JOURNAL OF SURGICAL RESEARCH 190 (2014) 391–398

Available online at www.sciencedirect.com

ScienceDirect

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Association for Academic Surgery

Hollow iron-silica nanoshells for enhanced high intensity focused ultrasound

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ARTICLE INFO

Article history:
Received 3 January 2014
Received in revised form
27 March 2014
Accepted 2 May 2014
Available online 10 May 2014

Keywords:
Nanoparticles
HIFU
Silica
Breast cancer
Histotripsy

ABSTRACT

Background: High intensity-focused ultrasound (HIFU) is an alterative ablative technique currently being investigated for local treatment of breast cancer and fibroadenomas. Current HIFU therapies require concurrent magnetic resonance imaging monitoring. Biodegradable 500 nm perfluoropentane-filled iron-silica nanoshells have been synthesized as a sensitizing agent for HIFU therapies, which aid both mechanical and thermal ablation of tissues. In low duty cycle high-intensity applications, rapid tissue damage occurs from mechanical rather than thermal effects, which can be monitored closely by ultrasound obviating the need for concurrent magnetic resonance imaging.

Materials and methods: Iron-silica nanoshells were synthesized by a sol-gel method on polystyrene templates and calcined to yield hollow nanoshells. The nanoshells were filled with perfluoropentane and injected directly into excised human breast tumor, and intravenously (IV) into healthy rabbits and Py8119 tumor-bearing athymic nude mice. HIFU was applied at 1.1 MHz and 3.5 MPa at a 2% duty cycle to achieve mechanical ablation.

Results: Ex vivo in excised rabbit livers, the time to visually observable damage with HIFU was 20 s without nanoshells and only 2 s with nanoshells administered IV before sacrifice. Nanoshells administered IV into nude mice with xenograft tumors were activated *in vivo* by HIFU 24 h after administration. In this xenograft model, applied HIFU resulted in a 13.6 ± 6.1 mm^3 bubble cloud with the IV injected particles and no bubble cloud without particles.

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http://dx.doi.org/10.1016/j.jss.2014.05.009

Conclusions: Iron-silica nanoshells can reduce the power and time to perform HIFU ablative therapy and can be monitored by ultrasound during low duty cycle operation.

1. Introduction

High intensity-focused ultrasound (HIFU) is an ablative technique that is currently used for treatment of uterine fibroids in the United States and is being investigated for other applications. [1–4] Less invasive techniques, which still provide good local control and prevent recurrence, are desirable for treating solid tumors. Silica nanoshells can accurately localize nonpalpable tumors [5–7] and are being investigated for HIFU ablation of small breast cancers without an operation or incision. Previous researchers have investigated magnetic resonance imaging (MRI)-guided HIFU of breast fibroadenomas. [8] However, MRI-guided HIFU is associated with patient discomfort of lying face down for over an hour and is not associated with complete ablation. [9,10] Ongoing clinical trials use thermal HIFU ablation for small breast cancers under MRI guidance. [11] With traditional HIFU therapy, some energy is converted to heat, which at the focal zone of the HIFU is sufficient to cause a thermal burn and induce coagulative necrosis of the tissue. For thermal ablation with HIFU, MRI is required to guide and monitor tissue temperature to minimize off target heating or over- or under-treatment. [12] Silica nanoshells could be used in a more convenient nonthermal technique of supine ablation under ultrasound guidance obviating the need for MRI monitoring while improving patient comfort and speed.

In addition to thermal damage, HIFU also causes mechanical damage by cavitation and can liquefy tissue; this is denoted as histotripsy. [13] Normally, for strictly mechanical damage to occur with HIFU, an intense pulsed ultrasound with a duty cycle below 4% with a time average intensity of 2 W/mm^2 is required to minimize tissue heating. [14] Due to the minimal tissue heating, mechanical damage caused with HIFU can be monitored by ultrasound instead of MRI. Xu *et al.* [15] demonstrated that during histotripsy *in vitro*, bubbles were generated that grew from $<$10 microns in size to $>$100 microns. Roberts *et al.* [16] applied focused pulsed high power, low frequency ultrasound for histrotripsy in rabbit kidneys. With 25 MPa peak negative pressure output, it was found that 1000 or 10,000 pulses resulted in formation of a 3 mm by 10 mm ellipsoidal cavity at the focal zone. Vlaisavljevich *et al.* [17] demonstrated that histotripsy can be performed on much larger volumes *in vivo* in porcine livers through intervening tissue and ribs. Although histotripsy without enhancement is a very promising technique, it uses very large pressures and insonation times.

