Experimental Study on a Large Animal Model of a New Thermoablation Technique

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Abstract. *Background: A novel technique of thermoablation, using a microtube to deliver pulses of hot water vapour, was tested on a large animal model in order to evaluate its efficacy and potential adverse effects. Materials and Methods: The medical device consisted of a microtube extension connected to a hydro-pneumatic pump. Pulses of pure water were injected though the microtube where they were heated and delivered as vapour into the target zone. The method was tested on the liver of 12 healthy pigs, either during open surgery or percutaneously under ultrasounds. Results: The technique was efficient and well-tolerated by the animals. Large volumes of necrotic tissue were created in a significantly short time compared to concurrent thermoablative techniques. Conclusion: Anticipating human application, this experimental study demonstrated a safe and efficient innovative thermoablation technique. The first human applications have been successfully performed and will be reported soon.*

As far as possible, a surgeon restricts the resection of a tumour to the malignant cells, although if normal and malignant cells cannot be distinguished by direct observation, a portion of healthy tissues around the lesion is also removed.

Surgical resection of liver metastases from primary colorectal cancer remains the best therapeutic method, as well as an excellent solution for the treatment of hepatocellular carcinomas (1, 2). Despite improvements in surgical techniques, resection is not always possible for anatomical reasons (3, 4). Moreover, it is an invasive procedure and alternative, minimally-invasive, treatments such as thermal ablation, localised chemotherapy and interstitial radiotherapy have been developed. These techniques deliver the correct dose of the active agents directly to the lesion.

Thermoablative procedures include cryoablation, radiofrequency (RF), interstitial laser photocoagulation (ILP), high-intensity focused ultrasound (HIFU) and microwaves. The liver is among the organs most frequently treated by thermoablation, mainly using radiofrequency. The extension of these methods to hepatic metastases is on the increase since few of these tumours are sensitive to chemotherapy (5). Thermoablative techniques are now being applied to other organs such as the lung, breast, bone, kidney, soft tissues, thyroid and prostate (6-10).

Several authors have stressed interest in combining heat and local chemotherapy (11-13). The innovative Targeted Multi Therapy (TMT) technique investigated in this paper has this capability of delivering various active agents through the same channel (microtube). The first field of development was the application of TMT to thermal ablation. The new method proposed comprises the delivering of pulses of calories under a small volume of water locally and minimally-invasively into the targeted region. The innovative aspect of this procedure is the use of wet heat to induce tissue necrosis.

Prior to treating liver tumours in humans, the new thermal ablation technique was tested *in vivo* on mice (14). The objectives of the present study were to assess the performance and the tolerance of delivering wet heat to the livers of living pigs for the destruction of hepatic tissues.

Materials and Methods

The medical device, developed internally by CERMA (Archamps, France), is composed of two parts: a controlled injection unit (or hydro-pneumatic pump) and a microtube extension connected to the injection unit.

The injection unit is a portable box working with pressurized air. It is made up of a controlled air piston, a water piston and a pure

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Key Words: Thermoablation, microtube, hot vaporized water.

water container (Figure 1). The air piston actuates the water piston, which pressurizes a constant volume of cold water (pulses <0.1 cm^3). The up and down movement of the pistons initiates two actions: the filling of the injection chamber with pure water (one pulse), and the propulsion of this agent through the microtube extension where it is heated. Then the pulse of vapour is directly delivered into the core zone to treat the tumour.

The microtube extension is a disposable device made up of a long flexible element that ends with a biopsy-like needle (Figure 1). The heating system is integrated inside the needle at the extremity of the tube. The liquid water flows through the heating tube, where it is transformed into vapour. The heat is generated only at the end of the needle, which is inserted into the centre of the tissue. Thus, the heat is delivered into the targeted zone and not lost along the needle path where it could damage the surrounding healthy tissue. The needle can be inserted into the tissue, either during open surgery or percutaneously under ultrasound, CT scanner or MRI guidance. The needle is perforated at its extremity, allowing the water vapour to reach the target: one single longitudinal hole and/or several radial holes of 50 μm each.

The overall device is controlled by an electronic-software system integrating two independent microprocessors. The power distributed to the heating system is monitored in real-time.

