Invited Paper

In situ treatment of liver using catheter based therapeutic ultrasound with combined imaging and GPS tracking

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ABSTRACT

Extensive surgical procedure or liver transplant still remains the gold standard for treating slow-growing tumors in liver. But only few candidates are suitable for such procedure due to poor liver function, tumors in unresectable locations or presence of other liver diseases. In such situations, minimally invasive surgery may be the best therapeutic procedure. The use of RF, laser and ultrasound ablation techniques has gained considerable interest over the past several years to treat liver diseases. The success of such minimally invasive procedure depends on accurately targeting the desired region and guiding the entire procedure. The purpose of this study is to use ultrasound imaging and GPS tracking system to accurately place a steerable acoustic ablator and multiple temperature sensors in porcine liver *in situ*. Temperature sensors were place at eight different locations to estimate thermal distribution in the three-dimensional treated volume. Acoustic ablator of center frequency of 7 MHz was used for the experiments. During therapy a maximum temperature of 60-65 °C was observed at a distance 8-10 mm from the center of the ablation transducer. The dose distribution was analyzed and compared with the gross pathology of the treated region. Accurate placement of the acoustic applicator and temperature sensors were achieved using the combined image-guidance and the tracking system. By combining ultrasound imaging and GPS tracking system accurate placement of catheter based acoustic ablation applicator can be achieved in livers in situ.

Keywords: ultrasound ablation, thermal therapy, image-guided liver ablation, high intensity ultrasound, ultrasound imaging, electromagnetic tracking

1. INTRODUCTION

Hepatocellular carcinoma is considered to be the third most common cause of cancer death in the world [1]. Liver is considered to be a common site for distant metastasis of several common types of cancer such as gastrointestinal cancer [2], breast, prostate [3], and melanoma [4]. Surgery procedures and liver transplantation are the most common options for treatment of the liver. Liver transplant is a very complex procedure and may lead to various infections such as hepatitis C [5]. Surgical procedure is an effective therapy but only a small percentage of patient are eligible for liver resection due to tumor location and other diseases present in the patient [2]. Minimally invasive ablative therapy has been investigated to successfully treat uresectable liver tumors [2].

Thermal ablation and hyperthermia are important treatment options for cancer therapy. Localized thermal ablation causes protein denaturization, necrosis and coagulation in the treatment region to kill tumor cells and spare the healthy

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tissue away from the tumor. Minimally invasive thermal therapies include radiofrequency, microwave, cyro and ultrasound ablation techniques to treat tumors. Thermal therapy using radiofrequency and microwave ablations are often used for patients who are not suitable for surgery and have unresectable colorectal or neuroendocrine hepatic metastasis [6]. Cryoablation technique freezes tissue rapidly at temperature below 0 °C to form intra- and extracellular ice crystals which results in cellular dehydration and loss of blood supply that leads to tumor cell deaths [7]. High-intensity focused ultrasound (HIFU) is a localized noninvasive ablation technique has been widely investigated to treat liver cancer [8]. The major drawback of radiofrequency or microwave ablation is the lack of control over the directionality and overall shape of the ablation zone. HIFU is an excellent technique to accurately control the treatment region but treated volumes are tiny and many zones are required to treat a clinically relevant volume, thus requiring considerable time to ablate a moderately large volume of tissue. Further, HIFU suffers from entry and exit burns due to the requirement for overlapping fields.

Minimally invasive catheter/needle based procedures are widely investigated for treatment of various diseases since it is one of the least invasive procedures with potential for minimal or no bleeding and can have good to excellent target accuracy. Ultrasound catheter/needle based devices have been created which Catheter based ultrasound therapy has been under investigation for treatment of prostate and uterine applications [9-11]. Synergistic therapy by combining catheter based ultrasound applicator delivery and radiation have shown excellent results [12, 13]. Interstitial ultrasound applicators have been under development, with demonstrated precise ablation patterns using single or multiple interstitial applicators to ablate *ex vivo* soft tissue [14, 15].

The purpose of the present study was to investigate the use of electromagnetic (EM) tracking in combination with ultrasound imaging to guide ultrasound interstitial applicator insertion for ablation of *in situ* porcine liver in human sized animals. The treatment was monitored by inserting several needle thermocouples at various distances from the ultrasound applicator. The dose distribution was estimated from the temperature recorded by each of the thermocouples. Finally, gross anatomical pathology of the ablation zone and surrounding region was performed and documented.

2. METHODS

2.1 Animal Protocol

The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC), University of Illinois, Urbana-Champaign and satisfied all University and NIH rules for the humane use of laboratory animals. Female pigs weighing 150-200 lbs. were used for the experiments. The pig was euthanized using with sodium pentobarb (Fatal plus 10 cc/100 lbs. IV). Most often the main blood vessel with trajectory through the jugular groove (usually, external jugular vein) was used. The ultrasound ablation experiments were conducted within 10 minutes from euthanizing the pig. Incision was made along the abdomen followed by cutting the rib cage to expose the liver *in situ* for treatment. After the treatment the liver was extracted from the body for gross pathology and visual inspection. After dissecting, the tissue was submerged into triphenyltetrazolium chloride (TTC) for staining. The TTC made the treated region appear in different color than the normal tissue for easier visual identification of the treatment region.

