Transrectal High Intensity Ultrasound Therapy of Localized Prostate Cancer.

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Abstract: Transrectal high intensity focused ultrasound (HIFU) has been successfully used for the treatment of localized prostate cancer in man. The method uses a wideband transducer sharply focused at 42.5 mm and operating in the frequency range 2.25 - 3.0 MHz. Thermal necrosis are induced with multiple shots of 4.5-s exposure repeated each 5-s. Since 1993, 50 patients have been treated in Lyon: a complete response was obtained in 56% of cases, a local control in 24% and only 20% justified additional treatment. Transrectal HIFU offers numerous advantages: it is minimally invasive, repeatable unlike radiotherapy and additional treatment can be easily performed.

INTRODUCTION

Prostate cancer is the most common cancer in men. We have been working since 1989 on a research project designed to perfect a method of treating localized cancers of the prostate as non-invasively as possible, using high intensity focused ultrasound (HIFU) emitted by transrectal route. The principle of tissue ablation by HIFU was demonstrated in the 50's (1). The ultrasound intensity and time constants required to obtain irreversible tissue lesions in in vivo conditions compatible with a clinical use, were established via a series of experiments on rat and dog kidneys (2). At the same time, by means of a study on an experimental fast-growing metastatic cancer, it was demonstrated that HIFU was capable of destroying tumor tissues and curing the cancer without provoking distant metastases (3). Lastly, a study conducted on dogs showed that it was possible to generate irreversible coagulation necrosis lesions in the prostate tissue by transrectal route without damaging the rectum wall (4). In 1992, the ethics committee approved a clinical study into the use of HIFU for treating benign (Study 1) and malignant (Study 2) tumors of the prostate. The purpose of Study 1 was to determine the ultrasound constants (ultrasound intensity and shot duration) required to produce irreversible lesions in human prostate tissue, in patients suffering from adenomas. The study was carried out with 10 patients and indicated that 4-s shots with an intensity (I_s,x, A) of 1000 Watts/cm² (1700 Watts/cm² I_s,x, A) at the focal point could be used to generate coagulation necrosis lesions without inducing lesions along the path of the beam, particularly in the rectum wall (5). Study 2 was then undertaken, from February 1993 onwards. The preliminary results obtained with the first 14 patients treated were published in 1996 (6).

TRANSRECTAL HIFU THERAPY TECHNIQUE

A convergent beam of high intensity ultrasound is emitted by a highly focused piezocomposite transducer in shots lasting a few seconds. The cavitation induced in the prefocal area leads to a sudden and intense absorption of the ultrasound that provokes a sharp temperature increase (> 70°C) and causes irreversible necrosis of tissue in the prefocal area. The ablated lesion is pear-shaped (conical) and measures about 2 mm in diameter by 18 mm in height. The short and sharp nature of the phenomenon means that there is little thermal diffusion. The entire volume of lesions can be ablated by firing repeatedly, with the focal point being moved between shots. The device uses a firing head that combines a rectangular wideband transducer focused at 42.5 mm with a commercial biplane transrectal ultrasound probe (Kretz RW 77 AK, Austria). Both elements are placed in a latex balloon filled with a cooled antiscavitation coupling liquid. A metal ring inside the balloon stabilizes the rectum wall during the rotational movements of the treatment transducer. During the imaging phase, the treatment transducer sweeps round on an eccentric axis and the imaging probe can then be located opposite the prostate in order to obtain the three-dimensional coordinates of the gland. During the treatment phase the imaging probe is retracted, and the treatment transducer is positioned parallel to the rectum wall. The ultrasound frequency is adjusted to between 2.25 MHz and 3 MHz according to the size of the prostate. Treatment then proceeds automatically, each shot lasting 4.5-s followed by a 5-s interval during which the firing head alters position in accordance with the rectum distance measured by A-mode scanning from a 5-mm diameter element located at the center of the transducer. Treatment continues layer by layer from the apex to the base, each layer being 1.6 mm thick. Usually 3 successive target volumes (apex, mid-part and base) have to be defined to treat an entire prostate lobe in one session.

