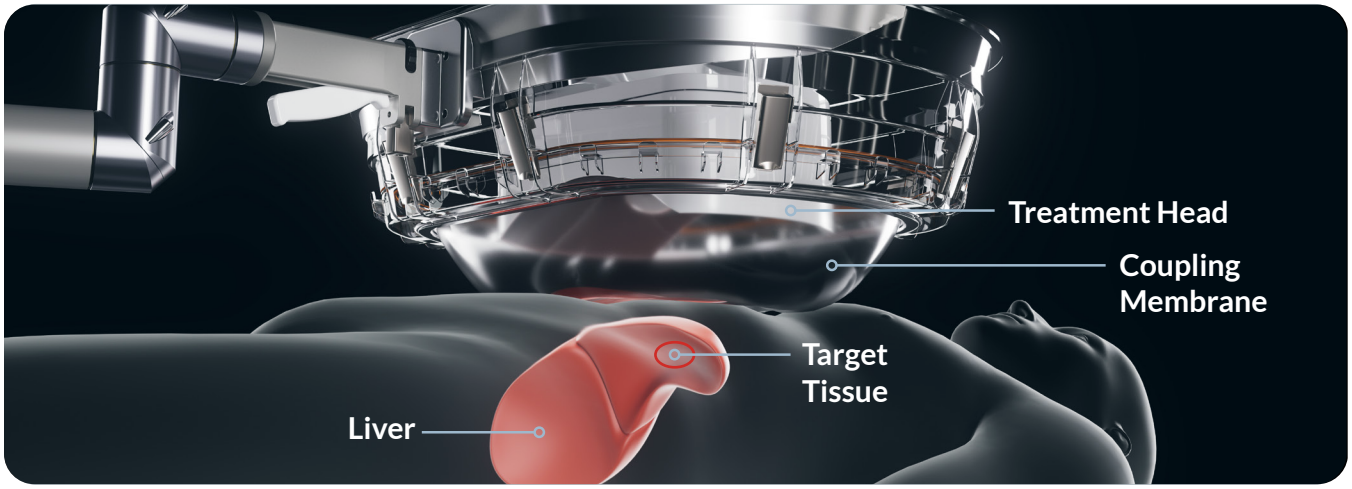
PATIENT EDUCATION

Histotripsy Procedure in Liver

WHAT IS HISTOTRIPSY?

Histotripsy uses high-intensity sound waves to destroy unwanted tumors in the liver. This procedure is non-invasive, which means it does not require incisions, needles, or anything to be inserted through the skin to treat the targeted liver tumors. A treatment head (the source that sends out the sound waves) is placed inside a soft, flexible membrane containing specially treated water that sits on your abdomen and is directed at the unwanted liver tumors. Your doctor will use diagnostic ultrasound to see and target the liver tumor they want to destroy, the sound wave energy is then turned on and focused to a singular point, creating a "bubble cloud", which destroys only the tissue your doctor has chosen.



HOW IS THE PROCEDURE PERFORMED?

- The histotripsy procedure may be performed under general anesthesia.
- Your doctor may require you to follow some dietary restrictions before the planned histotripsy procedure.
- During a histotripsy treatment, a soft, flexible membrane is positioned over the area where your liver is and filled with degassed water. The water helps the sound waves from the device pass to the target treatment area. There are no cuts made, needles used, or ionizing radiation involved in the procedure.
- Ultrasound imaging, which is like what is used to see a baby in the womb, and possibly previously taken MRI/CT scans, are used to locate the tumor and determine the size of the area that needs to be treated.
- During the procedure, the histotripsy therapy is delivered while your doctor monitors the treatment area real-time using diagnostic ultrasound.
- The procedure time will vary depending on patient specific variables and the number of histotripsy treatments delivered.

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Additional information about the science, treatment, and educational videos can be found at **HistoSonics.com.**

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WHAT HAPPENS AFTER THE PROCEDURE?

- You may feel some pain after treatment depending on the area treated, but there are no incision wounds and many times patients can return to normal activities quickly.
- Whether or not you need to stay overnight in the hospital after the procedure depends on several factors, including whether you are experiencing any pain and how you feel overall. The doctor will decide based on your individual situation. The doctor will determine when you return for follow-up.

