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3aBAb2. Thermal ablation by high-intensity-focused ultrasound using a toroidal transducer for the treatment of colorectal liver metastases during an open procedure.

Clinical results

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The objective of this clinical study was to validate the effectiveness, accuracy, tolerance and safety of a HIFU treatment developed for the treatment of liver metastases. Fifteen patients were included. The transducer has a toroidal shape (diameter: 70 mm, radius of curvature: 70 mm) and was divided into 256 ultrasound emitters operating at 3 MHz. A 7.5 MHz ultrasound imaging probe was placed in the centre of the device. All HIFU ablations were obtained in 40 seconds. The demarcation between ablated and non-ablated tissue was clearly apparent in ultrasound images and histology. In Phase I (6 patients) we demonstrated that the dimensions of HIFU ablations measured on ultrasound imaging were correlated ($r=0.88$) with dimensions measured during histological analysis. The average dimensions obtained from each HIFU ablation were a diameter of $21.0 \pm 3.9$ mm and a depth of $27.5 \pm 6.0$ mm. In Phase II (9 patients), the HIFU ablations were centered on a target previously identified with a precision of 1-2 mm. It was demonstrated that HIFU ablations can be precisely located at $7.0 \pm 2.3$ mm from the target (expected distance 7.5 mm). This toroidal HIFU transducer achieved fast, selective, safe and well-tolerated large volume liver ablation.

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INTRODUCTION

Colorectal cancer is the fourth most common cancer in men and the third most common cancer in women worldwide. Resection of liver metastases, when possible, is the gold standard and is the only treatment that can ensure long-term survival and a cure in some cases. However, only 10 to 20% of patients with liver metastases are suitable for resection. The overall 5-year survival rates are in the range of 35%–58% in several studies reporting on the results of resection. High Intensity Focused Ultrasound (HIFU) is a treatment modality which has been validated clinically for many diseases and which presents many advantages for the treatment of liver metastases. Although HIFU produces small single lesions, previous studies have been conducted to enlarge the ablated region by using, for example, cavitation, phased arrays systems, split focus or optimization algorithm for the focus pattern. Nevertheless, the main limitation to widespread clinical use of HIFU has been the length of time required to treat tumors of several cubic centimeters in volume. In our study, a toroidal-shaped HIFU medical device, developed for the treatment of liver metastases during surgery, is proposed to be used as a tool for assisting liver resection. The principal interest lies in the possibility of treating hepatic parenchyma in a short period of time (ablation of 5-7 cm³ in 40 seconds) without organ penetration. The selected approach for the toroidal HIFU treatment is surgical laparotomy. It makes it possible to reach all regions of the liver without penetrating the hepatic capsule. Such an intraproperative approach enables the protection of surrounding organs and eliminates the risk of secondary lesions. Tumor ablation using this toroidal HIFU device is not to be viewed as a replacement for resection but as a tool to complement resection that may be used during surgery in otherwise unresectable patients.

Here we report the first clinical results obtained with this device. The principal objective was to validate the effectiveness, tolerance and safety of the HIFU parameters defined during preclinical studies. In addition, the response to HIFU was assessed using ultrasound imaging and compared directly with histological analysis.

MATERIAL AND METHODS

Ultrasound equipment

The HIFU apparatus is composed of driving equipment (N'Djin et al. 2011) and a sterilizable treatment probe that has been previously described (Melodelima et al. 2007). The therapeutic transducer is a 1–3 piezocomposite material operating at a frequency of 3 MHz with an electroacoustic efficiency of 60%. The transducer has a toroidal shape of 70 mm in diameter and is divided into eight radial ultrasound emitters of 4.16 cm² each. The radius of curvature is R = 70 mm, and each of the eight emitters is divided into 32 individual transducers (Figure 1a). The surface of each individual transducer is 13 mm². Because of its toroidal geometry, the transducer focal zone and the lesion induced were shown to be cone-shaped with a diameter of 2 cm, a major axis of 2.5 cm and is placed at 7 cm from the emitting surface to enable treatment of the deepest regions of the liver. A sectorial ultrasound imaging probe working at a frequency of 7.5 MHz (Vermont, Tours, France) was placed in the center of the device and connected to a BK HAWK 2102 EXL scanner (B-K Medical, Herlev, Denmark) for guiding the treatment. The imaging plane was aligned with the HIFU focal zone. The HIFU probe was brought into contact with the liver using an ultrasonic sterile cooling and coupling liquid (Ablasonic®, Edap-Technomed, Vaulx en Velin, France) contained in a sterile polyurethane envelope (Civco, Kaloma, Iowa, USA). Software developed in our laboratory made it possible to define the treatment zone by HIFU from a two-dimensional ultrasound image.

