patients, and whether surgeons remove most lymph nodes during surgery

- Dr. Jones explained that the surgical procedure naturally yields a high number of lymph nodes, typically dozens. He noted that from an immunological perspective, lymph node yield is valuable for prognostic purposes but does not actually impact patient survival.

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Radiotherapy for Localized Pancreatic Cancer

Robert Owens, MBBcH, MRCP, FRCR, described challenges related to delivering radiotherapy in patients with pancreatic cancer, including respiratory motion and the radioresistant pancreas. At the same time, other nearby organs are radiosensitive (i.e., bowel) and have an elevated risk of micrometastatic disease. Several clinical trials have studied the role of radiotherapy in pancreatic cancer.[6-10] In the neoadjuvant chemoradiotherapy setting, there may be some benefit for radiotherapy.[8, 9] There was no overall survival benefit in the adjuvant setting, but there could be some benefit regarding local recurrences.[10] In the locally-advanced pancreatic cancer setting, there were no benefits to overall survival.[6, 7]

Next, the potential role of stereotactic ablative radiotherapy (SABR), which delivers high-dose radiotherapy in 1 to 5 fractions, was discussed. A systematic review determined that there was no overall benefit.[11] However, a systematic comparison of stereotactic body radiotherapy (SBRT) with conventionally fractionated radiation therapy suggested that SABR improved 2-year overall survival.[12] A study of SABR in the neoadjuvant setting suggested that SBRT was worse than surgery.[13] The NCCN recommends SBRT in patients with locally-advanced or borderline resectable pancreatic cancer after a course of induction chemotherapy or as a stand-alone modality for patients unsuitable for chemotherapy.[1] It is not recommended for metastatic disease (except oligometastatic), large tumors, multiple locoregional lymphatic nodules, or gastrointestinal mucosal infiltration.

SABR should be avoided in patients with clear involvement of the gastrointestinal (GI) tract because of the elevated risk of perforation or GI bleeding in these patients. The challenges with delivering SBRT include movement between the planning CT and the cone beam CT on the day of treatment, and geographic miss is also associated with movement. To improve treatment, the team introduced a MR Linac system, ViewRay MRIdian, which combines MRI imaging with radiation therapy. This allows daily treatment plan adaptation and real-time tumor tracking by providing superior image quality compared with cone beam CT, enabling precise recontouring and replanning before each treatment fraction to ensure accurate tumor targeting while avoiding critical structures like the bowel. Early research suggests low toxicity and high local control rates with MR Linac.[14,15] A feasibility study showed the potential to deliver higher doses of SABR while maintaining organ tolerances, but the trial closed early because the manufacturer went out of business. Early-stage research looked at using radiosensitizers in combination with SBRT, but early results failed to show benefit, and the trial was closed early.

SABR is also under investigation in the palliative setting for quality of life and symptom palliation (pain related to the tumor) and gives patients time off from systemic therapy. Preliminary work suggests a symptomatic response and a reduction in analgesia use. The PANCOSAR study looks at best supportive care versus SBRT in patients who were either unfit or declined surgery with ongoing enrollment. In the EXTEND trial, patients were randomized to metastasis-directed therapy (MDT) to standard-of-care systemic therapy for patients with some oligometastatic solid tumors, reported increased progression-free survival but not overall survival in patients treated with SBRT as well as showing an increased immune activation.

Questions

Q. How often is MRI used to detect micrometastases?

- Dr. Owens replied that despite having access to advanced MR-guided radiotherapy, there are challenges in demonstrating its benefits due to limited patient numbers and treatment centers, making it challenging to convince oncology colleagues to adopt new radiotherapy approaches like SABR.

Q. Why should we continue exploring immunotherapy in cancer treatment when studies across multiple tumor types show improved local control but no survival benefit?

- Dr. Owens emphasized the importance of patient selection, upfront chemotherapy, and recent imaging to identify suitable candidates before treatment delivery.

Q. What is the optimal timing for SBRT

- Dr. Owens said that the timing has yet to be determined, but they have already found that patients should remain on chemotherapy until treatment with SBRT.

Q. Is surgery following radiation more challenging in the pancreas than elsewhere?

- Dr. Reddy reported that this is the case; clinical trial evidence shows poorer survival outcomes, and radiotherapy is rarely used before or after surgery for operable patients following chemotherapy.

Q. Which imaging modality is most effective at predicting tumor response to chemotherapy?

- Dr. Owens responded that they generally use CT at 3-, 6-, 9-, and 12-months post-treatment, but it is quite challenging to determine what is tumor versus fibrosis.

Q. MR guidance for FUS and SBRT is similar, but how is tracking accomplished with SBRT?

- Dr. Owens stated that the system can track tumors and critical organs like the bowel in three planes in real-time to ensure precise treatment delivery while avoiding overdosing on sensitive structures.

Reimagining Signal-Seeking Trials for Pancreatic Cancer

Chris Cabanski, PhD, provided a brief overview of the Parker Institute for Cancer Immunotherapy (PICI), and two PICI-sponsored pancreatic cancer trials: PRINCE and REVOLUTION. PICI's mission is to accelerate the development of immune therapies to turn all cancers into curable diseases. The PICI model is to accelerate research from the bench to the bedside, and then into clinical development, hoping to reach the patient. PICI funds basic research and helps translate these findings into clinical studies by partnering with BioPharma. PICI funds a select number of academic centers throughout the US. PICI has partnered with these institutions to run clinical trials and has held multiple Investigational New Drug (IND) applications. They have also focused on collecting biopsies and samples to create a large data repository. The PRINCE trial evaluated immunotherapy combinations with chemotherapy in first-line metastatic pancreatic cancer across three arms: nivolumab plus chemotherapy, sotigalimab (CD40 agonist) plus chemo, and the combination of both plus chemotherapy.[16,17] This phase 2 trial notably omitted a chemotherapy-only control arm to speed enrollment, instead relying on historical controls for comparison.[17] Although not powered to directly compare between arms, the results showed that nivolumab plus chemotherapy had the best survival with a 50% response rate, while surprisingly, the triple combination performed the worst. Published data suggest biomarkers that could predict survival and might be used for patient selection in future trials.[18] PICI0044 REVOLUTION trial is a pancreatic platform study to test new immunotherapy combinations. The goal was to enroll the same patient population (n=15 per cohort) to look at novel therapies on top of chemotherapy with an adaptive trial design. After enrolling the initial 15 patients and evaluating safety, efficacy, and biomarker data, a cohort could be expanded to include an additional 15 patients, or the cohort could be closed. A drug selection committee vetted proposals for scientific merit and prioritized cohort proposals accordingly. A variety of patient samples were collected and analyzed. To date, three cohorts have been fully enrolled, and results will be published in the future. In 2023, PICI shifted away from holding the INDs for clinical trials to forming partnerships, and the Cancer Research Institute (CRI) and the Lustgarten Foundation assumed oversight of this platform trial, but in 2025 a decision was made to discontinue this effort. Dr. Cabanski mentioned the PORTER platform study in patients with metastatic prostate cancer that combined immunotherapy with multiple modalities, including radiation therapy and chemotherapy.

Questions

Q. Can you comment on the rationale of using the anti-CTLA-4 rather than anti-PD-1 in this setting?

- Dr. Cabanski replied that CTLA-4 inhibitors are used to enhance T-cell priming and activation, which is crucial for converting "cold" tumors to "hot" by increasing CD8+ T-cell counts. In contrast, PD-1 inhibitors help reinvigorate exhausted T cells within the tumor microenvironment (TME). In pancreatic cancer, the dense stroma and

immunosuppressive microenvironment significantly impede T-cell trafficking and infiltration, as imaging data frequently show T cells fail to reach the tumor site despite treatment. This unique TME provides a rationale for targeting the early activation of T cells with CTLA-4 inhibitors as a potential strategy to overcome these barriers.

Q. Do any of these trials incorporate molecular imaging?

- Dr. Cabanski stated that they imaged tumor biopsies in both trials (Vectra in PRINCE and Ultivue in REVOLUTION).

Q. What other imaging is collected?

- Dr. Cabanski said that they only collect typical CT images.

Q. Is there a reason you are also not trying to initiate new adjuvant surgical trials?

- Dr. Cabanski reported that the focus was on first-line treatment for metastatic disease, and the study population was limited to these patients.

Q. Is there a specific immunotherapy that seems promising to combine with chemotherapy beyond pancreatic cancer?

- Dr. Cabanski said that the most promising immunotherapy agents combined with chemotherapy so far have been anti-PD-1 agents. However, anti-PD-1 and chemotherapy combinations have been ineffective in patients with pancreatic cancer.

Q. What are your thoughts on including a small control arm (15 patients) in platform trials to serve as a baseline comparison across different treatment options, given how the lack of a control arm made the PRINCE trial results difficult to interpret?

- Dr. Cabanski commented that a small control arm of 15 patients would be more valuable for biomarker analysis than clinical efficacy comparisons, helping distinguish treatment-specific biomarkers from general chemotherapy-related markers.

Q. There might be a mismatch between the preclinical work and the clinical trial and the biopsies may not be helpful, given that they only sample a tiny portion of a larger tumor or from a distant metastasis site. The immunity paper by Li et al. showed that CD40/PD1/CTLA4 combined well to produce remarkable responses in mouse pancreatic tumors described as "T-cell inflamed" but was largely ineffective against "Non-T-cell inflamed" tumors.[19] The patients likely represent a mix of this biology. Some patients may have garnered benefit from the immunotherapy but identifying those patients a priori has been challenging.

- Dr. Cabanski agreed with this and said that follow up will focus on circulating biomarkers because of this issue.

