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(54) TRANSCRECTAL ULTRASOUND PROBE FOR BOILING HISTOTRIPSY ABLATION OF PROSTATE, AND ASSOCIATED SYSTEMS AND METHODS

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(56) References Cited

U.S. PATENT DOCUMENTS
4,526,168 A 7/1985 Hassler A61B 8/0833

FOREIGN PATENT DOCUMENTS
CN 106267593 A 1/2017

OTHER PUBLICATIONS

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(57) ABSTRACT

Transrectal ultrasound probe for boiling histotripsy ablation of prostate are presented herein. In one embodiment, a method for a transrectal ultrasound treatment uses high intensity focused ultrasound (HIFU). The method includes: generating a boiling histotripsy (BH) therapy ultrasound by a therapy transducer in a frequency range of 1 MHz to 2.8 MHz and a surface intensity range of 10 W/cm2 to 80 W/cm2. The therapy transducer may be about 50 mm long and about 35 mm wide. The method also includes applying the therapy ultrasound by directing ultrasound pulses having ultrasound shock waves to a target tissue at a focal depth of 2.5 cm to 5.5 cm; generating at least one μm-scale vapor

(Continued)
bubble at a target region; growing the at least one vapor bubble to at least one mm-scale bubble; and mechanically disintegrating a surrounding tissue by interactions between mm-scale bubbles and the ultrasound shock waves within a pulse.

20 Claims, 11 Drawing Sheets

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(56) References Cited

U.S. PATENT DOCUMENTS

2015/0750015 A1 12/2015 Cain 600/439
2017/0001376 A1 1/2017 Parthenen 600/439

FOREIGN PATENT DOCUMENTS

KR 20180074235 A 7/2018
WO 2013/033975 A8 7/2013
WO 2017/190159 A1 11/2017

OTHER PUBLICATIONS


Daoudi, K., “In vivo photoacoustics and high frequency ultrasound imaging of mechanical high intensity focused ultrasound (HIFU) ablation,” Biomedical Optics Express, Mar. 2017, [https://doi.org/10.1364/BOE.8.002235] [retrieved Feb. 10, 2021], 10 pages.


Khokhlova, T., “In vivo tissue embalization using millisecond boiling induced by high intensity focused ultrasound,” The Journal of the Acoustical Society of America, Apr. 2011, [https://doi.org/10.1121/1.3588149] [retrieved Apr. 21, 2021], 2 pages. (Meeting abstract only—no PDF available).


(56) References Cited

OTHER PUBLICATIONS


* cited by examiner
FIG. 5A

FIG. 5B
FIG. 7A

1-20 MS HIFU pulse
pause 0.1-1 s
boiling

60-100 MPa
10-16 MPa

FIG. 7B

64
μm
mm

74
TRANSRECTAL ULTRASOUND PROBE FOR
BOILING HISTRIPTIONS ABLATION OF
PROSTATE, AND ASSOCIATED SYSTEMS
AND METHODS

CROSS-REFERENCE TO RELATED
APPLICATION

This application claims the benefit of U.S. Provisional
Application No. 62/846,267, filed May 10, 2019, the
disclosure of which is expressly incorporated herein by refer-
eence in its entirety.

STATEMENT OF GOVERNMENT LICENSE
RIGHTS

This invention was made with government support under
R21 CA219793, R01 EB023910, R01 GM122859, and R01
EB007643, awarded by the National Institutes of Health.
The government has certain rights to the invention.

BACKGROUND

Thermal ablation of prostate tissue with high intensity
focused ultrasound (HIFU) has recently received FDA
approval as a non-invasive treatment alternative to first-line
prostate cancer treatment options. However, conventional
clinical transrectal HIFU systems have certain limitations. In
particular, conventional transrectal HIFU systems may
cause collateral damage due to nearfield heating and heat
diffusion from the focus. For example, conventional HIFU
treatment of a region of prostate generates heat inside the
tissue, which then diffuses into other regions of the prostate
and the surrounding tissue, potentially causing thermal
damage to otherwise healthy tissue. The conventional sys-
tems also suffer from insufficient real-time ability to monitor
treatment efficacy. Accordingly, systems and methods are
needed for improved ablation and imaging of the prostate or
other target tissue.