Calibration tests. Calorimetric tests have been completed so as to calibrate and establish the calories carried per volume of water injected, and to demonstrate the reliability of the thermoablation device.

The experiment was as follow: 10 vials containing approximately 150 g of water (M) were weighed and the initial temperature was measured. This volume of water was chosen in order to minimize the additional volume of water injected as vapour. Then, the microtube extension was introduced into each of them during a constant number of pulses. The vials were then weighed and the final temperature measured. The number of calories delivered per cm^3 of water injected was calculated in a first approximation as $Q = M * C * \Delta T / \Delta M$, where C is the specific heat of water, and ΔT and ΔM, respectively, the temperature and mass differences.

This experiment was repeated 4 times with the injection of 8, 16, 32 and 40 pulses, corresponding to 0.56 ± 0.03 cm^3, 1.10 ± 0.05 cm^3, 2.27 ± 0.07 cm^3 and 2.94 ± 0.10 cm^3 of water, respectively ($p < 0.05$). Thus the volume of water injected per pulse was calculated to be $V = 0.071 \pm 0.005$ cm^3/pulse ($p < 0.05$). On average, the calories delivered per cm^3 of water injected were $Q = 523 \pm 14$ cal/cm^3 ($p < 0.05$) and, by extrapolation, the calories delivered per pulse were $Q' = 36.4 \pm 1.0$ cal/pulse.

Ex vivo calibration on anatomical tissue: bovine liver. Vapourized water was injected into excised specimens of bovine livers in order to evaluate the volume of tissue affected by a calibrated number of calories. Bovine and not pig liver was chosen because more homogeneous pieces of tissue could be obtained.

For each volume of water, the thermoablation procedure was repeated up to 10 times in different parts of the liver. The experiment was conducted for four volumes of water: 0.56 cm^3, 1.1 cm^3, 2.27 cm^3 and 2.94 cm^3, corresponding to 8, 16, 32 and 40 pulses (equivalent to the calibration tests), and a total of 36 lesions were treated. The three dimensions of each lesion were measured by visual observation of the necrotised tissue and the volume was calculated using the formula $\{Volume = 4*\pi\ (a*b*c)/3\}$, where a, b and c are the radius of the hemiellipse.

Tests on the liver of healthy pigs. The experimental protocol was approved by the ethical board of the University Hospital of Geneva, Switzerland (number 31.1.1068/2050/II).

Twelve female pigs of "grand blanc" race were treated by thermoablation with wet heat. Their average weight was 45 kg. The main objectives of these tests were: (i) to validate the feasibility of the medical procedure on vascularized liver; (ii) to verify the tolerance to the treatment; (iii) to estimate the volume of necrosis according to the volume of injected water vapour; and (*i.v.*) to demonstrate cell death in the necrotized tissue as proof of the efficacy of this new technique.

The pig liver is divided into four lobes: the extreme left, the middle left, the extreme right and the middle right. These lobes are thin, maximum 4 to 5 cm and, as a consequence, it is sometimes difficult to obtain a large zone of necrosis within the lobe since the boundaries are easily reached.

The pigs were sedated by intramuscular injection using Stresnil®, Dormicum® and Atropin® in order to diminish anxiety, to reduce vagal reflex and prepare for the general anaesthesia. Then the animals were anaesthetized with a mixture of 5% of isoflurane in 100% of oxygen. For the duration of the treatment, the animals were kept under 2% isoflurane. An endotracheal intubation was installed. For the pigs no.4 to no.12, a catheter was placed in the jugular vein to take blood samples at regular intervals during the procedure.

Three pigs (no.1 to no.3) were treated *via* laparotomy and sacrificed immediately after the end of the thermoablation to observe its immediate effects. Specimens of tissues for biological tests and anatomopathological investigations were extracted.

The subsequent nine pigs (no.4 to no.12) were treated by a percutaneous procedure (15, 16) and kept alive for 14 days on average. The pigs were sacrificed from D+6 to D+21 after treatment. Among these nine pigs, 4 were treated with a single injection of water (no.4 to no.7). For the remaining 5 animals (no.8 to no.12), several lesions were induced, each one divided into two injections performed at one-to-two minute intervals.

