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A New Method of Thermoablation with Hot Water Vapour for Localized Tumours

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Abstract. *Background: A new method of thermoablation with hot water vapour based on a new type of microtube was developed. This approach allows tumours, with volume and anatomical positions not accessible to other techniques (cryoablation, radiofrequency ablation, laser ablation) to be treated. Materials and Methods: The method was tested on a human colon carcinoma grafted subcutaneously in Swiss nude mice and the experiment monitored under magnetic resonance imaging. Results: It was found that 2.52 cal s^{-1} per cm^3 of tumour were necessary to reduce tumour size. The microtube is built to withstand a large range of temperatures and pressures and is biocompatible. Conclusion: A specific feature of this technique is that, besides hot vapour, several types of drugs can be delivered through the same microtube depending of the location, type or size of the tumour. These properties make it a unique device for multi-therapeutic treatments.*

In most pathologies showing physical alterations of a tissue, surgery has demonstrated its therapeutic efficacy by direct resection of the lesions. The discovery of X-rays introduced a major improvement in the non-invasive localization and delineation of lesions.

Despite its remarkable results, surgery remains an invasive solution and radio-oncology has been a valuable alternative for several decades. The incidence of primary cancer of the liver ranks fourth worldwide. It has been estimated that 130,000 new cases of colorectal cancer are diagnosed each year in the United States and that more than 50% of these patients will develop liver metastases (1,2). This represents 95% of all liver tumours operated in the United States. Only 5% to 10% of hepatic metastases from colorectal cancer have been found to be resectable (3,4). Due to the major dysfunction of the organ in the case of chronic hepatitis or cirrhosis on the one hand and bad localization or large size of the tumour on the other, only a small amount of them are operable. It is estimated that nearly 50% of patients referred for hepatic resection do not actually undergo surgery (5,6). This has led to the development of minimally invasive techniques for treating liver tumours: percutaneous ethanol injection, radio frequency ablation (RFA), high intensity focused ultrasounds, cryoablation with liquid nitrogen (CRY), thermal ablation with lasers *etc.* The new and accurate imaging modalities (mainly computerized tomography and magnetic resonance imaging, MRI) are standard procedures nowadays in radiology departments. They permit not only an active device to be guided accurately, but also the visualization of the area to be treated. In fact, both of these advances played an important role in the development of these minimally invasive treatments. All these efforts have a common aim: to treat the lesion – and just the lesion – with an optimal efficiency and minimal side-effects.

However, each of the minimally invasive techniques mentioned above has some limitations (7-11). RFA and CRY have an upper limit to the volume which can be treated: namely, 5 cm diameter, but non-resectable tumours are often above this volume. Further, respiratory motion, blood pulsatility, peristaltic motion and the involuntary motions of the patient are drawbacks for most of these techniques. For instance, therapies with neutrons or protons have to be monitored by sophisticated motion-tracking software. The same problem occurs with focused ultrasounds (8); moreover, this latter technique has a high power deposit and side-effects that might prevent its use.

The new technique proposed here is based on a microtube, which categorizes it as minimally invasive. In the present work, a prototype of a microtube, made of biocompatible material in order that it can remain implanted for a long period of time, has been developed. It

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can be inserted percutaneously or during open surgery. This permits the active agent to be delivered when it is required according to the evolution of the lesion. Through the microtube can be administered several types of drugs, *e.g.* antibiotics, immunotherapeutic agents, drugs liberating free radicals (12) (like oxygen peroxide) or, as will be shown in this work, water vapour. The doses can be injected at the required localization and the release rate and quantity can be adjusted adequately (9). Finally, the direct positioning of the microtube in the lesion itself overcomes the adverse effects encountered with body movements (breathing, peristaltic movement, *etc.*).

On the practical side, if the tumour is small it can be treated by injecting conventional drugs through the microtube. If the tumour is large, these conventional therapeutic agents may be inefficient. For this reason the technique proposed here permits either the complete ablation of the tumour with water vapour, or the reduction of its volume such that it will become susceptible to the action of conventional drugs.