SUMMARY

This summary is provided to introduce a selection of
concepts in a simplified form that are further described
below in the Detailed Description. This summary is not
intended to identify key features of the claimed subject
matter, nor is it intended to be used as an aid in determining
the scope of the claimed subject matter.

Briefly, the inventive technology uses boiling histoptripsy
(BH) to cause precise mechanical tissue ablation, thus
destroying a target tissue (e.g., cancer tissue). In operation,
a sequence of nonlinear ms-long pulses, each having mul-
tiple relatively high amplitude shock fronts, heat target
tissue up to boiling temperatures within a μm-scale volume
during each pulse and causes localized evaporation bubbles
at the focus. Thus-generated evaporation bubbles relatively
rapidly grow into a nm-scale vapor bubble and cool down.
The interaction between the remaining ultrasound shocks of
the pulse and the ensuing vapor bubble results in a precise
mechanical tissue ablation.

Furthermore, the bubbles generated by BH and the result-
ing hyperechogenicity of the sonicated tissue allow for
reliable real-time targeting and monitoring the treatment
with B-mode ultrasound. Moreover, the loss of structure of
mechanically ablated tissue results in hypoechogenicity of
the treated volume in B-mode images and allows for evalu-
ation of the treatment outcomes. Owing to the rapidity of
tissue ablation bioeffects (e.g., on milliseconds scale), low
repetition rate of the pulses, and the mechanical mode of
action, BH minimizes nearfield heating, heat-sink effects
and thermal spread which otherwise complicate conven-
tional HIFU treatments.

In some embodiments, a shaped ultrasound therapy trans-
ducer for BH is about 50 mm long and about 35 mm wide,
therefore being suitable for a transrectal use. In different
embodiments, the therapy transducer may have a focal
length of about 40 mm and an aperture of 35x50 mm. The
ultrasound therapy transducer may include a central opening
for an ultrasound imaging transducer. In some embodiments,
the opening is circular having a diameter in a range of 20
mm to 25 mm.

In some embodiments, the therapy ultrasound waves are
generated as bursts of waves that are separated by non-
overlapping periods of time. In some embodiments, the BH
pulses have 5 ms duration, 2 Hz pulse repetition frequency,
and 20 pulses/second. These pulses may be delivered to a
rectangular grid (6x6 mm with 2 mm spacing) within target
tissue using a 1.5 MHz transducer. The surface intensity
of the therapy transducer (defined as the power generated per
surface area of the transducer) may range from 10 W/cm² to
80 W/cm². Based on this level of the surface intensity, the
ultrasound shock waves may reach a shock amplitude of
about 100 MPa at a focus depth of 40 mm. Such shock
amplitude suffices to initiate BH (e.g., to initiate bubble
activity). In some embodiments, the therapy transducer
operates in a frequency range of 1 MHz to 2.8 MHz.

In one embodiment, a method for a transrectal ultrasound
treatment using high intensity focused ultrasound (HIFU)
includes: generating a boiling histoptripsy (BH) therapy ultra-
sound by a therapy transducer in a frequency range of 1
MHz to 2.8 MHz and a surface intensity range of 10 W/cm²
to 80 W/cm², where the therapy transducer is about 50 mm
long and about 35 mm wide; applying the therapy ultrasound
by directing ultrasound pulses having ultrasound shock
waves to a target tissue at a focal depth of 2.5 cm to 5.5 cm;
generating at least one μm-scale vapor bubble at a target
region; growing the at least one vapor bubble to at least one
mm-scale bubble; and mechanically disintegrating a sur-
mound tissue by interactions between the at least one
mm-scale bubble and the ultrasound shock waves within a
pulse.

In an embodiment, a focal region for the therapy ultra-
sound at the target tissue is 0.1 mm to 1 mm wide and 2 mm
to 10 mm long.

In another embodiment, a shock amplitude of the therapy
ultrasound at a focus depth of 40 mm is about 100 MPa. In
an embodiment, a power of the therapy ultrasound is about
200 Watt at the focus depth of 40 mm.

In one embodiment, the therapy transducer is a phased
array therapy transducer comprising a plurality of phased
array elements.

In an embodiment, the phased array elements are ring-like
structures of an annular array. In another embodiment, a
phased array therapy transducer comprises 8 phased array
elements. In an embodiment, the phased array elements are
tile-like structures of a mosaic array.