The treatment was divided into three main steps: (i) first, under ultrasound (US) imaging, the targeted zone was located; (ii) secondly, the thermoablation needle was inserted into the liver under US and the treatment was carried out with a series of pulses of vapour; (iii) finally, the thermoablation probe was withdrawn and the morphology of the lesion was observed under US for a few minutes.

For the nine pigs kept alive after the treatment, two supplementary US imaging controls were carried out, on average on D+2 and D+6, with finally a third one just before sacrifice. The gross pathology included an intra-abdominal exploration in order to determine whether secondary effects, such as burns and abscesses, had occurred. After sacrifice, the liver was completely removed for additional tests. The tolerance of the hepatic, renal and hematological functions was evaluated by comparing the results of different blood tests on samples taken before the treatment (control samples), at the time of the two US-imaging controls and before sacrifice.

Statistical analysis. When simple linear regression analyses were performed, 'b' and 'r^2' represented the regression coefficient and the coefficient of determination, respectively.

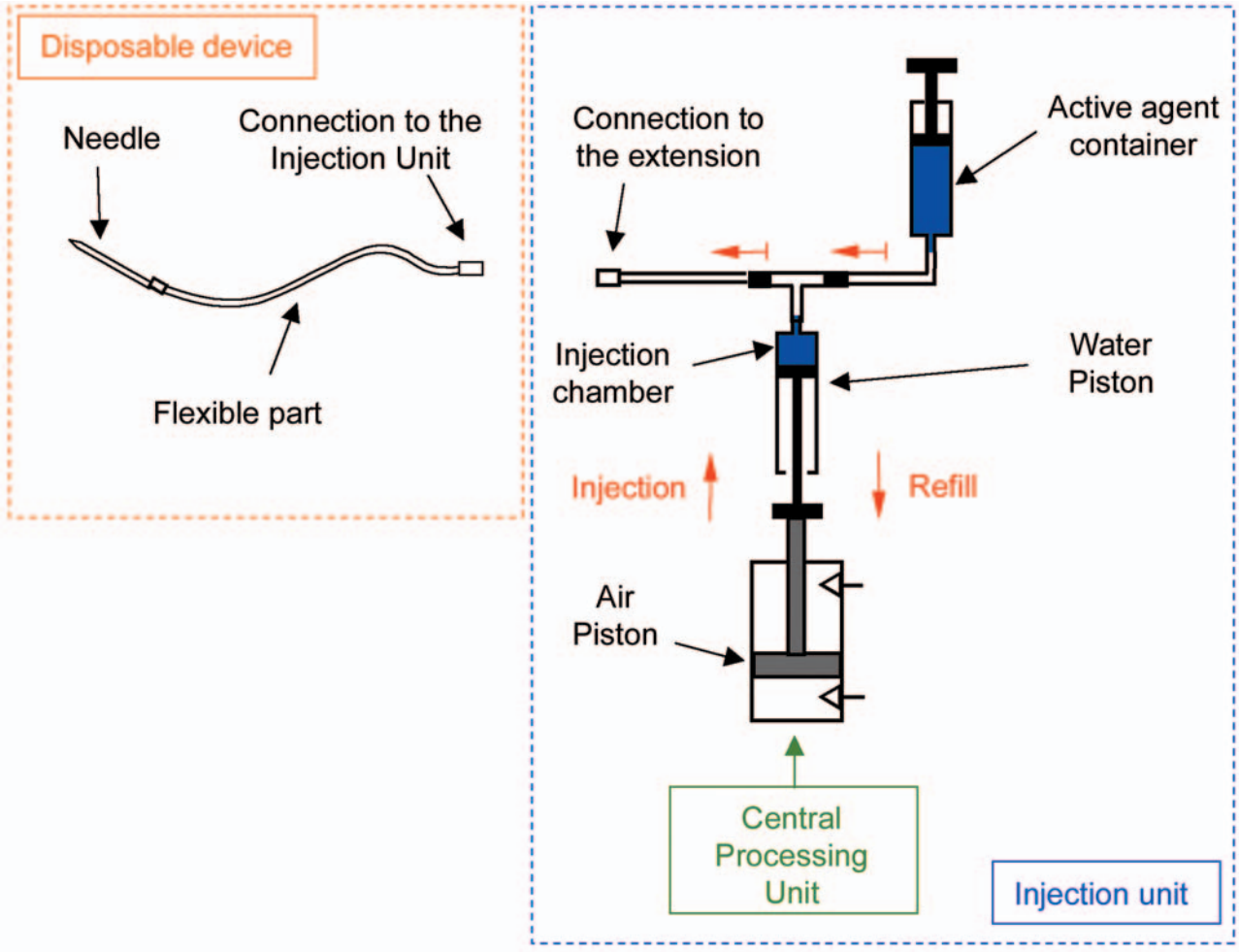

Figure 1. *Functional principle of the new thermoablation medical device developed by CERMA (Archamps, France).*

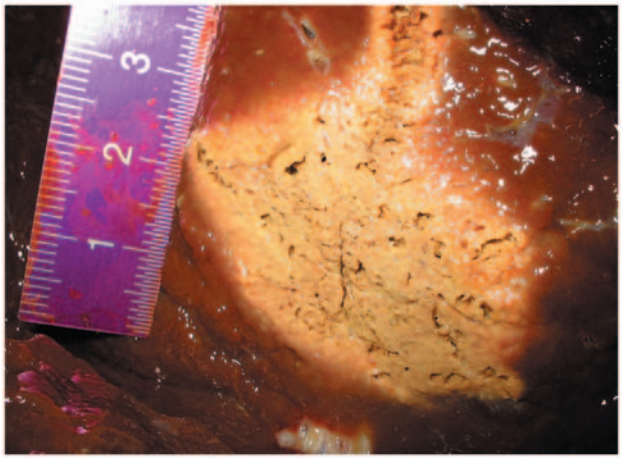