Ultrasound contrast agents such as microbubbles and nanoemulsions can enhance thermal and mechanical HIFU ablation. [18–22] Kaneko *et al.* [23] performed HIFU on rabbit livers *in vivo*, which had been dosed with Levovist (Schering AG, Berlin, Germany) microbubbles and doubled the burn volume compared with saline control rabbits after 60 s of HIFU application. Tran *et al.* [24] performed cavitation in canine kidneys with and without (Optison, GE Healthcare, Buckinghamshire, UK) microbubbles; continuous perfusion of microbubbles during insonation reduced the ultrasound intensity and exposure time needed. For microbubbles, the rapid clearance from circulation due to their large sizes suggests that for practical use it would be necessary to administer large doses or have multiple or continuous dosing. [25] Nanoemulsions and nanodroplets are particularly attractive because they have a small size until acoustic excitation induces droplet vaporization, which greatly increases their size. *In vitro*, perfluoropentane (PFP) core nanodroplets have the potential to substantially reduce the threshold for cavitation and histrotripsy. [26] The minimum pressure to generate cavitation bubbles in the presence of nanodroplets was ~3 MPa *versus* ~15.6 MPa without the nanodroplets.

Silica nanoparticles and nanoshells have been shown useful as ultrasound contrast agents [5–7] and as sensitizing agents for HIFU therapy. [27–29] Although the *in vivo* lifetime of ultrasound contrast agents is only minutes for microbubbles or several hours for nanodroplets, silica nanoshells have been shown to retain the loaded perfluorocarbon *in vivo* over the course of 10 d and remain in xenograft tumors after intravenous administration over the course of several days from a single dose of nanoshells. [5–7] In contrast to both microbubbles and nanodroplets, silica nanoshells have an almost infinite shelf life and facile surface functionalization. Previous studies used perfluorohexane liquid-filled silica nanoparticles and very short insonation times at high ultrasound power to cause thermal damage. The present study uses biodegradable 500 nm PFP-filled Fe-SiO_2 nanoshells for applications in histotripsy and thermal ablation at relatively modest peak negative pressures. Furthermore, it is demonstrated *ex vivo* in human mastectomy tissue that the use of the Fe-SiO_2 nanoshells may be used to ablate small and targeted tissue volumes as detailed by color Doppler imaging. Finally, it is shown that intravenously (IV) injection of the nanoshells, which accumulate in Py8119 tumors grown in mouse flanks, ablate tumors *in vivo*. To the best of our knowledge, this is the first report applying silica nanoparticle for a strictly histotripsy type therapy.

2. Materials and methods

2.1. Materials

Tetramethyl orthosilicate was purchased from Sigma–Aldrich (St. Louis, MO); iron (III) ethoxide was obtained from Gelest Inc (Moorisville, PA), 500 nm aminated polystyrene templates were purchased Polysciences (Warrington, PA); PFP was procured from Strem Chemicals (Newburyport, MA). All ultrasound imaging was performed using a Siemens Sequoia 512 (Mountainview, CA) with an Acuson 15L8 imaging transducer. HIFU was performed using a Sonic Concepts Inc (Bothell, WA) H-102 single element transducer, driven by ac AG 1006 Amplifier/Generator (Rochester, NY). FGEN Soft Front Panel version 2.6

software by National Instruments (Austin, TX) was used to generate the waveform and control the HIFU. Tissue sectioning and hematoxylin and eosin staining was performed by the University of California, San Diego Histology core.

