Treatment of liver metastases using High Intensity Focused Ultrasound (HIFU)

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Introduction

Colorectal cancer: Fourth most common cancer in men and the third most common cancer in women worldwide.

The development of liver metastases is the main cause of death.

Only 10 - 20% of patients are suitable for resection.
Why resection is not possible in most patients?

Tumor ablation using intra-operative HIFU is not viewed as a replacement for resection, but as a complementary tool that may be used in otherwise unresectable patients.

Our long-term objective is to develop a HIFU device that can be used during surgery, for treating unresectable liver metastases.

Tumor ablation using intra-operative HIFU is not viewed as a replacement for resection, but as a complementary tool that may be used in otherwise unresectable patients.
High Intensity Focused Ultrasound (HIFU)

Focused Ultrasound = Mechanical vibration, 1 – 20 MHz (Non ionizing, non invasive)

In a way analogous to the focusing of light, ultrasound waves can be focused at a given point.

The high energy levels carried in a HIFU beam can therefore be magnified further and delivered with precision to a small volume, while sparing surrounding tissues.
High Intensity Focused Ultrasound (HIFU)

Focused Ultrasound = Mechanical vibration, 1 – 20 MHz (Non ionizing, non invasive)

Predominant mechanisms of tissue damage the conversion of mechanical energy into heat

Immediate thermal toxicity occurs if tissue temperatures are raised above a threshold of 56°C for at least 1 second, leading to irreversible cell death through coagulative necrosis.
High Intensity Focused Ultrasound (HIFU)

Focused Ultrasound = Mechanical vibration, 1 – 20 MHz (Non ionizing, non invasive)

The volume of ablation (‘lesion’) following a single HIFU exposure is typically in the order of 1–3 mm wide by 8–15 mm in length.
The lesions must be placed side by side systematically to cover the tumor and some of the surrounding normal tissue margin.

High Intensity Focused Ultrasound (HIFU)

Focused Ultrasound = Mechanical vibration, 1 – 20 MHz (Non ionizing, non invasive)
High Intensity Focused Ultrasound (HIFU)

Rapid advances in HIFU over the last three decades have now made image-guided ultrasound therapy a clinical reality.

EDAP-TMS

Focus Surgery

HAIFU

Insightec - GE

PHILIPS
Major innovations were needed for treating liver metastases using HIFU

Liver metastases: several cubic centimeters
Enlarge the coagulated volume over short periods of time

- 2 Patents under licence
- Toroidal geometry
- 8 sectors - 256 transducers (3 MHz)
- An ultrasound imaging probe (7.5 MHz) allows real-time monitoring
Major innovations were needed for treating liver metastases using HIFU

The focal zone is located at 70 mm
Each transducer focuses on a distinct 1/8 arc of ring to ablate the liver

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Major innovations were needed for treating liver metastases using HIFU

Energy deposition in the focal plane (70 mm from the surface of the transducer)

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Lesion of coagulative necrosis at focus

7 cm³ in 40 seconds

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Toroidal geometry

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An ultrasound imaging probe (7.5 MHz) allows real-time monitoring
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Liver ablation created in 40s *in vivo* using the toroidal HIFU device

Ablation rate: 11 cm³ / minute

Liver ablation created in 10s *in vivo* using conventional HIFU device

Ablation rate: 0.003 cm³ / minute

This device is capable of achieving fast and selective ablation of predefined liver regions.
Major innovations were needed for treating liver metastases using HIFU.

The treatment of metastases inaccessible to any other technique (surgery, physical means ...) is conceivable using this HIFU device.
# Clinical study

## Phase I
- **6 patients**
- Validate the effectiveness, tolerance and safety of the treatment
- Assess the response to HIFU using ultrasound imaging
- Normal liver, 2 single HIFU lesions (one superficial, one deep)

## Phase IIa
- **6 – 12 patients**
- Demonstrate the accuracy of the treatment
- Normal liver, 2 single HIFU lesions

## Phase IIb
- **20 patients**
- Treatment of liver metastases (diameter $\leq$ 20 mm)
- Safety margins

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Patients planned for a standard curative hepatectomy

No modification of the planned surgery

Independent review board
Patients:
6 patients have been included between March, 2010 and Sept, 2010.
Age: 62 ± 6 years
Informed consent
Follow-up: 30 postoperative days

Exposure conditions:
Frequency: 3 MHz
Acoustic power: 70 - 90 W
Total exposure time: 40 s (one single lesion)
All elements working in phase

Objectives of the study:
Effectiveness, tolerance and safety
Assess the response to HIFU using the ultrasound imaging probe integrated in the device
Results – Phase I

Two single HIFU lesions were performed in each patient
Results – Phase I

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In 83% of the cases (10 out of 12), ebullition was created in liver tissues treated during HIFU single exposures.
Results – Phase I

Two single HIFU lesions were performed in each patient.