Figure 2. *Necrosis observed on an excised specimen of bovine liver after the injection of 2.94 cm^3 of water.*

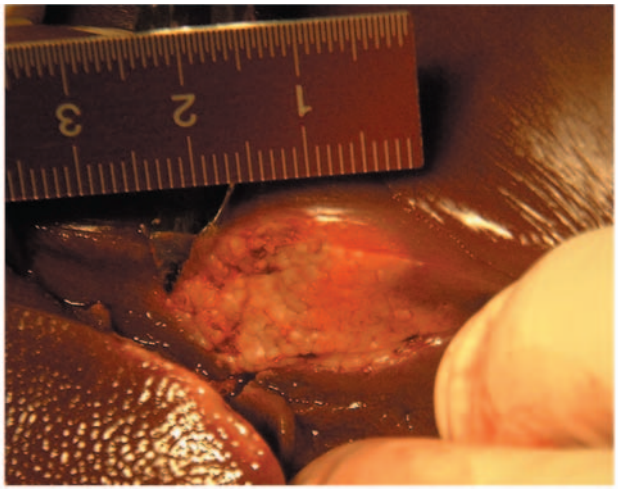

Figure 3. *Necrosis observed on the in vivo liver of a pig after the injection of 0.54 cm^3 of water.*

Table I. *Thermoablation on excised specimen of bovine liver; test parameters and results.*

Experiment no.	Nb of samples	Nb of pulses	Volume of water injected [cm^3]	Mean volume of the lesion [cm^3]
1	9	8	0.56	2.58±0.46 ($p<0.05$)
2	10	16	1.1	3.60±0.47 ($p<0.05$)
3	10	32	2.27	9.16±1.21 ($p<0.05$)
4	6	40	2.94	12.18±2.94 ($p<0.05$)

Results

Ex vivo experiment. Table I summarises the preliminary experiments in which different quantities of water vapour were injected into excised specimens of bovine livers. The average times to obtain these necroses were 16 seconds, 33 seconds, 66 seconds and 84 seconds for experiments no.1, no.2, no.3 and no.4, respectively. It was apparent that a linear relationship existed between the volume of water injected and the size of the lesion. In *ex vivo* experiments, the ratio between the volume of water injected and the size of the necrotic tissue was 4.05.

Due to the configuration of the needle, ellipsoid lesions were created (Figure 2) around the tip of the needle. A small cylindrical necrosis was also observed along the path of the needle, but was not taken into account for calculation of the size of the lesion. Some blood vessels were totally surrounded by necrotic tissue without any macroscopic lesions of the vessel wall itself.

