Transoesophageal ultrasound applicator for sector-based thermal ablation: first in vivo experiments.

David Melodelima, Cyril Lafon, Frédéric Prat, Yves Theillère, Alexei Arefiev, Dominique Cathignol

Transesophageal ultrasound applicator for sector-based thermal ablation: First *in vivo* experiments

David Melodelima, Cyril Lafon, Frederic Prat, Yves Theillère, Alexei Arefiev and Dominique Cathignol.

INSERM, U556, F-69003, Lyon, France

Pho. : (33) 4-72-68-19-30 Fax: (33) 4-72-68-19-31 E-mail: melodelima@lyon.inserm.fr

Running title: Transesophageal plane transducer

Hal-Inserm Author manuscript

Hal-Inserm Author manuscript

Transesophageal ultrasound applicator for sector-based thermal surgery: First *in vivo* experiments

Abstract

New curative and palliative treatments must be proposed in order to respond to the bad long-term prognosis of esophageal cancers. It has been demonstrated that High Intensity Ultrasound (HIU) can induce rapid, complete and well-defined coagulation necrosis. For the treatment of this cancer, we designed an applicator that uses an intraductal approach. The active part is an air-backed plane transducer. It has an external water-cooling system and operates at 10 MHz. *Ex vivo* experiments conducted on pig liver demonstrated the ability of this applicator to generate, by rotating the transducer, circular or sector-based coagulation necroses at predetermined depths up to 13 mm with an excellent angular precision. The treatment of sector-based esophageal tumour may be critical where both malignant and healthy tissues are covered by the ultrasound beam. Thus, *in vivo* trials were conducted on five healthy pig esophaguses in order to determine the maximal thermal dose that will not induce a perforation of the esophagus or surrounding tissues. From the results of previous studies, this dose is high enough in order to treat pathological tissues. These promising results indicate that this ultrasound system represents a safe and effective tool for the clinical treatment of esophageal tumours.

Key words: Ultrasound, thermal ablation, coagulation necrosis, intraductal therapy, sector-based, plane transducer, high intensity ultrasound

Hal-Inserm Author manuscript

INTRODUCTION

Esophageal tumours develop inside the circumference of the lumen and are very difficult to treat for two reasons. They are sometimes sector-based and the tumour thickness can vary significantly from one point to another. Furthermore, most occurrences of this type of cancer are not amenable to curative resection because of the extent of the tumour at diagnosis and the presence of a comorbid condition. Radiochemotherapy has not demonstrated any survival advantage so far. Photocoagulation by laser is used sometimes (De Palma et al. 1999; Sharma et al. 1999), but it is relatively expensive and demanding, because tissue destruction is superficial and several sessions are generally needed to achieve symptomatic improvement. Thus, for this form of cancer, a minimally invasive local treatment, leading to an immediate, in-depth and complete destruction of the targeted tissue, should be envisaged as both curative and palliative strategy for a large number of patients. Among the interstitial heating modalities for therapeutic thermal ablation, ultrasound presents two major advantages. Ultrasound penetrates deep into tissues allowing some extent of the coagulated volume (ter Haar and Robertson, 1993). Treatments by ultrasound are well-delimited; damages to surrounding tissues are minimal. In the past, high intensity ultrasound has proved to be highly efficient, both experimentally and clinically, in inducing homogeneous and reproducible tumour destruction by thermal coagulation necrosis (Fry and Johnson 1978, Chapelon et al. 1999, Gelet et al. 2000). World-wide clinical applications of focused ultrasound surgery (FUS) include the treatment of glaucoma (Burgess et al., 1986), benign prostatic hyperplasia (BPH) (Madersbacher et al., 1995 Uchida et al., 1998, Diederich et al., 2000) and treatment of localised prostatic cancer of the prostate (Chapelon et al. 1992) bladder (Vallancian et al., 1996) and breast (Hynynen et al. 1996). In addition, therapeutic ultrasound can be used intraductally (Lafon et al. 1999a), which makes it an approach that is particularly appropriate for carcinoma of the esophageal ducts.

Hal-Inserm Author manuscript

Most interstitial ultrasound applicators use a tubular transducer inducing simultaneous coagulation necrosis of the whole periphery of the applicator (Hynynen et al. 1997). Sector-based necroses are generated by remodelling irreversibly a tubular transducer and the radiated acoustic field. The method consists in cutting or paralysing part of the transducer (Diederich et al. 1996a, Nau et al. 1998, Deardorff and Diederich 2000). In contrast, a plane transducer generates elementary parallelepiped-shaped lesions in front of the emitting face. As the ultrasonic beam does not diverge in the near field, the pressure drop along the ultrasonic axis is only dependent on the energy attenuation in tissues (Diederich 1996b, Lafon et al. 1999b). Each elementary lesion can be induced in less time (10 s), to a greater depth, and with less perfusion-dependence (Billiard et al. 1990) than lesions produced by tubular transducers.

The aim of this study was first to conduct *ex vivo* experiments on pig liver in order to demonstrate the ability of the applicator to generate any angular sector-based shapes of coagulation necroses and to link the depth of the cylindrical lesions with the exposure conditions. In the case of sector-based tumours, both cancerous and thin healthy zones are irradiated. The deposited thermal dose should not induce perforation in the healthy zone, yet it should still coagulate the immediately adjacent cancerous tissues. Consequently, the second aim of this study was to determine the maximal thermal dose that can be delivered to a healthy esophagus without causing perforation. Finally, the thermal dose determined by these in vivo trials was compared with recent studies (Lafon et al. 1999c) to verify whether or not the dose was high enough to necrose malignant cells.