In one embodiment, the method also includes generating
an imaging ultrasound in a frequency range of 7 MHz to 15
MHz by an imaging transducer. In an embodiment, the
imaging transducer is placed within a circular hole in the
therapy transducer, and wherein a diameter of the hole in the
therapy transducer is in a range of 20 mm to 25 mm. In
another embodiment, the imaging transducer is configured
within a rectangular hole in the therapy transducer, and wherein the hole in the therapy transducer is about 13 mm wide and about 16 mm long.

In one embodiment, a transrectal high intensity focused ultrasound (HIFU) device, includes: a boiling histotripsy (BH) ultrasound probe having a generally rectangular therapy transducer configured to emit therapy ultrasound in an ultrasound frequency range of 1 MHz to 2.8 MHz at a surface acoustic intensity of in a range of 10 W/cm² to 80 W/cm², the therapy transducer being about 50 mm long and about 35 mm wide and having a centrally located opening, wherein the therapy transducer is configured to generate shock waves at a focal depth of 2.5 cm to 5.5 cm.

In an embodiment, a focal region of the therapy ultrasound at the target tissue is 0.1 mm to 2 mm wide and 2 mm to 10 mm long.

In another embodiment, the shock waves have an amplitude of the therapy ultrasound of about 100 MPa at a focus depth of 40 mm.

In one embodiment, a power of the therapy ultrasound is about 200 Watt at the focus depth of 40 mm.

In one embodiment, the device also includes: generating an imaging ultrasound in a frequency range of 7 MHz to 15 MHz by an imaging transducer.

In one embodiment, the device also includes an imaging transducer configured to generate an imaging ultrasound in a frequency range of 7 MHz to 15 MHz, where the imaging transducer is configured within a central opening in the therapy transducer, and where the dimensions of the opening are in a range of 15 mm to 25 mm.

In one embodiment, an imaging transducer is configured to generate an imaging ultrasound in a frequency range of 7 MHz to 15 MHz, where the imaging transducer is configured within a rectangular hole in the therapy transducer, and where the hole is about 13 mm wide and about 16 mm long.

In one embodiment, the therapy transducer is a phased array therapy transducer comprising a plurality of phased array elements, and the phased array elements are ring-like structures of an annular array.

In one embodiment, the therapy transducer is a phased array therapy transducer comprising a plurality of phased array elements, and the phased array elements are tile-like structures of a mosaic array.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages of this inventive technology will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, wherein:

FIG. 1 is a schematic diagram of a system for transrectal ultrasound boiling histotripsy ablation in accordance with an embodiment of the present technology;

FIG. 2 is a front view of an ultrasound probe in accordance with an embodiment of the present technology;

FIG. 3 is a diagram of an ultrasound field generated by a HIFU transrectal transducer for treating prostate tissue in accordance with an embodiment of the present technology;

FIGS. 4A-4D are different views of a HIFU transrectal therapy transducer in accordance with an embodiment of the present technology;

FIGS. 5A-5D are different views of phased array HIFU transrectal therapy transducers in accordance with embodiments of the present technology;

FIGS. 6A and 6B illustrate ultrasound wave propagation according to prior art and present technology, respectively.
boiling histotripsy conditions, the focal area for the shock amplitude of the pulse is about 2.5 mm by 0.1 mm.

FIGS. 4A-4D are different views of a HIFU transrectal therapy transducer in accordance with an embodiment of the present technology. Illustrated therapy transducer 12 may operate at a frequency range of 1-3 MHz, 1.5-2.8 MHz, 1-2.8 MHz, 2-2.8 MHz, or similar. In some embodiments, the therapy transducer 12 generates ultrasound shocks of about 60-140 MPa in a target tissue located at a focal region about 35-55 mm away from the transducer. In different embodiments, a surface intensity of the therapy transducer (defined as the power generated per unit surface area of the transducer) may range from 10 W/cm² to 80 W/cm² or from 10 W/cm² to 40 W/cm². In some embodiments, the therapy transducer includes a central opening having a diameter of up to 25 mm. Such central opening may be suitable for an imaging transducer.

FIGS. 5A-5D are different views of phased array HIFU transrectal therapy transducers in accordance with embodiments of the present technology. In each case, the therapy transducer 12 has a generally rectangular shape with 50 mm length (L₁) and 55 mm width (L₂). A radius of curvature (i.e., the focal length) of the therapy transducer is 40 mm. In other embodiments, other curvatures are possible. In some embodiments, the therapy transducers may have curved edges with about 10 mm radius.