ARE THERE CLINICAL STUDIES SHOWING ITS EFFECTIVENESS IN THE LIVER?

Doctors and researchers have researched and studied histotripsy for over 20 years, including in clinical trials. In a clinical trial conducted in 2019, it was used successfully in humans to destroy liver tumors[1].

The **#HOPE4LIVER** trials also demonstrated successful use of histotripsy in patients with primary and metastatic tumors in the liver in the US and EU[2,3].

1. THERESA Trial, 2019. https://clinicaltrials.gov/ct2/show/NCT03741088
2. #HOPE4LIVER US https://clinicaltrials.gov/ct2/show/NCT04572633
3. #HOPE4LIVER https://clinicaltrials.gov/ct2/show/NCT04573881

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Meet **Edison®**

System overview and technical specifications

Edison treatment head with bubble cloud (enlarged).

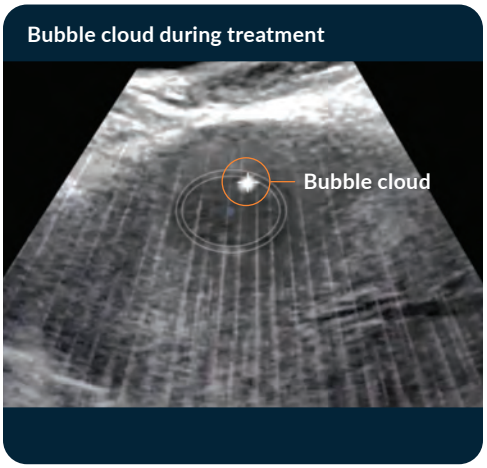
Histotripsy
Mechanism of Action

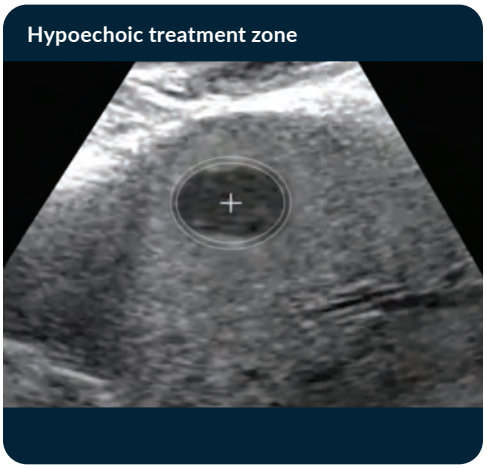
Histotripsy is a novel form of focused ultrasound that uses high amplitude, very short pulses designed to mechanically destroy and liquefy targeted tissue.

Specifically, as the focused ultrasound energy converges at a known focal point, high pressure causes extremely small, naturally occurring gas bubbles to expand many times larger through a phenomenon called acoustic cavitation.

During planning, the physician also establishes the minimum threshold voltage required to sustain the bubble cloud in the targeted tissue — this leverages histotripsy's "threshold effect" that removes targeted liver tumors, while tending to preserve collagenous vessels and ducts.[1]

The histotripsy mechanism of action is non-thermal, non-ionizing and is designed to destroy only the targeted tissue in the planned treatment volume.





In-vivo histotripsy treatment porcine liver

- **The bubble cloud generally has a bright, visible echogenic appearance as seen with the Edison real-time ultrasound imaging.**
- **The Edison System automated treatment arm dynamically and precisely moves the treatment head and bubble cloud throughout the targeted treatment volume under the watchful eye of the treating clinician.**

Edison Design Overview and Key Components

A User interface control panel

B Automated treatment arm

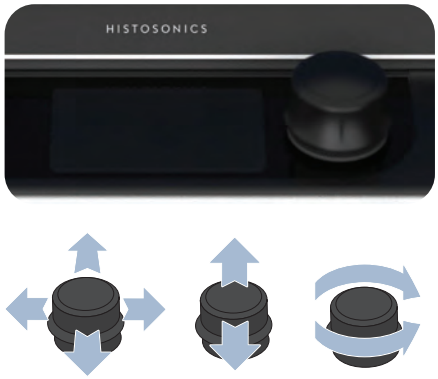
C Treatment head

Treatment Head Overview

The Edison System treatment head houses a concave therapy transducer which generates a localized bubble cloud at a known focal point to destroy targeted tissues and cells.