MATERIALS

The active head of the applicator is made of brass and round-shaped to permit transesophageal application without risk of injury (Fig. 1). The active surface is a 15×8 mm^2

piezoceramic plane transducer (Quartz & Silice, P7-62, Nemours, France) which operates at 10.35 MHz. This air-backed transducer was sealed with epoxy resin (Emerson & Cuming, Stycast 2651, Westerlo, Belgium) to ensure the applicator was watertight. The rotation of the active head is controlled remotely with negligible angular loss using an 80-cm long, 10-mm OD, flexible metallic shaft. A biocompatible envelope (1.3 mm thick) covers this metallic shaft. Connections for the transducer supply are done with a PVC casing attached on the opposite end of the applicator. This casing is mounted on an UR 100 microcontrol unit (Microcontrol, Evry, France) to monitor the rotation of the applicator. Electrical connections were realised via a miniaturised 50-Ω coaxial cable that was 80-cm long with a 0.9-mm OD. A tube (1-mm o.d.) over the whole length of the applicator is for holding a guide wire previously introduced in the esophagus. The active part of the applicator is covered by a 65-µm thick latex balloon attached with 2/0 polydioxanone (PDS) suture thread (Ethnor, Neuilly, France) and covered by watertight seal. This envelope introduced approximately 9% of ultrasonic pressure losses (Lafon et al. 1998a). The transducer is cooled by a continuous flow of degassed water at room temperature (25°C) at a rate of 21 mL/min. A peristaltic Masterflex pump (Cole-Parmer Instruments Co., Chicago, IL, USA) circulated the water around the closed cooling circuit and through a 1-liter watertight tank of degassed water. The water of the cooling circuit also ensured ultrasonic coupling between the transducer and target tissues. This balloon can be inflated via a syringe connected to the tank. At least, the cooling circuit shifts the maximum temperature slightly away from the applicator surface, thereby increasing the depth of therapeutic heating.

The electrical power was delivered in continuous mode via a Kalmus model 150 CF power amplifier (Engineering International, Woodinville, WA, USA) driven by a Hameg HM8131 sinusoidal wave generator (Hameg, Frankfurt, Germany). Directional power meter (wattmeter/reflectometer (Rohde & Schwarz, Munich, Germany) fitted with a NAP

Hal-Inserm Author manuscript

bidirectional coupling device probe (Rohde & Schwarz, Munich, Germany) were inserted into the line between the amplifier outpout and the applicator to determine with the aid of a built-in directional coupler the incident and reflected electrical power. The generator was controlled by a timer, which enabled emissions to be triggered manually and cut off automatically at the end of the desired shot time. Using the acoustical balance technique, an electro-acoustic efficiency of 61% at 10.35 MHz was measured from the radiation force (Davidson 1991).

METHODS

Ex vivo experiment

These *ex vivo* tests were conducted on pig liver. Before experiment, each sample of liver was degassed in a vacuum pump (0.7 bars for 30 min) at room temperature to remove bubbles (which can reflect the beam) initially present in the tissue and vessels. During the tests, each sample was immersed in a tank of degassed water maintained at 37°C. A thermocouple was introduced into each sample to ensure that temperature was close to 37°C before commencing the firings. A hole is produced into the center of each sample with a PVC awl (12-mm OD). The ultrasound applicator was introduced into the centre of each parallelepiped-shaped section of liver (100 x 100 x 30 mm^3) through the hole (Fig. 2). 20 shots were done with 18°-increments of angular rotation in order to induce cylindrical zone of coagulation necrosis. The time between the end of one shot and the beginning of the next shot after the rotation is 10 s. These exposure conditions come from our experience in the treatment of biliary cancers (Prat at al. 1999). This method provides a homogeneous necrosis across the complete circumference. The duration of the elementary exposures was set to 5, 10, 15, and 20 s and the acoustic intensity to 12, 14, and 16 W/cm^2. A set of three experiments

Hal-Inserm Author manuscript

was carried out for each combination of exposure duration and acoustic intensity to ensure reproducibility of the results. A total of 36 circular lesions were created.

Identical exposure conditions were chosen to induce sector-based lesions but the number of increments depended of the treated angle. The acoustic intensity in this case was fixed at 14 W/cm² for 10 s, with the same length of pause between shots. The sectors of necrosis chosen were 72, 108, 198, and 216°. A total of 12 sector-based lesions were produced. The coagulation necroses were inspected macroscopically.

The distinction between the surrounding non-treated tissues can clearly be seen in a medium like pig liver; the lesion has an off-white colour, sometimes dark at the most heated points, similar to that of cooked liver. Liver samples were frozen just after treatment to make the lesion easier to cut and examine. When the tissue temperature was close to –6°C, the tissues were sliced along a plane perpendicular to the applicator rotation axis situated at mid-height from the transducer. The depth of the lesion was measured only for circular-type lesions. To account for the fact that the depth is not constant around the whole circumference, the measurements taken along two orthogonal axes in the cutting plane were averaged (Fig. 3). Two axes issuing from the centre of the applicator and touching the outer edges of the lesion allowed the value of the angular section of each sector-based lesion.

In vivo trials

In vivo trials were carried out on five healthy pig esophaguses. Male pigs with an average weight of 30 kg were used for the study. Anaesthesia was obtained with a mixture of 4 ml of ketamine (50 mg/ml) and 6 ml of 2% xylazine, administered intramuscularly behind the ear, followed by a slow intravenous infusion of nesdonal (0.4 g/100 ml). Oxygenation was supplied with an assisted ventilation system. The coupling balloon was inflated via a syringe after the applicator's introduction in the esophagus. Ultrasound exposures started at 20 mm

from the cardia. They were realised without visual controls every 50–60 mm. The target zone was considered as a cylinder, whose treatment required twenty shots for 5, 10 or 15 s, separated from each other by an 18°-rotation angle. Acoustical intensities tested were 12, 14 and 16 W/cm^2. During these firing sequences, proper functioning of the cooling circuit was verified by the reflected power reading on the wattmeter. A significant rise in reflected power is typical of the appearance of microbubbles across from the transducer, as well as all other effects of vaporisation by overheating. The pigs were sacrificed under general anaesthesia. The times between treatment and euthanasia were staggered at 48h (one pig), 72h (one pig) and 96h (three pigs). Autopsy was performed to observe the development of the thermal damage administered. The esophagus was then removed and sliced lengthwise. The effects of ultrasound were firstly visually inspected. The height of the lesions was measured and thermal damage (homogeneity of the lesion, perforations…) were observed macroscopically. Secondly, if there is no perforation, histological sections were carried out. Nucleus, cytoplasm and collagen of the cells were stained with Hemalun-Eosine and Saffron (HES) respectivly to determine the effective treatment depth on the esophagus, the homogeneity of the thermal damage, the presence or absence of perforation and the ability of the tissue to heal after treatment.

