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INTERSTITIAL AND INTRACAVITARY THERAPEUTIC ULTRASOUND

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The non invasive nature of High Intensity Focused Ultrasound (HIFU) for thermal ablation of in-depth tumors is very promising and several medical devices are currently commercially available. Techniques using intracavitary or interstitial applicators have been proposed because extracorporeal HIFU techniques are not always suitable for deep-seated tumors. Bones or gaseous pockets may indeed be located in the intervening tissue. The objective is to bring the ultrasound source as close as possible to the target through natural routes in order to minimize the effects of attenuation and phase aberration along the ultrasound pathway. Under these circumstances, it becomes possible to use higher frequency, thus increasing the ultrasonic absorption coefficient and resulting in more efficient heating of the treatment region. In contrast to extra-corporeal applicators, the design of intracavitary probes imposes additional constraints relative to size and ergonomy.

When associated to modern imaging modalities, these minimally invasive therapeutic devices offer very promising options for cancer treatment.

1. Introduction

Thermal ablation of localized tumors using high intensity focused ultrasound (HIFU) is now an accepted therapeutic method and several devices are currently marketed. The most satisfactory method uses non-invasive, extracorporeal ultrasound sources, such as those used in lithotripsy. Using a big focalized transducer increases the pressure gain between the surface of the transducer and its focal point, thus preserving the intervening tissue. But methods using intra cavitary or interstitial applicators have been proposed because extracorporeal HIFU is not always suitable for deep-seated tumors. Bones or gaseous pockets may indeed be located in the intervening tissues. In tissue, the ultrasound wave is naturally attenuated and deformed on meeting structures with different geometric and acoustic properties. Attenuation or phase aberration during treatment of deep-seated tumors results in a decrease in pressure gain. In this case, pressure can be increased at the surface of the transducer in the hope of supplying sufficient energy to the focal point, but this increase is to the detriment of intervening tissue whose temperature will also rise. The objective of minimally invasive interstitial and intracavity methods is to bring the ultrasound source as close as possible to the target via natural routes in order to minimize the effects of attenuation and phase aberration. It then becomes possible to use higher frequencies, thus increasing the ultrasonic absorption coefficient which results in a more efficient heating of the treatment region. In contrast to extracorporeal applicators, probes impose additional design constraints with regard to size and ergonomy.

In this paper, the clinical research carried out by Unit 556 of the French National Institute for Health and Medical Research (INSERM) over the last fifteen years will be presented. This research is carried out within the context of developing minimally invasive applicators to treat deep-seated tumors that are inaccessible from the outside. More specifically, two major projects will be presented. One aims to develop a transrectal applicator for the treatment of prostate cancer and the other involves ultrasound endoscopic applicators to treat cancers of the esophagus and biliary ducts.

2. Projet #1: Treatment of prostate cancer using a transrectal focused ultrasound transducer,

Prostate cancer is the leading cancer among men in the USA and the second most common malignancy in males worldwide after lung cancer. In 1989, INSERM unit U556 (National Institute for Health and Medical Research), the Urology service of the Edouard Herriot Hospital Lyon, France and EDAP Technomed joined efforts and initiated a research project in France [1]. This project was to develop an efficient and minimally invasive treatment for localized prostate cancer (stages T1-T2). After ten years of development, the Ablatherm was CE marked (European approval) and the FDA gave approval for the United States to conduct a clinical study. The Ablatherm is a combination of various components:

- A table for the patient to lie on during the treatment.
- An ultrasound imaging system, which allows the visualization of the prostate by the surgeon.
- A transrectal head consisting of the imaging probe and the treatment transducer, which emits the focused ultrasound. These two elements are placed in a latex balloon filled with cooled liquid.
- A computer, which controls and aims the shots according to the firing plan established by the surgeon.
- Many safety devices are connected to the equipment to guarantee the patient's security and the optimal effectiveness of the treatment

The Ablatherm treatment is performed transrectally, generally under spinal anesthesia with a HIFU probe placed in the rectum (Figure 1). This probe emits a beam of high intensity convergent ultrasound. The ultrasound waves travel through the rectal wall and are focused in the prostate. In the point where the ultrasounds are focused (focal point) the sudden and intense absorption of the ultrasound beam creates a sudden elevation of the temperature (from 85 to 100°C), which destroys the cells located in the targeted zone. The targeted zone destroyed by each shot is tadpole-shaped and measures about 22 mm in height by 2 mm in diameter. Repeating the shots, and moving the focal point between each shot, it is possible to destroy a volume that includes the whole tumor without damaging surrounding tissues. The treatment (1 to 3 hours) can be performed under spinal anesthesia.

