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Development of an endoluminal high-intensity ultrasound applicator for image-guided thermal therapy of pancreatic tumors

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Abstract

An ultrasound applicator for endoluminal thermal therapy of pancreatic tumors has been introduced and evaluated through acoustic/biothermal simulations and *ex vivo* experimental investigations. Endoluminal therapeutic ultrasound constitutes a minimally invasive conformal therapy and is compatible with ultrasound or MR-based image guidance. The applicator would be placed in the stomach or duodenal lumen, and sonication would be performed through the luminal wall into the tumor, with concurrent water cooling of the wall tissue to prevent its thermal injury. A finite-element (FEM) 3D acoustic and biothermal model was implemented for theoretical analysis of the approach. Parametric studies over transducer geometries and frequencies revealed that operating frequencies within 1-3 MHz maximize penetration depth and lesion volume while sparing damage to the luminal wall. Patient-specific FEM models of pancreatic head tumors were generated and used to assess the feasibility of performing endoluminal ultrasound thermal ablation and hyperthermia of pancreatic tumors. Results indicated over 80% of the volume of small tumors (~2 cm diameter) within 35 mm of the duodenum could be safely ablated in under 30 minutes or elevated to hyperthermic temperatures at steady-state. Approximately 60% of a large tumor (~5 cm diameter) model could be safely ablated by considering multiple positions of the applicator along the length of the duodenum to increase coverage. Prototype applicators containing two 3.2 MHz planar transducers were fabricated and evaluated in *ex vivo* porcine carcass heating experiments under MR temperature imaging (MRTI) guidance. The applicator was positioned in the stomach adjacent to the pancreas, and sonications were performed for 10 min at 5 W/cm² applied intensity. MRTI indicated over 40°C temperature rise in pancreatic tissue with heating penetration extending 3 cm from the luminal wall.

Keywords

ultrasound ablation; pancreatic cancer; endoluminal; thermal modeling; MR guided ultrasound; catheter-based ultrasound; thermal therapy

1. INTRODUCTION

Pancreatic cancer is responsible for the 4th highest number of cancer-related mortalities in the United States, and has a 5-year survival of only 4%.¹ Surgical resection is currently the only potentially curative treatment option, but cannot be performed in over 80% of patients due to the advanced stage of their disease at clinical presentation.¹ For these advanced-stage patients, clinical treatment goals are to prolong survival and alleviate pain and other symptoms. Chemotherapy with or without adjuvant radiation therapy are standard treatment regimens, but have minor palliative and survival benefit.²

Thermal ablation has been demonstrated to provide palliative relief to patients with advanced pancreatic cancer through denervation and tumor debulking mechanisms.^{3,4} It may also extend survival in patients with early-stage and localized disease, potentially serving as an alternative to invasive major surgery. Many ablative modalities, including radiofrequency ablation, microwave ablation, cryoablation, high-intensity focused ultrasound (HIFU), photodynamic therapy, and electroporation are currently being investigated and clinically evaluated for treatment of pancreatic cancer.³ Apart from HIFU, these applied techniques are all percutaneous or interstitial. Both means are highly invasive and difficult to safely perform in the pancreas due to the risk of inducing pancreatitis and the close proximity of sensitive bowel tissue and vasculature. While HIFU can be applied completely non-invasively, its application is limited due to long treatment times and the challenging delivery of the acoustic energy into the tumor. It is encumbered both by the proximity of bowel gas, which limits the acoustic window, and respiratory motion.⁴ There is also interest in developing hyperthermia treatments for advanced pancreatic cancer. Hyperthermia has been clinically demonstrated to enhance the therapeutic benefit of chemotherapy and radiation therapy for many other cancer models, and may increase the drug delivery of thermally sensitive liposomes into desmoplastic pancreatic tumors.^{5,6}