These animal experiments conform to the requirements of the INSERM Office of Animal Experimentation and are in accordance with the legal conditions of the National Commission on Animal Experimentation.

RESULTS

Ex vivo results

Thirty-six circular lesions and twelve sector-based lesions were created. The dimension of the lesions along the applicator axis corresponded to the height of the transducer i.e. 15 mm. Cuts perpendicular to the axis of the applicator (Fig. 3) allowed measurement of the radius of the coagulation necrosis volumes, which represents the maximal lesion depth along the acoustic propagation axis. This cross-section demonstrates that the therapeutic depth is constant around the applicator. Figure 3 shows a typical lesion induced by a series of 20 ultrasound shots at an acoustic intensity of 12 W/cm² for 10 s. The average value of the treatment depth, with standard deviation, is given in fig. 4 as a function of intensity and exposure duration (12, 14, and 16 W/cm² for 5, 10, 15, and 20 s). Cylindrical 13 mm-deep lesions can be induced applying 16 W/cm² for 20 s. Figure 5 shows sector-based lesions. These results were obtained by rotating the transducer over angles of 72, 108, 198 and 216° respectively. The correspondence between the desired angle and the experimental result is given in table 1. The most significant deviation was measured at ±9°.

In vivo results

Table 2 summarises the results obtained on the pig esophaguses and proposes a synthesis of the influence of exposure parameters. The effects of the different firing parameters on the healthy esophagus were examined according to the homogeneity of the thermal damage, the treatment of a circular area, the presence or absence of perforation and the proper functioning of the cooling circuit. These experiments show (Fig. 6 and 9) that it is possible to deliver thermal doses that do not prevent healing of healthy exposed tissues. On fig. 6, the scar does not appear perfectly cylindrical as a reject from the pig made the applicator move slightly along the esophagus during treatment. The corresponding thermal dose consisted of a series of 20 shots, one shot every 20 s at an acoustic intensity of 14 W/cm² for an exposure duration of 10 s. An identical firing sequence with a longer exposure time (15

Hal-Inserm Author manuscript

s) or a higher acoustical intensity (16 W/cm^2 for 10 s) results in esophageal perforations (fig. 7). For all other firing sequences, esophageal and adjacent tissues were preserved. The height of the thermal damage was measured as being the same as the height of the transducer (15 mm). A constant reflected power reading on the wattmeter confirmed an effective cooling of the transducer and a good coupling with the targeted tissues. The highest thermal dose that can be safety delivered to the part of the esophagus adjacent to the trachea was found to be 10 s at 12 W/cm² for circular-type lesions. For this shot sequence, the depths of *ex vivo* thermal damage were 5±1 mm and 4±1 mm in the esophagus. This latter value is close to the thickness of the esophagus and was determined by histological analysis. In the other parts of the esophagus, the maximum safety thermal dose was found to be 10 s at 14 W/cm² for circular-type lesions. This dose is known to be sufficient to induce the necrosis of tumor tissue (Prat 1999). This shot sequence is associated with the recovery of healthy tissue. The safety of this HIU treatment was confirmed by histological analysis. It was proved (Fig. 8) that the underlying muscle layers were intact. Figure 8 also shown that, as it was observed for all the firing sequences, mucosal layers are necrosed. Figure 9 shown the very well defined boundary between healthy and necrosed cells.

DISCUSSION

Ex vivo experiments have shown that the 360° lesions induced are circular in shape when the applicator is rotated through an angle of 360°. Moreover, the height of the zone of necrosis is close to that of the transducer, as was reported previously (Lafon 1998b). The depths of lesions are reproducible with a standard deviation of less than 10 %. Lesional tissue was clearly distinguishable from untreated tissue with the border even perceptible at the macroscopic level. A relationship was established between the radius of the cylindrical lesion

and the parameters of sonication (intensity and shot duration). The greatest depths which we were able to generate were 8, 10 and 13 mm for surface intensity levels of 12, 14, and 16 W/cm^2 respectively, all with a sonication time of 20 s. Beyond 20 s, the depth of the lesion does not increase very much because thereafter, the rate at which the heat is being delivered is close to the rate of thermal diffusion. For this reason, it is preferable to choose a sonication time in the shallow region of the curve, which describes the variation of lesion radius as a function of shot parameters. It is also important to bear in mind that increasing the sonication time tends to render the lesion more susceptible to the effect of blood flow.

Furthermore, these *ex vivo* experiments show that mechanical rotation of the applicator makes it possible to induce coagulation necrosis with a well-defined angle. The difference between the angle chosen and the angle experimentally obtained was no greater than ±9° meaning that sector-based tumors can be treated accurately. The round shape at the edge of the lesion and the difference between the planed treatment angle and the observed result can be explained, firstly by small angular losses during the mechanical rotation of the applicator, and secondly by thermal diffusion, i.e. the heat delivered beyond the treatment margin. The constancy of the reflected power shows that the flow rate of 0.21 liters per minute provides adequate transducer cooling, which is confirmed by the fact that the tissue near to the transducer was not vaporized. An even higher flow rate would cool the superficial layer of the tissue being treated and increase penetration.