In vivo experiment. A total of fifteen lesions were usable in twelve pigs. In Figure 3, a typical result shows the lesion produced with the injection of 0.54 cm^3 of vaporized water into the middle left lobe of a liver 2 cm thick.

Clinical aspect: From a clinical point of view and during the general anaesthesia, the pigs tolerated the treatment very well. Only two of the test animals (pigs no.2 and no.3) encountered some respiratory problems for a few minutes, probably due to a small embolism at the base of the hepatic veins. The nine pigs which were not sacrificed immediately had normal surgical follow-up, based on their behaviour and feeding.

Biological investigations: Tests on NFP (numerical formula of platelets), TP (prothrombin time), TCK (creatine kinase), CRP (C-reactive protein), hepatic assessment (GOT, GPT -transaminases, alkaline phosphatase, gamma GT), urea and creatinine were performed. The controls were carried out on a regular basis. On average, the nine pigs were controlled four times. Besides a slight increase of the gamma GT up to 63 UI/l, seen in pig no.4 on D+9 (data not shown), all the other blood tests were normal.

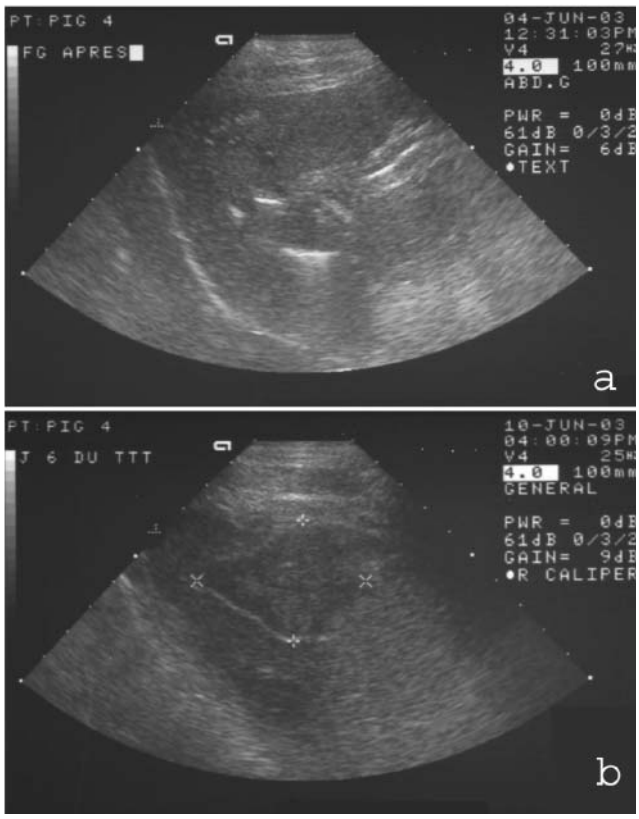

Figure 4. *Echographic images of the liver of a living pig (a) during the thermoablation treatment and (b) 6 days after treatment.*

Ultrasound imagery: Before the treatment, the liver appeared homogeneous under US imaging with a regular structure. During treatment, the liver constitution was heterogeneous. Some hyperechoic centres (foci) became visible on the picture, probably due to some small haemorrhagic sites (Figure 4a). Just after thermoablation, the lesions had oblong shapes of different sizes. A few days after the treatment, a re-organization of the necrotic zone could be seen. The previous hyperechoic centres became hypoechoic, probably due to tissue degradation. The lesion appeared on the US screen as a superposition of concentric layers, like onion skin, with an encapsulation of the treated zone compared to the healthy parenchyma (Figure 4b). The US device used was an Acuson™ 128 R/F (Acuson Corp., Mountain View, CA, USA). Unfortunately, this basic apparatus did not offer sufficient spatial resolution to position the needle with precision and to accurately evaluate the necrotic zone.

Anatomo-pathology: The anatomo-pathological examinations were performed on the liver of ten pigs. The lesions were first macroscopically located, removed with a thick outer layer of healthy tissue, then measured and fixed in formalin.