Materials and Methods

The whole system. It consists of a conventional High Pressure Liquid Chromatography (HPLC) pump used to carry the cold water towards a homemade "boiler". The terminal part of the system is the microtube hooked up at the output of the "boiler" on one of its extremities, the other one being inserted in the lesion to be treated.

Microtube device. A stainless steel prototype (ISO 316L) with an outer diameter of 200 μm and an inner diameter of 100 μm is shown in Figure 1. The tube is biocompatible and meets the basic mechanical requirements of sturdiness and elasticity. These mechanical characteristics should facilitate surgical implantation or percutaneous insertion. The microtubes were 45 cm in length. In Figure 1 (insert) is shown a macro image of the tiny hole of 50 microns drilled at the extremity of the microtube.

Heat system. The "boiler" is composed of a heat tank around which is wound a stainless steel tube (inner diameter/outer diameter = 0.3/1.6 mm) through which the water circulates. Water vapour is obtained up to 400˚C at the output of the "boiler"; a thermostat regulates the temperature.

Injection device. The HPLC pump (Perkin-Elmer, series 10, Norwalk, CN, USA) delivers the cold water into the "boiler" at a rate of 37 pulses per minute. To calibrate the flow and heat rate delivered by each pulse, 8 vials containing approximately 9 ml of water were weighed. Then, the microtube was introduced into each of them during 10 pulses or up to 45 pulses by incremental steps of 5 pulses. The vials were then weighed again. This experiment was repeated five times.

At the same time, the temperature of the water contained in the vials was measured, by means of a thermocouple (BAT-12, Physitemp Instrument, Clifton, NJ, USA), to evaluate the calories delivered by the injection system.

The values corresponding to the quantity of water delivered by the system as a function of the number of pulses were measured. From the slope of the linear regression ($p<0.05$) the quantity of water delivered was calculated to be 0.034 ± 0.002 ml/pulse.

An increase in temperature of 9 ± 0.42 ml of water (M) as a function of the number of pulses was found. From the slope of the linear regression ($p<0.05$) the increase of temperature per pulse was found to be 1.12 ± 0.09˚C/pulse (ΔT). The number of calories delivered per pulse (Q) by the system was calculated in a first approximation as: $Q = C * M * \Delta T$, where C is the specific heat of the water. Considering that the HPLC pump works at 37 pulses per minute, the time per pulse was 1.62 s. This leads to a Q value of 10.18 cal/pulse (42.65 J/pulse), *i.e.* 6.29 cal s^{-1} (26.36 J s^{-1}).

Magnetic resonance imaging. The experiments were performed under MRI, which permitted the effects of temperature during the injection to be monitored (13-17). The machine used is an open system operating at 0.23 T (Marconi Proview™). The receiving coil was a head coil for *ex vivo* experiments and a wrist coil (15 cm diameter) for *in vivo* experiments.

Ex vivo protocol. All animal experiments (*ex vivo* and *in vivo*) were performed according to the Swiss legislation and approved by the official Committee of Ethics for animal experimentation. One of the requirements was to observe the effects of the treatment. With water vapour, MRI is a unique tool for monitoring the effects of the calories delivered with an acceptable spatial and time resolution in order to circumscribe the tissue alteration only around the lesion. Trials to estimate the most appropriate MRI parameters for the spin-echo (SE) sequence were performed on excised porcine muscle and liver obtained from the Experimental Surgery Department of the Hospital (CHIREX) immediately after the animal was sacrificed. Then, the excised tissue was installed in the head coil at the centre of the open magnet.

MRI assessment: in a first experiment, ~0.51 ml (15 pulses) of hot water vapour was injected in the porcine skeletal muscle. Each pulse lasted 1.6 sec, resulting in a total injection time of 24 seconds. The image acquisition started simultaneously with the injection. Three contiguous slices of 4 mm thickness were obtained every 33 second during the injection. The central image was positioned exactly along the path of the microtube. Before starting the procedure a batch of three reference images were acquired.