Patients

Previous animal experiments led to an open pilot trial which was conducted between March, 2010 and September, 2010, after institutional review board approval. Informed consent for the study was obtained from all patients and conformed to world medical association declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects, 2004. A non-randomized Phase II study protocol was designed to evaluate the use of HIFU in this clinical context. According to the clinical trial protocol, patients with liver tumours that had been identified as being suitable for surgical resection were recruited for HIFU treatment. Criteria for inclusion were the presence of resectable liver metastases from a colorectal cancer, without invasion to other organs on CT-scan or MRI. It was planned to include 6 patients in this Phase I trial to confirm preclinical results and demonstrate...
effectiveness, tolerance and safety. Ablations must have been successfully performed in 85% of the cases to continue the study. Secondary endpoint was preciseness of ultrasound imaging to visualize HIFU ablations.

**Surgical procedure**

Two thermal ablations were created in each patient. Ablations were performed in the part of the liver that will be removed from resection and at distance from the metastases. The ultrasound exposures conditions were established from preliminary *in vivo* studies \(^{13}\). The free field acoustic power that has been used was 70-90 watts according to the depth of the focus and the sonication time was 40 seconds. Tolerance during treatment was evaluated using a continuous evaluation of hemodynamic status and blood oxygen saturation. After the HIFU procedure, the dimensions of all ablations were measured in sonograms using the 7.5 MHz ultrasound imaging probe located in the center of the device. A 12 MHz ultrasound imaging probe was also used to observe the lesions with higher resolution. After liver resection, ablations were cut along the HIFU acoustic axis was cut for histological analysis. Samples were fixed in 10% formalin after ablation and stained with standard hematoxylin-eosin. Regarding tolerance studies, follow-up was performed up to one month after the treatment.

**RESULTS**

All ablations were visible on ultrasound images. In 10 cases over the 12 ablations, ebullition appeared as a hyperechoic conical-shaped zone on sonograms in liver tissues treated during single HIFU exposures. The hyperechogenicity due to bubble formation disappeared 1-3 minutes after a HIFU exposure. However, changes in liver echogenicity (different from the hyperechogenicity due to bubble formation) remain present (up to the end of the total procedure) at the position of the ablation as a conical-shaped region with a hypoechoic boundary and a central hyperechoic zone in all groups. In all cases, the demarcation between ablated and non-ablated tissue was clearly visible in gross pathology \(^{13}\). The correlation between ablations observed in ultrasound imaging and gross pathology was \(p=0.92\). The average difference between the dimensions of ablations in sonograms and gross pathology was \(0.42 \pm 3.33 \text{ mm}\). Measurements on sonograms of the ablations included all changes of echogenicity (i.e., the hyper- and hypoechoic zones).

Each ablation was created in 40 seconds. The average coagulated volume was \(5.6 \pm 2.6 \text{ cm}^3\) (1.9 – 11.4) with an average diameter of \(21.6 \pm 4.5 \text{ mm}\) (12.0 – 28.0) and an average depth of \(28.4 \pm 6.3 \text{ mm}\) (20.0 – 43.0). The patients have tolerated the treatment well over the experimental period. There was no hemodynamics and respiratory changes. No HIFU-related complications occurred during surgery and 30 days postoperatively. It was shown that on average 93% of the liver was accessible for HIFU treatment using this device.