Technical Aspects of FUS for Pancreatic Cancer

Session chairs
Gail ter Haar and **Chrit Moonen**

Overview of Beam Path Issues/ Extracorporeal Approaches for Hyperthermia, Ablation

Holger Grüll, PhD, provided some preliminary results with MR-guided HIFU (MR-HIFU) for pancreatic cancer with the Sonalleve MR-guided system. The system has a phased array with 256 elements and has a capability of 1.2 MHz with MR-thermometry for real-time feedback. The challenges of treating pancreatic cancer with HIFU are the depth of the pancreas and location behind bowel and stomach tissue (air pockets), the presence of heat-sensitive structures close to the pancreas, and the complex motion patterns of the pancreas. The trial, HIFU PANC, is recruiting patients with metastatic disease of locally-advanced non-resectable tumors and is a proof-of-concept of ablation to demonstrate feasibility and safety. The primary endpoint is tumor destruction by thermal ablation, along with an optional research arm collecting blood and tumor biopsies before and after ablation to examine immune responses.

The general safety and treatment guidelines considerations were acoustic contact and acoustic window availability (no air pockets or bone blocking path), 1 cm safety margin with crucial organs, scar tissue (minimum of 6 weeks after surgery), metal clips ≥ 1 cm, and stents ≥ 1 cm. Patient preparation was the same as for gastrointestinal surgery. The first evaluated patient had an out-of-reach tumor; a gel pad reduced the distance by 2.5 cm due to compression, but it was still out-of-reach. The first treated patient had metal clips, but they were not in the far field. During treatment, there was a 4 mm treatment cell with a max temperature of 67.8°C, 150 W, 32 seconds duration. The patient had a grade 1 skin burn that healed within two weeks. It is unclear why the skin heated, but it may have been scar tissue related. Following treatment, the patient had a decrease in tumor markers at 28 days.

The second patient had a 4 mm treatment cell, power ranged from 100 W to 190 W, duration ranged from 16 to 36 seconds, and frequency was 1.2 MHz with a treatment duration of 1 hour and 18 minutes. There were no adverse events or serious adverse events, and the patient went home the day after treatment. The third patient had an air pocket in the pylorus that blocked the ultrasound beam to the tumor, but massage removed the air pocket. Dr. Grüll noted that blood flow in a nearby artery can create false temperature readings, but placing a saturation band over the artery eliminates these artifacts and improves the reliability of temperature measurements. The intended treatment volume was 3.7 mL, and the effective ablated total volume was 3.0 mL.

Next, Dr. Grüll discussed MR-HIFU-induced drug delivery for treating unresectable soft tissue sarcoma. Temperature-sensitive drug carriers are stable at body temperature and rapidly release at hyperthermic temperatures, and heating the tumor can result in direct delivery to the tumor. A trial will include six patients per group with either three cycles of temperature-sensitive drug delivery (doxorubicin) for 30 minutes or three cycles of doxorubicin alone. Previous research has determined how to treat large areas with MR-HIFU.[20] Safety concerns for hyperthermia were addressed in a porcine model by implementing new algorithms for heating control, heating larger volumes, improving MR-thermometry (field drift corrections), and heating bone. They also addressed bone heating with bone-embedded phantoms. They found that bone strongly absorbs and heats, requiring a safety margin of approximately 3 cm between the treatment target and any bones to prevent overheating.

Questions

Q. How many patients were screened versus the number treated?

- Dr. Grüll replied that three patients were screen failures out of six patients total. Failures were usually risky structures that were too near the target.

Q. Do you use a gastric tube to remove air from the stomach?

- Dr. Grüll said that a gastric tube was placed in one patient to remove air; it can also be used to fill the stomach with water or pineapple juice if necessary.

Q. Is this procedure possible without anesthetics?

- Dr. Grüll responded that this is not possible because the ablation is performed in the apneic phase (temporary pause in breathing) while patients are ventilated under anesthesia and can be maintained for 3 to 4 minutes.

Q. Can ablative treatments be done without anesthesia?

- Dr. Grüll explained that he was unsure if ablative treatments could be done without anesthesia as patients with pancreatic cancer experience pain in the prone position and cannot withstand more than 15 minutes on the table.

Q. How far do you need to be away from the artery?

- Dr. Grüll said that they maintain a distance of 1 cm, but in pigs, they ablate on the artery without any adverse events.

Q. In your hyperthermia study, where temperature was monitored for one hour, were thermosomes required to achieve and maintain the target temperature, or were you exploring alternative technical approaches?

- Dr. Grüll replied that while traditional hyperthermia treatments typically last one hour to enhance radiotherapy or chemotherapy through biological processes, shorter durations (potentially as brief as 10 minutes) may be sufficient for drug delivery applications, leading to the current compromise of 30-minute sessions. They are looking at this in a parallel preclinical rat study to explore optimal timing combinations.

Feasibility and Safety of Non-Invasive Pancreas Ablation Using Histotripsy

Jessica Gannon provided an overview of histotripsy for ablation in the pancreas. Current ablative strategies have limitations such as a lack of targeting precision, lack of real-time feedback, risk of damage to critical structures, and the risk of inducing pancreatitis. Histotripsy is a non-invasive, non-thermal, and non-ionizing treatment method for cancer. Histotripsy uses FUS waves to generate significant peak negative pressure and create cavitation with microbubbles that rapidly expand and collapse, breaking down tissue into acellular homogenate. Histotripsy can be done with millimeter precision. Ultrasound B-mode imaging can monitor the treatment in real time as the histotripsy bubble cloud appears as a bright white hyperechoic region. CT or MRI can be used for immediate feedback.

The clinical feasibility and safety of histotripsy for liver cancer were demonstrated, and the HistoSonics Edison System was approved by the US Food and Drug Administration (FDA) in 2023.[21, 22] Additional clinical applications of histotripsy, including the treatment of the prostate and kidney, are in development, as well as multiple preclinical applications. A porcine model demonstrated the feasibility of histotripsy to target a healthy pancreas.[23, 24] Without dietary preparation, they did not consistently target the pancreas because of gas blockage, but this was solved by feeding a custard diet laced with simethicone and bisacodyl.[24] Tumor ablation in a pancreatic tumor porcine model was achieved with histotripsy with proper dietary preparation.[25] A recently completed study assessed local response and lesion generation in the pancreas in an in-vivo porcine model. Treatment parameters are a 1.5 cm diameter spherical volume with a 700 kHz transducer, with a treatment workflow involving freehand ultrasound imaging and coaxial ultrasound monitoring. Histotripsy bubble clouds were identified in five out of nine animals with clear acoustic windows and hypoechoic regions seen immediately post-treatment. Histotripsy lesions were identified on CT in all animals. Lesions were contained in the pancreas (6/9) with a clear acoustic window and visualization. CT lesions matched the planned treatment diameter. There was one observed case of vessel sparing of the gastroduodenal artery within the treatment zone. There were two adverse events: septic peritonitis (1/9) and GI blockage (1/9), suggesting the need for strategies to protect the bowel during histotripsy. Normal pancreatic function was observed post-treatment after one week (3/3) and five weeks in pigs (5/6). One animal had elevated amylase and lipase levels three times their baseline at one-week post-treatment.

Questions

Q. What specific conditions or situations during the procedure would be a go/no-go decision?

- Ms. Gannon replied that clear ultrasound visualization of the pancreas is essential for treatment, as relying solely on auditory cavitation feedback when visibility is obscured by gas is inadequate since the exact location of treatment effects cannot be confirmed.

Q. Have you looked at immune cell infiltration into normal tissue?

- Ms. Gannon acknowledged that they have not looked at immune cell infiltration in the current study but are evaluating this in other studies in collaboration with Dr. Coy Allen's group.

Q. How long does the treatment take, and during treatment, does the power level sometimes increase unexpectedly and obstruct what initially was a clear treatment path?

- Ms. Gannon indicated the total treatment time took 2 to 5 minutes. While there were no cases of bowel interference during treatment, one case involved misalignment with the bowel during targeting, highlighting the importance of clearly distinguishing between bowel and pancreatic tissue during alignment.

Q. When comparing in-vivo ablations to optimized in vitro systems, are the clear margins between treated and untreated tissue maintained, or are they more irregular?

- Ms. Gannon explained that there are clear boundaries between treated and untreated areas in liver tissue. However, assessing these margins in pancreatic tissue has been challenging due to the organ's ovoid nature and tissue loss during sectioning. While the partial reduction of pancreatic tumors was observable in tumor studies, better treatment parameter optimization is still needed. In subcutaneous mouse models, good delineation was achieved between treated and untreated areas.

Q. Was respiratory motion a problem for this type of treatment?

- Ms. Gannon stated that breath holds could only be maintained for about one minute during treatment. While respiratory motion was present, they ensured the lesion creation stayed within pancreatic tissue.

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Intraoperative FUS for Pancreatic Cancer

David Melodelima, PhD, shared results on using HIFU for pancreatic cancer. The team uses a toroidal HIFU transducer with an ultrasound imaging probe in the center.[26, 27] The toroidal shape allows a larger volume of treatment, ranging from 1 cm3 to 55 cm3. The first application of this technology was intraoperative treatment of liver metastases, and it demonstrated better control of the focusing effect, visualization, and staging of malignancies, since additional metastasis (hepatic or peritoneal) are discovered intraoperatively in 15–20% of patients, despite preoperative imaging and may contraindicate treatment.

The first study was a liver proof-of-concept (NCT 01489787) phase I/II study (35 patients) that showed ease of targeting, reliable guidance with clear contrast between treated and untreated tissues, effective ablation and possible use for liver metastases in difficult locations such as the ones close to large vessels.[28, 29] This was repeated with the pancreas in pigs.[30] A safety procedure was developed to prevent occlusion of mesenteric vessels, based on Doppler signals.[31] A proof-of-concept clinical study for pancreatic cancer, focusing on locally-advanced tumors, was initiated with 26 patients and is ongoing. Studies on the ultrasonic properties of pancreatic tissues were conducted to develop patient-specific, non-invasive treatments.

