Our group has been working since 1989 on a research project designed to perfect a method of treating localised cancers of the prostate as non-invasively as possible, using focused ultrasound (HIFU) emitted by endorectal route. The principle of tissue destruction by HIFU was demonstrated by Fry et al. in 1955 [1]. In 1992 we established the ultrasound intensity and time constants required to obtain irreversible tissue lesions in a reproducible manner using a predominant thermal phenomenon, via a series of experiments on rat and dog kidneys [2]. At the same time, by means of a study on the R3327 Dunning experimental adenocarcinoma of the prostate, which is a fast-growing metastatic cancer (2 months), we demonstrated that HIFU was capable of destroying tumor tissues and curing the cancer without provoking distant metastases [3]. Lastly, we used a study conducted on dogs to show that it was possible to generate irreversible coagulation necrosis lesions in the prostate tissue by endorectal 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 second shots with an intensity of 1000 watts/cm² 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]. In this paper we report the results obtained up to now with 47 patients suffering from clinical stage T1 or T2 cancer with an average of 364 days of follow-up.

MATERIALS AND METHOD

Principle of treating by HIFU

The principle of treating localised cancers of the prostate by HIFU has been described previously [6]. A convergent beam of high intensity ultrasound is emitted by a highly focused piezocomposite transducer. Ultrasound is emitted in shots lasting several seconds. The sudden, intense absorption of the ultrasound beam at the focal point provokes a sharp temperature increase (about 85°C) that destroys the cells in the target area. The target area is ellipsoidal and measures about 18 mm in height by 2 mm in diameter. The shortness and sharpness of the phenomenon prevents thermal diffusion around the focal point. Volumes can be destroyed by firing repeated shots, with the focal point being moved between shots.

Materials

Two prototypes were used successively. Prototype 1.0, used to treat the first 20 patients with localised cancer, was based directly on the device used for the experiments on canine prostates and on adenomas of the prostate. The device uses a firing head that combines a rectangular treatment transducer focused at 45 mm and operating at a frequency of 2.25 MHz with a biplane endorectal probe (Kretz RW 77AK, Austria). Both elements are placed in a latex balloon filled with an anticavitation coupling liquid. During the imaging phase, the treatment transducer sweeps round on an eccentric axis: it takes up a position on a sagittal plane, and the imaging probe can then be located opposite the prostate in order to obtain the three-dimensional co-ordinates of the prostate gland. During the treatment phase the endorectal ultrasound probe is retracted, and the treatment transducer is positioned parallel to the rectum wall and hence to the posterior surface of the prostate.
Prototype 1.1, used for subsequent treatments, featured a number of improvements:
— a metal ring inside the balloon stabilises the rectum wall during the rotational movements of the treatment transducer;
— before each shot, an electronic device measures the exact distance between the treatment transducer and the rectum wall by ultrasound A-mode scan;
— the control software allows the operator to define the target volume, the contours of which are exactly the same as the prostate volume. In addition, before each shot the software corrects the distance of the transducer from the rectum in accordance with the distance measured by A-mode scan;
— a cooling system whereby the coupling liquid circulates in the balloon protects the rectal mucosa by removing the thermal energy released at the balloon-rectum interface on the firing of each shot;
— lastly, the ultrasound frequency can be set to between 2.25 MHz and 3 MHz as function of target area depth.

HIFU treatment procedure and Protocol

Almost all treatments are performed under spinal anaesthesia. Coupling between the balloon and the rectum is assured by ultrasound contact gel. The firing head is introduced into the rectum under manual control and the latex balloon then filled with 150 cc of anticavitation coupling liquid. Next the firing head must be put into the imaging position. The operator sets the boundaries of the target area firstly on the sagittal plane. The software then positions the ultrasound probe transversely and alters the position of the probe, plane by plane, from the apex to the base. For each prostate “slice”, the operator defines the treated area using the computer mouse, marking the left- and right-hand boundaries of the target area. The future lesions appear on the control screen as a line of ellipses. The software detects the position of the rectum and aligns the shots along the posterior capsule of the prostate, allowing a 3 mm margin of safety relative to the rectal mucosa. Once the three-dimensional co-ordinates have been set, the software retracts the biplane ultrasound probe and positions the treatment transducer parallel to the posterior surface of the rectum. The treatment then runs automatically. Each shot lasts 4.5 seconds, followed by a 5 second interval during which the firing head alters position. Treatment occurs layer by layer from the apex to the base, each layer being 1.6 mm thick. Once the treatment of one layer is finished, the firing head treats the immediately adjacent layer until the entire target volume has been treated. Usually 3 successive target volumes (apex, mid-part and base) have to be defined to treat an entire prostate lobe in one session. At the end of the session the balloon is deflated and the firing head withdrawn. The contralateral lobe is treated according to the same procedure one month later.