2.2. Animals and tissue

Female, 3–4 kg New Zealand White rabbits were housed individually in a UCSD-approved vivarium and fed Harlan Teklad (Indianapolis, IN) pelleted commercial feed. Before experimentation, each animal was anesthetized with 2% isoflurane gas through a nose cone. Particle injections took place through the ear vein of each animal under anesthesia. Animals were monitored in accordance with UCSD guidelines throughout all procedures. After experimentation, each animal was euthanized with an IV injection of sodium pentobarbital through the ear vein. All procedures performed on rabbits were approved by the UCSD Institutional Animal Care and Use Committee board.

Female, 4–6 wk old nude mice from UCSDs in-house breeding colony were housed in UCSD approved vivarium on a 12 h light–dark cycle and fed Harlan Teklad rodent feed. All tumor cell injections took place under anesthesia induced by inhalation of 1%–2% isoflurane. Each animal received two injections of 10^6 Py8119 cells in a single cell suspension in growth media, one over each hind limb. Animals were weighed and tumors were measured regularly in accordance with UCSD animal welfare policies until the tumors approached 1000 mm^3 in volume. Particle injections took place through the tail vein of each animal under anesthesia. After the conclusion of treatments and scans, all animals were euthanized by CO_2 inhalation. All procedures performed on mice were approved by the UCSD Institutional Animal Care and Use Committee board.

Human breast invasive ductal carcinoma and fibroadenoma tissues were received postoperatively and in full cooperation and consent of UCSD institutional review board protocols. Tissues received were ~1 cm^3 in volume but varied in disease type and state. Particles were injected directly into the tissue and after extraction of tissue sample.

2.3. Methods

2.3.1. Nanoparticle synthesis and perfluorocarbon filling process

Biodegradable 500 nm iron-silica nanoshells were synthesized as described previously. [6,30] A sol-gel reaction was performed on a 500 nm aminated template using tetramethyl orthosilicate and iron (III) ethoxide in ethanol. After collection by centrifugation, the particles were calcined at 550°C to remove the template and dehydrate the gel. After calcination, particles were stored, dried until needed and, subsequently, filled with PFP gas or liquid. Gas filling was performed as previously described. [31] For perfluorocarbon liquid filling, nanoshells were first placed under vacuum in an amber vial with a self-sealing silicone top. After 30 min under vacuum, the vacuum line was removed, and the vial filled with PFP gas using a gas syringe filled with vaporized PFP to equalize the pressure in the container such that the inserted liquid PFP does not vaporize in the container. With a syringe, 25 μL PFP/mg of particles was added to the container, and the container was briefly bath sonicated to disperse the particles. After the particles were filled with PFP liquid or gas, the particles were resuspended in MilliQ (EMD Millipore, Billerica, MA) water at a concentration of 4 mg/mL.

2.3.2. Ex vivo *HIFU of rabbit liver*

Two milligram (500 μL) of gas-filled Fe-SiO_2 nanoshells were administered to the rabbits IV via the marginal ear vein and allowed to circulate for 15 min. The rabbits were sacrificed and the livers were removed and partitioned for HIFU application. Liver partitions were placed in a water bath within the focal distance of the HIFU transducer, and HIFU was applied at 800 KHz with 100% duty cycle at 3 MPa for variable amounts of time. After HIFU, the livers were coarsely sectioned to reveal the damaged sections. A total of six rabbits were used, three rabbits received particle injections and three were used as a control group. Two insonations per time point were performed in each animal for a total of six insonations per time point. Effected volumes were measured by calipers.

2.3.3. Ex vivo *HIFU of excised breast tumor*

Patients underwent their standard procedures for resection of their benign or malignant tumor. A UCSD pathologist examined the tissue; after determining that removing this tissue would not interfere with their analysis, they removed a portion for experimentation. Two hundred microgram (50 μL) of PFP liquid-filled Fe-SiO_2 nanoshells were injected directly into the provided tumor tissue. The tissue was placed inside a plastic disposable transfer pipette bulb to aid handling. The bulb containing the tissue was placed in a water bath at the focus of the HIFU transducer. The HIFU transducer and the ultrasound imaging transducer were arranged orthogonal to one another in a water bath for simultaneous HIFU and US imaging. HIFU was applied for 1 min at 1.1 MHz with a 2% duty cycle at 3.5 MPa. After HIFU, tissues were flash frozen and stored at −80°C until they were submitted to histology for sectioning and hematoxylin and eosin staining. Human tissue experiments were repeated six times with tissues from six different patients, but were not analyzed numerically due to large variations in tissue type and difficulty injecting consistent amounts of particles because of the variations of the tissue.