FIG. 5A illustrates a phased array therapy transducer 12 having eight ring-like elements 12-1 (also referred to as sections or rings) of equal area. The total area of the illustrated therapy transducer 12 is 1353 mm². In other embodiments, different numbers of elements may be used, and the elements may have different areas. For the phased annular array therapy transducer, the focus can be electronically steered along the axis. In some embodiments, the phased array therapy transducer 12 may be controlled to provide a range of steering such that the focal area stays within a region limited by at most 80% decrease of the focal intensity. In different embodiments, other restrictions to steering angle or depth may be implemented. The illustrated therapy transducer has a central opening with a 15-25 mm diameter (D).

FIG. 5B illustrates a phased array therapy transducer 12 having 128 mosaic- or tile-like elements 12-1 of equal area. In operation, elements 12-1 may be controlled individually or in predetermined groups.

The therapy transducers illustrated in FIGS. 5C and 5D generally correspond to those of FIGS. 5A and 5D except for the rectangular openings for the imaging transducer. In some embodiments, these openings may be 16 mm wide (D₁) and 13 mm high (D₂), leaving a total area of the therapy transducer at 1648 mm².

FIGS. 6A and 6B illustrate ultrasound wave propagation according to prior art and present technology, respectively. Both FIGS. 6A and 6B illustrate ultrasound waves generated by therapy transducers 12. The ultrasound waves target tissue 62 (e.g., tumor, blood vessel).

FIG. 6A illustrates the conventional technology that uses smooth waves having generally same peaks of the positive pressure and negative pressure (P⁺ and P⁻). The conventional technology has certain shortcomings. For example, the smooth ultrasound waves slowly heat tissue and, when applied over a period of time, the heat diffuses to tissues that surrounds the target tissue at the focus. In many applications, such heating must be minimized or controlled by, for example, by limiting the exposure time or energy of the therapy ultrasound. In general, with conventional smooth wave technology a heat generated by the ultrasound scales with square of pressure peaks of the ultrasound (P²).

FIG. 6B illustrates an embodiment of the inventive technology. With the inventive technology, the emitted smooth therapy ultrasound waves develop into nonlinear shock waves as they propagate through the tissue. These nonlinear shock waves are characterized by their positive pressure (P⁺) being significantly higher than the negative pressure (P⁻). Furthermore, ultrasound shock waves heat the target tissue relatively fast, since the heat generation scales with the ultrasound shock wave amplitude to third power (A³). As a result, a boiling temperature may be reached relatively fast, for example within several milliseconds, thus limiting the undesired heating of the surrounding tissue. The vapor bubble initiated by the localized µm-scale boiling relatively quickly grows into larger vapor cavity and cools down while expanding from the hot focus. In some embodiments, relatively small vapor bubble having µm-scale may grow into mm-scale bubble within milliseconds. The remaining shock wavefronts within the same pulse keep interacting with these bubbles. As explained above, interaction of upcoming shocks with large scale bubble mechanically destroy (ablate) target tissue.

FIG. 7A is a graph of HIFU pressure pulses in accordance with an embodiment of the present technology. In some embodiments, the pulses of HIFU may extend over 1-20 ms, followed by a pause of 0.1-2 second. As explained above, the ultrasound shock waves within a given pulse may cause localized boiling in the target tissue, therefore generating vapor bubbles at the focal area. Next, these vapor bubbles may rapidly grow into significantly larger vapor bubble during the same pulse of the HIFU operation. These bubbles interact with remaining shock wavefronts within the same pulse. An example of such rapid growth in the bubble size is illustrated in FIG. 7B, which shows an initially generated vapor bubble 64 at µm-scale growing into a mm-scale gas bubble 74.