The effect of the treatments has been assessed by monitoring the PSA level and by randomised control biopsies one month, three months, six months and one year after treatment. 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

Table I summarises the results obtained since 1993 with 47 assessable patients. The data can be divided into 3 categories:

**Complete response**

With 27 patients (57.4%), control biopsies show no residual cancerous foci. The average PSA level of such patients fell from 7.1 ng/ml before treatment to 1.2 ng/ml after treatment. Their PSA level is perfectly stable (see for example fig. 1), and they simply have 6-monthly PSA check-ups and annual control biopsies.

<table>
<thead>
<tr>
<th>Nbr</th>
<th>Âge</th>
<th>PSA Pre</th>
<th>Nadir</th>
<th>Last</th>
<th>Prostatic Volume Pre</th>
<th>Last</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>47</td>
<td>70.7 ± 0.7</td>
<td>9.6 ± 1.1</td>
<td>1.6</td>
<td>37.2 ± 2.8</td>
<td>28.4 ± 3.6</td>
<td>364</td>
</tr>
<tr>
<td>G2</td>
<td>27</td>
<td>69.6 ± 0.8</td>
<td>7.1 ± 0.9</td>
<td>0.8</td>
<td>38.6 ± 3.7</td>
<td>24.2 ± 3.0</td>
<td>448</td>
</tr>
<tr>
<td>G3</td>
<td>12</td>
<td>71.5 ± 1.0</td>
<td>9.9 ± 2.0</td>
<td>1.3</td>
<td>37.1 ± 6.6</td>
<td>40.6 ± 11.6</td>
<td>364</td>
</tr>
<tr>
<td>G4</td>
<td>8</td>
<td>72.8 ± 2.1</td>
<td>17.9 ± 3.4</td>
<td>4.8</td>
<td>32.6 ± 3.8</td>
<td>24.5 ± 3.9</td>
<td>236</td>
</tr>
</tbody>
</table>


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Incomplete response

With 12 patients (25.5%), prostate control biopsies revealed the presence of residual cancerous tissue (1 or 2 positive biopsies out of 6). The residual cancerous tissue is usually located behind the prostate in contact with the capsule. The average PSA level of such patients fell from 9.9 ng/ml before treatment to 1.6 ng/ml after treatment. As the PSA level of these patients is gradually increasing, once it is above 3 ng/ml a complementary HIFU session is proposed, directed at the areas where the residual cancer has been detected. Iterative treatments are quite possible and effective, even though there is a long time between initial and additional treatments (fig. 2).

Failure

With 8 patients (17%), treatment was considered to have failed: persistence of numerous positive biopsies and an non-normalised average PSA level (4.8 ng/ml). Such patients were given additional treatment, either hormone treatment (3) or conformational external radiotherapy (5). The average PSA level after radiotherapy for patients in this group is 0.96 ng/ml. It should be noted that the average PSA level of patients in this “failure” group was 17.9 ng/ml before HIFU treatment and that 7 of these patients belong to the first 20 patients.

Changes in PSA level

Immediately after treatment, the PSA level rises sharply with a peak 12 hours after treatment which rises to an average maximum of over 5 times the base level before treatment. It then falls rapidly and stabilises about 2 months after treatment (Nadir point).

Changes in the prostate tissue

Hyperechogenic zones appear in the target volume immediately after treatment. These images are sometimes intense, masking the contours of the prostate. At times they are absent, however, but this gives no indication of the therapeutic result. They probably correspond to microbubbles of gas induced by a cavitation phenomenon in the treated area. In fact, such images are labile and disappear a few minutes after the end of treatment. In the weeks after treatment, most patients notice that necrotic debris is eliminated through the urethra, leading to a gradual reduction in the prostate volume. If treatment is 100% effective, the control biopsies in the months after treatment show coagulation necrosis lesions with the cells completely destroyed. The biopsies from the 3rd month onwards show more or less inflammatory prostatic fibrosis lesions.