2.2 Catheter based interstitial ultrasound applicators

Two element tubular PZT transducers were used to manufacture the catheter based ultrasound interstitial applicator as shown in Figure 1. The transducers were mounted on a hollow polyamide tube. The PZT transducers were 10 mm long with 1.5 mm outer diameter. The applicator was inserted into the tissue for treatment using a 13g implant catheter. Degased water was circulated through the applicator and the catheter for cooling the transducer during ablation. Degased water was used to minimize the presence of bubbles. Transducers with either 360° or 180° active zones as shown in Figure 1(b) and (c), were used for the experiments.

Using electrical impedance and radiation force balance measurements, the center frequency and efficiency of each transducer was determined. The center frequency of each individual transducer was used to excite the respective transducer to maximize energy output. Continuous wave operation was used to excite the transducers. Typically transducer center frequency ranged from 6.5 – 7.5 MHz with acoustic efficiency of 50 – 60 %. Here the transducer closer to the tip of the catheter was be referred to as Tx1 and the second transducer as Tx2 as shown in Figure 1.

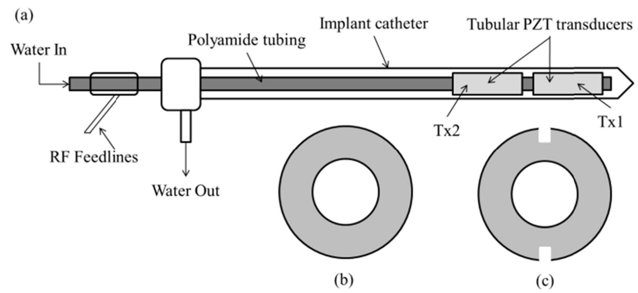


Figure 1: (a) Schematic of a catheter based ultrasound interstitial applicator, (b) cross-sectional view of a 360° tubular transducer, and (c) cross-sectional view of a 180° tubular transducer.

2.3 Thermometry and dose estimation

Needle thermocouples of Type T (Physitemp, New Jersey, USA) with multiple sensors along the length were used for monitoring temperature. Each needle was 100±2 mm long and 0.82 mm in diameter with 0.1 °C accuracy in temperature estimation. Thermocouples were placed at different distances from the ultrasound applicator and dose was calculated for each thermal sensor. A custom template was used to insert the applicator and thermocouples as shown in Figure 2. The template helped in registering the location of each thermocouple with respect to the ultrasound applicator precisely. The temperature from each thermocouple was recorded at every 1 second. The thermal dose calculated form the thermocouple reading is given by [16, 17]

$$t_{43} = \sum_{t=0}^{t=final} R^{(43-T_t)}\,\Delta t, \qquad \begin{cases} R = 0.25 \text{ for } T < 43℃ \\ R = 0.50 \text{ for } T \geq 43℃ \end{cases} \tag{1}$$

where T_t is the average temperature recorded by the thermocouple during time Δt. The unit of thermal dose is equivalent minutes at 43° C. Typically thermal dose of 50 – 240 equivalent minutes at 43° C can cause necrosis in soft tissue [18].

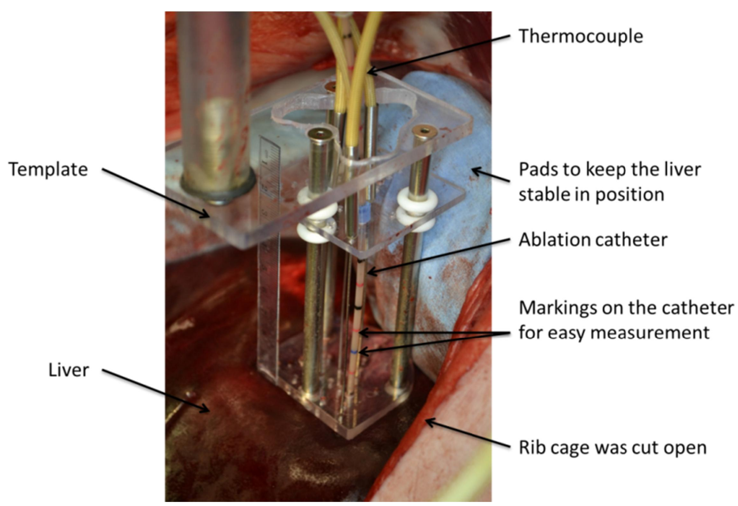


Figure 2: The placement of thermocouples and the ultrasound applicator using the custom template