2.3.4. In vivo *HIFU of Py8119 tumor bearing mice*

Eight hundred microgram (100 μL at 8 mg/mL) of PFP liquid-filled Fe-SiO_2 nanoshells were injected IV via the tail vein into Py8119 tumor bearing nude mice (2 tumors per mouse), and the nanoshells were allowed to circulate for 24 h before HIFU. The tumors were pressed against the HIFU transducer in a water bath for ease of focus. The HIFU transducer and the ultrasound imaging transducer were arranged orthogonal to one another in a water bath for simultaneous HIFU and US imaging. Three mice received particles, and an additional two mice served as a control group. In sum, six tumors were insonated with presence of particles and four tumors were insonated without particles. Raw ultrasound data was analyzed with Osirix (Pixmeo, Geneva, Switzerland) software and then numerical data was imported into Microsoft Excel (Redmond, WA). All data was analyzed with the analytical and statistical package

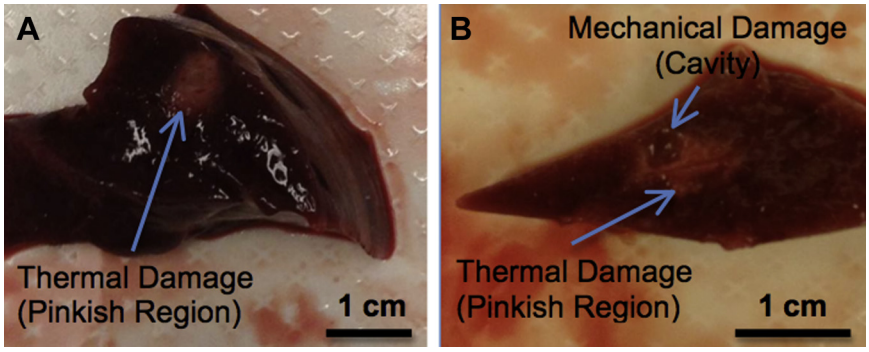

Fig. 1 – *Ex vivo* nanoshell-enhanced ultrasonic ablation. (A) A thermal lesion is produced by highly energetic ultrasonic ablation without nanoshell enhancement after 60 s of exposure. (B) Both mechanical and thermal damage are produced with nanoshell enhancement after only 30 s of ultrasonic ablation at an equivalent power. The thermal damage is the pink region compared with the dark red of the healthy liver tissue. The mechanical damage is seen as a physical cavity that was generated from nanoshell cavitation. (Color version of figure is available online.)

available in Microsoft Excel. HIFU was applied for 1 min at 1.1 MHz with a 2% duty cycle at 3.5 MPa. After HIFU, tissues were flash frozen and stored at −80°C until they were submitted to histology for sectioning and H&E staining.

3. Results and discussion

PFP-filled Fe-SiO_2 nanoshells have been evaluated as a sensitizing agent for HIFU ablative therapies. New Zealand white rabbits received a 2 mg IV injection of PFP gas-filled Fe-SiO_2 nanoshells. After 15 min of particle circulation, the rabbits were sacrificed, and the livers were removed for HIFU application to overcome the attenuation and scattering of the rabbit skin and for more precise ablation of multiple distinct zones. It was found that at a given power of ultrasound energy, using a continuous 800 KHz pure tone waveform with a peak negative pressure at 3 MPa, nanoshell enhancement could reduce the amount of time necessary to achieve a measurable response in tissue. As can be seen in Figure 1A, highly energetic ultrasound alone can cause thermal damage in the liver after 60 s of exposure at 100% duty cycle. However, an equally sized lesion, approximately 100 mm^3 can be produced in 30 s at 100% duty cycle with nanoshell enhancement with the addition of mechanical damage (Table for time reduction and lesion volume data). Note within the ablated region, there is an area of mechanical damage and there is a zone of thermal ablation showing that the nanoshells enhance both processes because the ultrasound is strongly scattered by the nanoshells. HIFU causes thermal injury and coagulative necrosis, which can be macroscopically viewed by tissue discoloration. [27,28,32] For these rabbit studies, the mechanical damage is differentiated from the strictly thermal injury by the presence of a large cavity within the thermally damaged region. The high degree of thermal damage as shown by macroscopic tissue necrosis in these rabbit studies is also attributed to the continuous use of the HIFU, which increases the deposition of thermal energy relative to pulsed HIFU. In the pulsed HIFU experiments in mice and human tissue below, the degree of thermal injury was assessed with H&E stained histology.