In vivo evaluation in a porcine model treated 45 pigs, 12 to 14 weeks old, weighing 25 to 35 kg, with energy escalations of 35, 40, 45, and 50 kJ.[31] The duty cycle was 40% (10 seconds HIFU and Doppler + signal processing 15 seconds), and HIFU exposure was 370 seconds. Doppler signals were used to prevent spasms in mesenteric vessels, with a threshold set to predict spasms 50 seconds before occurrence. The study demonstrated successful HIFU ablation treatment with controlled lesion sizes (25-45 mm) and no damage to surrounding organs, showing a strong correlation between imaging and pathological measurements while maintaining safe energy levels below 40 kJ. Additionally, reliable visualization of B-mode imaging with HIFU ablation was confirmed by MRI.

A multicentric phase I/II clinical study is underway for locally-advanced, non-progressive pancreatic cancer after chemotherapy: phase I (monocentric, n=3-6) and phase II (multicentric, n=20-23). The main goal for the phase I study is safety; for the phase II trial, it is one-year overall survival with success defined as 60%. Four patients were screened since July 2024, but none were treated due to the discovery of peritoneal or hepatic metastasis.

A non-invasive patient-specific treatment approach is in development. This has involved measuring acoustic properties, particularly tissue attenuation, to estimate how much energy will reach tumors. Variations in attenuation values were observed between normal and tumoral tissues, requiring specific treatment parameters. The team is developing a new small transducer for the non-invasive treatment of the pancreas. The small size aims to avoid complications related to surrounding organs with an acoustic window validated in real time. The new device will use toroidal geometry to create HIFU while minimizing complications to surrounding organs.

Questions

Q. How do bile duct cancers differ from liver cancers in terms of treatment effectiveness since liver cancers are affected by blood vessel cooling (heat sink effect) while bile duct cancers typically obstruct the bile duct and don't have this cooling mechanism?

- Dr. Melodelima stated that their research found that blood flow (heat sink effect) doesn't significantly impact their treatment's effectiveness for two reasons: 1) their fast treatment time (1-6 minutes) prevents cooling effects, as demonstrated in studies with and without blood flow restriction, and 2) they achieved successful ablation even near major blood vessels. However, there are limitations in evaluating treatment effects due to anatomical differences between pigs and humans, and they'll need to monitor bile duct complications in clinical trials carefully.

Q. How do you control the amount of energy delivered during treatment, do you use real-time energy feedback measurements, or do you rely on experience?

- Dr. Melodelima explained that they use two reference points to control energy delivery: 1) the initial energy output from the transmitter in a free field and 2) the estimated energy reaching the target based on tissue attenuation measurements and electrical power measurement during sonication.

Q. How do your tissue attenuation measurements account for the changes in tumor and pancreatic tissue characteristics after neoadjuvant chemotherapy, given that these changes make it difficult to differentiate between tumor and normal tissue?

- Dr. Melodelima acknowledged that this is a key limitation. They made several measurements in human tissue samples treated after chemotherapy, showing high variability in attenuation values between patients. They are working on new methods to estimate attenuation in situ before treatment, but this might not be possible if the tumor is not visible on ultrasound images. Rather than trying to treat all cases, they aim to identify patients most suitable for this treatment approach; this method will not be effective for all tumors.

Panel Discussion

Panelists
Jessica Gannon, **Holger Grüll, David Melodelima**, **Gail ter Haar**, and **Eli Vlaisavljevich**

Throughout the discussion, participants emphasized the importance of careful patient selection, the need to understand long-term outcomes better, and the potential benefits of combining different treatment approaches.

A key topic was the treatment of tumors near blood vessels, particularly around the superior mesenteric artery (SMA). While some participants suggested getting closer to vessels to make tumors resectable, others cautioned about the risks. Another participant shared that their experience with complications coming not from direct thermal damage but from post-treatment swelling around diseased vessels in patients with pancreatic cancer. Researchers should use caution with animal models using healthy vessels, as these do not adequately represent the challenges of treating actual patients with diseased vessels encased by tumors.

The discussion also covered various ablation technologies, including thermal ablation, histotripsy (non-thermal ablation), and ultrasound-guided approaches. A significant advantage of histotripsy was its tissue selectivity, allowing treatment around sensitive structures like vessels and bile ducts. However, experts noted that different parameters and doses might be needed for various tissue types and locations.

Regarding imaging guidance, participants discussed challenges with visualization, particularly for deeper tumors. While ultrasound guidance can work well with proper bowel preparation, some noted difficulties in tumor delineation, especially after chemotherapy. MRI fusion and contrast agents were discussed as potential solutions. Tumors without pretreatment may be easier to visualize.

The panel also addressed the development of new tools, with updates on progress toward smaller instruments for endoscopic and laparoscopic approaches. Dr. Vlaisavljevich mentioned that they plan to test these new transducers in large animal studies by early 2025, while surgical probes are already being optimized for various applications.

A fundamental question emerged about the ultimate goal of ablation in pancreatic cancer treatment. Some questioned whether complete tumor eradication through thermal ablation is realistic, suggesting that patients eligible for complete ablation might also be surgical candidates. This led to a discussion about alternative treatment models, including using partial ablation to induce immune responses. The immunological aspects of different ablation techniques were also discussed, with thermal ablation noted to be less immunogenic than cryoablation. Some preclinical studies suggested partial ablation might produce better immune responses than complete ablation. However, the relationship between antigen preservation and actual immune response remains unclear, as evidenced by decades of cryoablation experience.

Preclinical FUS Studies of Pancreatic Cancer Therapy

Session chairs
Petros Mouratidis and **Tatiana Khokhlova**

Tumor Microenvironment, Interstitial Pressure, and Elasticity in Pancreatic Cancer

Cyril Lafon, PhD, presented the impact of mild ultrasonic cavitation on the stiffness of pancreatic tumor models to promote drug delivery. The pancreatic cancer tumor microenvironment has a dense fibroblast-rich stroma, leading to a poor immune response, high interstitial pressure, and limited vascularization that hinders chemotherapy delivery and reduces tumor permeability. Prior research suggests that stromal depletion accelerates cancer advancement and reduces survival rates. Ultrasound-induced cavitation enhances the effectiveness of gemcitabine in cells from a pancreatic mouse model (KPC) while preserving fibroblasts.[32] Their system generates controlled cavitation using a dual-output computer setup with a gel-surrounded transducer and a hydrophone to monitor bubble oscillation noise. It features a rapid feedback mechanism that maintains both inertial and stable cavitation levels by adjusting power based on recorded noise.[33] The results show that inertial cavitation reduces the stiffness of the spheroids, while stable cavitation maintains this effect. The combination of inertial cavitation, stable cavitation, and gemcitabine had a synergistic effect on cell viability in the 3D in vitro tumor model.

The same experiments were performed in vivo in mice. The experimental setup combines an ultrasound system with two confocal transducers, an imaging probe at the center to visualize the cavitation cloud and a hydrophone for cavitation quantification and regulation. Passive elastography estimated tumor stiffness before and after treatment (Verasonics Vantage 256, L12-5 (50 mm) probe). The results showed that the stiffness of large tumors decreases after treatment, while smaller tumors become stiffer. There was a correlation between elasticity and collagen network density, with greater collagen density leading to stiffer tumors. Smaller tumors have higher collagen density. In summary, inertial cavitation interacts with the collagen network but needs further investigation.

Questions

Q. Have you looked at other mechanical properties of tumors, such as strength, etc.? The tumor exhibits non-linear viscoelastic behavior, meaning its stiffness (Young's modulus) at low strain rates doesn't accurately represent the overall tissue strength.

- Dr. Lafon said that they tried to measure the interstitial pressure of the tumor, acknowledging uncertainty due to inconsistent interstitial pressure measurements across experiments. He suggested adjusting energy levels based on tumor characteristics

rather than using fixed exposure conditions. In their rat study, they used preset parameters instead of closed-loop cavitation control.

Q. Is the differential treatment response between large and small tumors potentially influenced by varying levels of released compressive residual stress, which accumulates more in larger tumors rather than just tissue stiffness differences?

- Dr. Lafon acknowledged that larger tumors have necrotic cores that may be more susceptible to modification.

Cavitation-based Disruption/permeabilization of Pancreatic Tumors for Enhancing Systemic Therapies

Tatiana Khokhlova, PhD, provided an overview of her work with pulsed FUS (pFUS)-induced cavitation in pancreatic cancer. There are various anatomic barriers to systemic therapies, including dense fibrous stroma, high interstitial pressure, and hypovascularity/poor perfusion. Mild cavitation with pFUS could produce inertial cavitation that disrupts the tumor and increases diffusivity for drug delivery. The initial studies used genetically engineered KPC mice with pancreatic tumors. Fluorescent doxorubicin was administered with pulsed ultrasound before or after drug administration.[19] Cavitation was observed at peak negative pressures of 8.5 mPA, leading to enhanced drug uptake of 1.5- to 4.5-fold in the tumor, which was better if the drug was given after FUS. Cavitation leads to collagen disruption and hyaluronic acid, which reduces interstitial pressure.

MRI studies on different mouse models (genetically engineered (KPC), orthotopically grafted, and subcutaneously grafted) showed significant changes in diffusion, particularly in the KPC model.[34] Increased diffusivity correlates with better prognosis and response to therapy. Treatment response is poorly reflected by radiologic size evaluation due to tumor fibrosis, necrosis, edema, etc.[35] An increase in the apparent diffusion coefficient after chemotherapy was associated with a histopathologic response, likely because fibrotic tissue was replacing cellular tumor tissue.[36]

They also investigated the response in a chronic setting with pFUS cavitation and gemcitabine in the KPC mouse model. The treated area became hyperechoic, indicating cavitation. Histological analysis revealed that the treated area had dead cells and increased fibrosis, while the untreated tumor portion continued to grow. The combination of gemcitabine and pFUS showed intense staining for granzyme B but no CD8+ T cells in the pFUS-treated area. In a gene expression analysis, genes responsible for immunosuppression, tumor support, and chemotherapy resistance were downregulated after combining pFUS and gemcitabine treatment. There was also a downregulation of PD-L1, suggesting modulation of the tumor microenvironment.