The macroscopic examination of the various lesions showed whitish coagulation areas of regular shape. In the majority of cases, ellipsoid lesions were observed and, more rarely, spherical lesions. The volume of the necrotic areas varied from 0.59 to 16.49 cm^3 (Figure 5) and were proportional to the volume of water vapour injected (0.45 to 7.5 cm^3). From the linear regression equation {y=2.36x} in *in vivo* experiments, the injection of a calibrated volume of water generated, on average, a volume of necrotic tissue equal to 2.36 times the volume of the water injected.

The following hepatic lesions (data not shown) were observed: partial or total necrosis organized into foci often in multiple lesions with other unclear, superficial or deep boundaries. The necrosis could be homogeneous, oxyphile and was more regularly observed on large parenchymal areas than on isolated cells. The hepatocytes had a condensed aspect and their cytoplasm was dense, eosinophilic and grainy. The cores were homogeneous, retracted in the process of pycnosis. Councilman elements (bodies) were not seen. The necrosis was due to ischemia or to coagulation. Cell death was complete and frequently found in vast zones of parenchyma with poorly-defined margins of the cell and pycnotic cores. Moreover, some sectors with autolytic necroses were seen.

In some cases, granular inflammatory lesions were also observed at the edge of the necrotic foci. In others, a polymorphic granuloma was present at the rim of the autolytic foci, made of giant macrophagic cells, spumous histiocytes, deteriorated polynuclears and purulent foci. Sometimes, vascular lesions were noted with inflammatory remodelling of the vessel wall and a few recent thrombi.

On the histopathological section (Figure 6), the hollow space left by the needle shaft can be visualized. This path is surrounded by an important inflammatory granuloma along with abscesses and macrophagic resorption. Deeper in the tissue, the hepatic necrosis is total in conjunction with some small recent vascular thrombi.

Therefore, the gross pathological study confirmed that, most of the time, the injection of water vapour achieves extensive area of necroses with inflammatory granuloma. Cavitations were never detected, as reported for other techniques (17).

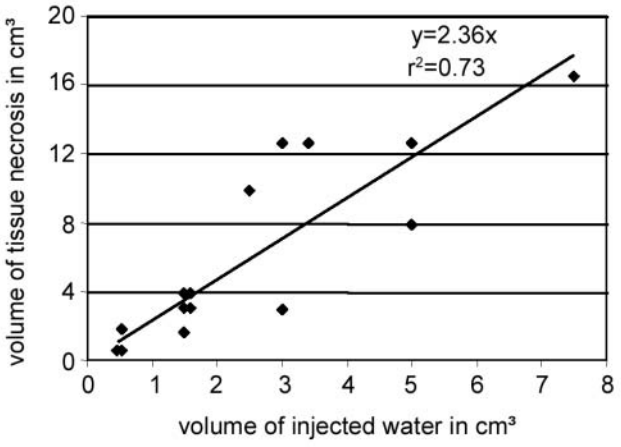

Figure 5. *Scatter plot of linear relationship between the volume of tissue necrosis ($b=2.36$, $r^2=0.73$) and the volume of injected water in the liver of 12 healthy pigs.*

Discussion

The TMT technique has multitherapy capabilities, but this study was restricted to the evaluation of thermoablation with vaporized vapour.

Other techniques. The application of heat to treat living tissues (cautery) has been used for a long time. More recently, hyperthermia techniques have been developed at temperatures below 50˚C (18). In addition, malignant cell destruction with water at temperatures between 70˚C and 87˚C has been reported with mitigated success (19, 20).

Radiofrequency (RF) thermoablation utilizes an alternating current (350-500 KHz) to generate ionic agitation, that results in heat and produces coagulative necrosis. The direct heating due to RF is limited to the close vicinity of the needle. The heat is then distributed by conduction into the tissue to form a more or less spherical zone of necrosis around the electrode (21). To date, the main application of RF is the treatment of hepatic metastases from primary colorectal cancers, owing to their spherical shape. This advantage might be a serious drawback if the needle is not inserted in the centre of the tumour, or the tumour is not spherical, as frequently occurs.

During RF thermoablation, the tissue temperature is kept below 110˚C to minimize adverse effects such as tissue boiling, vaporization and carbonization (22, 23). The production of gas bubbles and char acts as a heat and electrical insulator, resulting in incomplete ablation. Some manufacturers of RF equipment have circumvented this disadvantage by infusing cooling liquid to reduce the temperature at the needle surface area (24). It is observed that the infusion of liquid improves the electrode tissue interface and that direct ablation is generated *via* the heated liquid diffusing into the tissue (25, 26).