Table – HIFU Application at 100% duty cycle on rabbits treated with and without nanoshells.

Time (s)	Nanoshell enhanced ablated volume (mm^3)	Standard deviation	Control ablated volume mm^3)	Standard deviation
2	1.3	1.9	0.0	0.0
5	12.5	10.9	0.0	0.0
10	24.0	17.0	0.0	0.0
20	27.7	13.8	0.7	1.5
30	107.1	74.9	17.2	10.7
60	171.3	128.5	94.9	47.1

Nanoshell-enhanced ablation can dramatically reduce the amount of time required for HIFU especially for HIFU, which contains a thermal component. When HIFU alone was focused on a rabbit liver using a continuous 800 KHz pure tone waveform with a peak negative pressure at 3 MPa at 100% duty cycle, no measurable response could be observed visually with <20 s exposure. However, after giving a rabbit a dose of particles at 0.5 mg/kg and allowing for a 15 min circulation time, a measurable response could be detected with as little as 2 s of HIFU exposure at 100% duty cycle. Table shows the average volumes of the affected areas in the rabbit livers at times where HIFU alone would have no effect. As shown in the Table, in only 2 s a response can be observed. The large standard deviations are attributed to a short circulation time resulting in an uneven distribution of particles. Alternatively, it is possible that the large standard deviations are due to regions, which have a selectively higher accumulation of particles, which when insonated result in a larger ablated area. These issues can be potentially overcome by changing the concentration of the delivered dose or increasing the circulation time. For the studies described in the following, the duty cycle was reduced to 2% to avoid thermal damage and to allow for more precise ultrasound imaging as thermal injury is not always readily visible under B-mode imaging. The lower duty