Histologic evaluation of formalin fixed paraffin-embedded sections of excised HIFU ablation in liver tissues revealed evidence of tissue necrosis and cell death in the treated zone. Edges of the coagulated area were clearly delimited. The demarcation between the coagulated zone and the untreated regions was approximately 100 μm. Tissue damage was confined to regions that had been given HIFU exposure, whereas in the sharply demarcated surrounding tissue there was no evidence of cell damage.

**DISCUSSION**

This study demonstrated clinically that the combination of a toroidal geometry with electronic beam steering allows the creation of large lesions (up to 5 – 6 cm³) in a very short amount of time (40 seconds). When conventional spherical transducers are used, the volume of the ablation following a single HIFU exposure is small and will vary according to the transducer characteristics, but it is typically ellipsoidal with dimensions on the order of 1–3 mm (transverse) \(\times 8–15 \text{ mm}\) (along beam axis). To clinically ablate tumors with safety margins, many of these lesions must be placed side by side by electronically moving the focal volume and/or by moving the transducer mechanically. Therefore, the long time required to treat tumors of several cubic centimeters in volume using HIFU is the main technical limitation to the widespread clinical use of this technique. For example, using conventional spherically shaped HIFU devices, thermal therapy requires significantly long treatment times; 149 min for prostate cancer \(^{12}\) and 32–135 min for uterine leiomyomas \(^{15}\). This fact compromises the technique for most of the prominent applications (i.e., liver cancers where the tumors may measure up to several cubic centimeters in volume and where the therapeutic options are limited). To fill this therapeutic gap, we have designed a new geometry of HIFU transducers and have developed a new method of treatment that can rapidly induce large lesions. The HIFU
approach presented in this study is characterized by the brevity of the treatment16 (40 seconds for one ablation of about 5-6 cm³), which makes it possible to reduce treatment dependence from blood perfusion.

The ultrasound imaging probe placed in the center of the HIFU device provides real-time control of the treatment. Ultrasound imaging was accurate for both targeting the area to be coagulated and to assess the area of ablation accurately as previously demonstrated17. Each ablation induced by HIFU is visible with high contrast on sonograms, and the ablation ultrasound size correlates well with pathologic ablation size. This represents a major advancement in the improvement of treatment efficacy since the dimensions of the treatment zone can be enlarged by accurately juxtaposing single lesions without leaving untreated liver in the ablated zone.

The selected approach for this toroidal HIFU treatment of liver metastases is surgical laparotomy. This approach makes it possible to reach all of the regions of the liver without penetrating the hepatic capsule. Furthermore, such an intraoperative approach enables the protection of the surrounding organs and eliminates the risk of secondary lesions18. In addition, as suggested for radiofrequency ablation (RFA) or cryosurgery ablation (CSA), combining hepatic resection with HIFU ablation could expand the number of patients who may be candidates for liver-directed surgical therapy19, 20. The open procedure used in this study appears to be ideally suited for HIFU ablation. Compared to an extracorporeal device, an open procedure facilitates the protection of adjacent viscera and the intra-abdominal staging of malignancies. The lesions not detected with preoperative imaging may be discovered intraoperatively21, 22. Nevertheless, the use of an extracorporeal HIFU device is clinically feasible, as demonstrated by the treatment of hepatocellular carcinoma23, but only a small part (approximately 30%) of the liver is accessible using a noninvasive HIFU device unless a partial rib resection is performed24. In addition, attenuation, phase aberration and liver movements can produce secondary lesions (such as skin burns or gastric lesions) if a completely extracorporeal treatment is performed in the liver25. To date all these difficulties are not solved. Therefore, the device was developed and evaluated for use during an open procedure to provide a complementary tool to surgeons for hepatic resection. This allows a first evaluation before developing an extracorporeal device.

In conclusion, this HIFU treatment using a toroidal transducer is feasible, safe and well tolerated. This device is capable of achieving selective ablation of predefined liver regions. Ultrasound imaging evidence of complete ablation of the target region can be taken to infer histological success.

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REFERENCES