Discussion about the experiments. From a technical point of view, the reliability of the medical device with hot vapour was excellent. For water quantities injected, ranging from 0.56 cm^3 to 2.94 cm^3, the number of calories per ml of water at the exhaust point was constant and equal to 523 ± 14 cal/cm^3 ($p<0.05$).

The dimensions of the coagulation zones created with the injection of water vapour were compared between

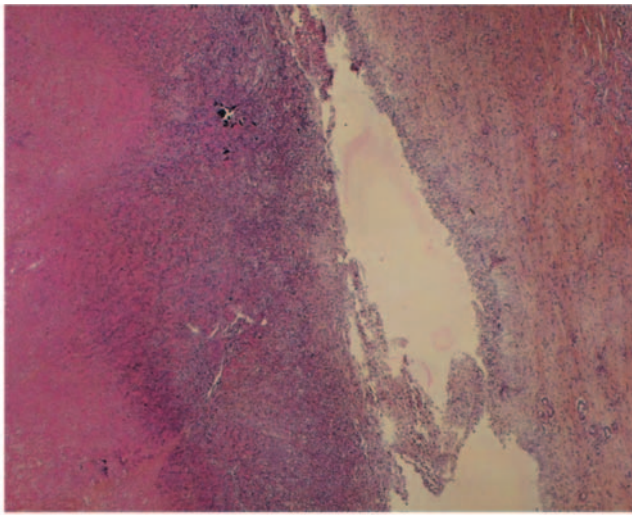

Figure 6. *Histological section observed at a magnification of 4 showing the necrotic zone and the remodelling of the adjacent cells.*

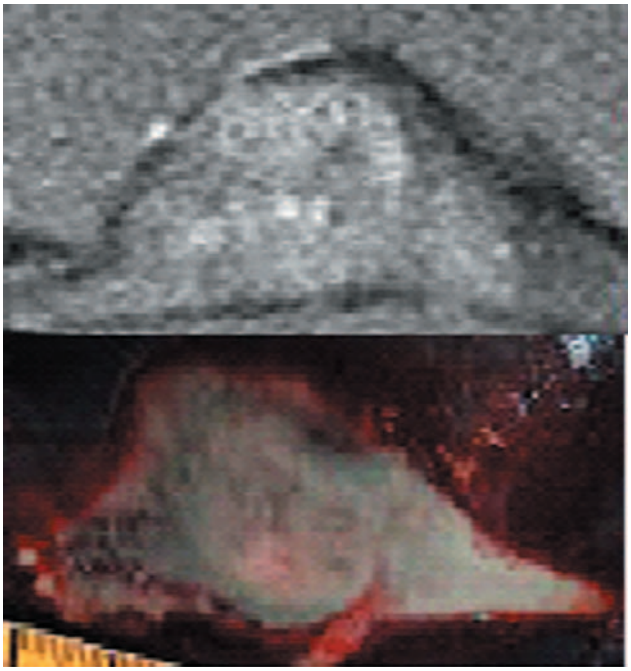

Figure 7. *MRI image (Proview 0.23T, Marconi Medical Systems, Cleveland, USA) obtained with an Inversion-Recovery sequence (90/90/16) and the image of the excised specimen of liver after thermal treatment in vivo.*

experiments performed on excised specimens of bovine livers and on livers from healthy pigs in *in vivo* experimentation. It was found that the ratio of the volume of necrosis induced over the volume of water injected had a factor 4.05 for *ex vivo* tests and a factor 2.36 for *in vivo* tests. This difference can certainly be attributed to the effect of the bloodstream when large blood vessels are close to the targeted region, as reported by various authors (25, 27, 28). Additionally, since the water vapour is injected into the parenchyma, the heat confinement due to the "capsule effect" surrounding the tumour is lost. This effect was clearly observed on a specimen of bovine shin where the calories were contained within the fascia. These figures correspond to the volume of tissue necroses observed by gross pathology for a calibrated amount of calories injected. These results do not compare with data reported in a previous work where the optimum amount of calories required to destroy a tumour were observed on an *in vivo* model (14). In these latter experiments, the destruction of malignant tissues can take several days, depending on the temperature distribution during the thermoablation procedure (29).