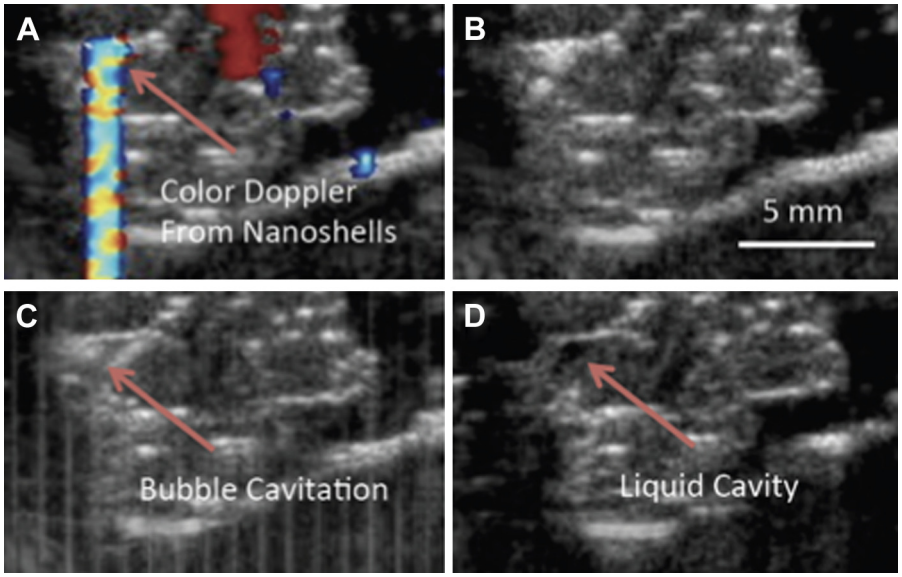

Fig. 2 – *Ex vivo* HIFU of excised mastectomy tissue. Fifty microliter at 4 mg/mL of PFP liquid filled 500 nm nanoshells were injected intratumorally *ex vivo*. (A) Color Doppler ultrasound displays the location of the nanoshells allowing for better targeting of the HIFU transducer. (B) B-mode image of tissue before HIFU. (C) HIFU was applied for 1 min at 1.1 MHz and 3.5 MPa with a 2% duty cycle. Bubble cavitation/formation is readily observed. (D) After HIFU a pocket (black spot) filled is created, which is filled with the liquefied tissue. (Color version of figure is available online.)

cycle is also expected to increase the relative enhancement with silica nanoshells while remaining innocuous to off target tissues. Furthermore, to potentially gain an increased effect from the pulsed HIFU, which is less energetic than continuous HIFU, the particles in the following experiments used PFP-liquid filled particles. The advantage of using the PFP-liquid filled particles is that when the liquid is converted to gas under HIFU, the volume occupied by the PFP increases substantially and generates multiple gas bubbles from a single liquid droplet, which can cavitate and cause mechanical damage. The increased number of bubbles from the conversion from liquid to gas also allows for very facile monitoring during ultrasound even in noncontrast specific imaging modalities.

To demonstrate that nanoshells could potentially be used for histotripsy HIFU therapy in humans, PFP liquid-filled 500 nm nanoshells were injected intratumorally into excised human mastectomy tissue and HIFU was performed at 2% duty cycle. It has been previously shown that 500 nm silica nanoshells remain sequestered to the injection site during intratumoral or intramuscular injections and do not extravasate. [6,7] It was hypothesized that due to the low functional

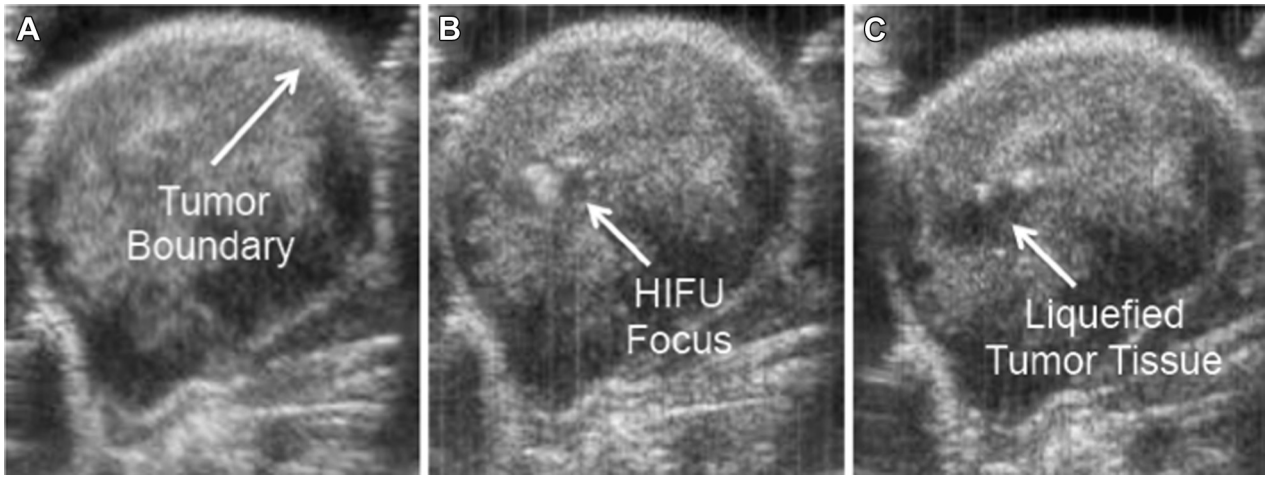

Fig. 3 – Nanoshell enhanced HIFU *in vivo* in Py8119 tumor bearing nude mice. Eight hundred microgram of 500 nm liquid PFP-filled nanoshells were administered IV. HIFU was applied 24 h after administration for 1 min at 3.5 MPa and 1.1 MHz with a 2% duty cycle. (A) Before HIFU (B) during HIFU, bubble movement/generation was noticed at the focal zone. (C) After HIFU. Blackened area at HIFU focus was liquefied tissue.