An integrated ultrasound imaging probe with encoded rotation and translation allows continuous visualization for localizing, planning and monitoring treatment.

Freedrive handle buttons for load-assisted gross positioning.

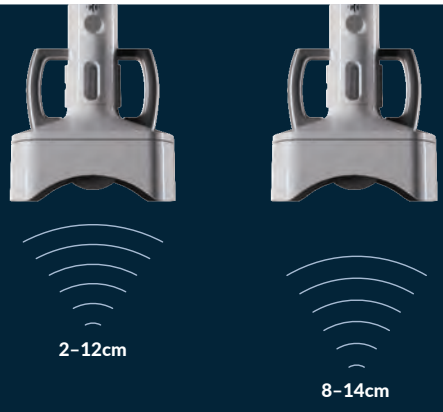


Space mouse moves the treatment head in six degrees of freedom (x, y, z, pitch, roll and yaw) at the desired speed and allows precise, fine tune positioning of the treatment head.

OPTIONS

Treatment heads are designed and optimized for a specific treatment depth range.

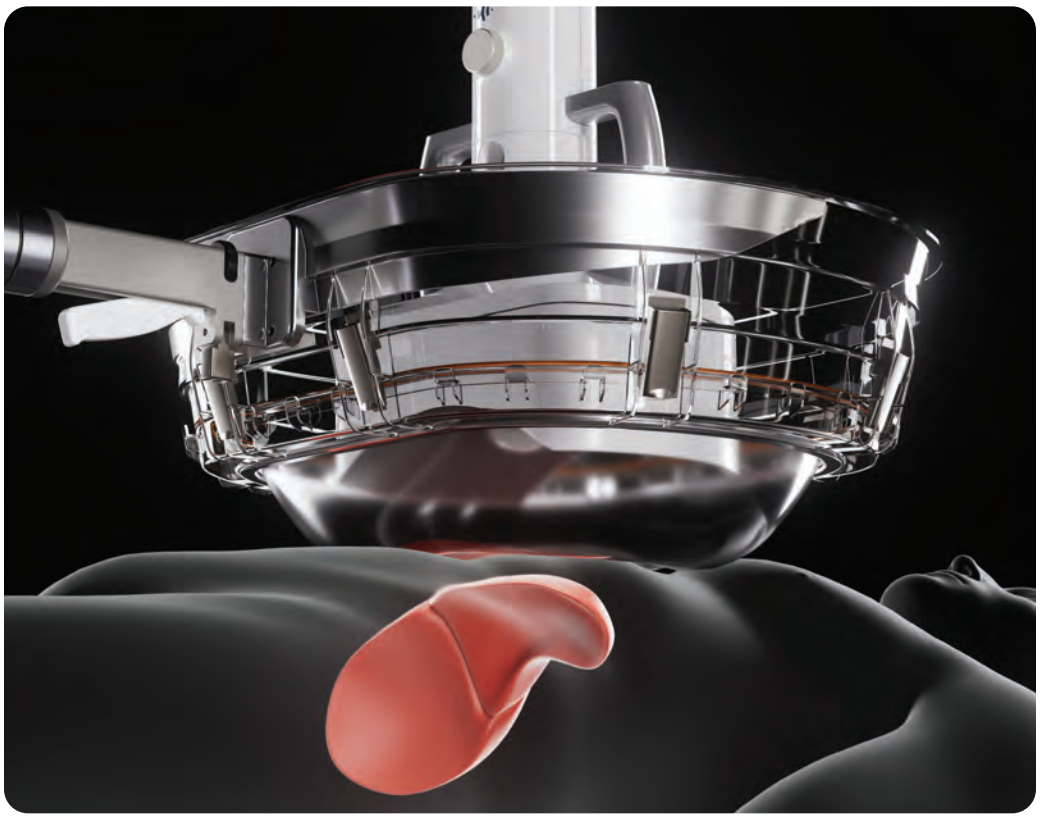
Treatment heads are designed for quick and easy exchange.