Volume assessment: To assess the capability of the technique in terms of volume to be treated

a) 3.4 ml of water vapour was injected during 160 sec (100 pulses) in an excised porcine skeletal muscle, repositioning the tube at the centre of a predetermined region eight times. The tube was perforated at the tip and had additional holes (10) extending from 1 cm of the extremity to 5 cm and drilled along a spiral path. The total time to reposition the microtube did not exceed 10 sec.
b) 2.55 ml of water vapour was injected during 120 sec (75 pulses) in an excised porcine liver, repositioning the tube at the centre of a predetermined region three times . The tube was perforated at the tip and had additional holes (10) extending from 1 cm of the extremity to 5 cm and drilled along a spiral path. The total time to reposition the microtube did not exceed 10 sec.
c) 0.4 ml of water vapour was injected during 20 sec (12 pulses) in an excised porcine liver, positioning the tube at the centre of a predetermined region. The tube was perforated only at the tip.

In vivo protocol. The efficiency of the technique *in vivo* was assessed with water vapour on 6 Swiss nude mice (Iffa Credo, L'Arbresle, France) grafted on the right flank with human colon tumours (T-380) (18). The animals were kept under aseptic conditions in cages fitted with paper filters and fed with standard, vitamin-supplemented irradiated food. In addition, drinking water was supplemented with a polyvitamin preparation (Oranol Roche Basel, Switzerland, 0.3 ml/300 ml) during 4 days of each second week. The growth of the tumour was measured in two dimensions and the tumour volume (volume = L x $l^2/2$) determined as described in Poupon *et al.* Measurements were made every other day up to a dimension corresponding to one tenth of the weight of the mouse (27-32 g). At that point, the animals were anaesthetized with isofluran (Forene, Abott, AG Baar, Switzerland, 1.5-2% in O_2) and freely installed on a bed set in the MRI couch, the head close to the anaesthetic exhaust. Based on the tissue lesions observed in *ex vivo* experiments, it was anticipated that 0.5 ml of hot water vapour should be an acceptable volume to start treatment of the tumour. As an additional precautionary measure, the temperature of the region receiving the hot pressurized water was measured externally with a calibrated laser beam (Raytec Inc., Santa Clara, CA, USA) to ensure that the external temperature of the subcutaneous tumour remained below 50°C. During the procedure, SE sequence was used to monitor temperature effects. The choice of the parameters was based on *ex vivo* experiments (see Results). After treatment, the evolution of tumour' volume was measured as described above. The animals were sacrificed after fifteen days following treatment or at tumour relapse.

Image analysis. Signal amplitudes of the untreated regions of the animal (abdomen), the thermal lesion and the background (noise) were measured. Measurements were made on the same anatomical level for each image sequence of the mice. Three separate regions of interest (ROIs) were sampled from different areas of the same region and the results were averaged. For aIl images, the signal-to-noise ratios for untreated regions of the body (SA*body*) and the thermal lesion on the grafted tumour (SA*tumour*) were determined. Due to the small size of the animal, the measured area was 90 ± 10 pixels. The lesion-to-body contrast-to-noise ratio (CNR) was calculated as:

$$CNR = (SA_{tumour} - SA_{body})/SA_{noise}$$

The images were transferred from the MRI system to a PC using the hospital network. The signal intensity for the ROI was measured using a custom program written in MATLAB 5.2 (The MathWorks Inc. Natick, MA, USA) running on an IBM-compatible PC.

Results

Ex vivo experiment. MRI assessment: From the results of preliminary experiments in which water vapour was injected to specimens of porcine skeletal muscle, it was found that the MRI sequence best suited to observing the effects of temperature on the tissue with an acceptable spatial resolution is a spin echo sequence with a TR/TE of 260/22 respectively; a matrix of 128 x 256 and a slice thickness of 4 mm. With these values, a batch of 3 images was collected every 33 sec. Figure 2 represents successive temporal images of the centre slice where the microtube is inserted (arrows). The arrow shows the centre of a spherical region representing the grafted tumour. The time between the first image – the reference, which is obtained before the hot pressurized water was injected – and the last one, is about three minutes. A significant difference is seen between the first and the following slices, showing the effects of temperature on the tissue. On the second image, a shadow due to the temperature change is seen and it slowly disappears from one slice to the next. On the last image, alteration of the tissue is readily apparent. This demonstrates that ~0.51 ml of water vapour produces an alteration in the tissue of ~3 cm, a value which corresponds to the average dimension of the tumour expected from preliminary experiments.