Complications

Table II summarises the complications observed, and their treatment. Most complications, and all severe complications, occurred between 1993 and 1995. Complications have become less frequent (16%) and there have been no rectal complications since the introduction of various safety measures.

Patients treated after failure of radiotherapy

Two patients in this group correspond to radiotherapy failures. In both cases, no complications arose during treatment, and the treatment resulted in the PSA level being normalised and stabilised (fig. 3).
DISCUSSION

The aim of treating cancer of the prostate is to ensure patient survival with a minimum of side effects. These preliminary results show that trans-rectal HIFU treatment can enable local control of cancers of the prostate to be achieved in 83% of cases (57.4% complete, 25.5% incomplete). The failures (17%) appear mainly to be with patients where the level of seriousness (stage) had been underassessed, as their initial PSA level was much higher (17.9 ng/ml) than those making a complete or partial recovery (7.1 ng/ml and 9.9 ng/ml respectively). The PSA of patients who have made a full recovery is stable at around 1 ng/ml. For the moment, however, not much time has elapsed since treatment (only 5 patients were treated over 3 years ago). It is therefore possible that, with time, we will see local recurrences from possible residual cancerous foci undetected by the biopsies. But we can reasonably believe that the patients treated by HIFU and having a PSA level of below 1 ng/ml will make positive progress. However, the most important prognostic factor appears to be the stability of the PSA level rather than its absolute value. The situation in the case of recurrence after HIFU treatment is radically different from that for radiotherapy failures [7]. Either the HIFU treatment can be repeated, as there are no maximum doses, or one can turn to a different treatment (external radiotherapy).

The treatment of localised cancers of the prostate by HIFU needs therefore to be evaluated against external radiotherapy, brachytherapy and transperineal cryotherapy. A phase II multicenter study is currently in progress in 6 European centres (3 in France, 2 in Germany, 1 in Netherlands).

CONCLUSION

It is still far too early to predict the place of HIFU treatment in treating localised cancer of the prostate. We can simply say that this treatment has numerous 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 this is unsuccessful, one can have recourse to an adjuvant treatment.

The treatment of localised cancers of the prostate by HIFU needs therefore to be evaluated against external radiotherapy, brachytherapy and transperineal cryotherapy. A phase II multicenter study is currently in progress in 6 European centres (3 in France, 2 in Germany, 1 in Netherlands).

REFERENCES

SUMMARY

Our group has been working since 1989 on a research project designed to achieve local control of localised prostate cancers using a relatively non-invasive process: high intensity focused ultrasound (HIFU) emitted via the transrectal route. The HIFU transducer consists of a sharply focused (40 mm focal length) wideband transducer operating in the frequency range 2.25-3.0 MHz. Ultrasound is emitted in shots lasting 4.5 second followed by a 5 second interval. Each shot induces at depth a localised thermal necrosis corresponding to an ellipsoidal lesion of about 18 mm high and 2 mm in diameter. Volumes can be destroyed by firing repeated shots, with the focus of the transducer being moved between shots. The HIFU transducer is coupled to a retractable 7.5 MHz biplane ultrasound imaging probe. A computer controlled positioning device moves the probe in the rectum to ablate the volume defined with the image. For patient safety, the system includes a power monitoring circuitry combined with a real time A-mode ultrasound detection of rectal wall. The head is covered by a latex balloon filled by 150 cc of a cooled anti-cavitation liquid which circulates to cool both the therapy transducer and the rectal mucous membranes. Since 1993, 47 patients have been treated in Lyon. The preliminary results show that transrectal HIFU treatment can enable local control of cancers of the prostate to be achieved in 83% of cases with a complete response in 57.4% and incomplete in 25.5%. Only 17% justified additional treatment. Transrectal HIFU offers numerous advantages: it is minimally invasive requiring only a short hospital stay; it is repeatable unlike radiotherapy and additional treatment centred on insufficiently treated area can be performed. In 1996, a multicenter study has been initiated with six different sites in Europe.

Key-words: Ultrasound therapy. Focused ultrasound. HIFU. Prostate cancer. Transrectal ultrasound.