2.4 Ultrasound imaging, EM tracking and ultrasound ablation

The ultrasound imaging was acquired using a SonixTouch (Ultrasonix, Richmond, BC, Canada) system, which is a FDA approved clinical ultrasound system with an L14-5/38 GPS probe. The SonixGPS system built into SonixTouch system was used for tracking. The in-house software architecture was developed to communicate with the hardware, ultrasound imaging and tracking system. Specifically the ultrasound imaging and tracking was performed using the PLUS software [19, 20] and Open IGT Link. A screen-view of the application software is shown in Figure 3. The left column of the screen shown in Figure 3 was used for displaying two and three-dimensional ultrasound imaging with tracking information. The temperature and the dose versus time were displayed in the central columns of the screen. The right column was used for displaying the controls and experimental parameters used for the experiment. The buttons at the left and the right end of the screen were used for controlling the ultrasound imaging/tracking and treatment/monitoring hardware, respectively. The menu items at the top were used for administrative purpose such as patient management, file management and other tasks. The software has the functionality to create and execute treatment plans.

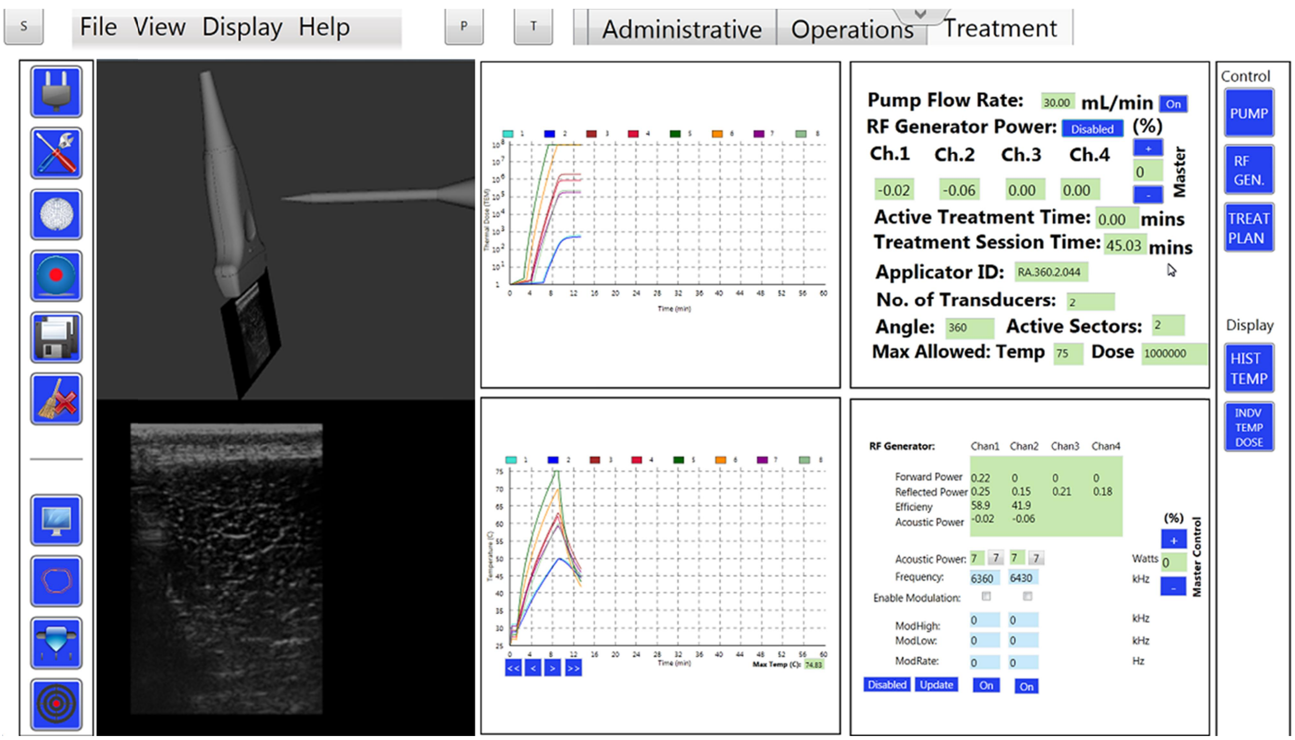
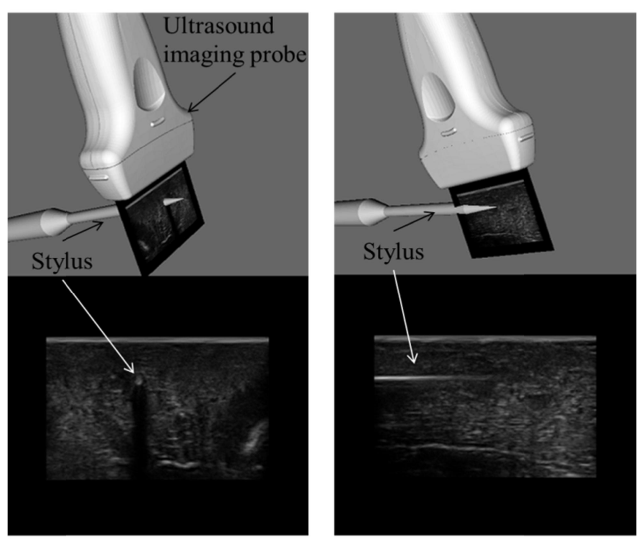


Figure 3: The treatment guidance/control/monitoring application software operation screen view.