Thermal therapy and hyperthermia treatments of pancreatic cancer could be performed in a minimally invasive manner using an endoluminal ultrasound applicator, as conceptualized in Figure 1. This applicator would be inserted into the esophagus orally and manipulated to the stomach or duodenal lumen adjacent to the tumor-bearing region in the pancreas. Sonication would be directed into the tumor through the gastrointestinal (GI) luminal wall, and cooling of the active transducers and adjacent wall tissue would be achieved by circulating water through a balloon covering the transducers. Ultrasound confers many advantages over other modalities, including directionality and high spatial control over the energy deposition through selecting the appropriate transducer geometry and operating frequency. This approach is also inherently compatible with image-guidance, including ultrasound or MR, allowing a means of providing direct treatment monitoring and feedback control during the course of the therapy. In order to validate this treatment strategy, a theoretical evaluation

was performed using 3D acoustic and biothermal modeling. Parametric studies for ablation treatments using a generalized anatomical model were used to identify favorable design parameters of the applicator transducers. These results were used for modeling thermal ablation and hyperthermia treatments in patient-specific models of pancreatic cancer to evaluate feasibility and safety of the approach. Preliminary prototype devices were fabricated and experimentally evaluated in *ex vivo* porcine carcass studies using MR guidance and MR temperature imaging (MRTI).

2. THEORETICAL PARAMETRIC INVESTIGATION

2.1 Development of a 3D acoustic and biothermal model

3D transient temperature distributions produced by the endoluminal ultrasound applicator in tissue were calculated by using an implicit FEM solver (COMSOL Multiphysics 4.3) to solve Pennes bioheat equation (Equation 1):

$$\rho C_t \frac{dT}{dt} = \nabla [k \cdot \nabla T] - \omega_b \cdot C_b \cdot [T - T_b] + Q_{ac} \quad (1)$$

where ρ is density, C_t is the specific heat of tissue, T is tissue temperature, k is thermal conductivity, ω_b is blood perfusion, C_b is the specific heat of blood, and T_b is blood temperature. Q_{ac} is the acoustic heat deposition in tissue, derived from the acoustic intensity calculated for each transducer configuration using the rectangular radiator method.⁷ The transducer geometry was modeled as 20 mm length $\times$ 10 mm width, and four separate configurations were investigated: planar, tubular (with radius of curvature of 6 mm and 80° sector angle), curvilinear along the transducer width (lightly focused), and curvilinear along the transducer length (strongly focused). Temperature profiles were calculated with the direct implicit stationary solver (PARDISO) in COMSOL, and Dirichlet boundary conditions were set to 37°C at the tissue domain extremities and 10-25°C at the balloon-tissue boundary. Thermal dose (t_{43}) was calculated using the Sapareto-Dewey formulation, and a threshold of 240 equivalent minutes at 43°C (EM) was used as the tissue ablation threshold.⁸ Heterogeneous thermal and acoustic tissue properties were incorporated: pancreas attenuation = $11 \times f^{0.78}$ Np/m and perfusion = 10 kg/m³/s, pancreatic tumor attenuation = 1.25 $\times$ (normal pancreas attenuation) and perfusion = 4.5 kg/m³/s, and duodenal wall attenuation = 5 f and perfusion = 16 kg/m³/s, where f is the ultrasound frequency in MHz. The duodenal wall was modeled as 2 mm thick. Perfusion was dynamically set to 0 kg/m³/s during heating when tissue temperature exceeded 52°C or dose exceeded 300 EM. A proportional-integral (PI) feedback controller of the applied power was integrated into the thermal modeling to simulate control under MR temperature imaging (MRTI) guidance, with the set-point being the maximum tumor temperature.

2.2 Parametric studies of transducer parameters

Parametric studies for thermal ablation of pancreatic head tumors were performed using a generalized anatomical model to determine the effects of transducer configuration and frequency (1–5 MHz) on lesion volume, penetration depth, and sparing of duodenal wall tissue from thermal injury. The dimensions of the anatomical model were 50 $\times$ 50 $\times$ 73.5 mm, and the tissue compartments are shown in Figure 2. The applicator transducer was

positioned 6.5 mm from the luminal wall, and the central portion of the wall above the transducer was modeled as being cooled by 10°C water. The normal pancreatic tissue-tumor tissue boundary was situated 5 mm from the inner wall surface. Transient temperature solutions at a single applicator orientation were obtained every 15 seconds for a 5 minute total treatment time, followed by 3 minutes of cooling. The PI controller parameters were tuned for a 5 min rise time to a maximum temperature of 80°C.