Histotripsy Coupling Kit Overview

FEATURES

- Proprietary single-use design for easy setup and disposal.
- Ergonomic, easy fill and drain method to quickly couple the therapy transducer to the patient.
- Flexible membrane conforms to the patient's anatomy and allows uninterrupted ultrasound delivery.

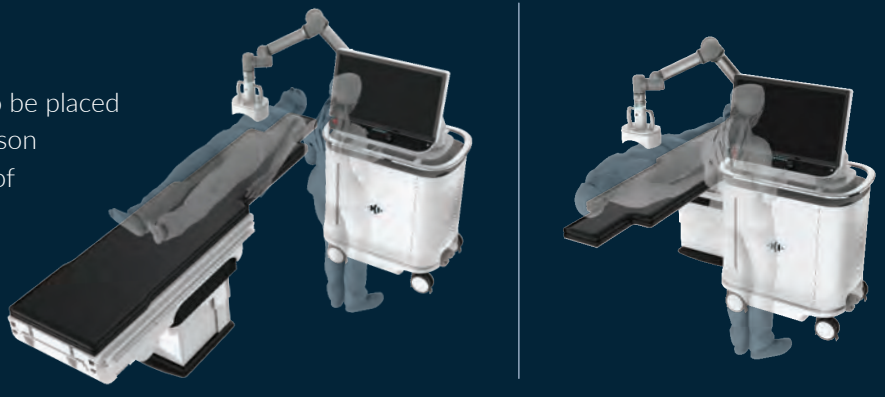


The Edison System patient membrane holds the ultrasound medium and contours to the patient, acoustically coupling the treatment head to the patient.

Flexible membrane

SETUP

With its small footprint and ability to be placed on either side of the patient, the Edison System is compatible with a variety of rooms and room configurations.



Workflow Overview

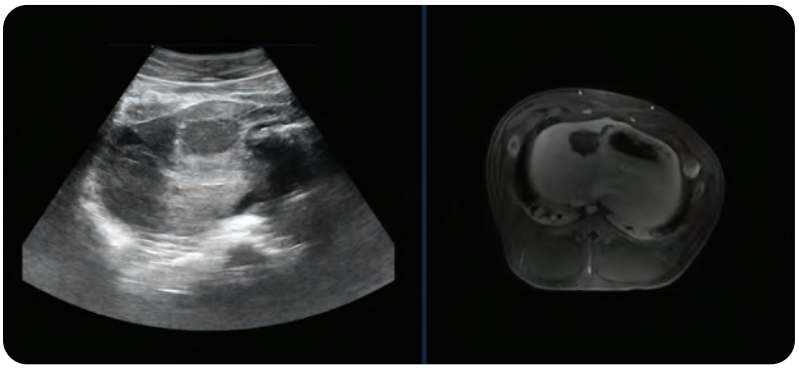
FOCUS

Designed around the three phases of the histotripsy procedure (Localize, Plan, Treat), the Edison System user interface provides step-by-step instructions and seamless workflow so that physicians can focus on the task at hand.

1 LOCALIZE

View MRI or CT imaging alongside real-time diagnostic ultrasound with 2D and 3D views.

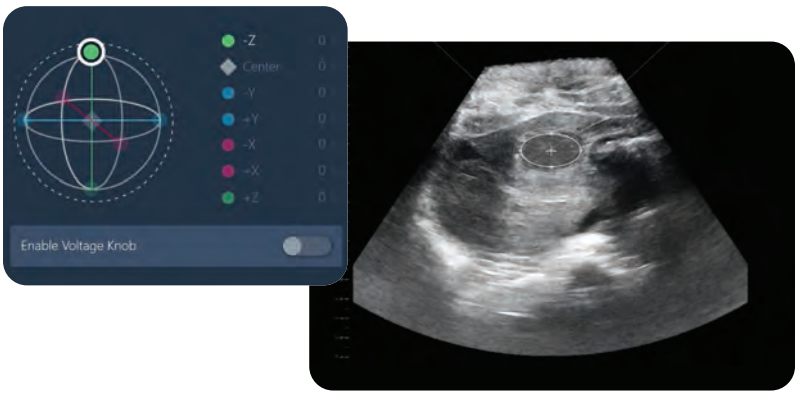
- Evaluate both the target and other critical anatomy in the area of interest.
- Multi-planar viewing with the rotating and translating diagnostic ultrasound supports full volumetric targeting.