A series of *in vivo* experiments were performed to assess the effects of different thermal doses delivered to healthy esophageal tissue. The specific effects depended on the region of the esophagus being treated. Tracheal tissue contains extensive cartilage and has a far higher attenuation coefficient than does esophageal tissue. In consequence, coagulation necrosis is induced by smaller doses in this area, a phenomenon which can lead to a life-threatening situation if the organ is perforated. A thermal dose of 12 W/cm^2 for 10 s for

Hal-Inserm Author manuscript

circular-type lesions does not cause perforation in either the esophagus or the trachea and allows regeneration of healthy tissue yet it is known to induce necrosis in tumor tissue (Lafon 1999). For this shot sequence, the depth of *ex vivo* and *in vivo* thermal damages are close together because the sonication times are so short that blood flow is only a minor factor when it comes to lesion formation. Other parts of the esophagus can tolerate much higher thermal doses (10 s at 14 W/cm^2 for circular-type lesions) because other neighboring tissues do not attenuate as efficiently as the trachea. All these experiments were conducted on healthy tissue. For the treatment of tumors, an acoustic intensity of 12 W/cm² will be used for esophageal tissue near the trachea, and one of 14 W/cm² will be used for other parts of the esophagus. Sonication times will be chosen on the basis of the dimensions of the tumor being treated. The *in vivo* short-term study has determined, by the way of histological studies, the maximal thermal dose, which never induce a perforation in healthy esophagus. As the underlying muscle layers were intact, the probability that at long term a perforation will appear in the esophagus is very low. Moreover, Chen et al. 1999 clearly shown in a long-term study (4 months) a regeneration of tissues if an underlying structure was intact after a high intensity focused ultrasound treatment.

According to these satisfactory results, the present method could be used for the curative ablation of superficial tumors in high-surgical risk patients as well as for palliation in patients with advanced disease in combination with radio- and chemotherapy, or in patients with tumor recurrence after successful chemoradiotherapy

CONCLUSION

Ex vivo experiments conducted on pig liver demonstrated the ability of the applicator to generate any angular sector-based lesion with a good angular accuracy by rotating the transducer and juxtaposing elementary lesions. Moreover we associated the depth of the

cylindrical lesions with the exposure conditions. The experiments undertaken *in vivo* allowed the determination of the maximal thermal dose that can be administered to different regions of the esophagus. These doses are well known to be sufficient to necrose cancerous tissues.

Based on these very encouraging results, an independent hospital ethics comitee has given approval to start treatment on patients with histologically confirmed cases of esophageal cancer.

ACKNOWLEDGEMENTS

This work was partially supported by a grant from the French Ministry of National Education, Research, and Technology (MENRT), grant N° 2000/102 (ACI telemedecine and technologies) and by a grant of the Agency for Research on Cancer (ARC), grant N° 4443.

Hal-Inserm Author manuscript

Hal-Inserm Author manuscript

REFERENCES

Billard B.E., Hynynen K., and Roener R.B. Effects of physical parameters on high temperature ultrasound hyperthermia. Ultrasound Med. Biol., 1990;16:409-420.

Burgess S.E.P., Silverman R.H., Coleman D.J., Yablonski M.E., Lizzi F.L., Driller J., Rosado A.L., Dennis P.H. Treatment of glaucoma with high intensity focused ultrasound. Ophtalmology 1986;93:831-838.

Chapelon J.Y., Margonari J., Vernier F., Gorry F., Ecochard R., Gelet A. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. Cancer Research, 1992;52(22):6353-6357.

Chapelon J.Y., Ribault M., Vernier F., Souchon R., Gelet A. Treatment of localised prostate cancer with transrectal high intensity focused ultrasound. European Journal of Ultrasound: Official Journal of the European Federation of Societies for Ultrasound in Medicine and Biology, 1999;9(1):31-38.

Chen L., ter Haar G., Robertson D., Bensted J. and Hill C. Histological study of normal and tumor-bearing liver treated with focused ultrasound. Ultrasound in Medicine and Biology, 1999;25(5):847-856.

Curiel, L, Chavrier, F, Souchon, R, Birer, A, Chapelon, J Y. 1.5-D high intensity focused ultrasound array for non-invasive prostate cancer surgery. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control 2002;49:231-242.

Davidson F. Ultrasonic power balances. In Preston R.C., Output measurements for medical ultrasound , Springer Verlag, Berlin, Germany, 1991;75-90.

De Palma G.D., Galloro G., Siciliano S., Donisi M., Cantanzano C. Endoscopic palliation of locally recurrent esophageal and gastric carcinoma after surgery. Gastroenterology International 1999;12:69-72.

Deardorff D.L. and Diederich C.J. Axial Control of Thermal Coagulation Using a Multi-Element Interstitial Ultrasound Applicator with Internal Cooling. IEEE Trans. Ultrason. Ferr. Freq. Contr. 2000;47(1):1541-1545.

Diederich C.J. Transurethral ultrasound array for prostate thermal therapy: initial studies. IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control 1996a;43(6):1011-1022.

Diederich C.J. Ultrasound applicators with integrated catheter-cooling for interstitial hyperthermia: theory and preliminary experiments. Int. J. Hyperthermia. 1996b;12(2):279-297.

Diederich C.J., Nau W.H., Burdette E.C., Khalil Bustany I.S., Deardorff D.L. and Stauffer P.R. Combination of transurethral and interstitial ultrasound applicators for high-temperature prostate thermal therapy. Int. J. Hyperthermia 2000;16(5):385-403.

Hal-Inserm Author manuscript

Fry F.J., Johnson L.K. Tumour irradiation with intense ultrasound. Ultrasound Med. Biol. 1978;4:337-341.

Gelet A., Chapelon J.Y., Bouvier R., Rouvière O., Lasne Y., Lyonnet D., Dubernard J.M. Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. Journal of Endourology / Endourological Society 2000;14(6):519-528.

ter Haar G.R. and Robertson D. Tissue destruction with focused ultrasound *in vivo*. Eur. Urol. 1993;23(1):8-11.

Hynynen K., Freund W.R., Cline H.E., Chung A.H., Watkins R.D., Vetro J.P. and Jolesz F.A. A clinical, noninvasive, MR-imaging monitored ultrasound surgery method. Radiographics 1996;16(1):185-195.

Hynynen K., Dennie J., Zimmer J., Simmons E., He W.N., Marcus and Aguirre M. Cylindrical ultrasonic transducers for cardiac catheter ablation. IEEE Transactions on Biomedical Engineering 1997;44:144-151.

Lafon C., Chapelon J.Y., Prat F., Gorry F., Theillère Y. and Cathignol D. Design and *in vitro* results of a high intensity ultrasound interstitial applicator. Ultrasonics. 1998a;36:683-687.