The ultrasound imaging and tracking system for insertion of catheter was first tested in freshly *excised* chicken breast tissue for verifications as shown in Figure 4. The EM sensor was located at the tip of the stylus and the stylus was inserted into the *excised* chicken breast tissue using the ultrasound image guidance. The three-dimensional and two-dimensional views of the stylus being perpendicular and parallel to the imaging plane are shown in Figure 4(a) and (b), respectively. It can be easily noticed that the appearance of the stylus in the B-mode images correlates accurately with the three-dimensional view and vice versa. The combination of the three-dimensional view along with B-mode images guided the insertion of the catheter into the tissue as planned.

For the *in situ* liver experiment, the EM sensor was first inserted into the implant catheter. The implant catheter with



(a) (b)

Figure 4: Ultrasound imaging and tracking in excised chicken breast tissue with (a) stylus perpendicular to the imaging plane, (b) stylus parallel to the imaging plane.

the EM sensor at its tip was inserted into the tissue guided by ultrasound imaging and GPS tracking. After the implant catheter was positioned at the treatment location, the EM sensor was taken out of the catheter and the ultrasound applicator was inserted into the implant catheter. A custom template was used to position the applicator and thermocouples as shown in Figure 5(a) and (c). The B-mode images corresponding to the ultrasound imaging transducer position with respect to the application and the thermocouples were shown on Figure 5(b) and (d).

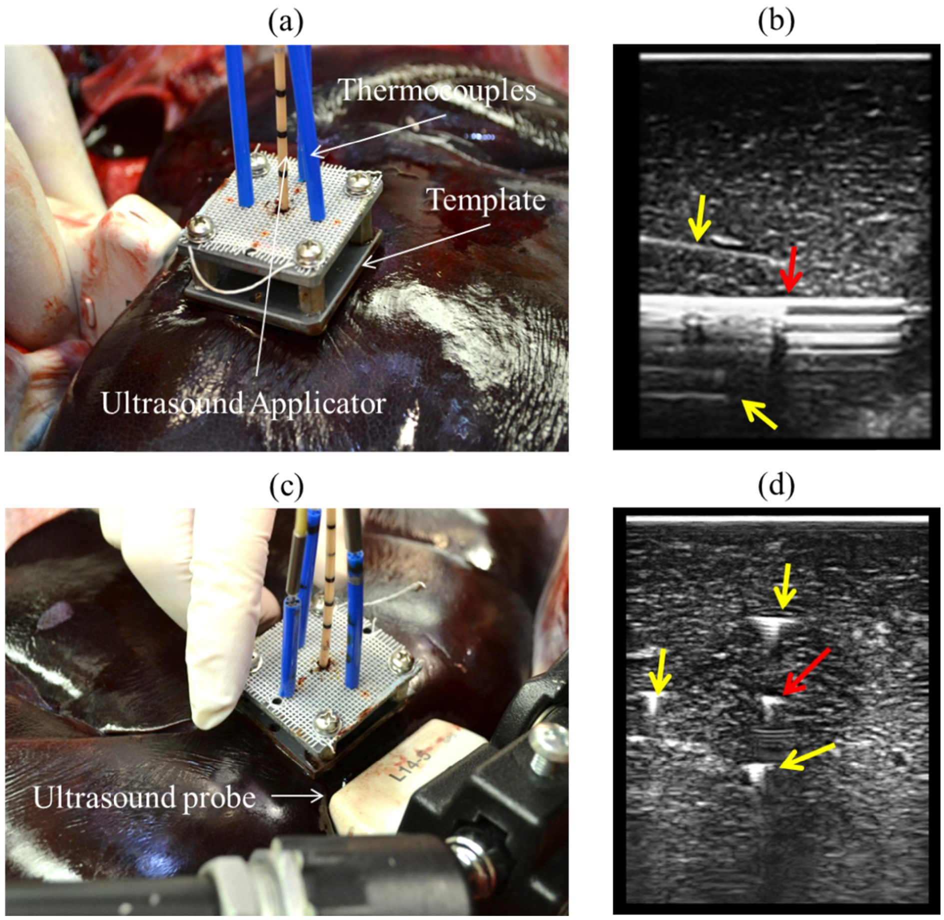


Figure 5: (a) Ultrasound imaging plane parallel to applicator, (b) B-mode image corresponding to imaging transducer position in (a), (c) ultrasound imaging plane perpendicular to applicator and thermocouples, and (d) B-mode images for corresponding imaging array position shown in (c). (The red and the yellow arrows in the B-mode images (b) and (d) represent the ultrasound applicator and thermocouples, respectively)

Typically 7 W (acoustic) was delivered to the tissue by the ultrasound applicator. The acoustic wattage was estimated by considering the system efficiency, transducer efficiency and the transmission through the catheter to the tissue. Water flow rate of 30 ml/min was used for each treatment for cooling the ultrasound ablation transducers in the applicator.