The relationships between transducer frequency and penetration depth, lesion volume, and maximum duodenal wall temperature for each configuration (planar, tubular, lightly focused – 30 mm ROC, and strongly focused – 30 mm ROC) are shown in Figures 3 (a)-(c). As expected, increasing the frequency resulted in shallower penetration and consequently both smaller lesions volumes and higher duodenal wall temperatures. In order to stay below a wall temperature of 45°C, it is necessary to operate within the lower frequency spectrum, from about 1-3 MHz, and to disqualify tubular transducers for ablative purposes. At 2 MHz, about 30-35 mm penetration depth from the duodenal wall is possible using a planar or focused configuration, with a corresponding lesion volume of 3-6 cm³. As the transducer geometry becomes more focused, the sparing of the duodenal wall and penetration depth are improved at the cost of smaller lesion volumes. To promote fast treatment times afforded by high lesion volumes, low frequency planar and lightly focused transducers would be most appropriate for ablation of tumors with boundaries close to the duodenal wall. For tumors located deeper in the pancreas away from the duodenum, strongly focused transducers would be preferential, providing enhanced penetration and wall sparing.

3. PATIENT-SPECIFIC MODELS OF THERMAL ABLATION AND HYPERTHERMIA

Three axial CT image studies of patients with pancreatic head tumors were used to generate 3D patient-specific anatomical models. In each model, relevant anatomical structures, including the tumor, duodenum, duodenal wall, pancreas, pancreatic duct, and nearby major vasculature, were segmented using Mimics (Mimics Innovation Suite, Materialise). These were converted into 3D finite element meshes in 3-matic (Mimics Innovation Suite, Materialise). In each model, the applicator, enclosed in a 2 cm diameter balloon, was positioned in the duodenum adjacent to the tumor. The rectangular radiator method was used to calculate acoustic intensity distributions from simulated transducers onto the anatomical model mesh. After converting intensity to heat deposition, Pennes bioheat equation was solved in COMSOL Multiphysics to determine temperature and thermal dose distributions. Model parameters were the same as for the parametric studies (see section 2.1). For models incorporating vasculature, heat flux boundary conditions were incorporated at the inner surface of each vessel, with heat transfer coefficients calculated for each using the method described by Haemmerich et al.⁹ Thermal ablation simulations were solved transiently with PI control, while hyperthermia treatments were simulated as steady-state solutions to constant transducer input power. The maximum tumor temperature for all hyperthermia simulations was set to 45°C, and cooling water temperature was 20-25°C.

3.1 Patient Specific Model #1

Model 1 is shown in Figure 4 (a) and constitutes a small ($21 \times 19 \times 18$ mm, 4.3 cm^3) head tumor in contact with the duodenum. The nearest and farthest distances of the tumor boundaries from the transducer surface were 7.7 mm and 28.0 mm, respectively. Thermal ablation treatments were simulated using two different 20×10 mm transducer configurations – 2 MHz planar and 2 MHz lightly focused curvilinear with a 25 mm ROC. For both cases, the maximum temperature set-point in the tumor for the PI controller was set to 70°C , and the cooling water flow was 10°C . Rotation of the applicator was necessary for both cases to maximize volumetric coverage of the tumor. Thermal dose contours for both cases are shown in Figure 4 (b). For the planar case, after a 20 min total treatment time, 92.9% of the tumor was ablated. The maximum temperature and thermal dose of the duodenal wall were 44.3°C and 5 EM, and for the pancreatic duct were 46.8°C and 30 EM. The lightly focused case required a longer treatment time and resulted in better sparing of sensitive structures at a slight tradeoff of tumor ablation volume. 90.3% of the tumor volume was ablated after a 24 min treatment time. The maximum thermal stresses on the duodenal wall were 41.8°C and 0.4 EM, and for the pancreatic duct 46.2°C and 16 EM.

A hyperthermia treatment was simulated using a 1 MHz tubular transducer, as the angular coverage afforded by this configuration spanned the full extent of the tumor boundaries. At steady-state, 95.0% of the tumor volume was elevated above 40°C as shown in Figure 4 (c).