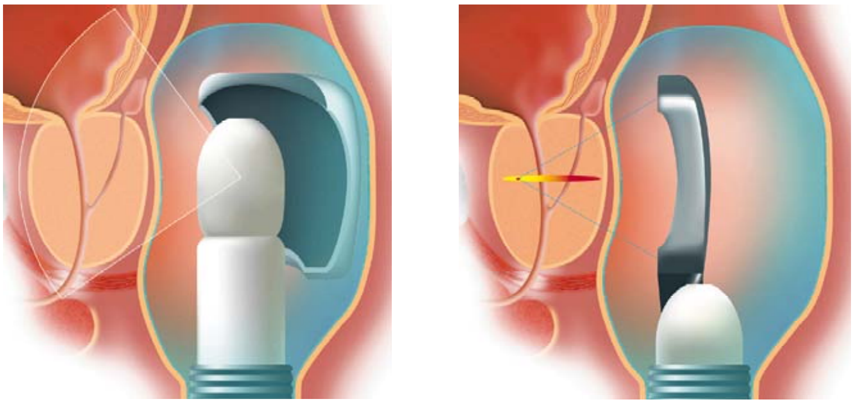

Fig. 1. Once Imaging of the prostate is performed (left), the imaging probe is removed and the focused transducer is set for treatment (right).

The first patient with prostate cancer was treated in Europe in February 1993 [3] and in the United States in July 1999. More than 4500 patients have been treated so far. It is a technology with which thousands of patients have already been treated in prestigious European institutions. It is a treatment alternative for a pathology of high incidence, with a low morbidity, minimal hospital stay and that represents an alternative to surgery and radiotherapy. Additionally, it can be used for patients who have local recurrence after external radiotherapy ("salvage" treatment) [4].

Promising results from the European sites show up to 92% of negative biopsy and stable PSA following Ablatherm treatment in localized prostate cancer. A European multicenter study has been completed on 402 patients with localized prostate cancer. The results of this study show that after an Ablatherm treatment more than 8 patients out of 10 have negative biopsies (87.2%) and a normal PSA level (81.4%). These results are based on an average follow-up at 13 months. According to the data available as of today, only about 1 patient out of 10 (9,8%) will need an additional treatment option to be administered after Ablatherm treatment (Studies carried out in Lyon - France, with more than 5 years follow-up).

We can say that ultrasound surgery of prostate cancer is safe and effective with low risks : even if this is a non-surgical treatment, there are still a few risks associated with HIFU therapy (most are temporary): immediate post treatment urinary retention (requiring a catheter for a few days), urgency, stress incontinence, urinary infection and decreased sexual functioning.

The treatment of localized prostate cancer with High Intensity Focused Ultrasound is a new treatment with many advantages:

- ✓ Destruction of the cancerous tissue without lesion of the surrounding organs
- ✓ Absence of irradiation
- ✓ Shorten hospital stay
- ✓ Treatment performed under spinal anesthesia in one session
- ✓ Treatment can be repeated
- ✓ Other therapeutic alternatives can be considered in case of incomplete results
- ✓ The treatment can be used for the treatment of local recurrences after external radiotherapy