Generally three or four sets of needle microprobes were inserted at different distances from the applicator to monitor temperature profile during treatment. Thermocouples at 5 mm, 10 mm and 15 mm radially from the applicator were inserted using the custom template shown in Figure 6, where the distance between the thermocouples was 10 mm.

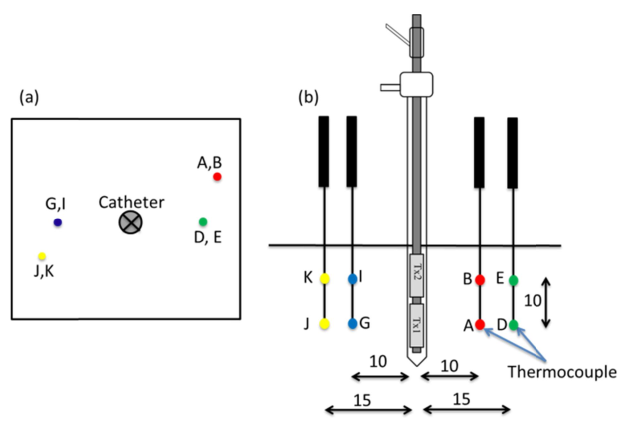


Figure 6: Location of the high-intensity US applicator and the thermocouples in both (a) top view and (b) view along the depth of the applicator

3. RESULTS

Experiments were performed to ablated pig livers *in situ* using ultrasound image-guided tracked interstitial catheter based ultrasound ablation. Acoustic power of 7 W was delivered to the tissue by each of the ultrasound ablation transducers (Tx1 and Tx2) to the tissue. The tissue was exposed to high intensity ultrasound for approximately 9 minutes as shown in

Figure 7(a). The temperature recorded by the different thermocouple was shown in

Figure 7(b), where the location of each thermocouple with respect to the applicator was shown in Figure 6. The dose calculated from each of the thermocouple readings was shown in

Figure 7(c). The legend for each of the temperature and dose curve shown in

Figure 7 corresponds to the thermocouple label (A, B, D, E, G, I, J and K) shown in Figure 6. The temperature increased monotonically with increase in exposure time and decreased after the power was turned off.

After exposing the tissue either in one or multiple location, was extracted from the body for gross pathology and visual inspection. The tissue was stained with TTC before gross pathology and visual inspection. An example of the gross pathology images after sectioning the liver tissue were shown in

Figure 7(d) and (e) at two different views. The tissue was treated at two different locations as indicated by two white arrows in

Figure 7(e). From visual inspection and differentiating treated region with respect to discoloration, the treatment region depth (along the length of the applicator) was 20-25 mm and was laterally (perpendicular to the applicator) 55-60 mm long. Thermocouples located at 15 mm radially from the applicator showed a peak temperature of 55-60 C and thermal dose of $10^3 – 10^5$ EQ mins. Necrosis occurs at 240 EQ mins and hence a minimum radius of 15 mm lesion can be obtained successfully. The uniform discoloration of the treated zone indicates uniform ablation was obtained within the planned target zones as shown in

Figure 7(d) and (e).