Volume assessment: For a specimen of muscle the volume necrotized in 160 seconds was estimated to be 350 cm^3, a value confirmed by gross pathology. On the liver, the volume destroyed was about 250 cm^3 if the needle was correctly inserted in the thickest part of the liver, a prerequisite difficult to achieve because of the morphology of the porcine liver. The experiment with 0.4 ml (c) is closely related to what is anticipated in a human treatment of liver lesions. A volume of 20 cm^3 was destroyed in a time not exceeding 20 seconds (Figure 3).

In vivo experiment. Experiment I. Twelve Swiss nude mice were grafted. Out of these twelve animals, one graft did not grow and two had to be sacrificed immediately after injection because of an inappropriate dose of calories. Due to its poor health, a mouse had to be sacrificed at J2.

On adjusting the dose, ~0.31 ml (9 pulses) of water, for the next seven animals, the expected reduction in tumour size was observed. This is apparent in Figure 4 on the image of a mouse with a tumour of 2.5 cm^3 before injection (J0) and on two subsequent images obtained respectively at 10 and 15 days after injection. The volume of the tumour at 10 days was 0.8 cm^3. At 15 days only necrotic tissue surrounded by a tiny rim of remaining tumour tissue was observable. The volume was estimated at less than 0.15 cm^3 (the accurate measurement of the tumour size after treatment was difficult because of the shape of the necrotic zone).

The animals were injected under MRI in order to observe, during the injection, the effects of temperature. A batch of 3 images was collected every 66 sec. Figure 5 demonstrates, on transaxial MRI images, the effect produced by the temperature during the injection. The first image is the reference before injection. From the second image, "on line", significant change in pixel intensity due to the effects of temperature was observed. On the last image, the intensity does not return to the reference values due to

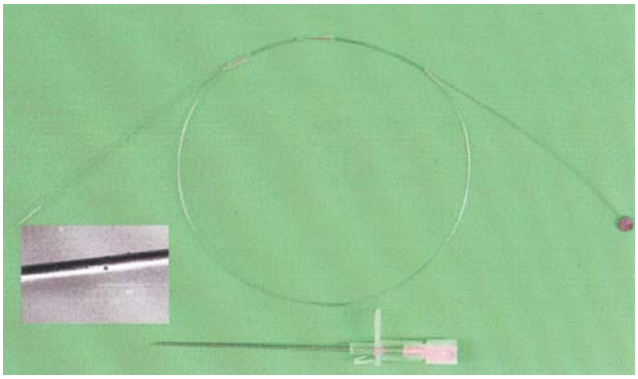

Figure 1. *Stainless steel (AISI 316L) microtube of 100 μm inner diameter and 200 μm outer diameter (compare to a 16-gauge needle).*

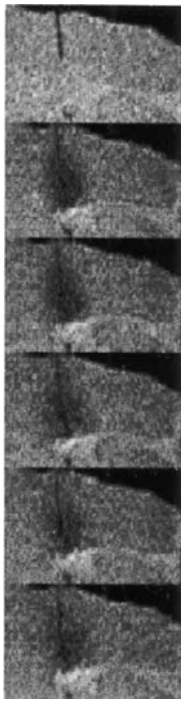

Figure 2. *Set of MRI images, acquired every 33 sec, showing the effect of temperature on a specimen of pig skeletal muscle. The first image is the reference image before the injection of hot vaporized water.*