Lafon C, Chapelon J.Y., Prat F., Gorry F., Margonari J., Theillère Y. and Cathignol D., Design and preliminary results of an ultrasound applicator for interstitial thermal coagulation. Ultrasound in Med. & Biol. 1998b;24(1):113-122.

Hal-Inserm Author manuscript

Lafon C., Prat F., Arefiev A., Theillère Y., Chapelon J.Y., Cathignol D. Ultrasound Interstitial Applicator for Digestive Endoscopy: *In Vivo* Destruction of Biliary Tissues. IEEE Ultrasonics Symposium in Lake Tahoe, USA 1999a;2:1447-1450.

Lafon C., Chavrier F., Prat F., Chapelon J.-Y. and Cathignol D. A theoretical comparison of two interstitial ultrasound applicators designed to induce cylindrical zones of tissue ablation. Medical & Biological Engineering & Computing. 1999b;37(3):298-303.

Lafon C., Prat F., Gorry F., Margonari J., Theillère Y., Chapelon J.-Y. and Cathignol D. *In vivo* effects of interstitial ultrasound plane applicator on Dunning tumours. Proceedings of the Congress IEEE Ultrason Ferr Freq Control, Sendaï, Japan, 1999c;1423-1426.

Madersbacher S., Pedevilla M., Vingers L., Susani M., Marberger M. Effect of high intensity focused ultrasound on human prostate cancer *in vivo*. Cancer. Res. 1995;55:3346-3351.

Nau W.H., Diederich C.J., Stauffer P.R., and Deardorff D.L. Investigation of directional interstitial ultrasound applicators for thermal coagulation of tissue. Surgical Applications of Energy, T.P. Ryan, Ed. Proc. Int. Soc. Opt. Eng. (SPIE-BIOS). 1998;3249:13-19.

Prat F., Lafon C., Margonari J., et al. A high-intensity US probe designed for intraductal tumor destruction: experimental results. Gastrointestinal Endoscopy. 1999;50(3):388-392.

Sharma P., Jaffe P.E., Battacharyya A., Sampliner R.E. Laser and multipolar electrocoagulation ablation of early Barrett's adenocarcinoma: Long-term follow-up. Gastrointestinal Endoscopy 1999;49:442-446.

Uchida T., Muramoto M., Kyunou H. et al. Clinical outcome of high-intensity focused ultrasound for treating benign prostatic hyperplasia: preliminary report. Urology 1998 ;52 :66-71.

Vallancien G., Harouni M., Guillonneau B., Veillon B. and Bougaran J. Ablation of superficial bladder tumors with focused extracorporeal pyrotherapy. Proc. Eur. Assoc. Urol. 1996;47(2):204-207.

Hal-Inserm Author manuscript

Figures captions

Figure 1: Schematic diagram of the applicator.

Figure 2: Experimental set up and electrical equipment for *in vitro* experiments.

Figure 3: Liver tissue treated *ex vivo* (section perpendicular to the axis of the applicator): 20 shots of 10 s duration with, between each shot a 18°-angle rotation and a rest period of 10 s; 12 W/cm².

Figure 4: Depth of circular lesions in function of the acoustical intensity (◆ 12 W/cm², ■ 14 W/cm², ♦ 16 W/cm²).

Figure 5: Shape of sector-based lesions generated by the plane transducer. Several shots of 10 s duration at 14 W/cm² with a 18°-angle rotation between each shot and a rest period of 10 s. (a) 5 shots, (b) 7 shots, (c) 12 shots, (d) 13 shots.

Figure 6: Pig esophageal tissue treated *in vivo*. 20 shots of 10 s duration with, between each shot a 18°-angle rotation and a rest period of 10 s; 14 W/cm². Autopsy 72 h after treatment. The healthy treated tissues are healing

Figure 7: Esophageal tissue treated *in vivo*. 20 shots of 10 s duration with, between each shot a 18°-angle rotation and a rest period of 15 s; 14 W/cm². Autopsy 72 h after treatment. Two esophageal fistulas appear.

Figure 8: Histological view (×30) of an esophagus sonicated with 20 shots of 10 s duration with, between each shot a 18°-angle rotation and a rest period of 10 s; 14 W/cm². Autopsy 48 h after treatment.

Figure 9: Histological view (×125) of an esophagus sonicated with 20 shots of 10 s duration with, between each shot a 18°-angle rotation and a rest period of 10 s; 14 W/cm². Autopsy 72 h after treatment.

Table 1: Comparison between the experimental and the desired angles of sector based lesions.

Table 2: Summary of *in vivo* experiments.