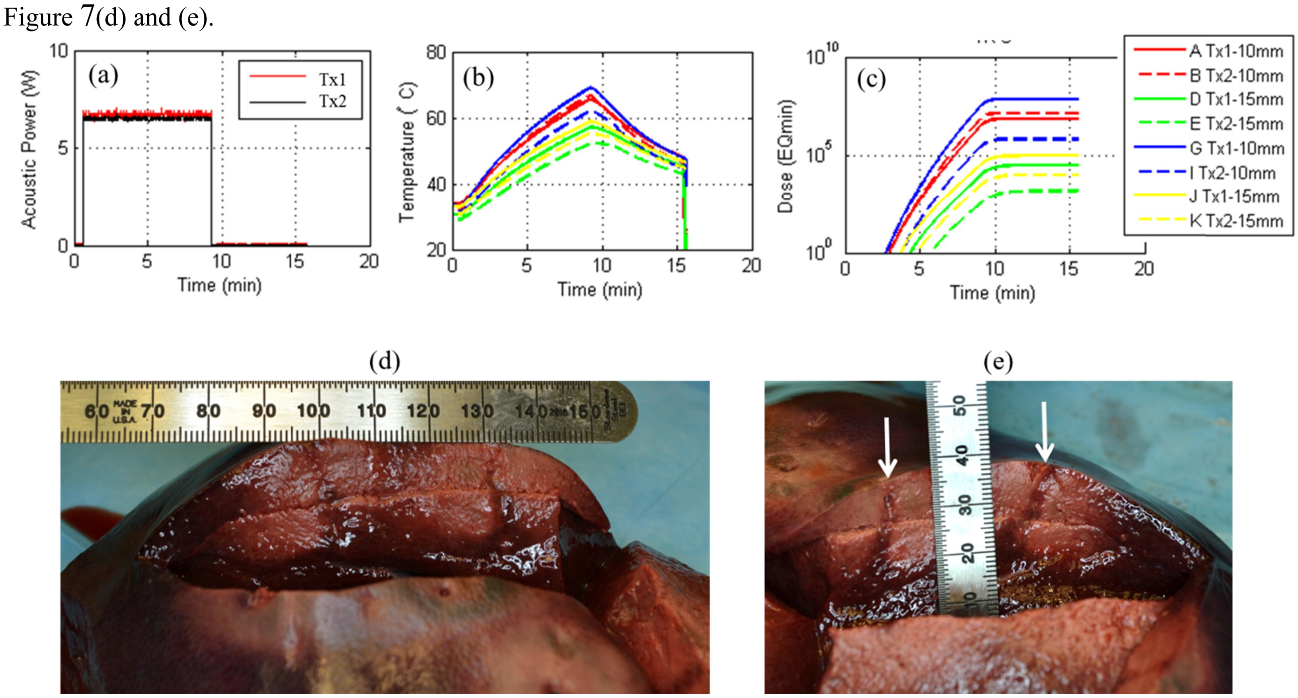


Figure 7: (a) Acoustic power output from the applicator during the treatment, (b) temperature profiles recorded by the thermocouples during the treatment, (c) cumulative dose calculated from each of the thermocouple readings, (d) gross pathology of the ablated zone with scale showing the linear extent of the treatment zone, and (e) gross pathology of the ablated zone with the scale indicating depth of treatment (the white arrows indicate the position of the applicator during the treatment).

Additional experiments were performed to form different ablation patterns as per planned treatment. The gross pathology images of two different treatment patterns were shown in

Figure 8(a) an (b) using multiple insertion of 360° applicators. Similarly, gross pathology images of treatment patterns were shown in Figure 8(c) an (d) using single insertion of 180° sectored applicators. The first treatment produced a liner a curved pattern from four insertion of the ultrasound applicator and extends to length of 100 mm as shown in

Figure 8(a). Another treatment produced an approximate equilateral triangular pattern of size 50 mm using three insertion of the applicator as shown in

Figure 8(b). Angular sectored pattern are useful to treat soft tissue and also avoid destroying nearby vessels/veins.

Figure 8(c) shows a treatment area where the surrounding major veins were not affected by the exposure using a 180° ultrasound applicator. It was clearly identified that the tissue outside the ultrasound beam was not affected by the exposure. Gross pathology image from another experiment is shown in

Figure 8(d) using a 180° ultrasound applicator.