In addition to diffusion, pFUS can increase the plasma abundance of tumor-derived microRNAs, often circulating in concentrations below detection.[37] These microRNAs are promising prognostic markers of tumor response to treatment. Dr. Khokhlova highlighted the challenges with scaling up FUS mouse studies to humans, such as the limited acoustic

window for treating deeper and larger targets. A major limitation is that ultrasound imaging provides only a 2D view while the therapy beam is conical. To address this, researchers developed a dual-use pFUS imaging probe with an array that combines imaging and FUS capabilities—a 64-element, 1 MHz probe that can both image targets and deliver sufficient pressure (7 mPa) for cavitation. Initial pig liver studies demonstrated successful homogeneous disruption of blood vessels across the treated volume.

Questions

Q. Why is there no immune response in the untreated area?

- Dr. Khokhlova explained that while there was some positive immune response, it wasn't sufficient by itself to be fully effective. She also commented that this was a mouse model and could not adequately model human disease.

Q. What lessons can we learn from comparing previous enzymatic stroma disruption approaches (like hyaluronidase) and their failures with FOLFIRINOX to your current mechanical/ultrasound-based approach to improving drug delivery?

- Dr. Khokhlova replied that the key difference is that pFUS is localized to the tumor site. In contrast, hyaluronidase is administered systemically and affects the entire body, including blood vessels and micrometastases.

Q. Are their specific particle size characteristics or molecular weight ranges that show enhanced effects from cavitation?

- Dr. Khokhlova answered that this has not been studied; pFUS globally increases diffusion, but larger molecules would likely be affected less than smaller molecules.

Immunological Effects of FUS in Pancreatic Preclinical Models

Irving Allen, PhD, focused on immunology and tumor ablation techniques, particularly histotripsy. The lab uses mouse and rat studies and also conducts canine cancer models and human studies with various ablation methodologies. The key challenge is optimizing and making a predictable immune response after tumor ablation, as this could help prevent metastatic lesions that often lead to patient death or cancer recurrence. Histotripsy and ultrasound treatments destroy cancer cells and immunosuppressive cells, which potentially limit the recognition of the tumors by the immune system. However, these cell populations typically re-emerge. After histotripsy, they usually see increased neutrophils, increased macrophages, reduced myeloid-derived suppressor cells (MDSCs), and variable changes in T-cell populations.[38] After histotripsy, damaged cells release molecular signals (like HMGB1 and ATP) that trigger an inflammatory response. This leads to the production of pro-inflammatory cytokines, which, if adequately resolved, can help stimulate beneficial immune responses against the tumor. In animal studies, treating one tumor with histotripsy can trigger a systemic immune response that stops growth in untreated tumors elsewhere in the body. As expected, this effect only occurs in immunocompetent mice.[39–42] Histotripsy eliminates cancer cells through multiple cell death mechanisms while triggering beneficial immune responses, though the precise details are still under investigation.[38] The immune system responds through a cascade of processes from damage-associated molecular pattern (DAMP) molecules to innate immune activation and cytokine release that ultimately generates a robust systemic antigen response.[38]

Questions

Q. Are you ablating the entire tumor?

- Dr. Allen replied that his group does partial ablation so that there is tumor remaining to allow for the study of tumor responses to histotripsy. Optimal responses have been seen after 50% ablation. This technology allows for multiple treatments over time to optimize the immune response.

Q. What is the role of IFNγ after histotripsy since IFNγ appears to be important as PD-L1 is IFNγ-inducible?

- Dr. Allen stated that the choice of what to target in clinical trials needs to be carefully evaluated—CTLA4, PD-1, PD-L1, or others.

Panel Discussion

Panelists
Irving Allen, **Holger Grüll**, **Tatiana Khokhlova**, and **Cyril Lafon**

Participants discussed how tumor volume significantly impacts treatment response, noting that even slight differences in size (5–10 mm) can alter outcomes. They emphasized the challenges of analyzing treatment effects, particularly when using bulk analysis methods like RNA sequencing or flow cytometry, which may not effectively differentiate between different zones within the tumor. More expensive techniques like spatial analysis were recommended for better resolution of treatment effects.

There was also a discussion on developing standardized metrics to measure and report cavitation effects in treatments. Quantifying the actual treatment impact rather than only documenting the input parameters was emphasized. The discussion explored different ablation approaches, including thermal and non-thermal methods. The participants debated the effects of heat on immune responses, with some arguing that thermal ablation may be detrimental as it denatures proteins and destroys blood vessels and lymphatics. Non-thermal approaches like histotripsy were noted to preserve antigens, potentially leading to better immune stimulation.

The conversation then turned to the challenges of achieving abscopal effects (systemic responses affecting untreated tumors) in human patients despite consistent success in mouse models. Mouse studies are suitable for mechanistic studies, but need follow up with veterinary models, such as pig, to further the research. The participants acknowledged that single-modality treatments are unlikely to be successful alone, suggesting that combination approaches with immunotherapies or chemotherapies might be more effective. There was a suggestion for a comprehensive study of the abscopal effect, beginning with animal models and progressing to human trials, potentially through the FUSF.

The panel discussed measuring tumor stiffness in clinical settings, particularly in organs like the pancreas, and explored potential drug combinations for future preclinical studies. The participants also discussed potential combination treatments, including radiosensitizing agents such as gemcitabine and 5-FU, and the current standard-of-care.

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Immunotherapies of Pancreatic Cancer
Challenges and Opportunities I

Session chairs
Timothy Bullock and **Sarwish Rafiq**

Challenges and Opportunities for Immunotherapy in Pancreatic Cancer

Gregory Beatty, MD, PhD. Immunotherapy has become a standard-of-care for many cancers but has produced limited benefit for patients with pancreatic cancer. Patients that benefit are those classified with high microsatellite instability and high tumor mutational burden. Pancreatic cancer's resistance to immunotherapy is attributed to low mutational burden, poor immunogenicity, a hostile microenvironment, and a compromised patient immune system fitness. Biomarkers can predict treatment response, and treatment assessments may help refine the approach to identifying patients who will best respond to immunotherapy treatments.[43] In patients with pancreatic cancer, the immune contexture of tumors associates with short- and long-term survival in patients with treatment-naïve surgically-resected pancreatic cancer.[44] Pancreatic cancer shows spatial heterogeneity in cellular components indicating that different parts of the same tumor may use different immune-evasion tactics. Cellular neighborhoods, rather than cellular abundance, may best define the immune response in pancreatic cancer.[44] A composite index of immune and tumor neighborhoods is associated with survival.[44]

A phase II study investigated gemcitabine combined with nab-paclitaxel and indoximod in patients with treatment-naïve metastatic pancreatic cancer. Treatment shifted the transcriptional profile of tumors, notably reducing the proliferation marker Ki-67, but this did not alone correlate with clinical outcomes.[45] Several key determinants, such as higher tumor mutational burden, neoantigen burden, and immune phenotype influence immunotherapy efficacy. The presence of liver metastases and systemic inflammation also correlate with worse survival.[46] The neutrophil-to-lymphocyte ratio indicates liver inflammation, correlating with increased levels of pro-inflammatory cytokines and acute-phase reactants. Serum amyloid A (SAA) was associated with liver metastasis and worse outcomes in pancreatic, colorectal, and lung cancer.[47] A study using wild-type versus SAA knockout mice orthotopically injected with pancreatic cancer cells showed improved survival in SAA knockout mice.[48] These observations suggest a link between liver inflammation, T-cell infiltration, and survival outcomes in patients with pancreatic cancer. Further research showed that both SAA production and STAT3 signaling were elevated in the livers of patients with pancreatic cancer patients and liver metastasis.

Dr. Beatty said this research suggests that patient selection matters and that the immunotherapy response rate for patients without liver metastasis is between 10% and 25%. CD40 immune activation correlates with response to chemotherapy. He proposes the term inflammostat as a cancer biomarker and therapeutic target.[49] The term encompasses

the complex interplay of the inflammatory contexture within and outside the tumor microenvironment (TME) regarding the type, polarity, intensity, and location of immune cells along with functional factors.[49] Increased inflammation leads to immune evasion and poor therapeutic responses. Understanding and manipulating inflammatory components, such as IL–6, is crucial for developing more effective strategies to overcome treatment resistance.

Advances in the Use of CAR-T Cells in Solid Tumors

Sarwish Rafiq, PhD, focuses on improving the efficacy of engineered cell therapies. Chimeric antigen receptors (CAR) are synthetic receptors based on T-cell receptors and are MHC independent.[50] The design of CAR involves combining immunological motifs to drive T-cell recognition, activation and proliferation.[51, 52] CAR consist of a binding domain, hinge, transmembrane domain, and intracellular signaling domains for T-cell activation and costimulation. CAR-T cells are a highly personalized form of medicine with a process involving a blood draw, T-cell separation, genetic engineering, and reintroduction post-chemotherapy. There are currently seven FDA-approved CAR-T cell products, and all of these are for B-cell malignancies.[53]

CAR-T cells have limited efficacy in solid tumors.[54] Studies in pancreatic cancer have used various targets, such as mesothelin, EGFR, HER2, claudin, and CD133, with limited efficacy. However, there are some signals for clinical responses emerging. A recently published trial of a personalized RNA neoantigen vaccine in the adjuvant setting of pancreatic cancer demonstrated that patients with vaccine-expanded T cells showed no relapse of their cancer up to 30 months from surgery.[4] Another trial studying mesothelin-targeted CAR-T cells in combination with anti-PD-1 antibodies, had some patients that showed a long-term response.[55] Despite these promising results, distinct challenges remain for CAR-T cell therapies for solid tumors including manufacturing a high-quality autologous CAR-T-cell product that can traffic to and specifically recognize the tumor.[52] Once the cells reach the tumor, physical barriers, inhibitory ligands, immunosuppressive cells, and excessive costimulation can hinder T-cell function in the TME.