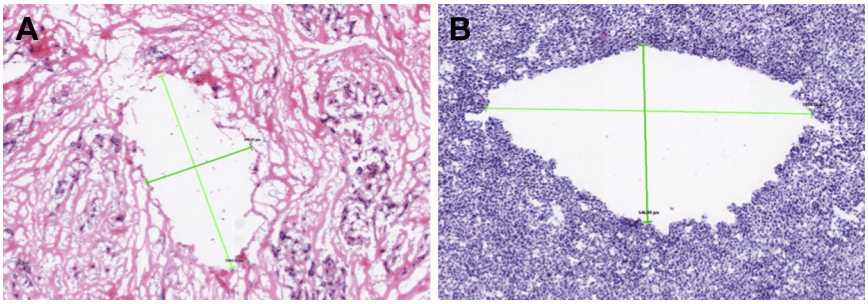

Fig. 4 – Histologic evaluation of tissues after nanoshell administration and insonation. (A) H&E stained image of human mastectomy tissue after HIFU at 4× magnification. Crosshairs measure a cavity found in the tissue at ~1600 × 800 μm. (B) H&E stained image of Py8119 tumor tissue after HIFU at 10× magnification. Crosshairs measure a cavity found in the tissue at ~1000 × 550 μm. (Color version of figure is available online.)

porosity of tissue (approximately 10 nm) that fluids and small molecules can easily diffuse from the injection site, but the nanoshells remain stationary. As shown in Figure 2A, the nanoshells are clearly visible under color Doppler ultrasound imaging. The long tail from the Doppler image seen in Figure 2A is due to shadowing from the high reflectivity of the particles. Once the HIFU is activated (Fig. 2C), the cavitation and bubble generation can be observed at the site where the color Doppler signal originated. Comparing the images before (Fig. 2B) and after HIFU was applied (Fig. 2D), a cavity is clearly formed within the tumor. This effect is seen in the change in color of the injection site between Figure 2B and D, as can be seen in it goes from white to black after insonation. This change in color is indicative of a change of local echogenicity, which was due to the formation of a liquid pocket. It is hypothesized that the relatively small volume that was ablated was due to the relatively small volume occupied by the directly injected nanoshells and the small focal zone of the transducer (cross-sectional area $\approx$1.44 mm^2). However, the small volume overlap between the focal zone of the HIFU and the volume occupied by the nanoshells allows for very precise ablation and may be advantageous in delicate therapies to avoid damaging sensitive or off target tissues.

It was previously demonstrated with 500 nm nanoshells that it is possible to detect Py8119 epithelial breast cancer tumors in nude mice by gamma scintigraphy. [6] Because nanoshells can accumulate in this tumor model, nanoshells were administered IV into the same Py8119 breast tumor bearing nude mice. PFP liquid-filled nanoshells were allowed to circulate and accumulate in the tumors for 24 h before HIFU administration. HIFU was applied for 1 min at 3.5 MPa and 1.1 MHz with a 2% duty cycle. As HIFU was applied, the nanoshells were fractured and the liquid PFP within the nanoshells underwent acoustic droplet vaporization (Fig. 3B) and began to cavitate. This cavitation liquefied the tissue within the focal zone (Fig. 3C) whereas tissues outside the focal zone remained unaffected. The affected region in Figure 3C is black, identical to the region in Figure 2D despite the different injection types. The average size of the bubble cloud generated in response to insonation was found to be 13.6 $\pm$ 6.1 mm^3 with the particles and no bubble cloud was observed without particles. Control mouse tumor insonation without particles can be seen in Supplemental Figure 1. Figure 3 demonstrates that PFP-filled 500 nm Fe-SiO_2 nanoshells can be used as HIFU sensitizing agents, specifically for enhancing mechanical cavitation and liquefaction of tissue *in vivo*. Previous results in an identical mouse xenograft model showed that only ~2.5% of the injected dose, approximately 20 μg of nanoshells, actually reach the tumors. [6] Despite the low concentration of nanoshells within the tumors, it was sufficient to generate a nanoshell dependent response when exposed to HIFU. This indicates that very few nanoshells are necessary to reduce the cavitation threshold and cause mechanical ablation.