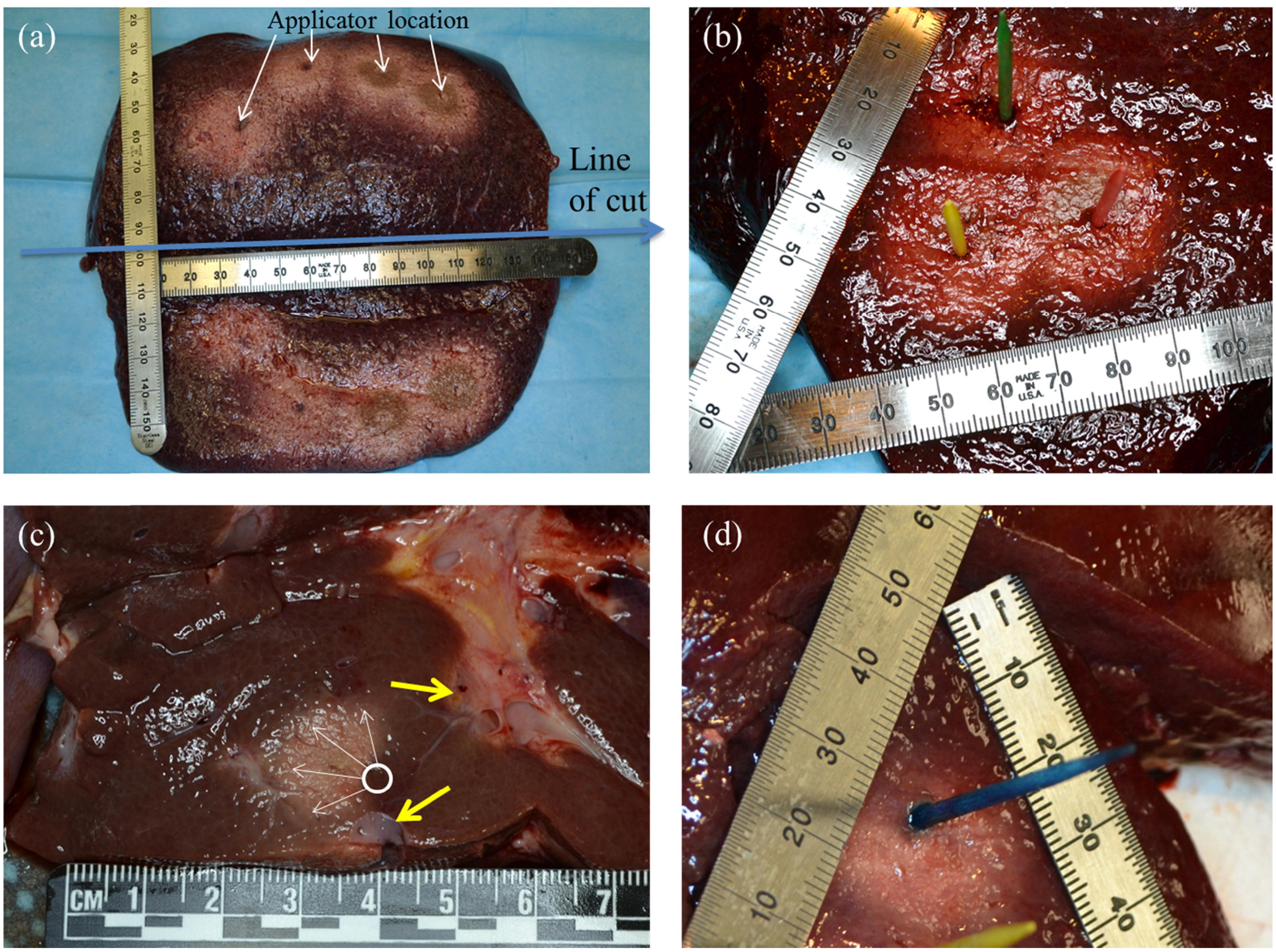


Figure 8: Gross pathology of the ablated pig liver tissue with (a) curved pattern using four insertion of 360° applicator and (b) triangular pattern using three insertion 360° applicator (applicator location indicated by wooden sticks), (c) angled pattern using single insertion of 180° applicator (applicator position indicated by the white circle, white and yellow arrows denote the ablated zone and major vessels respectively), and (d) angle pattern using single insertion of 180° applicator of the ablated zones (applicator location indicated by blue wooden stick).

Maximum and average temperature recorded by the thermocouple at distances 5 mm, 10 mm and 15 mm radially from the applicator from ten exposures is shown in Figure 9. Similar acoustic power and exposure times were used for all the exposures. The average peak temperature of 72.9 °C, 63.1 °C and 54.1 °C were observed at radial distance of 5mm, 10 mm and 15 mm, respectively from the applicator. Similarly peak cumulative dose of 5.49×10^8, 1.31×10^6 and 5.58×10^3 equivalent minutes at 43 °C were observed at radial distance of 5 mm, 10 mm and 15 mm, respectively. The average values and standard deviation of peak/minimum temperature recorded by the thermocouples at 5 mm, 10 mm and 15 mm were shown in Figure 10. Average temperature of more than 55 °C was observed at 15 mm radial distance from the applicator as shown in Figure 10. The average peak temperature decreased monotonically with increasing radial distance from the applicator.