The effect of HIFU treatments was assessed by monitoring the PSA levels and by randomized control biopsies. Complementary treatment can be given several months or even several years after the initial treatment if the control biopsies indicate that the cancer is still present.
RESULTS OF THE CLINICAL STUDY

So far, the clinical study (7) is composed of 50 patients including 2 patients with local recurrence after definitive external radiotherapy. After a median follow-up time of 22 months, results can be divided into 4 groups:

- G1: with 28 patients (56%) control biopsies showed no residual cancerous foci. The average PSA level of these patients was normalized to 0.8 ng/ml. The treatment then was considered as a success.

- G2: with 3 patients (6%) control biopsies showed no residual cancerous foci but the final PSA level was higher than 4 ng/ml. A complementary HIFU sessions will be scheduled when residual cancer foci are precisely localized.

- G3: with 9 patients (18%) the average PSA level prostate was normalized to 0.9 ng/ml but control biopsies revealed the presence of residual cancerous tissue (<2-mm) located behind the prostate in contact with the capsule. As the PSA levels of these patients are slowly on the increase, once a level of 3 ng/ml is reached, it is proposed to resume HIFU directed at the areas where residual cancer has been detected. Iterative treatments are quite possible and effective, even if there is a long interval between the initial and repeat sessions.

- G4: with 10 patients (20%), treatment was considered to have failed: persistence of numerous positive biopsies and an abnormally high average PSA level (8.9 ng/ml). These patients were given other form of treatment (hormonotherapy or radiotherapy). It should be noted that 7 of them were among the first 20 patients treated.

DISCUSSION

These clinical results show that transrectal HIFU treatment can result in the local control of 80% of cases of local prostate cancer (56% complete, 24% incomplete). Failure (20%) appears to be most common in patients where the extent of the disease had been under-assessed. Two assumptions can explain the partial responses observed in patients of groups 2 and 3. In group 2 it is likely that cancerous tissue remained untreated in the anterior part of the gland due to the large prostate treated in this group. In group 3 the residual cancerous foci were located beyond or adjacent to the capsule. In an experimental study performed on rabbit liver (unpublished data), it was noticed that the focal lesion could be shifted toward the transducer by increasing the transmitted frequency. Since the frequency has been adjusted to between 2.25 MHz and 3 MHz according to the size of the prostate, no posterior focus of residual cancer has been found in sextant biopsies. A possible explanation for this phenomenon is that tissue attenuation is highly increased by cavitation bubbles which appear in the transducer prefocal field. Hyperechogenic zones indeed appear in the target volume immediately after treatment. These images which are sometimes intense, masking the contours of the prostate, are labile and disappear within a few minutes of the end of treatment.

It is clear that the main problem is how to ablate the cancerous tissue in its entirety. The focal distance of the HIFU therapy transducer is currently constant (42.5 mm) so the treated area of the prostate corresponds to a strip located immediately in front of the posterior prostate capsule. The length of this strip is about 20 mm so, if the prostate is enlarged, its anterior portion is beyond the range of the device. This explains the poor activity observed against enlarged prostates. However, since initial HIFU treatment causes shrinkage of the prostate volume and thinning of the gland, an extra session can reach the anterior part, thus explaining the improved results observed after subsequent HIFU sessions. In order to correct this drawback and to preclude the need for repeat HIFU sessions, an annular array transducer which can electronically focus HIFU through the 30-55 mm range has been developed (8). This variable focusing transducer is at present under clinical evaluation and is expected to give significantly higher efficacy. Transrectal HIFU has a number of advantages: it is relatively non-invasive and requires only a short stay in hospital, it can be repeated, it can be used to make up lost ground after external radiotherapy has failed and, if unsuccessful, some other form of treatment can be performed. A phase II multicenter study is currently underway in 6 European centers including 3 in France, 2 in Germany and 1 in the Netherlands.

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REFERENCES