2 PLAN

Adjust the size, shape and location of the planned treatment volume with target and margin contours. Visual representation of the plan contours are overlaid onto real-time diagnostic ultrasound.

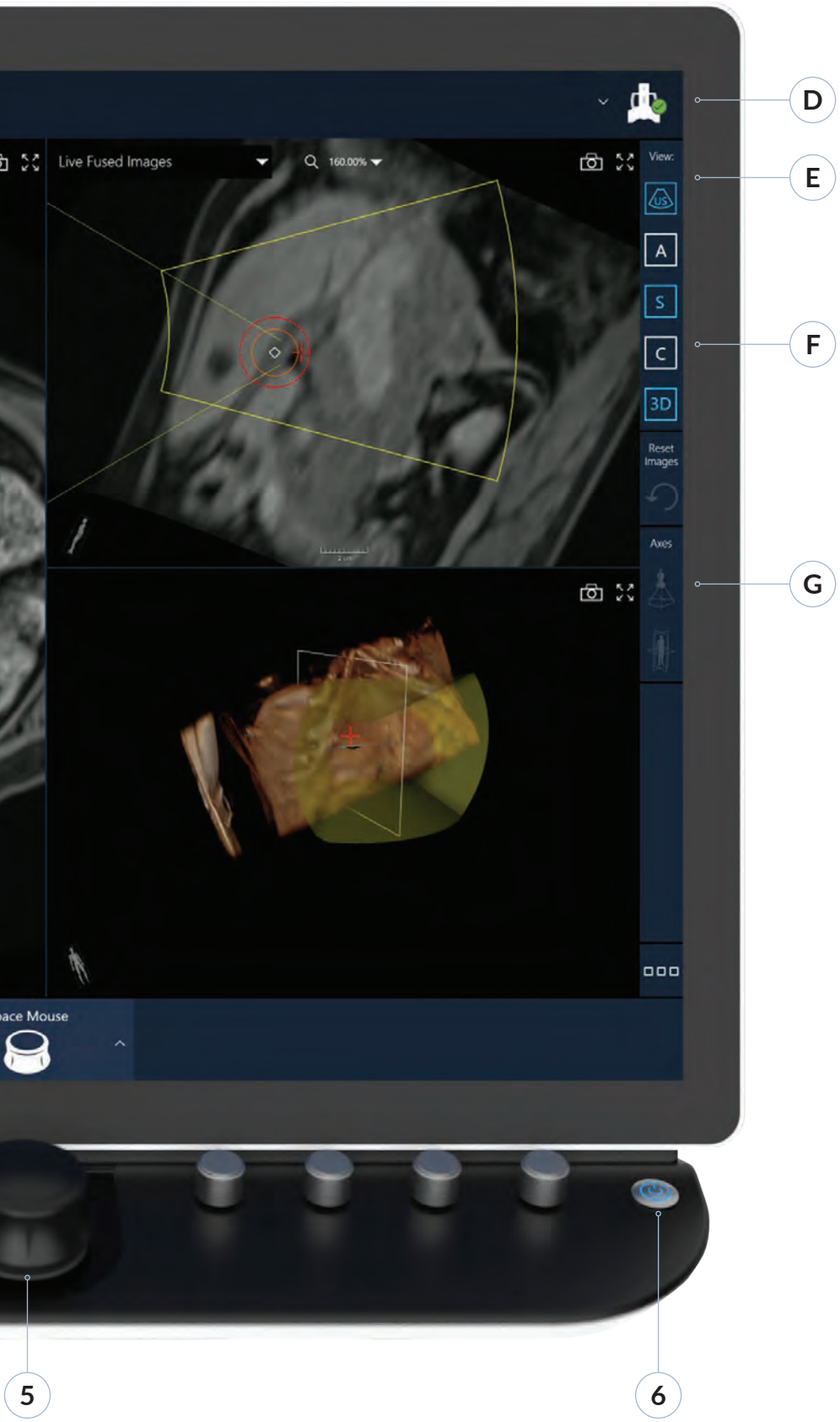
Edison's workflow allows the clinician to determine the precise amount of energy required to destroy the target. These measurements are performed inside each target at 7 discrete points and are used to determine the treatment parameters.



