High-Intensity Focused Ultrasound in Prostate Cancer: Results after 3 Years

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ABSTRACT

Background: Local high-intensity focused ultrasound (HIFU) is a minimally invasive method of coagulation (85°C) that ablates prostatic tissue with high precision.

Patients and Methods: Over a 3-year period, 184 patients with organ-confined prostate cancer have undergone 232 sessions of transrectal HIFU therapy (mean duration 90 minutes) under spinal anesthesia at 2.25 or 3.0 MHz, 50 W, with a penetration depth of 25 mm.

Results: Follow-up sextant biopsies (mean 1.9) were cancer free in 80% of patients, and in patients with residual cancer, the tumor mass was reduced more than 90%. The nadir value of prostate specific antigen (PSA) was <4 ng/mL in 97%, including 61% who had values <0.5 ng/mL. After primary HIFU, no severe side effects (fistula, grade 2 or 3 incontinence, rectal mucosal burn) were seen. All patients had a suprapubic tube (mean 29 days), and 33% needed transurethral resection of debris (mean 7 g). Hospital discharge was within 24 hours after treatment.

Conclusion: Transrectal HIFU enables minimally invasive local prostate tissue ablation with high rates of negative biopsies, low PSA nadir, and low complication rate. Further follow-up is needed to define the efficacy of disease control.

INTRODUCTION

Carcinoma of the prostate (CaP) is organ confined in 70% of men at the time of diagnosis. In Bavaria, 25% of these patients undergo local therapy (surgery 23%, radiation 2%), while 75% receive systemic hormonal ablation or no treatment; i.e., watchful waiting. The side effects, the “castrating” negative psychological impact, and the non-hormone-sensitive progression of the disease makes hormonal ablation not very attractive for most patients. The “wait and see strategy” leaves the patient with only a general statistical prognosis for his disease stage and does not address his personal fears regarding his untreated tumor. Consequently, this approach is not very well accepted, even if it is medically indicated.

The therapeutic goal for application of transrectal high-intensity focused ultrasound (HIFU) is postponement of hormonal ablation by local minimally invasive tumor coagulation. Non-hormone-sensitive progression and typical side effects of hormonal ablation should be avoided or postponed. In addition, local HIFU treatment provides a curative chance for the patient.

A first study objective was a review of the adverse events, side effects, complications, and patient satisfaction of HIFU. The data demonstrated an acceptably low rate of adverse events and complications. These data are separately reported in the accompanying article. This report describes the efficiency of transrectal HIFU for local disease in elderly men (>70 years) who were not candidates for radical prostatectomy (study arm A). Study arms B (treatment of local recurrence) and C (adjuvant debunking) are not reported in this publication.

PATIENTS AND METHODS

Techniques

The HIFU is performed in one session as day surgery or as an outpatient procedure. The HIFU device used is Ablatherm® (EDAP-TMS, Lyon, France) (Fig. 1). The evaluation of the patient consists of transrectal ultrasonography (TRUS) at 7.5 MHz, TRUS-guided sextant prostate biopsies, and total PSA (tPSA) assay. Free PSA (fPSA) is not evaluated in follow-up.

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A CT scan, magnetic resonance imaging (MRI), and bone scan are obligatory before HIFU. The outcome is monitored by PSA at day 1, 14, and 30 and every 3 months thereafter. Also, TRUS-guided sextant biopsies are performed routinely at months 3 and 12 and in cases of significant PSA elevations during follow-up. If there is evidence of disease progression, additional CT scans, MRI, and bone scans are obtained.

Treatment is performed with the patient in a right-sided position under spinal anesthesia with a suprapubic tube in place (Fig. 2). To enable precise treatment, the bladder is emptied, and the patient is secured on the table to prevent undesirable movements. Therapy planning is performed with the applicator in place. Planning starts in the transversal TRUS mode to define the anatomic apex of the prostate gland. It proceeds to the longitudinal mode and defines the apical treatment start point, which is 5 mm from the anatomic apex. The next step is to identify the bladder neck as the therapeutic boundary. A "security distance" is defined that consists of 3 to 6 mm between the rectal mucosa and the dorsal prostate capsule; the lesion length is 13 to 18 mm. All tissue within these boundaries is treated in sequential slices from apex to bladder neck.

As many as 1000 single HIFU lesions were created in the prostate at 2.25 MHz or 3.0 MHz using a therapeutic piezoelectric transducer (55 × 40 × 10 mm). Over a 3-year period, 232 local HIFU treatments in 184 patients have been performed and evaluated. A first series (N = 90 treatments) included significant therapeutic dose increases within the first year, as well as several technological changes. The HIFU technique, application mode and treatment strategy have been standardized since November 1997.

Between April 1996 and October 1997, the period of the learning curve, 90 treatments were given at 2.25 MHz. The energy was delivered with an 18-mm fixed focus in 4.5-second shots with a 12-second delay. The distance from the rectum to the capsule was fixed at 3 mm, and there were no security features. From November 1997 to April 1999, 94 treatments were given at 3.0 MHz. For these treatments, there was a flexible focus of 13 to 18 mm. The shots lasted 5.0 seconds with a 5-second delay. The distance from the rectum to the capsule was 3 to 6 mm, with autofocusing. The rectal tissue was cooled with 5°C inflow and 15°C outflow. There was a 5-mm security zone at the apex and detection of and correction for patient movement.

Patients

The inclusion criteria were unsuitability for surgery, biopsy-proven localized (Stage T1a N M0) prostate cancer of any Gleason grade, a gland volume of <30 cc by transrectal ultrasonography, no calcifications >5 mm, a total prostate specific antigen (PSA) concentration <20 mg/mL, a life expectancy of at least 5 years, normal rectal anatomy, and provision of informed consent. Typically, the patients had local progression of disease causing symptoms, were unable to tolerate the effects of systemic therapy, or were highly motivated to preserve their sexual potency.