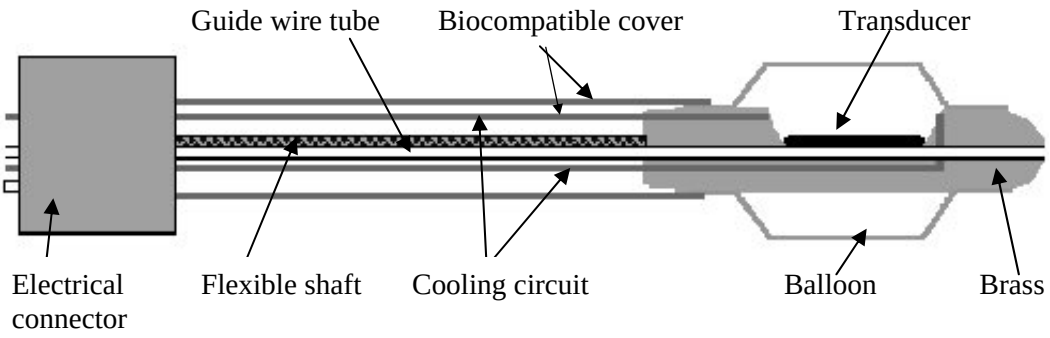

Figure 1 – D. Melodelima

Hal-Inserm Author manuscript

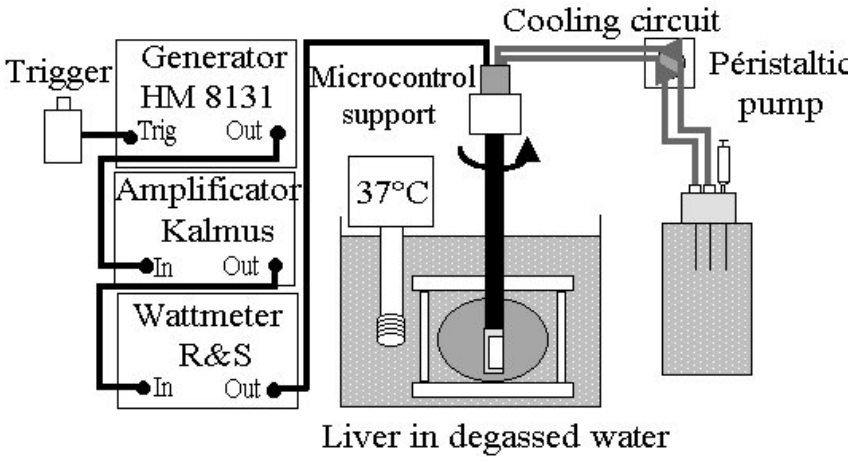

Figure 2 – D. Melodelima

Hal-Inserm Author manuscript

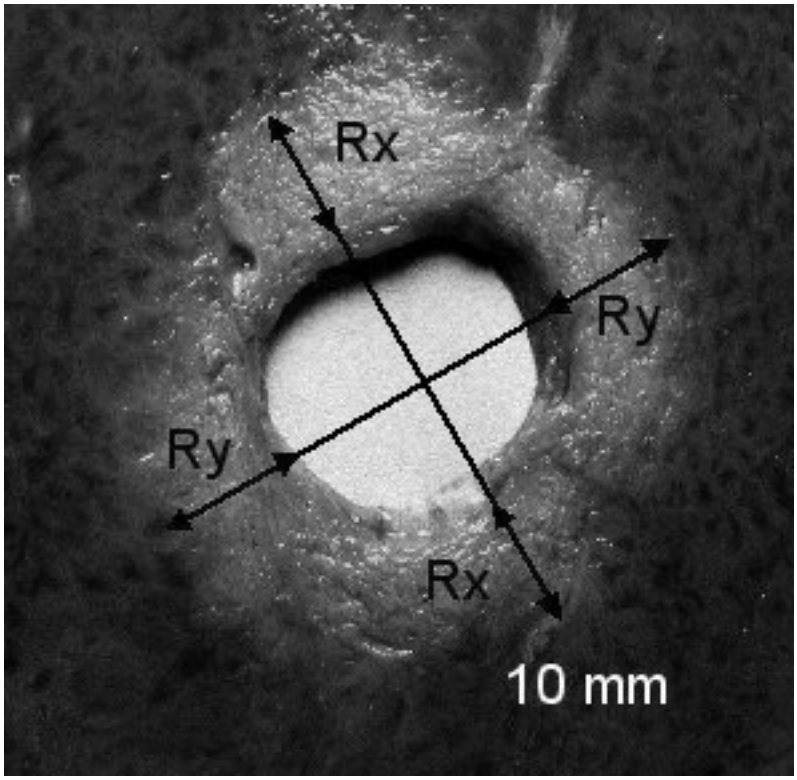

Figure 3 – D. Melodelima

Hal-Inserm Author manuscript

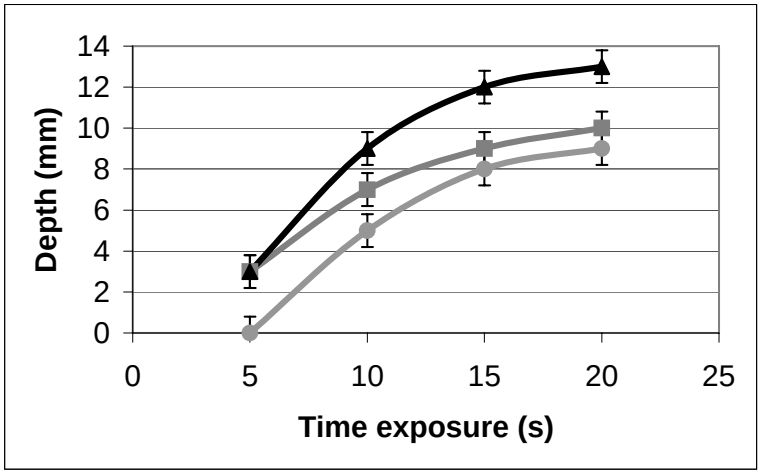

Figure 4 – D. Melodelima

Hal-Inserm Author manuscript

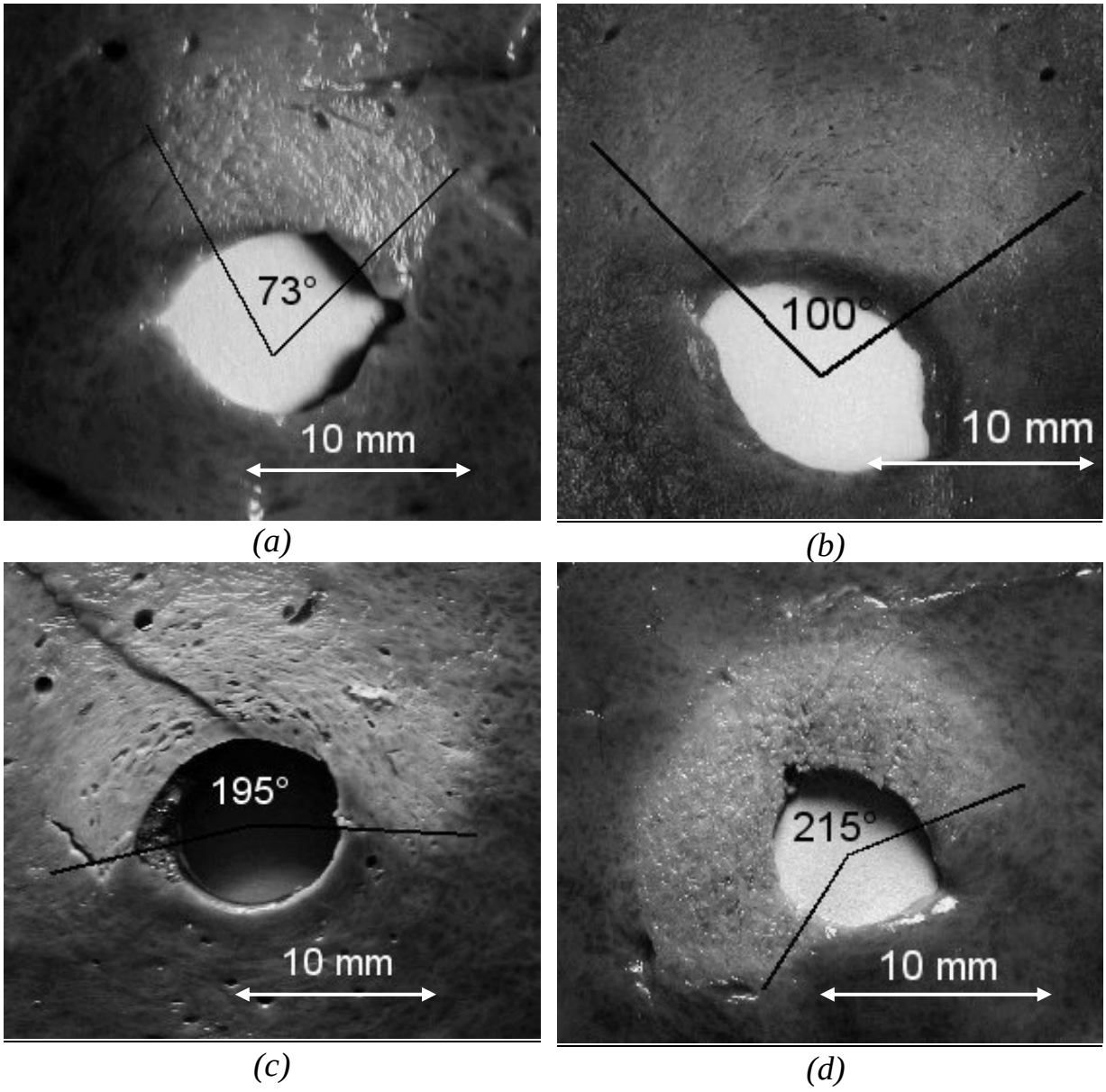

Figure 5 – D. Melodelima

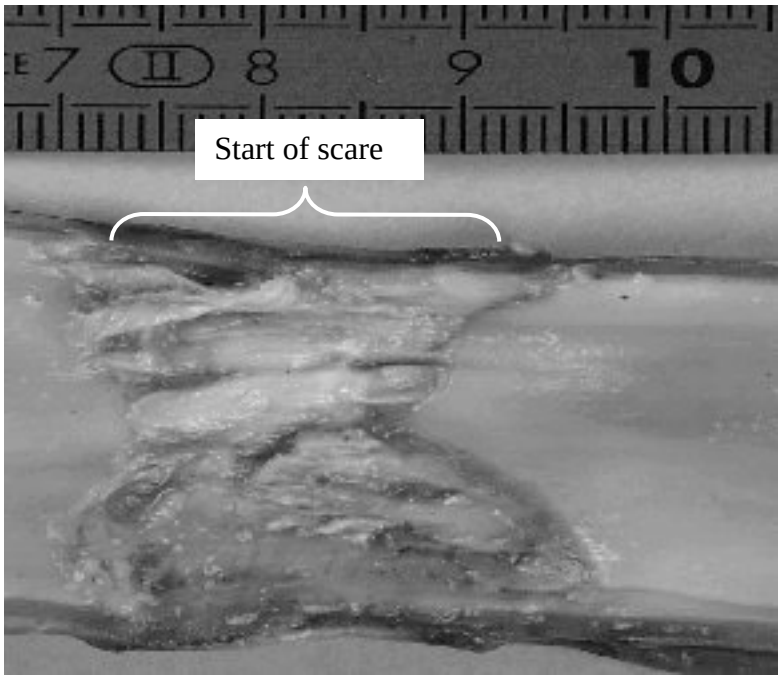

Figure 6 – D. Melodelima

Hal-Inserm Author manuscript