3. Projet #2: Endoscopic ultrasound applicators for the treatment of digestive tumors

Systemic treatments such as radiotherapy are not effective on most digestive cancers. Furthermore, very few patients are able to undergo surgery, the only curative treatment available, because of their general condition and the late diagnosis of these tumors. Prognosis is extremely poor and only palliative care (placing of prostheses) can be undertaken [2]. These tumors develop locally around the biliary or esophageal lumens and are therefore good candidates for treatment by intraluminal radiotherapy. Small applicators able to come into contact with the target tumor are required for this approach. When non-focalized transducers are used, coagulation necrosis develops from the surface of the transducer. To compensate for the absence of focalization, it is necessary to increase frequency (5 – 20 MHz) [5]. The treatment depth is directly related to the ultrasound frequency. The higher the frequency, the less the ultrasound penetrates the tissue, and the more intense is the heat. To necrose tissue with a low frequency, weakly attenuated wave requires increasing the power of the ultrasound whilst keeping it below the destruction threshold of the applicator. Even when coagulating volumes of cylindrical tissue, a rotary transducer was preferred to a tubular transducer. Indeed, the divergence associated with tubular transducers results in a rapid fall in pressure that limits the depth and/or the duration of treatment [6]. Consequently, various applicators were designed and tested in clinical studies. The shapes and characteristics of these applicators were adapted to the therapeutic objective. The common feature of all our endoscopic applicators is their plane transducer. The generated plane wave is oriented mechanically to cover the total volume of the tumor. In order to minimize the movement of the applicator, we have developed an ultrasound cylindrical phased array composed of 64 elements for transesophageal thermotherapy. Based on the principal of dynamic focalization, the 64 small transducers mounted on a tubular frame are excited successively. Depending on the delay times of the excitation of each element, a plane wave can be generated with a group of elements. Rotation of the plane wave is obtained by exciting a group of neighboring transducers [7]. Depending on the application, different guiding methods were tested: endoultrasound, MRI and fluoroscopy. The interest of MRI lies in the fact that this imaging modality can give in almost real time temperature monitoring whilst controlling the extent of coagulation necrosis. However, it requires constructing non-magnetic applicators that do not induce artifacts on the image.

A pilot study was carried out in 10 patients presenting with cholangio-carcinoma [8]. The applicator used was compatible with conventional gastrointestinal endoscopic equipment. A guide wire enabled the applicator to exit the endoscope and move up into the biliary ducts to the tumor. The method is minimally invasive since the duration of anesthesia was not significantly prolonged and both the treatment and the control examinations corresponded to the dates when the prostheses needed to be renewed. For some patients, who underwent surgery after ultrasound treatment, analysis of the removed tumor demonstrated 10 mm deep coagulation necrosis at the targeted point. In most cases, local tumor regression was observed with distal proliferation resulting from a pre-treatment under-estimate of tumor spread. In one case (Figure 2), the tumor was completely destroyed and bile flow restored. Future studies should determine whether this endoscopic ultrasound treatment of biliary tumors is a new palliative method, or whether it could be curative in high-risk surgery patients presenting localized tumors.

4. Conclusion:

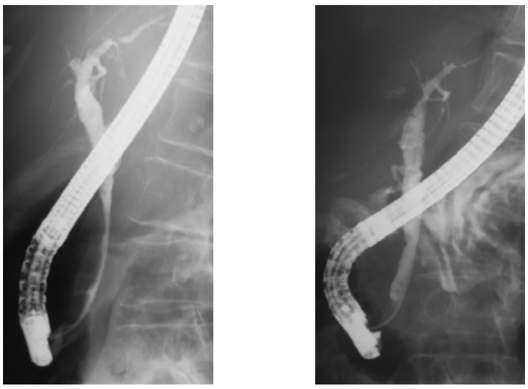

Fig. 2. Fluoroscopic image shows the stricture in the bile duct (left). Three months after ultrasound treatment, the flow in the bile duct is restored (right).

When associated to modern imaging modalities, these interstitial and intracavitary therapeutic devices offer very promising options for cancer treatment. These methods are suitable for treating deep-seated tumors, precise, safe, repeatable, bloodless and economic.

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EFFECT OF THE SHOCK WAVE ENVELOPE ON CAVITATION BUBBLE DYNAMICS

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The Rayleigh equation describing nonlinear oscillations of a gas bubble in a liquid has been analyzed using the theory of groups. The group of scale transformations was calculated and then used as the basis for constructing the solutions to the Rayleigh equation. The analytical description of the essentially nonlinear dynamics of a bubble allows one to use the aforementioned solutions as a model for analyzing such phenomena as shock wave propagation in liquids with phase inclusions. The study of effectiveness of expansion and collapse of a single bubble driven by periodically prolonged scaling acoustical field has been performed. The key to understanding the transition from weakly oscillating to strongly collapsing bubbles lies in the existence of a threshold for spontaneous bubble expansion known as the Blake threshold. Blake threshold is never achieved at this form of driving and this is the main reason for ineffectiveness of bubble extension.. The small, in comparison with the pressure drop at the leading edge, stretching