Five minutes after the exposure, the cloud of bubbles disappeared. However, a residual modification of liver echogenecity persisted at the position of the single lesion.
The high visibility of HIFU lesions on sonograms allows reliable determination of the ablated zone.
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Results – Phase I

Histological analysis

Clear demarcation of the treated zone

No hemodynamics and respiratory changes during treatment
Results – Phase I
Accessible hepatic volume

Objective: 80% of the hepatic volume
Average volume accessible: $94 \pm 9\%$ (67 – 100%)
Clinical study

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No modification of the planned surgery

Independent review board

Phase I

6 patients

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- Normal liver, 2 single HIFU lesions (one superficial, one deep)

Phase IIa

6 – 12 patients

- Demonstrate the accuracy of the treatment
- Normal liver, 2 single HIFU lesions

Phase IIb

20 patients

- Treatment of liver metastases (diameter ≤ 20 mm)
- Safety margins
Method – Phase Ila

Patients:
9 patients have been included between January, 2011 and November, 2011.
Age: 62 ± 10 years
Informed consent
Follow-up: 30 postoperative days

Exposure conditions:
Frequency: 3 MHz
Acoustic power: 70 - 90 W
Total exposure time: 40 s (one single lesion)
All elements working in phase

Objectives of the study:
Demonstrate the accuracy of the treatment
HIFU lesions centered on a target or placed at a fixed distance (7.5 mm) from a target
Results – Phase Ila

HIFU lesions centered on a surgical clip

6 patients included, 11/12 HIFU lesions were correctly centered with an accuracy of 1-2 mm
Results – Phase Ila

HIFU lesions placed at a fixed distance (7.5 mm) from a surgical clip

The distance between the target and the lesion was set to 7.5 mm (1 – 15)
6 HIFU lesions have been created
The distance that has been achieved was: 7.0 ± 2.3 mm (4.3 – 9.8)
## Clinical study

### Phase I
- **6 patients**
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- Assess the response to HIFU using ultrasound imaging
- Normal liver, 2 single HIFU lesions (one superficial, one deep)

### Phase IIa
- **6 – 12 patients**
- Demonstrate the accuracy of the treatment
- Normal liver, 2 single HIFU lesions

### Phase IIb
- **20 patients**
- Treatment of liver metastases (diameter ≤ 20 mm)
- Safety margins

Patients planned for a standard curative hepatectomy
No modification of the planned surgery
Independent review board
Results – Phase IIb

Treatment of liver metastases with safety margins

Liver metastasis treated with safety margins in one single HIFU ablation of 40 seconds
Results – Phase IIb

Treatment of liver metastases with safety margins

Liver metastasis treated with safety margins in one single HIFU ablation of 40 seconds
Results – Phase IIb

Treatment of liver metastases with safety margins

Liver metastasis treated with safety margins in one single HIFU ablation of 40 seconds
Discussion – Future work

No HIFU-related complications occurred during surgery and 30 days postoperatively.

This toroidal HIFU transducer achieved fast, selective, safe and well-tolerated large volume liver ablation, without puncture.

Ultrasound imaging evidence of complete ablation of the target region can be taken to infer histological success.

Liver metastases can be treated in a few minutes with safety margins
Funding and support

This project was funded in 2006 by Cancéropole Lyon Auvergne Rhône Alpes:

- Program Proof of Concept (PDC 2006.4.8)
  - Preclinical trials in animals to evaluate treatment capabilities of the device
  - Development of a device in accordance with European legislation for use during surgery
  - Clinical Proof of Concept

- Has allowed EDAP-TMS to obtain funding from Oseo-Anvar