3.2 Patient Specific Model #2

As shown in Figure 5 (a), the second anatomical model is a small head tumor ($17 \times 22 \times 24$ mm, 4.3 cm^3) located deeper in the pancreas and surrounded by sensitive anatomical structures, including a stented bile duct, the pancreatic duct, and the superior mesenteric artery (SMA). The nearest and farthest distances of the tumor boundaries from the transducer surface were 11.5 mm and 35.0 mm, respectively. To compensate for the deeper position of the tumor and its close proximity to sensitive structures, a 2 MHz strongly focused curvilinear transducer with a 32.5 mm ROC was used for ablation. To better preserve the stented duct, it was modeled as being infused with 33°C cooling water as a heat flux boundary condition during the duration of the ablation. Both rotation and minute translation of the applicator were necessary to increase volumetric tumor coverage, and the maximum tumor temperature was set to 75°C . After a total treatment time of 18 min, 81.3% of the tumor was able to be ablated, while sparing the ducts and vasculature from significant thermal damage, as shown in Figure 5 (b). The maximum temperatures and doses of all sensitive structures did not exceed 45.9°C and 18.9 EM.

Due to the deeper extent of the tumor, hyperthermia was simulated using a 1.5 MHz planar transducer that was rotated to span the tumor boundaries. At steady-state 86.5% of the tumor could be elevated above 40°C as shown in Figure 5 (c).

3.3 Patient Specific Model #3

The third anatomical model constitutes a large ($50 \times 44 \times 25$ mm, 37.2 cm^3) pancreatic head tumor that spans most of the head of the pancreas. It is close in proximity to the duodenum, aorta, vena cava, portal vein, superior mesenteric vein, and SMA, among lesser vasculature.

For adequate coverage of the tumor, it was necessary to reposition the applicator along the length of the duodenum. Three discrete applicator positions were incorporated, with rotation of the applicator performed at each position. A 2 MHz planar transducer was chosen for ablation due to its high penetrative and volumetric capabilities, and the maximum tumor temperature was set to 75°C. After a 48 min total treatment volume, 60.1% of the tumor volume could be ablated, with minimal thermal damage to sensitive tissues and vasculature, as shown in Figure 6 (a). The maximum temperature and thermal dose of the duodenal wall were 44.1°C and 11.8 EM, and for the pancreatic duct were 43.2°C and 2.3 EM. No blood vessel exceeded a temperature of 42.9°C or dose of 2.0 EM. Tumor coverage could have been increased by considering more discrete positions of the applicator along the duodenum, at the cost of further increasing the treatment time.

Hyperthermia was simulated in this case using a 1.5 MHz planar transducer, with the applicator confined to a single position in the duodenum. By rotating the applicator, about 7.6 cm³ of the tumor volume could be elevated above 40°C as shown in Figure 6 (c).

4. EXPERIMENTAL INVESTIGATIONS OF PROTOTYPE APPLICATORS

4.1 Prototype Endoluminal Ultrasound Applicator Design

Prototype endoluminal ultrasound applicators with two 10 × 10 mm 3.2 MHz planar transducers were fabricated. The transducers were mounted with air-backing onto a custom-designed transducer stage fixture, which had a 12 mm outer diameter, internal channels for wiring and circulating water flow, and platforms for integrating MR tracking coils. The fixture was 3D printed for ease of fabrication and secured onto the distal end of 8 mm catheter. A fixed-shape balloon was secured to the top of the fixture for water circulation during sonication, and additional features to augment the maneuverability of the catheter, including a hinge and guiding tip, were incorporated. Images of the fabricated devices can be seen in Figure 7.

4.2 Heating Experiments in *Ex Vivo* Porcine Carcass under MR Guidance

Device delivery and heating performance were evaluated in a 3T GE MRI scanner using 60-80 lbs. whole porcine carcasses. The prototype applicator was inserted directly into the porcine esophagus and manipulated into the stomach lumen. MR anatomical imaging guidance was used to precisely position the applicator against the stomach wall adjacent to the porcine pancreas, as shown in Figure 8 (a). Once positioned, multiple MRTI imaging slices were prescribed through the applicator to capture temperature change in the tissue. Sonications (5 W/cm², 10 min) were performed with real time multi-slice thermometry using the RTHawk platform (HeartVista, Inc.). As shown in Figure 8 (b)-(d), MRTI temperature profiles illustrate the capability of the applicators to heat through the stomach wall into the pancreas, with ~30 mm heating penetration and substantial volumetric temperature elevation ($T > 40^{\circ}\text{C}$).