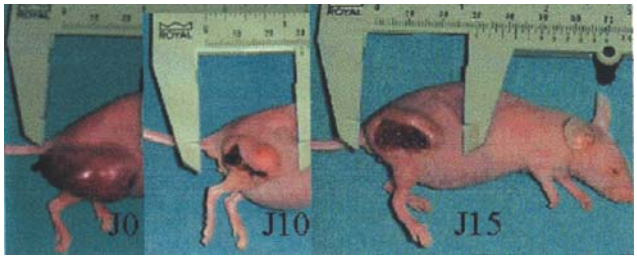

Figure 3. *A specimen of excised liver which had received vaporized water for 20 sec.*

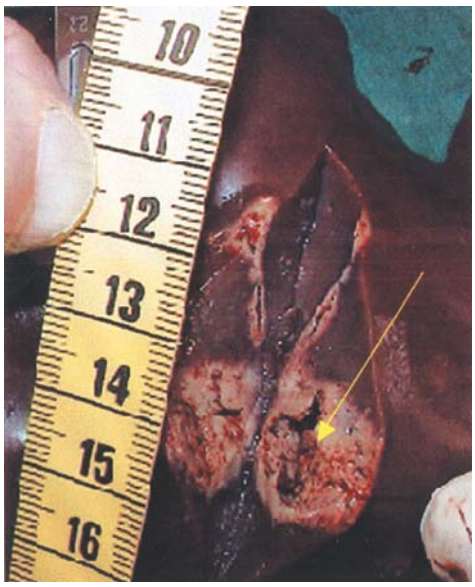

Figure 4. *Example of tumour before the treatment and post-treatment at 10 and 15 days.*

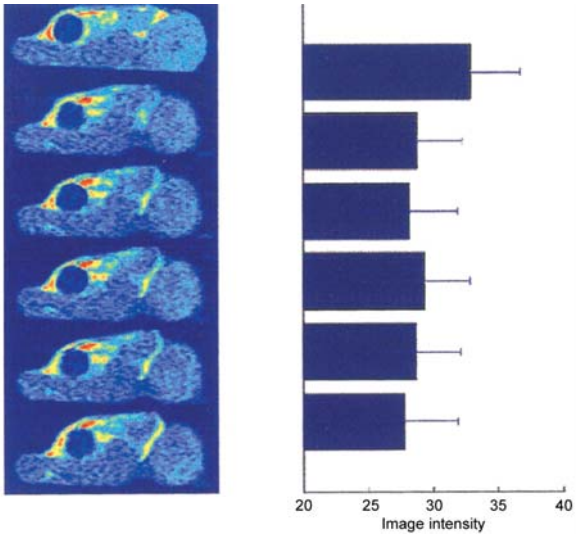

Figure 5. *Set of MRI images, acquired every 66 s, showing the effect of temperature on a tumour grafted on a mouse. The first image is the reference image before the injection of hot vaporized water. The graph shows the mean pixel intensity of the tumour appearing in the same order as images. Bars represent the standard deviation.*

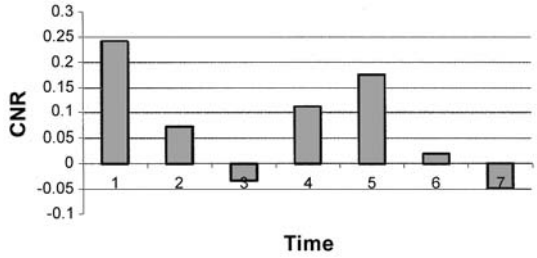

Figure 6. *Graph representing the contrast to noise ratio, corresponding to the graph in Figure 5.*

Table I. *Determination of the appropriate doses of calories to treat the tumour with injection in one location.*

animal	vol. max. cm^3	vol. min. cm^3	cal/ cm^3
1	1.2	0	141
2	1.1	0	177
3	2.7	1.5	45
4	1.4	1.2	70
5	1.6	1.3	73
6	1.0	1.1	118

Table II. *Determination of the appropriate doses of calories to treat the tumour with injection in one or two location.*

animal	vol. max.	vol. min.	nb of pulses	cal/cm^3	% reduction
1	1.03	0	4+2	59	100
2	4.8	1.18	6	13	75
3	1.22	0	3	25	100
4	2.95	0	5+4	31	100
5	1.92	0	4	21	100
6	2.14	0	4+5	43	100
7	2.25	0	5+4	41	100
8	5.4	0.75	6	11	86

tissue alteration, reflected in the relaxation times T_1 and T_2 changes. In Figure 6 is shown the effect on the CNR with time and which confirms the results presented on Figure 5. Indeed, there is a strong decrease of the CNR, followed by an increase during the first minutes, which most likely accounts for the temperature effects. Then, the CNR decreases corresponding to the modifications in the tissue structure (change in T1 and T2).