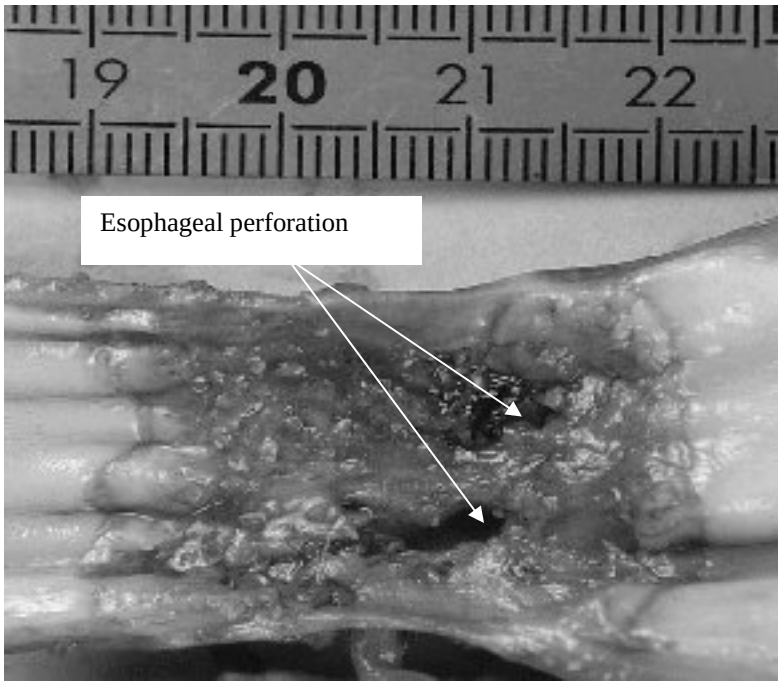

Figure 7 – D. Melodelima

Hal-Inserm Author manuscript

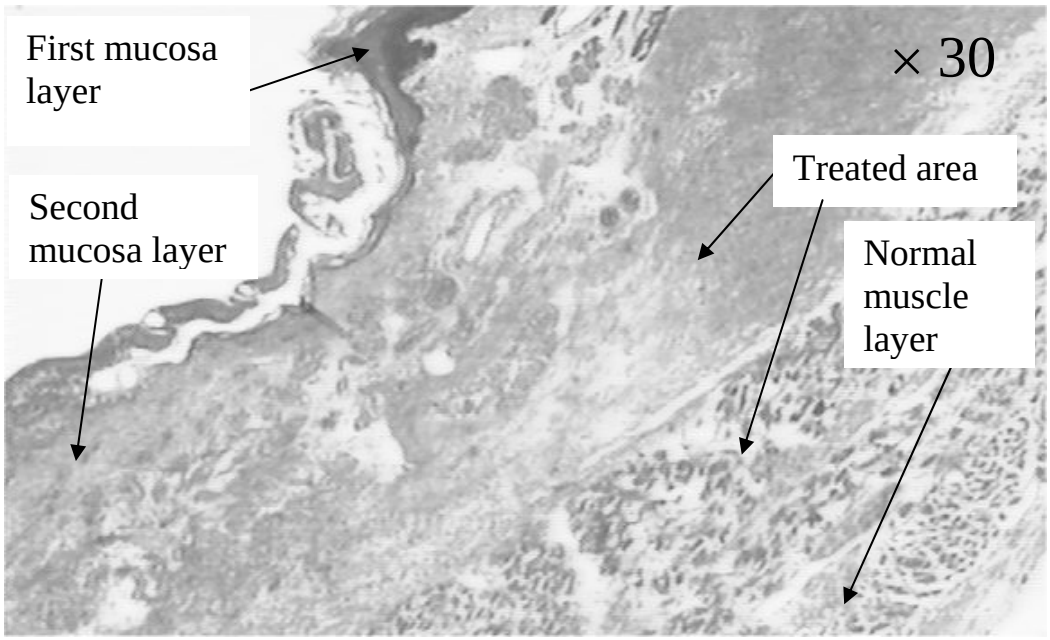

Figure 8 – D. Melodelima

Hal-Inserm Author manuscript

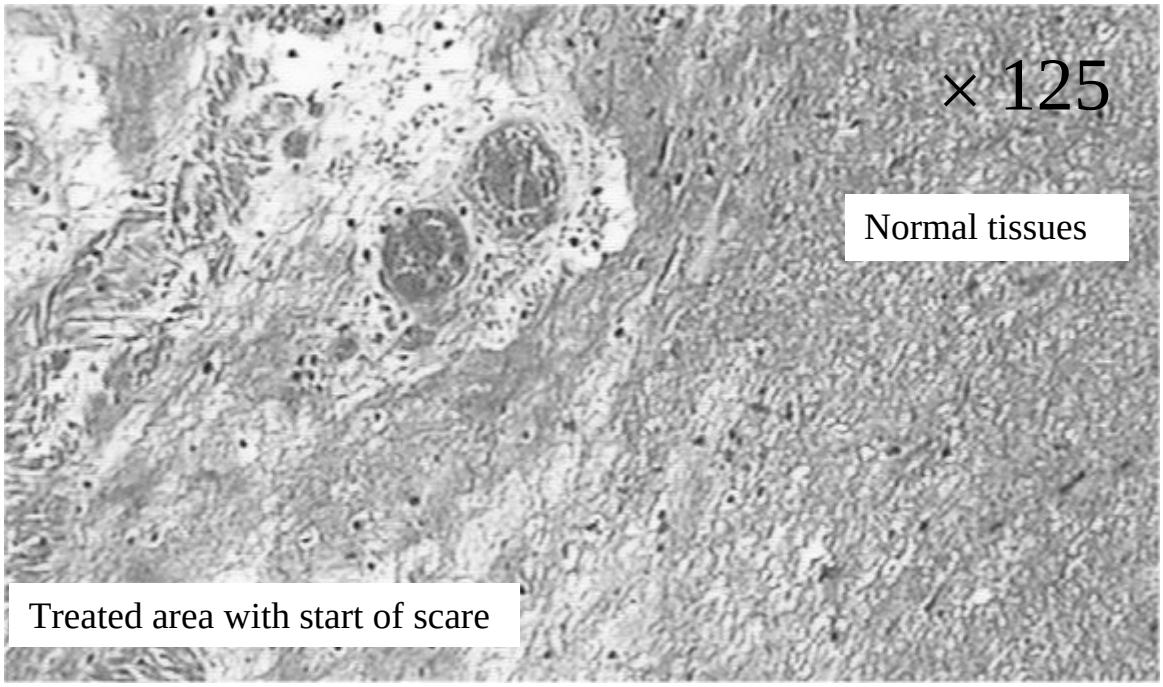

Figure 9 – D. Melodelima

Hal-Inserm Author manuscript

Preplanned treated angle (Degrees)	Experimental result (Degrees)
72°	(73±2)°
108°	(100±2)°
198°	(195±2)°
216°	(215±2)°

Table 1 – D. Melodelima

Hal-Inserm Author manuscript

Time between treatment and autopsy	48 h Circular treatment			72 h Circular treatment		96 h Circular lesions	
Acoustical intensity (W/cm^2)	14		16	12	14	12	14
Time exposure (s)	10	15	10	10	10	10	5
Esophageal perforation	No	Yes	Yes	No	No	No	No
Homogeneous thermal damages	Yes	Burned areas	Burned areas	Yes	Yes	Yes	Yes
Circular treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Efficient cooling	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tracheal perforation	Not tested	Yes	Not tested	Not tested	Yes	No	Not tested
Surrounding tissues	Intact	Lesion	Lesion	Intact	Intact	Intact	Intact

Table 2 – D. Melodelima