FIG. 8 is a graph of one cycle of HIFU focal waveforms in accordance with an embodiment of the present technology. The horizontal axis represents time elapsed, and the vertical axis represents pressure at the target area. FIG. 8 shows modeled focal waveforms in tissue produced by the HIFU probe 100. As explained above, the HIFU system 100 can generate ultrasound shock wavefronts in the focal region of the therapy transducer. In some embodiments, the pressure amplitudes of shock wavefronts (A) may range from about 60 MPa to about 140 MPa. In general, the pressure amplitudes of the shock wavefronts scale up with higher surface intensity and longer length of the therapy transducer. For example, for a focal length of 40 mm, probe length of 40 mm and surface intensity of 14 W/cm², the pressure amplitude A₁ is about 95 MPa. For a higher value of the probe length of 50 mm and the same surface intensity of 14 W/m², the pressure amplitude A₂ is about 140 MPa, at least in part because for transducers with larger focusing angle, the focal lobe is shorter, the ultrasound shock waves have a shorter distance to develop thus requiring higher pressures. Other values of illustrated parameters are also possible in different embodiments.

FIG. 9A is a graph of one cycle of HIFU focal waveforms in accordance with an embodiment of the present technology. The horizontal axis represents time elapsed, and the vertical axis represents pressure at the target area. The graph shows modeled pressure results in water for a therapy probe having 50 mm length and 35 mm width, at the focal length of 40 mm. Different curves in the graph represent surface intensity of the modeled probe in a range of 0.08 W/cm² to
14.26 W/cm². The resultant ultrasound pressures at the focus scale up with the increased surface intensity. Furthermore, for the modeled probe, the shock waves develop only after a certain threshold value of the surface intensity is reached, which in this case is about 10 W/cm². In other embodiments, other values of the parameters may apply.

FIG. 9B is a graph of HIFU peak positive and peak negative pressures of the focal waveform in accordance with an embodiment of the present technology. The horizontal axis represents surface intensity of the therapy probe, and the vertical axis represents peak pressures at the target area. The graph shows modeled pressure results for a therapy probe having 50 mm length and the focal length of 40 mm. Two therapy probes are modeled: one having a width of 30 mm (solid symbols) and another having a width of 35 mm (open symbols). Based on the simulation results, the positive peak pressure (P⁺) and the resultant ultrasound shock amplitude increases with increased probe width.

Many embodiments of the technology described above may take the form of computer- or controller-executable instructions, including routines executed by a programmable computer or controller. Those skilled in the relevant art will appreciate that the technology can be practiced on computer/controller systems other than those shown and described above. The technology can be embodied in a special-purpose computer, controller or data processor that is specifically programmed, configured or constructed to perform one or more of the computer-executable instructions described above. Accordingly, the terms “computer” and “controller” as generally used herein refer to any data processor and can include Internet appliances and hand-held devices (including palm-top computers, wearable computers, cellular or mobile phones, multi-processor systems, processor-based or programmable consumer electronics, network computers, mini computers and the like). From the foregoing, it will be appreciated that specific embodiments of the technology have been described herein for purposes of illustration, but that various modifications may be made without deviating from the disclosure. For example, in some embodiments the counter or controller may be based on a low-power buck regulator connected to a capacitor. Moreover, while various advantages and features associated with certain embodiments have been described above, it is recognized that some embodiments, other embodiments may also exhibit such advantages and/or features, and not all embodiments need necessarily exhibit such advantages and/or features that fall within the scope of the technology. Accordingly, the disclosure can encompass other embodiments not expressly shown or described herein.

The present application may also reference quantities and numbers. Unless specifically stated, such quantities and numbers are not to be considered restrictive, but exemplary of the possible quantities or numbers associated with the present application. Also, in this regard, the present application may use the term “plurality” to reference a quantity or number. In this regard, the term “plurality” is meant to be any number that is more than one, for example, two, three, four, five, etc. The terms “about,” “approximately,” etc., mean plus or minus 5% of the stated value.

The principles, representative embodiments, and modes of operation of the present disclosure have been described in the foregoing description. However, aspects of the present disclosure, which are intended to be protected, are not to be construed as limited to the particular embodiments disclosed. Further, the embodiments described herein are to be regarded as illustrative rather than restrictive. It will be appreciated that variations and changes may be made by others, and equivalents employed, without departing from the spirit of the present disclosure. Accordingly, it is expressly intended that all such variations, changes, and equivalents fall within the spirit and scope of the present disclosure as claimed.