3 TREAT

During fully automated treatment, Edison dynamically and continuously moves the treatment head through the optimized pattern of the planned treatment volume and provides continuous real-time monitoring of imaging and treatment status.

User Interface Overview



SOFTWARE ELEMENTS

A Procedure phase (Localize, Plan, Treat)

B Current task and instructions

C Planning controls

D Treatment head identifier/status

E Image plane customization

F DICOM View (Axial, Sagittal, Coronal)

G Axis perspective controls

PHYSICAL CONTROLS

1 E-stop (emergency stop button)

2 Planning knobs (X, Y, Z)

3 Voltage adjustment

4 Trackpad

5 Space mouse

6 Power button

Specifications

THE EDISON SYSTEM

Features

- 32 inch touchscreen display with 16:9 aspect ratio, 3840 x 2160 pixels (4K), scratch-resistant AR glass, super wide 179 degree viewing angle (horizontal and vertical) and aluminum chassis
- Fully-adjustable display arm
- Detachable treatment head with integrated GE LOGIQ™* E10s imaging probe
- Automated treatment arm
- Physical control knobs for setting planning parameters
- Physical control knobs for controlling imaging probe translation/rotation
- E-stop button
- Track pad
- 3D space mouse and freedrive treatment arm control
- Uninterruptible power supply
- Full-surround aluminum handrail
- Swivel lock/full lock castors

Dimensions (Transport)

- Height: 166cm (65.5 inches)
- Width: 100cm (39 inches)
- Depth: 64.6cm (25 inches)

Weight

- 264kg/582lbs

Electrical

- 120 V (US)/240 V (Europe)

GE LOGIQ™* E10s

Features

- 22 inch high-resolution anti-glare OLED display
- 12.1 inch, high resolution, color touchscreen display
- Fully-adjustable monitor arm
- Next-generation cSound™* architecture
- High frequency imaging
- GE LOGIQ™* E10s imaging probe
- Ergonomic floating keyboard

Dimensions (Transport)

- Height: 130cm (51 inches)
- Width: 58.5cm (23 inches)
- Depth: 90cm (35.5 inches)

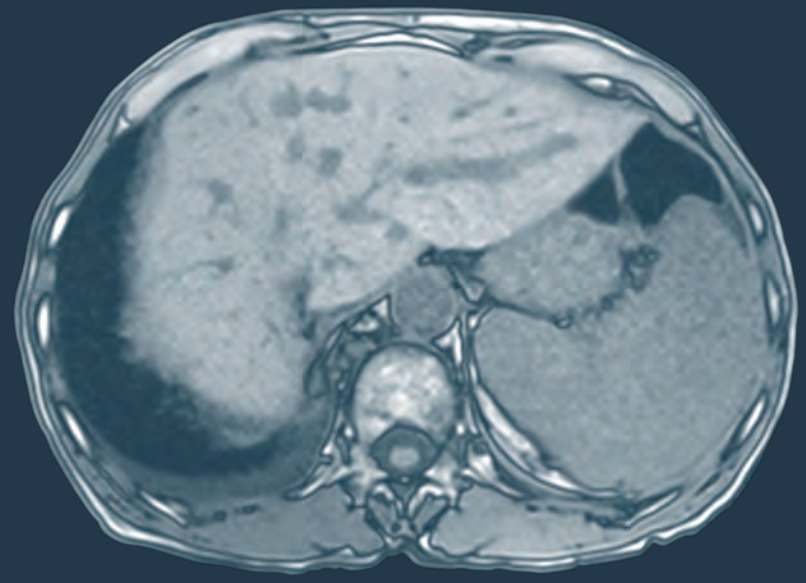
Weight

- 115kg (254 lbs)