There were 184 patients aged 59 to 81 (mean 72) years admitted to the study. The mean prostate volume was 26 cc. The Gleason score was 2 to 4 in 9.5%, 5 to 7 in 80%, and 8 to 10 in 10.5%. The mean serum PSA value on the day of HIFU was 2.2 ng/mL. This low value was a consequence of the prior administration of a single injection of LH-RH agonist by a community urologist in 48% of the patients. Hormonal ablation also had been used to reduce the prostate to a treatable size (<30 cc) in the patients. In patients not having hormonal therapy, the mean PSA value at diagnosis was 12.0 ng/mL (median 9.8 ng/mL).

The mean follow-up was 193 days, and the median was 112 days (range 0–903). All patients had at least one post-treatment biopsy.

RESULTS

Results using HIFU for local CaP are encouraging: 80% cancer-free biopsies, 97% PSA nadir < 4 ng/mL, and 61% PSA nadir < 0.5 ng/mL (Tables 1 and 2). Proctoscopic pathologic findings such as rectal burns occurred in 15% of the patients treated at 2.25 MHz but only 0.7% of those treated at 3.0 MHz. All rectal burns were asymptomatic. The incidence of rectourethral fistulas decreased from 3.1% at 2.25 MHz to 0.5% in primary treatment of local disease at 3.0 MHz. Prostate volume decreased a mean of 50%; quality-of-life scores (0–6 scale) did not change significantly (from 1.8 to 2.1). Micturition, assessed by the International Prostate Symptom Score (IPSS; 0–35 scale), changed from 5 to 4. This small change is probably because one third of the patients had significant obstructive symptoms before HIFU and had to undergo transurethral resection of necrotic debris within 6 to 8 weeks. All patients were

| Table 1. Incidence of Residual Cancer (%)²
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<tbody>
<tr>
<td></td>
<td>P</td>
<td>P + Z</td>
<td>Z</td>
</tr>
<tr>
<td>2.25 MHz</td>
<td>30</td>
<td>7</td>
<td>23</td>
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<td>2</td>
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²P = subcapsular; Z = central.

| Table 2. Mean PSA Concentrations (ng/mL)
<table>
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<th>Treatment day</th>
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<th>Last value</th>
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<tr>
<td>Min</td>
<td>0.1</td>
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</tr>
<tr>
<td>Max</td>
<td>20</td>
<td>100</td>
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<tr>
<td>Median</td>
<td>9.8</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Mean (3.0 MHz only)</td>
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<td>8.7</td>
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discharged less than 24 hours after HIFU treatment or were treated as outpatients. Urinary tract infections (UTI) occurred in 58% of the first 96 cases, but the rate of UTI decreased to 17% in the patients treated at 3.0 MHz because of low-dose antibiotic prophylaxis.

Potency was preserved in one third of the men in whom the entire prostate was treated. If potency was very important to the patient and his CaP was unilateral, 5 mm of tissue was excluded from treatment on the contralateral side near the neurovascular bundle, accepting a 15% higher rate of recurrence. This sparing of the neurovascular bundle resulted in potency preservation in two thirds of the men so treated. Mild stress incontinence was common in the patients treated at 2.25 MHz (24%) because we did not start the treatment with an apical security margin of 5 mm. Using this security margin, the stress incontinence rate decreased to 4% with no increase in apical residual cancer.

**DISCUSSION**

High-intensity focused ultrasound is a therapeutic alternative of minimally invasive local treatment of CaP. In local disease, HIFU treatment should postpone the need for hormonal ablation and reduce non-hormone-sensitive progression of CaP. Transrectal HIFU offers potentially curative treatment of local disease in a single session that can be performed on an outpatient basis. By comparison, radiation therapy is performed in 25 to 30 single sessions and requires nearly 6 weeks. The complications, side effects, and disease recurrence rates of radiation therapy stimulated the development of brachytherapy as a single-session treatment, external three-dimensional conformal radiation, and the combination of these treatment modalities. The possibility of local CaP ablation (study arm A; 80% of cases) in the experience reported here suggests new indications of HIFU beyond initial treatment of local disease. These include treatment of local recurrence after radiation or surgery or early hormonal ablation (study arm B; 10% of cases) and adjuvant local debulking in combination with hormonal ablation (study arm C; 10% of cases). These additional uses are now under investigation. Local symptoms and local progression of disease should be postponed. Better quality of life and a longer survival time should result.

Transrectal HIFU is a urologic treatment that needs the skill of surgical three-dimensional anatomic knowledge, diagnostic TRUS experience, and extracorporeal shockwave lithotripsy (ESWL)-based application experience to perform properly. A learning curve of only 10 treatments is needed to learn the technique of HIFU using the Ablatherm.

**CONCLUSION**

The efficacy of transrectal HIFU (3.0 MHz) in local CaP is demonstrated by an 80% negative follow-up biopsy rate. The PSA nadir was <4 ng/mL in 97% of patients and <0.5 ng/mL in 61%. No other therapy is excluded by HIFU. Treatment is possible as day surgery or on an outpatient basis. Side effects have diminished with improvement of the technique and application strategy. Auxiliary procedures are transurethral resection in one third of the cases and antibiotic treatment for UTI in one third of the cases. Under this regimen, all patients have returned to normal micturition (IPSS score remains stable). Potency is preserved in as many as two thirds of the patients who are potent before HIFU (40%), depending on the treatment strategy. Long-term follow-up will let us learn more about PSA elevations after nadir, rates of recurrence, and side effects from tissue shrinkage. Currently, HIFU is a local palliative treatment of CaP with curative potential.

**REFERENCES**


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