In both the mouse model and human mastectomy tissue, nanoshell-enhanced ablation resulted in the generation of a physical cavity. It should be noted that during gross examination, when the tumor was cut along the ablated region, the dark area was liquefied. In both human breast tissue and mouse tumor tissue (Fig. 4), the application of high-intensity ultrasound in the presence of nanoshells results in mechanical destruction and liquefaction of tissue. Furthermore, due to the low duty cycle of the ultrasound, which results in a low time-averaged intensity, no coagulative necrosis or thermal damage is observed in the surrounding tissue in H&E histology. Previous histology reported from histotripsy showed that the region ablated was a homogenated field of cellular debris. [14,17,33] It is hypothesized that the difference in the present study is due to a difference in handling the tissue after insonation. Previous reports fixed the tissue in formalin solution, which may have preserved the ablated region for examination, whereas flash freezing the sample resulted in the ablated region being lost during the tissue sectioning process.

4. Conclusions

Liquid PFP-filled Fe-SiO_2 nanoshells reduce the time and intensity needed to achieve visibly measurable damage in tissues in both standard and purely mechanical HIFU. With an insonation at 800 KHz and 3 MPa in healthy rabbit livers, the nanoshells could reduce the time to visually observed damage from 20 s to 2 s, while simultaneously accentuating thermal and mechanical damage. On gross examination of tissues, the

mechanical damage resulted in a cavity filled with liquefied tissue. By reducing the duty cycle of the HIFU to 2% while employing nanoshells, the thermal damage was eliminated and only mechanical ablation occurred. After injecting *ex vivo* human breast tumor tissue with 50 μL of nanoshells, the mechanical ablation was limited to the volume overlap between the focal zone of the transducer and volume occupied by the nanoshells with precise spatial control of ablation. *In vivo* liquid PFP-filled nanoshells, IV injected into Py8119 breast tumor-bearing mice could be activated by HIFU at 1.1 MHz and 3.5 MPa to enhance mechanical ablation 24 h after administration. Under these conditions, a $13.6 \pm 6.1\ mm^3$ bubble cloud response could be measured with the IV injected particles and no bubble cloud was observed without particles. Examination of breast and mouse tissues revealed similarly sized cavities from mechanical ablation of tissue. With intravenous administration in the *in vivo* model, a larger zone could be ablated by continuously moving the HIFU transducer throughout insonation. The Fe-SiO_2 nanoshells have a much greater *in vivo* stability and tumor retention time and nearly infinite shelf life compared with other sensitizing agents. HIFU based therapies offer the promise for local control with low morbidity for treating solid tumors such as breast cancer.

Acknowledgment

This study has been funded by the Samsung Advanced Institute of Technology grant number 20125011 and by the 1R21CA151140-01A2 IMAT grant from the National Institutes of Health. This study used the Small Animal Imaging Resource supported by the *In vivo* Cancer and Molecular Imaging Center (ICMIC) P50-CA128346. A.L. is supported by an R25 CA153915 training grant and 1F31CA174276 - 01A1 awarded by the National Institutes of Health. Z.W. was supported by a Career Development Award through the ICMIC and UCSD Academic Senate Grant RK131H. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. L.G.E. was supported by NCI grant K22CA118182. The authors wish to thank Siemens Medical Solutions USA, Inc for providing the Sequoia US system as equipment loans to UCSD.

Authors' contribution: A.L. wrote the article. A.L., Z.W., A.C.K., and S.L.B. did the analysis and interpretation. Z.W., L.G.E., R.F.M., W.C.T., A.C.K., and S.L.B. contributed to the conception and design. C.V.B. and R.D.V. did the data collection. J.W., R.F.M., and W.C.T. did the critical revision of the article. A.C.K. and S.L.B. obtaining the funding.

Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in the article.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jss.2014.05.009.

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