As expected, the coefficient of determination "r^{2}" for the *in vivo* experiments (r^2=0.73, Figure 5) was not as good as that for the *ex vivo* experiments (r^2=0.99) due to the influence of blood flow (heat sink). For the same amount of water injected, the volume of coagulation can be more or less, depending on whether the probe is inserted near a blood vessel or not. For this reason, the thermoablation procedure requires precise positioning of the probe under accurate guidance by ultrasound. However, pig liver lobes are significantly thinner than human liver and it was rather difficult to locate a portion thick enough to insert the tip of needle right into the centre.

Advantages of the TMT technique over concurrent techniques. The new thermal ablation technique with hot water has several advantages. (i) Although the quantity of energy delivered to the tissue was significant at Q=523 cal/cm^3 of water, no charring was ever observed. This can be attributed to the injection of wet heat. (ii) The volume treated per unit of time was greater for the TMT technique compared to the RF techniques. With the TMT thermoablation technique, necrosis was observed with a volume of up to 16.5 cm^3 for a treatment time of 3.5 minutes. Patterson *et al.* (28) have reported an average necrosis volume of 6.5 cm^3 (p<0.001) for a treatment time of 10 minutes on non-tumorous liver tissue of swine. Antoch *et al.* (30), using a cool-tip probe for 20 minutes on Göttingen mini pigs, found, on average, a necrosis of 3.9 cm in the large-axis diameter and 2.7 cm in the small-axis diameter. The use of hot water vapour to convey heat had two favourable effects on the coagulation dimensions. First, the natural vapour pressure used helped the diffusion of the calories deeply into the tissue. Secondly, after transformation into liquid water, the hot liquid

induced coagulation by direct thermal contact (23, 31). (iii) A fairly homogeneous destruction of cells was observed on the anatomo-pathological samples as well as on the MRI images (Figure 7). On the contrary, with RF thermoablation, the heat generated drops with the distance r from the probe tip (32), resulting in a non-homogeneous distribution of energy, hence a non-homogeneous necrosis. (iv) The animals tolerated the procedures during the treatment very well. All the blood tests were normal, except for pig no.9 on D+9 (data not shown) which had gamma GT slightly above normal. Further, this animal did not show any signs of pain. For the period after the intervention, the behaviour and feeding patterns of all the animals were satisfactory.

Minimally invasive procedures require adequate monitoring. The thermoablation procedure was carried out with ultrasound guidance, demonstrating that the percutaneous approach was operational. Nowadays, the trend for all minimally invasive techniques is the use of MRI, which offers a unique way to measure, non invasively, the internal temperature. Hence, the components of the TMT device were made from "MRI compatible" material (33).

The medical device was monitored by two microprocessors managing, in real-time, the different actions and sensors. The volume of water injected and the quantity of heat transmitted to the water were adjusted constantly. Indeed, the calorimetric tests corroborated that the energy conveyed per cm^3 of water was constant at±5%. However, each thermoablation treatment is unique and the tumour environment is constantly changing. Because necrosis is the consequence of high temperature, monitoring of the temperature at the tumour site can guarantee good reliability and predictability (34, 35). Consequently, a microscopic temperature sensor is currently being developed and will be incorporated at the tip of the needle to measure, in real-time, the tissue temperature.

Improvement of the TMT device. The first human applications of the thermoablation technique with hot water vapour have been successfully performed and will be reported soon. Currently, the technique is being developed towards the implantable version of the microtube, for the delivery of a variety of active agents. The anticipated strategy could include: first, tumour mass reduction by injection of hot water vapour and, then, *via* the same microtube, delivery of complementary treatments at the right time. It will be possible to use nano-encapsulated chemotherapy and/or interstitial radiotherapy with radioactive nano-particles. Some promising results were obtained with the injection of apoptotic products (33). Moreover, beyond oncology, the TMT can be used in antibiotherapy or for local delivery of pain killers, for example in back pain.

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Received July 28, 2005
Revised September 30, 2005
Accepted October 7, 2005