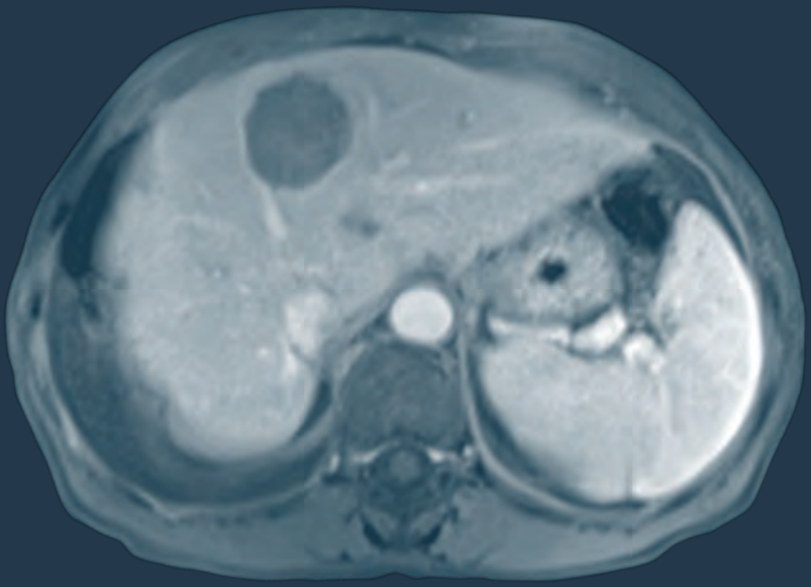
Electrical

- 120 V (US)/240 V (Europe)

Making the impossible, **possible.**



BEFORE



AFTER

MRI series from a single patient in the THERESA Trial.
Vidal-Jove J, et al. Int J Hyperthermia. 2022;39(1):1115-1123.

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician. The Edison System is intended for the non-invasive mechanical destruction of liver tumors, including the partial or complete destruction of unresectable liver tumors via histotripsy. The FDA has not evaluated the Edison System for the treatment of any disease including, but not limited to, cancer or evaluated any specific cancer outcomes (such as local tumor progression, 5-year survival or overall survival). The System should only be used by persons who have completed training performed by HistoSonics, and its use guided by the clinical judgment of an appropriately trained physician. Refer to the device Instructions for Use for a complete list of warnings, precautions and a summary of clinical trial results, including reported adverse events.

1. Vlaisavljevich et al. Phys. Med. Biol. 2014;59(2): 253-70

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FOCUS ON HISTOTRIPSY

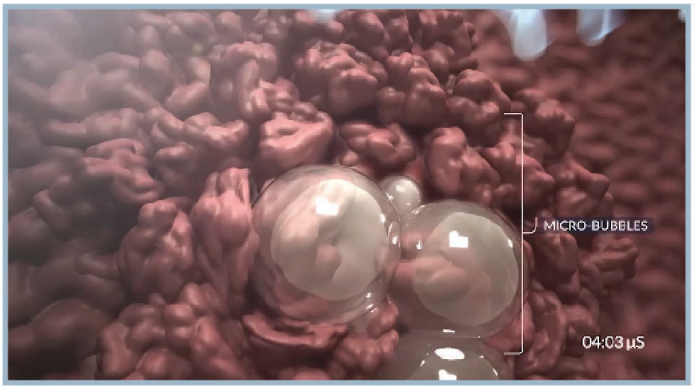
Bubbles have never been so powerful

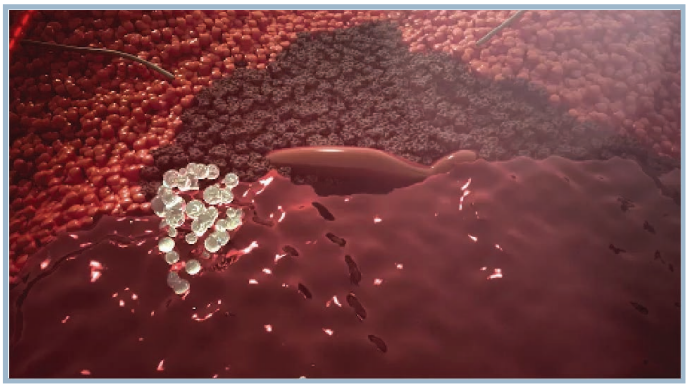
THE SCIENCE

Histotripsy is a novel form of focused ultrasound that uses high amplitude, very short pulses designed to mechanically liquefy and destroy targeted tissue.

Specifically, as the focused ultrasound energy converges at a known focal point, high pressure causes extremely small, naturally occurring gas bubbles to expand many times larger through a phenomenon called acoustic cavitation.