Approaches to using CAR-T cells for pancreatic cancer therapy include using classic second-generation CAR-T cells against tumor cells or cancer-associated fibroblasts, armored CAR-T cells such as those co-modified to express cytokines or antibodies, and CAR-T cells combined with systemic or local therapies. Systemic treatments include immune checkpoint inhibitors while local treatments include radiation therapy or cryoablation.[56] The armored CAR-T cell approach aims to alter the TME with a CAR-T cell that can protect itself from the immunosuppressive microenvironment, modulate the TME, and recruit an endogenous immune response. FUS can be used to thermally activate engineered CAR-T cells only at the tumor site, reducing off-target toxicities in animal studies.[57] Current pancreatic cancer clinical trials are exploring various antigens and combination therapies.

Questions

Q. How are CAR-T cells administered?

- Dr. Rafiq answered that administration methods may differ for each disease site. Intravenous, intraperitoneal, and intracranial are all modes of administration that have been used clinically.

Q. Was there a differentiation between host T cells in early disease versus post-chemotherapy latent disease to determine if T-cell characteristics remained consistent across both stages?

- Dr. Rafiq said they plan to analyze samples from newly diagnosed patients through collaborations, representing patients in their healthiest state. While this analysis wasn't done in previous studies, the timing of sample collection likely impacts T-cell product characteristics.

Q. After lymphodepletion, how long does it take for patients to regain a functional immune system, and what would be the optimal timing for initial immunostimulation?

- Dr. Rafiq replied that while lymphodepletion is standard practice for blood cancers and likely beneficial for solid tumors, the immune system begins recovering quickly and aligns well with the typical CAR-T-cell expansion timeline of approximately 14 days, during which there may be opportunities to optimize treatment through strategies like FUS for enhanced antigen expression.

Q. Was the chemotherapy a high dose?

- Dr. Rafiq answered that the practice of lymphodepletion originated in bone marrow transplantation, where, although its precise mechanism remains unclear, it is known to facilitate T-cell engraftment through potential mechanisms such as creating physical space for T cells and triggering cytokine release, with cyclophosphamide and fludarabine being the most commonly used conditioning chemotherapies used with CAR-T cells.

Q. Was this repeatable?

- Dr. Rafiq said that redosing with CAR-T cells is possible and has been done in the clinical trial setting if there is an extra product.

Immunotherapies for Pancreatic Cancer
Challenges and Opportunities II

Session chairs
Timothy Bullock and **Nancy Kren**

FUS-induced Immune Response in Animal Models

Timothy Bullock, PhD, explained that FUS (histotripsy) can delay tumor progression by promoting the presence of immunogenic tumor antigen in dendritic cells in the tumor-draining lymph nodes (TDLN) and synergize with the activation of antigen-presenting cells. Boiling histotripsy delays treated and untreated tumor outgrowth in a melanoma mouse model.[58] Boiling histotripsy treatment results in tumor antigen accumulation in TDLN that can enhance activation in dendritic cells and naive CD8+ T cells. Data indicates that antigen presence in TDLN after boiling histotripsy is independent of migrating dendritic cells. TDLN dendritic cells are still activated and promote T-cell expansion without dendritic cell migration from treated tumors. This suggests that boiling histotripsy could be impactful in tumors with a low density of dendritic cells.

Pancreatic cancer is known to be poorly infiltrated by dendritic cells.[59] The PG4 system with four transducers was developed to precisely treat small tumor volumes in orthotopic models. Boiling histotripsy resulted in cellular disruption and ablation in the KPC mouse model of pancreatic cancer. However, boiling histotripsy alone did not result in any change in tumor growth. There were minimal alterations in the adaptive immune response. Next, they combined a CD40 antagonist with boiling histotripsy in a mouse mode of pancreatic cancer, but there was no synergy between the treatments.[60] They observed increased CD8+ T cells with the combination treatment compared to the monotherapies. Dose de-escalation of anti-CD40 may be needed to reveal interaction with boiling histotripsy.

They also looked at potential reasons for the differential outcomes between melanoma and pancreatic cancer models. The melanoma model shows a robust lymphatic network, facilitating antigen drainage, while pancreatic cancer has a limited lymphatic network. Future research will explore whether altering tumor stiffness or promoting lymphangiogenesis could improve antigen drainage in pancreatic cancer models.

Questions

Q. Pancreatic cancer lacks antigens and is poorly immunogenic, and the question on TDLN could be answered by looking at ovalbumin. How was it demonstrated that dendritic cell trafficking is unnecessary when antigen levels are high, and whether CCR7 was used?

- Dr. Bullock answered that they used a CCR7 antibody, and they are in the process of a follow-up experiment using CCR7-knockout bone marrow chimeras to provide genetic confirmation of their findings, specifically looking at the activation of naive T cells in TDLN.

Q. How can dendritic cell trafficking to the tumor be increased, and is it necessary based on these data?

- Dr. Bullock indicated that dendritic cells were necessary, and they serve two valuable functions: enhancing T-cell priming in the TDLN through mass action and supporting effector T cells within the tumor microenvironment. Mobilization of DC can be achieved with inflammatory agents such as pathogen-associated molecular patterns

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Q. Were the pancreatic cancer cells used in these experiments typical?

- Dr. Bullock said that they used the less anti-CD40 responsive KPC7940b cells derived from KRAS/p53 mutant mice. They are considered quite representative of human disease.

Q. Would vaccinating dendritic cells be advantageous?

- Dr. Bullock said they aimed to activate dendritic cells through antigen release and CD40 stimulation. Additional dendritic cell mobilization might be helpful if the ability of FUS to bypass dendritic cell migration is not evident in the pancreatic cancer setting.

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T-cell Receptor Clonotype Tracking to Monitor Immune Responses in Pancreatic Cancer Clinical Trials

Stephanie Dougan, PhD, discussed using T-cell receptor (TCR) clonotype tracking to monitor immune responses in patients. T cells mediate anti-tumor immunity. TCRs are barcodes that can be used to track T cells over time. A T-cell clonotype encompasses all daughter cells originating from a single parent T cell, sharing identical TCRs, with populations ranging from hundreds of thousands to millions of distinct clonotype families, each representing the complete lineage descended from one initial T-cell. This was demonstrated in a clinical trial combining ribociclib and PD-1 blockade in patients, and ribociclib skewed newly emerging clonotypes to memory T cells.[61] TCRs from blood matched TCRs in the tumor.[61]

Pancreatic cancer is used in Dr. Dougan's research as a model of poorly immunogenic cancer. Some patients have PD-1 expressing T cells. PD-1 blockade induces the proliferation of pre-existing effector clonotypes; some were also found in the tumor.[62] Reinvigorated T cells from pancreatic cancer have a non-productive NF-κB response. Various parts of the same tumor can have different T-cell responses.

The team hypothesized that increased T-cell priming would increase the diversity of expanded clonotypes that could recognize tumor cells. This same hypothesis could be used to study the response to FUS.

Questions

Q. Were you able to identify any molecular or genetic characteristics that might explain why one tumor became unresponsive to treatment while the other maintained its response?

- Dr. Dougan explained that they conducted genomic analysis hoping to find obvious drivers like MHC class I loss but found no clear explanation for the differential response between the two cases. While they generated a list of potential neoantigens, they did not think they could identify the functionally relevant ones through bioinformatics approaches alone, particularly given the challenges in matching TCRs to antigens.

Q. Do you observe similar patterns of clonal diversity—either expansion or focusing—in both CD4+ T cells and CD8+ T cells, or is this characteristic predominantly observed in one T-cell population versus the other?

- Dr. Dougan said that they have not analyzed the data yet.

Q. Based on your findings about tumor heterogeneity, should window-of-opportunity clinical trials implement multiple-site tumor sampling to effectively analyze clonal variation through single-cell analysis?

- Dr. Dougan stated that the analysis can be conducted in two ways: either by comparing paired blood samples from the same patient at different timepoints, or by comparing post-treatment samples against a control group.

Immunogenicity of Low-Intensity FUS in Pancreatic Cancer

Nancy Kren, PhD, highlighted the collaborative nature of the effort to work on the immunogenicity of low-intensity FUS (LOFU). LOFU attempts to increase vascular permeability and release antigens, using microbubbles to enhance the effect.[63] An initial study applied LOFU, which resulted in a tumor volume decrease in a subcutaneous mouse model of pancreatic cancer.[63] Immune changes included increased macrophages (MHC II+), indicating an early response. There was no change in CD8+ T cells within the tumor, but there was an increase in HMGB1. The size of the tumor is important for the response to LOFU.[63] With a bigger tumor, there was no effect of a single or two LOFU treatment. They also found that two treatments of LOFU did not illicit the same or better immune response. Next, they combined CD40 with LOFU. However, results with CD40 as a single therapy were so good, no additive effect was seen with LOFU treatment.

The team aimed to move to an orthotopic mouse model and expand to other mechanisms, such as acoustic enhancement and cavitation. Early optimization involved using a chicken breast with a thermocouple to measure temperature changes, ensuring safe treatment parameters. The team used a machine with three imaging bays to treat the entire mouse. The team tested four modalities: LOFU with microbubbles, hyperthermia, high-intensity FUS with microbubbles, and thermal ablation in a KPC mouse tumor model. The study showed significant changes with high-intensity FUS, including coagulation and necrotic regions. Samples were barcoded for cytometry by time of flight (CyTOF), and the analysis showed an increase in total T cells and a trend towards increased CD8+ T cells with LOFU and hyperthermia. Lymph nodes showed decreased CD4+ T cells and increased dendritic cells with LOFU.

Future directions are to determine the types of cell death induced by different FUS modalities and how these can elicit an immune response, combination therapy with immunotherapy (orthotopic model), an antigen model to explore better the immune response, and the role of ultrasound treatments in metastasis.

Questions

Q. What FUS parameters were used for hyperthermia?

- Dr. Kren replied that they used a small spot-size treatment for two minutes to induce controlled damage rather than complete ablation.

Q. A comment specifically recommended using ovalbumin to measure T-cell priming and proliferation in the TDLN, suggesting this would better reveal differences between techniques compared to measuring tumor size or macrophage population changes.

- Dr. Kren agreed and added that this research is a work in progress and plans to conduct more experiments.