Table I summarizes the volume of the tumour at the injection time (J0) and the minimum volume measured after treatment, the quantity of calories injected and the calories per unit of volume and the reduction achieved. The estimated dose of hot water vapour necessary to reduce the tumour size according to these preliminary data is: 141 cal/ cm^3.

A control animal was injected with water at 30˚C following the same procedure used with water vapour. The tumour kept on growing and the animal had to be sacrificed five days later due to the size of the tumour.

Experiment II. In order to minimize the dose of calories delivered, the injection procedure was altered by adjusting the locations of injections according to the shape of the tumour, which was not necessarily spherical. Four animals received a unique dose in one location; four animals had two shots, the doses being delivered in each site as indicated by the number of pulses (column 4). Table II summarizes the results. Introducing the calories in two distinct locations has significantly improved the efficacy of the technique since a value down to 21 cal/cm^3 has completely removed the tumour. Below that value, only partial resection of the lesion was achieved. In one case the complete removal of the tumour was obtained with 59 cal/cm^3; possibly the same reduction had been achieved with half that quantity of calories as it can be anticipated if we compare it with the case 3 that has a comparable small volume of tumour. It must be pointed out that these values are applicable for the kind of tumour used, for other type of tumour or tissue, these values have to be adapted. Contrary to experiment I, the minimum volume was obtained between two days and five days.

Discussion

The aim of this study was the development of the appropriate hardware and adequate methodology required to reduce the size of a tumour using water vapour. It has been demonstrated that the technique proposed is effective in causing localized tissue alteration. It has also been shown that a microtube can be used with appropriate equipment to deliver water vapour *in vivo* into the tumour. Due to the small dimensions of the microtube, very limited heat loss occurred along its path with the concomitant limitation of tissue damage.

The method of treatment reported in this study differs from that proposed by Okuda *et al.* (20) by the fact that the temperature of the water is much higher. In fact, vapour is delivered instead of hot water. Therefore, in a short time, with a very limited quantity of liquid, a large amount of calories is deposited in the tumour by the transformation of vapour into water. Moreover, this work was extended to a living animals.

Hahn *et al.* (21) found that the diffusion of alcohol is heterogeneous. In this study, the problem was overcome using water vapour in order for heat diffusion to become almost independent of the structure of the tissue (22). On the type of tumour used in the experiment, a fairly homogeneous diffusion of the calories within the tumour tissue was observed by direct visualization and additionally confirmed by histology.

It can be anticipated that the microtube implanted percutaneously like a biopsy needle (17,23) will be accurately and stably positioned, independent of the motion of the tissue. The microtube could alternatively be inserted surgically, the surgeon adequately routing the microtube to reach the whole lesion. If necessary, it could stay in position inside the body for several days, or even months if properly protected from infection, so as to be ready for a new treatment in case of recurrence of the tumour.

With an adequate length and number of micro holes along the microtube, the technique proposed does not have a critical limit to the size of the lesion to be treated since

"wet heat" is used, avoiding the adverse effect such as tissue charring (17,24) and only small volumes of liquid are injected. Experiments performed with this technique on pig muscle and liver (25) have shown that in three minutes a volume of 500 cm^3 can be treated. This result compares favourably with those obtained by CRY and RFA ablation, which are well recognized as the best methods for treating very large tumours (26-29). Most of the experiments undertaken to evaluate the volume that can be treated were performed on *ex vivo* specimens, therefore, for *in vivo* applications some adjustments have to be anticipated to take into account the blood flow (26). Since this technique is able to treat with one needle, in one shot, a volume of 5 cm^3 in about 10 seconds, it is envisaged to apply it first to liver metastases (24) as an alternative technique to CRY and RFA. Ongoing experiments *in vivo* on the liver of pigs (25) allows one anticipate that there will be no major changes compared to the results obtained *in vitro*.

