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Developing an Interstitial Ultrasound Applicator for Thermal Ablation in Liver: Results of Animal Experiments

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Background. **In this project, an interstitial ultrasound applicator was developed for the treatment of primary and secondary cancers of the liver. Experiments on animals were used to check the destructive capabilities of this probe within the hepatic parenchyma of the pig *in vivo*, with a study of the physical parameters of the ultrasound treatment. In parallel, the possibility of visualizing the lesions induced by means of ultrasound imaging was also studied.**

Materials and methods. **Thirteen pigs were used in this project, which had received the prior approval of the ethics committee of Lyon Veterinary School. Ultrasound lesions were performed by varying the physical parameters of the treatment (acoustic intensity and shot time) with the aim of obtaining larger and larger areas of destruction. An operative device was developed to ensure precision in treatments. Two types of lesions were performed: elementary lesions corresponding to single shots at 40° to 50° rotation intervals, and cylindrical lesions obtained by a continuous rotary deployment of the probe. The effect of hepatic pedicle clamping on the size of ultrasound lesions was studied. The aspect and dimension of the lesions were analyzed by means of operative ultrasound imaging and macroscopic examination. Histological analysis showed the impact of the treatment on the hepatic parenchyma.**

Results. **This work made it possible to study the elementary ultrasound lesions produced by our probe. Seventy elementary ultrasound lesions were analyzed. Treatments could be performed on all pigs without any difficulty. There were no operative incidents. The ultrasound-induced elementary lesions showed complete necrosis, with lesion length of up to 37 mm obtained without resort to pedicle clamping; this must be considered as a radius of the final lesion obtained over a complete rotary deployment (360°), then a diameter of 7 cm of thermal ablation can theoretically be obtained. The effect of pedicle clamping was studied and showed improvement of the lesion length. Results of continuous rotary deployment of the probe were encouraging. Operative ultrasound imaging proved to be a simple tool for directing and positioning the applicator in the target zone on the one hand and which, on the other hand, enabled accurate, real-time visualization of the ultrasound lesions. On histological analysis, the ultrasound-induced necrosis was complete and well defined.**

Conclusion. **This work shows that it is feasible to treat cancers of the liver using interstitial ultrasound probe. Thermal damage obtained on the hepatic parenchyma of pigs *in vivo* is complete and can be monitored using simple diagnostic ultrasound. The ultrasound parameters can be adapted to obtain destruction of variable size.**

Key Words: **liver cancer; ultrasound therapy; interstitial; thermal ablation; porcine liver; pedicle clamping; real-time imaging; local treatment; computer-assisted.**

INTRODUCTION

The liver is the first metastatic site in the progression of colorectal cancers. Metastases to the liver are isolated in 50% of cases. Medium-term spontaneous survival is 4 to 21 mo, with at most a 5% survival at 5 y [1]. Hepatocellular carcinoma (HCC) represents the

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third greatest cause of mortality from cancer, with growing incidence in Europe and North America [2, 3]. Surgical resection is the only treatment that can potentially cure primary and secondary cancers of the liver. This is possible in 20 to 25% in cases of colorectal cancer metastases. Medium-term survival after resection is 30 to 42 mo, with a 20 to 50% survival at 5 y [4–6]. Without surgical resection, median survival is no more than 20 mo [7, 8].

Two interstitial treatments make it possible to increase the number of patients who are treated in a curative way [9, 10]. Radiofrequency ablation can be used to treat lesions through hyperthermia, ideally for lesions of less than 3 cm. This current upper limit of 3 cm is due to the high rate of local recurrence [11]. Unlike cryotherapy, operative monitoring of the volume treated by radiofrequency is not particularly reliable. Cryotherapy can be used to treat bigger lesions, but complications frequently arise in the case of large destruction volumes [9]. Pedicle clamping makes for increased efficiency, but can lead to biliary complications [10].

High-intensity ultrasound has proven its efficiency in destroying tumor tissue, particularly in clinical applications for the treatment of localized cancers of the prostate [12]. The extent of tissue necrosis produced by the ultrasound depends on several parameters: frequency (MHz), ultrasound intensity (W/cm^2), insonification time (s) and the size of the transducer used (mm). The aim of this project is to develop an interstitial ultrasound applicator that is fitted with a flat transducer, and then study the different lesions that are induced in the liver when the physical parameters are varied. This preliminary study on the livers of pigs *in vivo* must make it possible to define treatment data for obtaining larger, more complete, more precise necroses, and to study the effects of hepatic perfusion on lesion size. Operative ultrasound imaging was systematically used to check the positioning of the interstitial probe, and to study the aspect of the ultrasound lesions.