Panel Discussion

Moderators
Nancy Kren and **Timothy Bullock**

Panelists
Irving Allen, **Stephanie Dougan**, **Nancy Kren**, and **Sarwish Rafiq**

The group discussed the current state of research on immune parameters for clinical trials involving patients with pancreatic cancer, that it requires an academic research lab, and that there are no commercial options at this time.

The discussion also focused on the challenges and opportunities in treating pancreatic cancer using various therapeutic approaches, particularly comparing it to more responsive cancers like melanoma. A key topic was the fundamental differences between pancreatic cancer and melanoma in terms of their tumor microenvironment and immune response.
The participants discussed how pancreatic cancer presents unique challenges due to its dense fibroblast-rich structure and immunologically "cold" nature, compared to the more immunologically "hot" melanoma. They explored how these differences affect treatment efficacy, particularly concerning histotripsy and immunotherapy approaches. The conversation explored technical aspects of different histotripsy modalities, including cavitation versus boiling histotripsy, and how treatment parameters affect tissue breakdown and immune response. The speakers emphasized that treatment duration and intensity significantly impact outcomes, noting that longer treatment times don't necessarily yield better results.

A significant portion of the discussion centered on immune system responses, particularly regarding T-cell behavior in pancreatic cancer. The participants noted that while PD-1-positive T cells are present in pancreatic cancer, they often do not respond to PD-1 inhibitors, suggesting additional layers of immunosuppression that need to be addressed.
A participant wondered why certain treatments are ineffective, whether due to energy constraints in a dense TME or unique aspects of the immune environment in the pancreas.
The experts also explored the role of mutations and neoantigens in cancer treatment response, discussing how MSI-high tumors respond better to immunotherapy. They debated the minimum number of mutations needed for effective immune responses and considered the potential of RNA vaccines in treatment approaches.

The discussion concluded with considerations about CAR-T-cell therapy in solid tumors, focusing on successful applications in mesothelioma and brain tumors. The participants discussed the importance of timing when combining FUS treatment with T-cell therapies, noting the complex interplay between acute inflammatory responses and immunosuppressive cells.

Throughout the conversation, there was an emphasis on the need for further research to understand the mechanisms behind treatment responses and to optimize combination approaches for effectively treating pancreatic cancer. While progress has been made, the experts acknowledged that many questions remain about how to best leverage various treatment modalities for maximum therapeutic benefit.

FUS for Pancreatic Cancer Treatment

Session chair
Joan Vidal-Jové

HIFU Combined with FOLFIRINOX for Pancreatic Cancerr

Jae Young Lee, MD, PhD, discussed clinical trials combining FUS treatment with FOLFIRINOX chemotherapy for pancreatic cancer. The presentation covered three clinical trials investigating a novel combination therapy approach for pancreatic cancer treatment. The research aims to address the limitations of traditional chemotherapy, particularly the challenge of drug penetration due to dense fibrotic stroma and poor blood supply in pancreatic tumors.

The first trial was a single-arm study with 56 evaluable patients, combining four cycles of FOLFIRINOX with FUS treatment within 24 hours of starting the 5-flourouracil (5-FU) infusion every two weeks. FUS treatment was performed with an APIUS 900 (ALPINION, Seoul, South Korea), and treatment parameters were determined using a mouse model study.[64] FUS parameters were an intensity between 1.5 to 2.5 kW/cm2, 1% duty cycle, three sec/point exposure time, and 10 Hz pulse repetition frequency (PRF). These parameters were previously confirmed in a proof-of-concept study.[65] The single-arm study demonstrated an objective response rate of 64%, with no FUS-related adverse effects. The estimated two-year survival rate was 56%, with more than half of patients becoming eligible for surgical resection. A notable case showed a complete pathological response after treatment.

The second trial was a randomized feasibility study comparing FOLFIRINOX alone versus FOLFIRINOX plus FUS using a new compact device called IMD-10, developed primarily for drug enhancement. This trial involved 30 patients divided into two groups, control (FOLFIRINOX only) and experimental (FOLFIRINOX plus FUS), for four cycles (2-week intervals) followed by eight cycles of FOLFIRINOX or other anti-cancer treatment. The combination therapy group showed an objective response rate of 64% compared with 38% in the chemotherapy-only group. While not statistically significant, this trend suggested enhanced treatment efficacy with FUS. Mild adverse events were reported.

The presentation concluded by introducing an upcoming larger randomized confirmatory trial, a prospective, single-center, controlled, randomized trial. The plan is to enroll 280 patients, with overall survival as the primary endpoint. The trial aims to validate the promising results from previous studies with a more robust sample size and methodology, including independent evaluator blinding. The research suggests that combining FUS with FOLFIRINOX chemotherapy could potentially advance pancreatic cancer treatment, offering improved response rates without significant additional side effects.

Questions

Q. Were you able to analyze immune parameters for the patients who had surgery following FUS treatment?

- Dr. Lee replied that they could analyze blood from the first trial but did not find any changes, and it is not feasible at their institute to collect tumor tissue.

Q. Can you comment on how long each treatment takes?

- Dr. Lee said that the average treatment time is 30 minutes.

Q. Was the FUS energy used for ablation, drug delivery, or treatment, and could you achieve good margins?

- Dr. Lee mentioned that they refined the FUS targeting in large animal models. They found no evidence of tissue damage in humans, and FUS is used to enhance drug delivery.

Q. How many patients were screened before 60 patients were enrolled?

- Dr. Lee said that many patients were excluded because of a lack of a good acoustic window, and four patients were excluded because of gas.

Q. How many patients became resectable following treatment?

- Dr. Lee said that out of 56 patients, almost 60% were resected.

Q. How are the patients prepared prior to FUS?

- Dr. Lee said that patients fasted the night before.

Q. Were the patient types balanced?

- Dr. Lee said this was not accounted for in the second study but will be stratified by borderline resectability in the third trial.

Q. What was the BMI for the treated patients?

- Dr. Lee answered that they were non-obese with a BMI of around 20 or 21.

Q. Were there any changes in pain?

- Dr. Lee indicated that they did not collect data on pain, but patients did not report much pain prior to treatment.

Q. Have you looked at drug uptake on contrast-enhanced MRI?

- Dr. Lee reported that they have not performed an MRI, only a CT.

Q. Why did you only do four cycles of FUS?

- Dr. Lee admitted that this was partially because of scheduling.

Q. How long did it take to get comfortable with the targeting?

- Dr. Lee indicated that he felt confident with the targeting after doing about 10 cases.

Focused Ultrasound Therapy for Unresectable Pancreatic Cancer
Current Status and Future Directions

Feng Wu, MD, PhD, discussed FUS for unresectable pancreatic cancer, focusing on ablation and drug delivery. An early proof-of-concept trial for HIFU ablation in advanced pancreatic cancer.[66] All patients reported decreased pain following partial ablation. This was confirmed by another trial that reported pain relief with partial ablation.[67]

A retrospective trial in Shanghai involving over 500 patients demonstrated improved one-year survival rates with combined therapy approaches (gemcitabine alone and gemcitabine with HIFU). However, two-year survival rates showed no significant difference between treatment groups.[68] Another study reported a remarkable 33.5% four-year survival rate when combining chemotherapy with HIFU, representing one of the highest survival rates in pancreatic cancer treatment history.[69] Another study showed significantly higher survival rates when genetic testing to guide chemotherapy selection was combined with HIFU, with one-year survival rates mainly improving in the genetically guided treatment group.[70] A randomized controlled two-arm phase I/II trial of 40 patients with inoperable pancreatic adenocarcinoma is ongoing; group A will receive standard chemotherapy, and group B will receive standard chemotherapy plus local HIFU treatment.[71]

Next, Dr. Wu described FUS for drug delivery with thermosensitive liposomes, either with or without microbubbles. Thermosensitive liposomes (ThermoDox® = thermosensitive liposomal doxorubicin) have been used with FUS for drug delivery to the liver.[72] This approach uses temperature-controlled release mechanisms where drug capsules open at specific temperatures (39-42°C), allowing targeted delivery directly to tumor sites. This method can increase local drug concentration by 2 to 10 times compared with traditional delivery methods, with minimal systemic side effects. A trial for patients with pancreatic cancer is underway.[73] This clinical trial compares standard doxorubicin therapy or ThermoDox® combined with focused ultrasound-induced hyperthermia under general anesthesia, with allocation based on patient and tumor safety criteria. Dr. Wu described FUS drug delivery with microbubbles for liver cancer, but cavitation needs to be carefully controlled. FUS drug delivery without bubbles is also under study. In patients with pancreatic cancer, the tissue can be very stiff, which limits the permeability of drugs to the tumor.

Dr. Wu discussed the potential of HIFU ablation for treating pancreatic cancer. Partial ablation for palliative purposes could also be considered. Dr. Wu proposes “FUS plus” that integrates FUS drug delivery immediately followed by FUS ablation. Dr. Wu concluded that there may be other approaches for FUS, but the broader medical community needs to be convinced of the potential benefit.

Questions

Q. In some trials described, the patient populations were mixed; how will you show benefits for different population groups?

- Dr. Wu replied that the third planned trial will be a larger group of patients, and he hopes to be able to stratify patients.

Q. Doxorubicin is not the standard-of-care for pancreatic cancer, is the choice of this drug related to the thermal liposome?

- Dr. Wu agreed that the use of doxorubicin is related to the proof-of-concept with thermal liposomes and being able to demonstrate that it reaches the tumor. They support the development of a thermal liposome containing standard treatments for pancreatic cancer.

Q. What is the plan for the FUS plus trial?

- Dr. Wu explained that this would be a safety study with only partial ablation.

Q. Could a handheld FUS device work for the pancreas?

- Dr. Wu said that they are waiting on the data from the trial, but it seems promising for drug delivery.

Q. Is there animal data showing the efficacy of the FUS plus (drug delivery followed by partial ablation)?

- Dr. Wu said that they are uncertain as chemotherapy has been challenging for pancreatic cancer.
- Dr. Grüll reported that his group published a 2017 study using a mouse sarcoma, and they were able to demonstrate that hyperthermia enhanced drug delivery through temperature-sensitive liposomes. When combined with ablation, the effect was enhanced even further.