As the ultrasound waves converge on the targeted tissue, the rapid expansion and collapse of the micro-bubbles forms a "bubble cloud" which imparts mechanical forces on the cells, resulting in instantaneous cell destruction and leaving behind an acellular lysate.





Histotripsy's unique mechanism of action destroys targeted tissue only within the bubble cloud, which enables highly precise treatments while avoiding damage to non-targeted tissue. Histotripsy is performed non-invasively, and it does not use ionizing radiation or heat to destroy targeted tissue.

HARNESSING THE POWER

Using the Edison® System, the physician views real-time diagnostic ultrasound to localize the targeted tissue and to plan the treatment volume (including any margin the physician determines appropriate). During planning, the physician also establishes the minimum threshold voltage required to sustain the bubble cloud in the targeted tissue – this leverages histotripsy's "threshold effect" that removes targeted liver tumors while tending to preserve collagenous vessels and ducts.[1]

During treatment, the physician monitors treatment via real-time diagnostic ultrasound as the precision treatment arm continuously moves the bubble cloud automatically to encompass the entire planned treatment volume. The destructive effects of histotripsy is confined to the tissue within the planned treatment volume.

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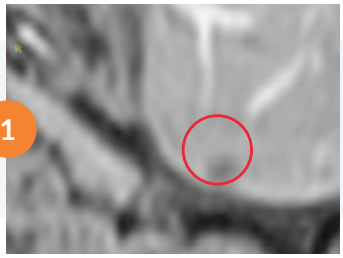
POST-TREATMENT

After treatment has concluded, the physician uses live ultrasound to confirm treatment. The volume where soft tissue was mechanically destroyed will typically appear hypoechoic (dark). The images below demonstrate histotripsy results in (A1) a patient MRI and contrast-enhanced ultrasound demonstrating precision treatment and (A2) an immediate tissue response with preserved patent vessel traversing the treatment zone. The final images (A3) are of an ex-vivo animal model and are representative of collagen structures and larger vessels which tend to remain preserved after histotripsy.

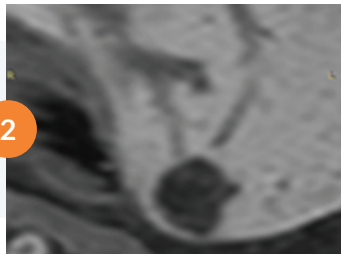
A1

THERESA Trial[2]

MRI images of pre and post liver tissue treatment.



Red circle designates the planned treatment area.



The treatment zone encompasses the planned treatment area but does not impact other tissue, including the adjacent liver capsule.

A2

THERESA Trial

Contrast-enhanced ultrasound (CEUS) pre and post liver tumor and tissue treatment.

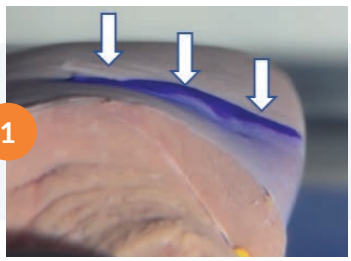
Red circle designates the planned treatment area.

Hypoechoic appearance post-treatment.

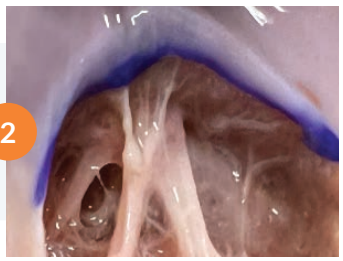
A3

Benchtop Bovine Liver

Post liver tissue treatment.



Histotripsy treatment completed just below liver capsule, which remains intact.



Patent vessels traversing through treatment zone visualized after washout of acellular lysate.

REFERENCES

1. Vlaisavljevich E, et al. Effects of tissue mechanical properties on susceptibility to histotripsy-induced tissue damage. Phys Med Biol. 2014;59(2):253-270. doi:10.1088/0031-9155/59/2/253
2. Vidal-Jove J, et al. First-in-man histotripsy of hepatic tumors: the THERESA trial, a feasibility study. Int J Hyperthermia. 2022;39(1):1115-1123. doi:10.1080/02656736.2022.2112309

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