What is claimed is:

1. A method for a transrectal ultrasound treatment using high intensity focused ultrasound (HIFU), the method comprising:
   generating boiling histotripsy (BH) therapy ultrasound by a therapy transducer operating in a frequency range of 1 MHz to 2.8 MHz and having a surface intensity of the therapy transducer in a range of 10 W/cm² to 80 W/cm², wherein the therapy transducer is about 50 mm long and about 35 mm wide;
   applying the therapy ultrasound by directing a plurality of ultrasound pulses having ultrasound shock waves to a target tissue at a focal depth of 2.5 cm to 5.5 cm;
   generating at least one mm-scale vapor bubble at the target tissue;
   growing the at least one vapor bubble to at least one mm-scale bubble;
   mechanically disintegrating the target tissue by interactions between the at least one mm-scale bubble and the ultrasound shock waves, wherein the interactions take place within a duration of individual ultrasound pulses of the plurality of ultrasound pulses, without thermally damaging a surrounding tissue.

2. The method of claim 1, wherein a focal region for the therapy ultrasound at the target tissue is 0.1 mm to 1 mm wide and 2 mm to 10 mm long.

3. The method of claim 1, wherein a shock amplitude of the therapy ultrasound at a focus depth of 40 mm is about 100 MPa.

4. The method of claim 3, wherein a power of the therapy ultrasound is about 200 Watts at the focus depth of 40 mm.

5. The method of claim 1, wherein the therapy transducer is a phased array therapy transducer comprising a plurality of phased array elements.

6. The method of claim 5, wherein the phased array elements are ring structures of an annular array.

7. The method of claim 6, wherein the phased array therapy transducer comprises 8 phased array elements.

8. The method of claim 5, wherein the phased array elements are tile structures of a mosaic array.

9. The method of claim 1, further comprising:
   generating imaging ultrasound in a frequency range of 7 MHz to 15 MHz by an imaging transducer.

10. The method of claim 9, wherein the imaging transducer is placed within a circular hole in the therapy transducer, and wherein a diameter of the hole in the therapy transducer is in a range of 20 mm to 25 mm.

11. The method of claim 9, wherein the imaging transducer is configured within a rectangular hole in the therapy transducer, and wherein the hole in the therapy transducer is about 13 mm wide and about 16 mm long.

12. A transrectal high intensity focused ultrasound (HIFU) device, comprising:
   a boiling histotripsy (BH) ultrasound probe having a generally rectangular therapy transducer configured to emit therapy ultrasound in an ultrasound frequency range of 1 MHz to 2.8 MHz at a surface acoustic intensity of the ultrasound probe in a range of 10 W/cm² to 80 W/cm², the therapy transducer being about 50 mm long and about 35 mm wide and having a centrally located opening, wherein the therapy transducer is configured to generate shock waves at a focal
depth of 2.5 cm to 5.5 cm, and wherein the therapy transducer is configured for mechanically disintegrating a target tissue by interactions between at least one mm-scale bubble and the shock waves, wherein the interactions take place within a duration of a pulse, without thermally damaging a surrounding tissue.

13. The device of claim 12, wherein a focal region of the therapy ultrasound at the target tissue is 0.1 mm to 2 mm wide and 2 mm to 10 mm long.

14. The device of claim 12, wherein the shock waves have an amplitude of the therapy ultrasound of about 100 MPa at a focus depth of 40 mm.

15. The device of claim 12, wherein a power of the therapy ultrasound is about 200 Watts at a focus depth of 40 mm.

16. The device of claim 12, further comprising: an imaging transducer configured for generating an imaging ultrasound in a frequency range of 7 MHz to 15 MHz.

17. The device of claim 12, further comprising an imaging transducer configured to generate imaging ultrasound in a frequency range of 7 MHz to 15 MHz, wherein the imaging transducer is configured within a central opening in the therapy transducer, and wherein a diameter of the hole in the therapy transducer is in a range of 20 mm to 25 mm.

18. The device of claim 12, further comprising an imaging transducer configured to generate imaging ultrasound in a frequency range of 7 MHz to 15 MHz, wherein the imaging transducer is configured within a rectangular hole in the therapy transducer, and wherein the hole is about 13 mm wide and about 16 mm long.

19. The device of claim 12, wherein the therapy transducer is a phased array therapy transducer comprising a plurality of phased array elements, and wherein the phased array elements are ring structures of an annular array.

20. The device of claim 12, wherein the therapy transducer is a phased array therapy transducer comprising a plurality of phased array elements, and wherein the phased array elements are tile structures of a mosaic array.