Ablation of Pancreatic Tumor Using Histotripsy

Joan Vidal-Jové, PhD, described histotripsy for pancreatic cancer. Histotripsy is a non-thermal tissue ablation method that uses high-pressure, short-duration acoustic pulses to create bubble clouds that mechanically break down targeted tissue. Unlike thermal ablation, which alters protein structure through heat, histotripsy physically breaks down tissue while preserving nearby vessels and ducts. The procedure uses the Edison System (HistoSonics), which includes a transducer with robotic control and imaging capabilities. Treatment planning involves defining multiple points in a spherical pattern and employing a histotripsy training tool that integrates MRI, CT, and PET scan data to optimize targeting. The procedure requires careful respiratory control through anesthesia with specific breathing protocols to manage patient movement. A master trial is being planned to collect comprehensive data on the device, as the initial device approval was based on only 50 patients.

An upcoming clinical trial named "Gannon" will focus on pancreatic cancer treatment using histotripsy to destroy the TME and potentially activate the immune responses. The trial will target patients with borderline, locally-advanced, or oligometastatic disease, excluding those with bone metastases. Animal studies have been carried out to help plan the histotripsy treatment for this trial. This safety study trial will include three cohorts receiving different amounts of histotripsy treatment (15, 20, and 25 mm partial histotripsy). Patient selection criteria include considerations such as stent placement and tumor location, with particular emphasis on treating tumors in the body of the pancreas.

Questions

Q. What kind of samples will be collected?

- Dr. Vidal-Jové said they will only collect blood as it is a safety trial.

Q. The pancreas is very dense, is it possible to visualize the treatment to check for accuracy between the treatment and the image?

- Dr. Vidal-Jové explained that they have demonstrated accuracy in the pancreas with large animal models, although these animals lacked tumors.

Q. Is the target volume always smaller than the tumor and how do you think about safety?

- Dr. Vidal-Jové replied that the treatment would be within the tumor, and three separate researchers would evaluate the images to ensure they were treating the tumor, not the pancreas.

Q. Will you treat it according to what you see, or will the aim be within a specific time?

- Dr. Vidal-Jové answered that the treatment time was very short, measured in seconds, with a set dose.

Q. Given that liver ablation treatments are already available, how do you make a business case for purchasing a new device?

- Dr. Vidal-Jové indicated several advantages to histotripsy, including that it is not toxic like radiotherapy and has the potential for immune system effects.

Q. Will approval be based on feasibility, or will there be data on response rates and clinical outcomes?

- Dr. Vidal-Jové replied that, based on FDA discussions, the approval would likely be based on feasibility, similar to that of the liver treatment.

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Panel Discussion

Panelists
Keaton Jones, **Srikanth Reddy**, **Feng Wu**, and **Jae Young Lee**

The panelists first discussed FUS for pain control. Researchers felt that these kinds of trials might be worthwhile, and there would need to be comparisons to current modalities. Regarding treatment strategies, the participants discussed the potential benefits of combining local treatments with systemic therapy. While complete tumor ablation alone may not be sufficient and feasible in patients with pancreatic cancer, there is interest in using FUS techniques to enhance chemotherapy effectiveness and partial destruction of the cancer either by ablation or histotripsy to potentially stimulate immune responses. However, the speakers noted that promising preclinical results often fail to translate effectively to human patients. Treatment for pancreatic cancer will involve many different treatments depending on the patient and their tumor. A key point of discussion is the challenge of treating pancreatic cancer as a systemic disease. The participants note that even when presenting with a small, localized tumor, most patients die from metastatic disease. This highlights a critical need for better biomarkers to differentiate between truly localized and systemic disease, as this would help guide treatment decisions.

The discussion included comparing medical practices between Korea and America, particularly regarding ultrasound diagnostics. Korean clinics benefit from having specialized radiologists perform ultrasound on generally thinner patients, while American practices face challenges with larger patients and varying technician skill levels.

The conversation concluded with practical considerations about implementing clinical trials. The participants discuss the importance of timing treatments properly, as patients often become too frail and weak and not fit for any anti-cancer treatment if there are delays. They also highlight a significant advancement: the demonstrated safety of combining local ablation with chemotherapy, which provides more treatment flexibility than previous protocols requiring gaps in chemotherapy treatment. This development is described as a potential “game changer” for patient care.

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Roadmap Discussion

Session chair
Keaton Jones

Regulatory Science Considerations; FDA Office of Science and Engineering Laboratories (OSEL) Perspective

Subha Maruvada, PhD, from the FDA's OSEL, discussed regulatory science considerations around medical acoustics and ultrasound devices, focusing on pancreatic cancer applications. The therapeutic ultrasound program recently changed to the medical acoustics program, which has two sub-programs on therapeutic and diagnostic ultrasound and transcranial. The medical acoustic program's role involves addressing scientific and safety questions for therapeutic ultrasound devices, working with international standards organizations, and supporting FDA reviewers.

A key focus of the presentation is the concept of "regulatory science tools," which are innovative, science-based methodologies to assess medical device safety and effectiveness or emerging technology. These tools can include phantoms, software, models, and best practices, which are publicly available to help manufacturers and innovators streamline their development process. Unlike mandatory standards, these tools are voluntary resources that bridge the gap between published research and formal standards development and are particularly useful for emerging technologies. Regulatory science tools are product development and assessment tools that expand the scope of science-based approaches to speed and improve the translation of technologies into safe and effective medical products. A catalog of regulatory science tools to help assess new medical devices is available on the FDA website (https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices).

Several potential areas for regulatory science tool development exist specifically for pancreatic cancer, including acoustic characterization tools, phantom models for device testing, determination of tissue properties, and development of safety thresholds. The importance of defining treatment parameters, standardizing dose measurements, and establishing clear relationships between acoustic inputs and treatment outcomes was emphasized.

Questions

Q. What is the FDA doing to share its work with regulatory agencies worldwide, particularly considering that the FUS industry is not primarily based in the US?

- Dr. Maruvada explained that they are sharing all their standards with scientists worldwide but not specifically with other regulatory agencies, and this is an area to investigate in the future.

Q. Does OSEL work with other parts of the FDA, such as the Center for Biologics Evaluation and Research, regarding device-driven drug delivery?

- Dr. Maruvada responded that OSEL does work with other parts of the FDA when combination drug/device applications are received. However, there could be broader collaboration across the FDA concerning research. Many reviewers are overburdened but inviting them to workshops could be beneficial.

Q. The field should consider the increasing importance of incorporating patient feedback and engagement throughout the medical device development process, from clinical trial design to product refinement.

- Dr. Maruvada indicated that the FDA has patient advisory panels and that collaborations with the FUSF could be helpful in the future.

Q. How can we proactively address potential safety concerns and establish collaborative frameworks for evaluating emerging medical technologies while ensuring their safety and effectiveness through ongoing assessment and stakeholder engagement?

- Dr. Maruvada replied that reviewers now understand the technology much better, and the concerns are about specific applications. The IEC 60601-2-62, the safety standard for therapeutic ultrasound, was published in 2013, but it is outdated and is being updated. One future consideration for this standard is to have application-specific standards.

Summary of Recommendations

Burning Questions

Participants were asked to discuss 'burning questions,' which were topics related to prioritizing future efforts by the FUSF to advance FUS for treating pancreatic cancer.

Pain Management and Palliation

- There is good quality evidence for pain relief after partial ablation.
- Pain management could be particularly beneficial for older patients (≥ 80 years of age) or those who are not candidates for surgery or chemotherapy.

Immune Response and Mechanisms

- There was a detailed discussion of how FUS might stimulate immune responses, and there is a need to obtain data from humans at there is a robust systemic immune response following FUS destruction of tumor either by histotripsy or ablation though there is a lot of data from preclinical models.
- The discussion highlighted that treating the primary tumor alone may not be sufficient, and the effects on metastases need to be considered. However, there was discussion whether FUS treatment of liver metastases would be as immunologically active systemically as FUS treatment of hepatocellular carcinoma (HCC) appears to be.
- A key mechanism involves activating dendritic cells, which interact with T cells in the TDLN. The question is whether dendritic cells are sufficiently activated after exposure to molecular patterns released from FUS-treated tumors, or whether additional interventions will be needed. Another key question is to determine the best FUS modality for activating dendritic cells to trigger an immune response to the tumor.
- Experts emphasized the need to understand whether the treatment triggers immunogenic cell death and that it is unrealistic to expect all tumors to behave similarly.
- Multiple preclinical models were suggested to study FUS in pancreatic cancer, as each model has distinct characteristics that illuminate particular aspects of the disease. They specifically suggest incorporating models that vary in their immune response (poorly and highly immunogenic) and different tumor development patterns (orthotopic and spontaneous), noting that this diversity in models remains valuable for comprehensive research.

Clinical Trial Design Considerations

- There was a debate over whether to include patients with borderline resectable versus locally-advanced pancreatic cancer; some participants hypothesized that converting borderline resectable patients to surgical candidates may show efficacy.
- A preliminary signal-seeking study could examine surgical conversion rates while simultaneously collecting survival data, enabling faster progression to a Phase 3 trail without waiting years for initial survival endpoints to mature.
- Window-of-opportunity trials were proposed for borderline resectable patients during the 6-to-8-week pre-surgery period. Patients would be treated with FUS before surgery, and biological endpoints would be used as outcome measures. This could be done in parallel with in vitro work while collecting samples.
- The suggested approach of starting with 10 to 20 neoadjuvant chemotherapy patients per treatment group for initial studies would allow differentiation between treatments; pre- and post-biopsy samples could reduce costs by reducing the need for a control arm.
- Careful biomarker and tissue collection strategies, including pre/post-treatment biopsies, are needed. Ideally the whole primary and draining lymph nodes will be needed for pathological analysis to get robust data regarding immune priming.
- Pain should be an outcome measure in clinical trials and is a significant area of interest for pancreatic cancer.
- There was a discussion of emerging treatments like KRAS inhibitors and potential combinations.
- Recognition that FUS alone is unlikely to be curative, and combination approaches are needed.
- The role of in-vivo imaging in monitoring treatment effects was emphasized.