MATERIALS AND METHODS

Materials

For this project, a tubular applicator, 4 mm in diameter, with a flat PZT-type 762 piezoceramic transducer (Quartz and Silice, Nemours, France) was developed (Fig. 1A). The array element consisted of an ultrasound transducer measuring 3 × 10 mm operating at a frequency of 5.7 MHz. An internal circuit of degassed water at 4°C cools the front face of the transducer during treatment and ensures ultrasonic coupling with the target zone. A pneumatic support is used to hold the probe implanted in the liver in position (Fig. 1B). This takes the form of an articulated arm that can be positioned according to the location of the probe within the liver. This support is fitted with a rotation device (Newport Corp., Irvine, CA) which turns the applicator around its axis using a micrometric screw. The rotation system is computer-controlled via a GPIB using a Testpoint

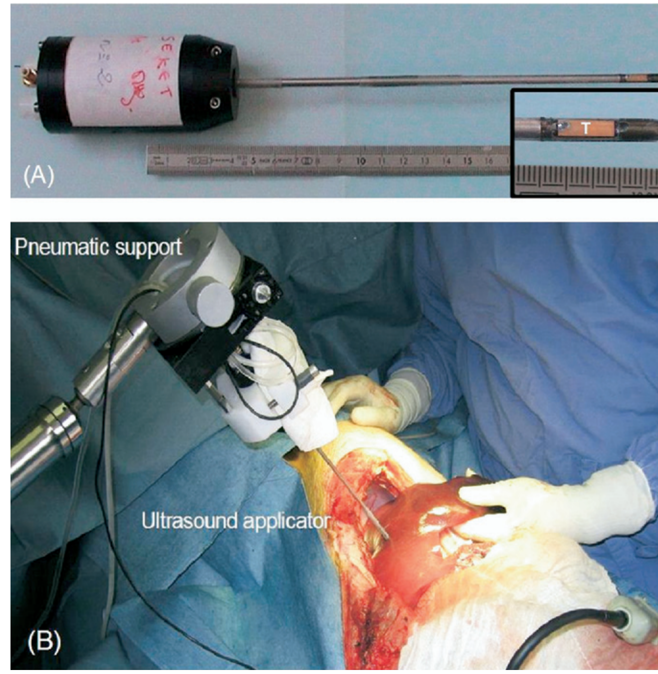

FIG. 1. (A) Interstitial ultrasound probe used in this project. The transducer (T) is aimed laterally. (B) Operative device with ultrasound probe positioned under ultrasound guidance and kept in place in the liver by the pneumatic support. (Color version of figure is available online.)

graphical interface (Keithley Instruments Inc., Cleveland, OH). All experiments were carried out under the guidance of an ultrasonograph (B and K Hawk, Gentofte, Denmark) with a 7.5 MHz multielement linear array probe. The interstitial probe is fed by a pulse amplifier (ADECE 50 W, Artannes-sur-Indre, France) from a function generator (HAMEG, Mainhausen, Germany). A wattmeter (Rhode and Schwartz, Böblingen, Germany) is used during manipulations to measure the electrical power delivered to the applicator.

Methods and Surgical Techniques

The protocol was submitted to the ethics committee of the Lyon veterinary school on June 28, 2004, and was accepted. The project required the use of 13 pigs. The animals were anesthetized using sufentanil (Sufenta; Janssen-Cilag, Issy-les-Moulineaux, France) 0.5 μg/kg/h and atracrium besylate (Tracrium, Glaxo-Wellcome, Marly-le-Roi, France) 0.5 mg/kg/h. Mechanical ventilation, provided by a respirator, was ensured by means of endotracheal intubation. Hemodynamic and intrarectal temperature data were gathered at regular intervals for each animal, enabling continuous checks on homeostasis. Following a bisubcostal laparotomy, the liver was liberated so as to be able to fully manipulate and explore it. The hepatic pedicle was systematically prepared to clamping. Operative ultrasound imaging first enabled the visualization of the intrahepatic vessels and the identification of the target zone. It was then used to guide the positioning of the probe avoiding the intrahepatic vessels. The target zone had to be more than 20 mm in thickness and located at least 40 mm from any interface in the direction of ultrasound propagation (inferior vena cava or hepatic veins, gallbladder, limits of the liver). The median sectors of the liver often fulfilled these criteria. The target zones in the same liver were enough distant to ovoid overlap between lesions (at least 8 cm between the insertion points).

Ultrasound Treatment Methods

The initial objective was to determine lesion length as a function of ultrasound intensity (30 to 45 W/cm^2) and shot duration (40 to