To strictly limit the thermal lesion to the grafted tumour and preserve the integrity of the animal was a main concern of the *in vivo* experiment described above. Before the appropriate dose of calories was found, two animals had to be sacrificed immediately. After some adjustments, the change in intensity of the images (Figure 5), better visualized directly on the console, provided an efficient monitoring that met the requirements of radiologists trying to assess "on line" the limits of thermal ablation. One salient feature of the procedure is the accuracy with which the adjustment was made during the injection, guided by the intensity of the yellow line at the interface between the tumour and the abdomen of the mouse. This yellow line changes slightly from the reference image to the second image, and is restored on the subsequent images as it was on the reference. After the animal was sacrificed, the integrity of the animal's tissue was confirmed by direct observation on the one hand and by the stability of the SAbody parameter on the other.

This preliminary work on mice is a first step toward applications in humans. In this context, delimiting the exact tumour volume reached by the calories will be less critical since it is common practice for the surgeon removing a tumour as well as for most of the minimally invasive techniques (30), to go beyond the strict limits of the pathological tissue. With the technique described here and the possibility for the microtube to remain implanted over a long period, the strategy that can be anticipated is, in a first pass to reduce the volume of the pathological tissue, then observe under MRI its evolution and, if necessary, either repeat the procedure with more calories or pursue the treatment with other active agents (31). Among the therapeutic agents which can be vectorized, are nanoparticles charged with a specific drug or radioisotopes. The technique described, delivering an active agent under pressure, can be beneficial in oncology too, for instance to slowly release chemotherapeutic agents, associated or not with radioactive products, when the tumour cannot be excised. Concerning bone infection in which treatment is difficult because of its poor vascularization, *in situ* delivery of low or non-soluble antibiotics and/or analgesic, should also enhance the efficiency of the drugs (32).

MRI has been introduced and all the equipment built from non-magnetic material to anticipate applications to humans. In this connection, it was observed that some stainless steel microtubes make a slight shadow (blurring) along its path, an artefact mainly due to a local distortion of the magnetic field. On the one hand, the artefact created might obscure the temperature effect, but on the other this might be an advantage, since it indicates the exact position of the microtube inserted in the tissue (33). An alternative choice might be an iridium/platinum alloy, currently under evaluation, which does not show any artefact. However, this will probably require some additional marker to make it visible in MRI and some compromise has to be found

The *in vivo* experiments performed on mice with subcutaneously grafted tumour permit the direct observation of the entire procedure *i.e.*, insertion of the microtube, injection of the water vapour as well as the effect of treatment. As the experiment is well visualized, no major investigation was conducted to optimise the quality of the magnetic resonance images. Such experiments are currently being performed on pigs (25). With the MRI system used, the choices adopted provide an acceptable spatial resolution in a reasonable time, a finding confirmed by similar studies (34). It must be noticed though that, if time resolution is not a restriction, inversion-recovery sequences may be the better choice (35). The improvements in the new MRI machines with more efficient sequences should provide better image contrast and spatial resolution, without a time penalty. The main goal to be achieved for clinical application is the assessment "on line" of the treatment as reflected by a global alteration of the tissue by the heat. Therefore, we did not investigate potentially better methods for accurate temperature measurements (36).

In conclusion, in the present work the feasibility of a new minimally invasive technique to focalise therapeutic agents has been demonstrated. This technique can deliver several drugs through the same channel with well controlled doses, advantages not provided by the other techniques. This technique with hot vaporized water is currently being evaluated (37). One hope is that this multi-therapeutic approach will give an additional choice for the treatment of both chemo- or radio-resistant tumours as well as inoperable tumours.

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