The FUSF is seeking feedback and ideas on the necessary clinical trials to demonstrate the efficacy of FUS in treating pancreatic cancer, and attendees were encouraged to reach out with ideas.

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Action Items

1. Design studies that specifically investigate the immune response/abscopal effect (rather than having it be an "incidental" finding).
    - In vitro studies of dendritic cell response to select FUS modality.
    - Primary and lymph node harvesting at surgery to gain evidence of dendritic and T-cell activation?
2. Consider a study to determine some of the dendritic cell results of FUS treatment. This can also include various levels of FUS intensity (boiling histotripsy, cavitation histotripsy, etc.).
3. Design a window-of-opportunity trial to understand the cellular effects of FUS in human pancreatic cancer.
4. Include pain management as an endpoint in future studies.
5. Publish the workshop proceedings in an open-access journal.

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Abbreviations

CAR	Chimeric antigen receptors
CRI	Cancer Research Institute
CyTOF	Cytometry by time of flight
DAMP	Damage-associated molecular pattern
FDA	Food and Drug Administration
FUS	Focused Ultrasound
FUSF	Focused Ultrasound Foundation
HIFU	High-intensity focused ultrasound
IND	Investigational New Drug
MDSC	Myeloid-derived suppressor cells
MDT	Metastasis-directed therapy
NCCN	National Comprehensive Cancer Network
OSEL	Office of Science and Engineering Laboratories
PA	Pancreatic adenocarcinoma
PICI	Parker Institute for Cancer Immunotherapy
PRF	Pulse repetition frequency
SABR	Stereotactic ablative radiotherapy
SMA	Superior mesenteric artery
TCR	T-cell receptor
TDLN	Tumor-draining lymph nodes

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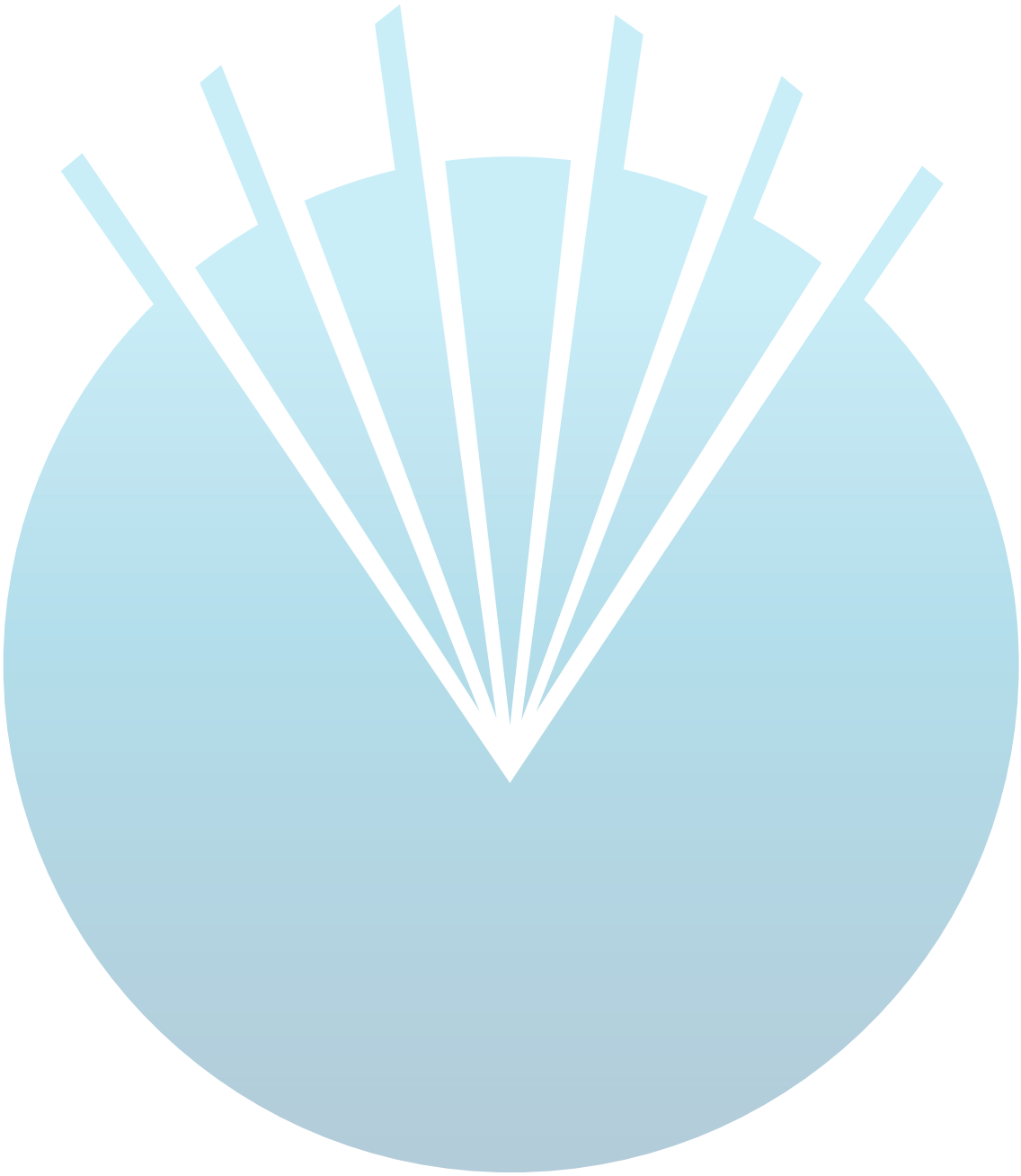
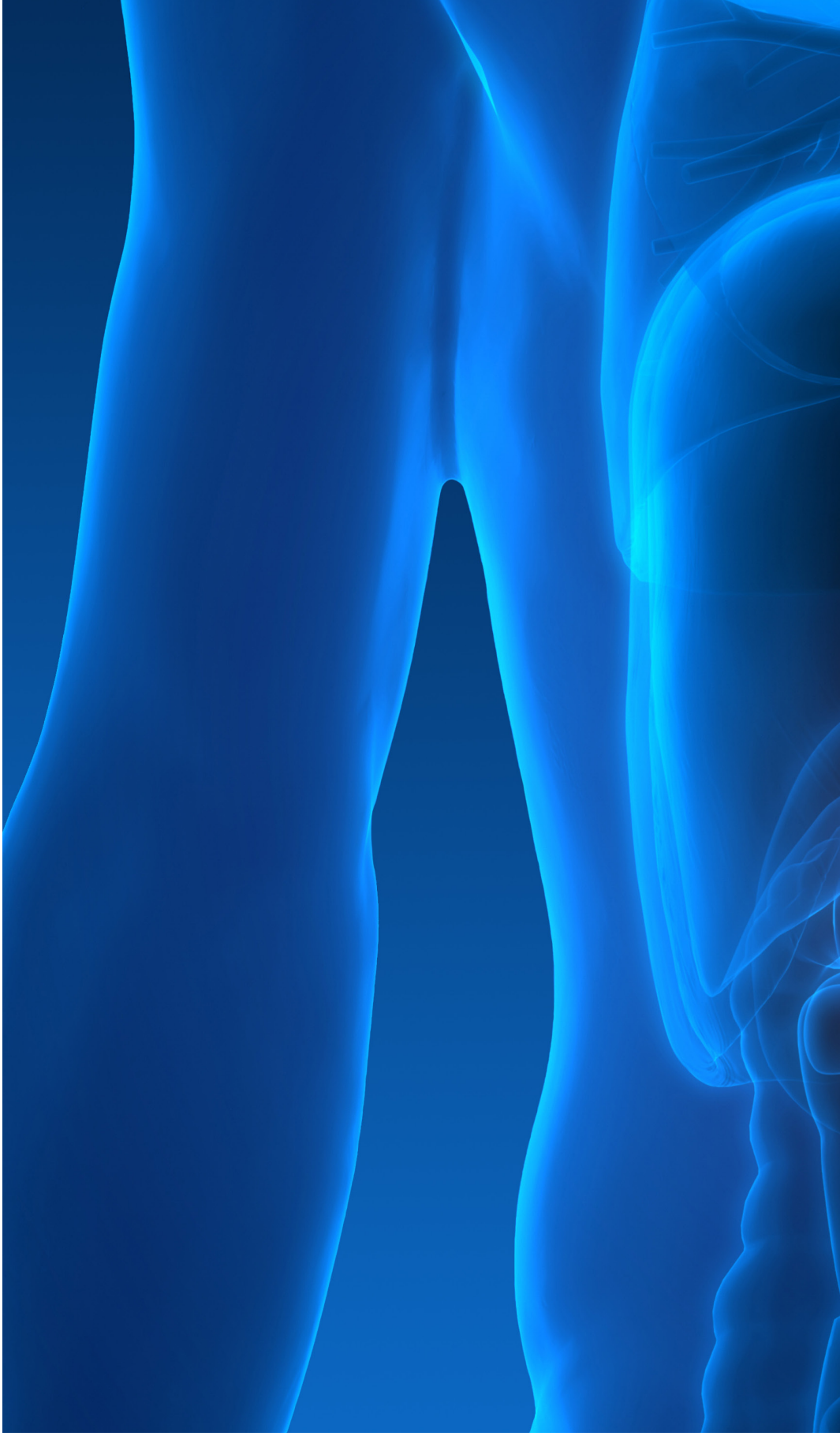
Acknowledgements

The Role of Focused Ultrasound in Pancreatic Cancer workshop was planned by The Focused Ultrasound Foundation in partnership with the meeting sponsors Haifu Medical, HistoSonics, IMGT, Profound Medical, and SONIRE Therapeutics. This summary was written by Heather Gorby, PhD. Tim Meakem and Chrit Moonen provided final approval of the summary.





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