5. CONCLUSIONS

Theoretical studies illustrate the feasibility of performing endoluminal ultrasound thermal therapy of pancreatic head tumors while preventing thermal injury to sensitive structures.

Parametric studies over transducer geometry and frequency indicate that operating frequencies in the range of 1-3 MHz maximize penetration and coagulation volume for ablation treatments while mitigating luminal heating. Thermal ablation modeling in patient-specific models of small tumors extending 35 mm from the luminal wall have demonstrated capability of debulking large portions of the tumor in short (< 30 min) treatment times without significant damage to non-tumor tissues. Elevation of large portion of these tumors above 40°C for hyperthermia was also demonstrated to be feasible. The larger tumor (~5 cm diameter) model required translation of the applicator during treatment for ablation of appreciable volumes of the tumor, and would be an unlikely candidate for hyperthermia using this approach due to limited coverage at a single position. Prototype endoluminal applicators were fabricated and contained two planar 1 cm square transducers operating at 3.2 MHz. These applicators were characterized in *ex vivo* porcine carcass heating experiments with MRTI guidance. The prototype applicators could be positioned in the stomach of the porcine adjacent to the pancreas, and exhibited sufficient heating of pancreatic tissue for ablative purposes, with a heating penetration of approximately 3 cm.

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Figure 1.
 Schema and concepts of an endoluminal ultrasound applicator positioned in the GI tract for thermal therapy of pancreatic tumors.

Figure 2. Cross-sectional slice of 3D generalized tissue block model for parametric studies of thermal ablation across transducer geometries and frequencies.

Figure 3.

Effects of transducer configuration and operating frequency on (a) penetration depth (as measured from inner luminal wall) of thermal lesion, (b) tumor lesion volume ($t_{43} > 240$ EM), and (c) maximum temperature of luminal wall tissue, after a single 5 minute sonication with a temperature set-point of 80°C .

Figure 4.

(a) Patient-specific model anatomy #1, consisting of a small pancreatic head tumor directly adjacent to the duodenum. The applicator was positioned in the duodenal lumen, and ablation treatments were simulated using 2 MHz planar and lightly curvilinear transducer configurations. The ablated tissue margins, as defined by the $t_{43} > 240$ EM margins, are shown across the central cross-section for both cases (b). Hyperthermia was simulated using a 1 MHz tubular transducer, with temperature distributions and contours shown in (c).

Figure 5.

(a) Patient-specific model anatomy #2, consisting of a small pancreatic head tumor adjacent to the SMA, stented bile duct, and pancreatic duct. (b) 240 EM dose contours for ablation, simulated by minutely translating and rotating a strongly focused curvilinear transducer to maximize tumor coverage while sparing all sensitive structures. (c) Tumor surface temperature distribution for a hyperthermia simulation, by rotating an applicator with a planar 1.5 MHz transducer.

Figure 6.

Patient-specific model anatomy #3, consisting of a large pancreatic head tumor. For ablation, the applicator was translated to three distinct positions along the length of the duodenum and rotated at each position. (b) 240 EM dose contours obtained for an ablation simulation using a 2 MHz planar transducer. (c) Hyperthermia was simulated by rotating a single applicator with a 1.5 MHz planar transducer at position 1, with temperature distributions and contours shown across the central cross-section.

Figure 7.

(a) Top view of distal tip of applicator, showing the transducer stage fixture with two mounted $10\text{ mm} \times 10\text{ mm}$ 3.2 MHz planar transducers. (b) Side view of distal tip of applicator, showing the frontal coupling balloon above the mounted transducers and guiding tip.

Figure 8.

(a) T2-weighted axial image of porcine carcass with the endoluminal ultrasound applicator positioned in the stomach lumen adjacent to the pancreas. Sonication was performed with real-time, multi-slice MRTI for a 10 min heating duration at 5 W/cm^2 applied intensity. Temperature elevation profiles are shown at the end of heating for a sagittal imaging plane (b) and two axial imaging planes (c)-(d) all with respect to the applicator.