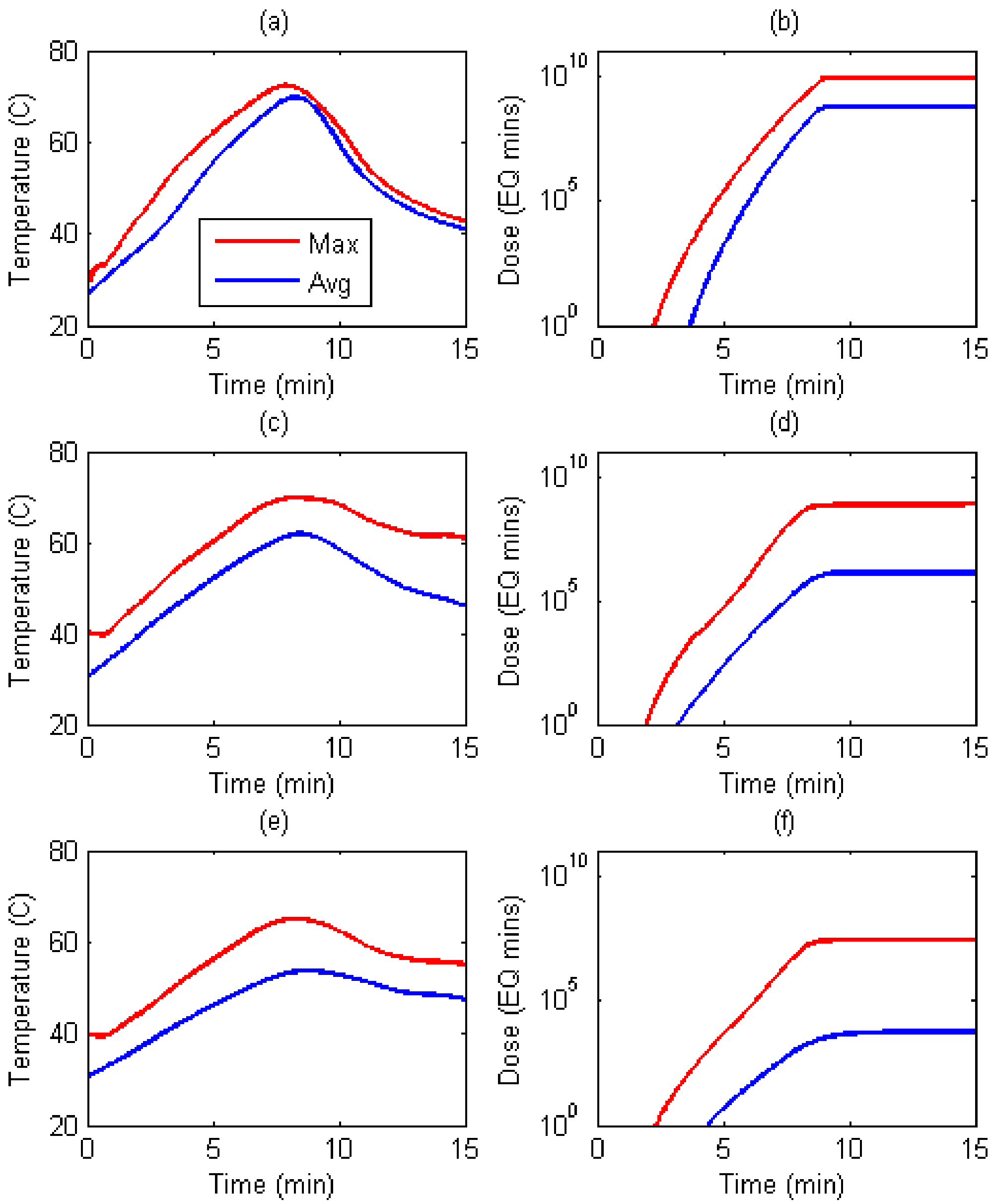


Figure 9: Maximum and average temperature and dose profiles: (a) temperature profile at 5 mm, (b) dose at 5 mm (c) temperature profile at 10 mm, (d) dose at 10 mm, (e) temperature profile at 15 mm and (f) dose at 15 mm radially from the applicator.

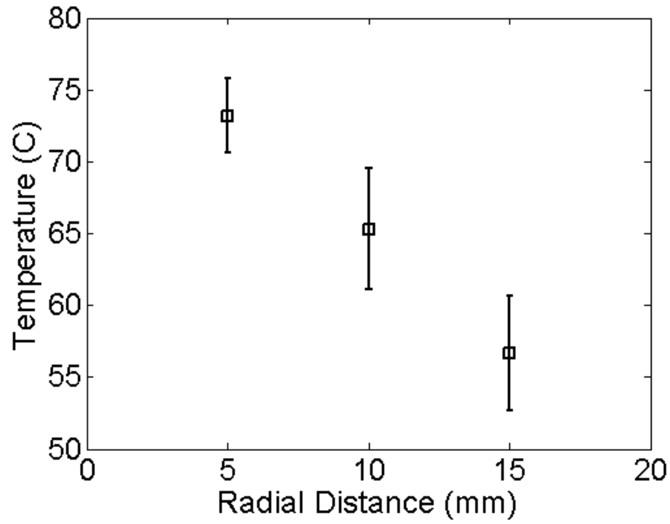


Figure 10: Mean and standard deviation of peak temperature recorded by the thermocouples at different radial distances from a single US applicator.

4. CONCLUSION

Experiments were performed to investigate the feasibility of using ultrasound imaging with EM tracking to guide catheter based ultrasound thermal therapy in pig livers *in situ* using human-sized animals. The main goal of this study was to induce necrosis in planned tissue volume (size with directionality) without damaging the surrounding soft tissue. One of the main challenges of modern thermal therapy is to precisely control the directionality and demarcation boundary of the ablation zones. The experimental results demonstrated that the directionality and shape of the ablation zone can be controlled using catheter based high intensity sectored ultrasound transducers. The 180° sectored transducers helped in creating ablation pattern without damaging the nearby vein/vessels in the tissue verified from gross pathology inspection.

In situ liver samples were used here to provide realistic anatomical constraints and accessibility requirements for this feasibility study. The ultrasound imaging and EM tracking system guided the insertion of the catheter into the tissue accurately as planned. The advantage of real-time imaging capability of ultrasound helped in guiding the treatment successfully. We plan to conduct future experimental studies using the proposed technique on *in vivo* pig livers and study the effects of blood flow on the results obtained and compare with this study. More exposure time may be needed for *in vivo* tissue compared to time needed for ablation in this study to achieve similar treatment volumes for both study cases since the blood flow will act as a coolant during the *in vivo* treatment.

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