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Results and Side Effects of High-Intensity Focused Ultrasound in Localized Prostate Cancer

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ABSTRACT

At the time of diagnosis, prostate cancer is organ confined in 70% of the cases. A quarter of these patients undergo local therapy (surgery/radiation); 75% risk disease progression by "watchful waiting" or systemic side effects through hormonal ablation. Local high-intensity focused ultrasound (HIFU), as minimal invasive tissue coagulation (85°C), ablates prostatic tissue with high precision. Since April 1996, 184 patients have undergone 232 sessions of transrectal HIFU therapy (average 90 min) under spinal anesthesia at 2.25/3.0 MHz, 50 W, and a penetration depth of 25 mm. The follow-up serum prostate specific antigen (PSA) concentration, sextant biopsies, International Prostate Symptom Score (IPSS), quality of life measures (QoL), and complaint registration provide the foundation for this clinical evaluation. Follow-up sextant biopsies (an average of 1.9) showed 80% of the patients to be cancer free. In men with residual cancer, the tumor mass was reduced more than 90%. The PSA nadir in 97% was <4 ng/mL, including 61% with values <0.5 ng/mL. After primary HIFU, no severe side effects (fistula, second or third grade incontinence, rectal mucosal burns) occurred. All patients had a suprapubic tube (average 29 days), and 33% needed a transurethral debris resection averaging 7 g. They were discharged within 23 hours. According to the short-term follow-up transrectal HIFU enables minimal invasive local prostate tissue ablation with high rates of negative biopsies, low PSA nadir, and low complication rate.

INTRODUCTION

HIGH-INTENSITY FOCUSED ULTRASOUND (HIFU) is under investigation as minimally invasive therapeutic option for men with prostatic cancer (CaP). The cancer is organ confined in 70% of men at the time of diagnosis.[1] In Bavaria, 25% of these men undergo local therapy (surgery 23%/radiation 2%), while 75% receive systemic hormonal ablation or no treatment; i.e., watchful waiting.[1,2]

The therapeutic goal for transrectal HIFU is postponement of hormonal ablation by local minimally invasive coagulation. Progression to hormone-insensitive disease and typical therapeutic side effects should thereby be avoided or postponed.[3–5] In addition, local HIFU treatment provides a curative chance for the patient.

This publication describes the efficiency and adverse events of transrectal HIFU for local disease in elderly men (>70 years) or in high-risk patients, who are not candidates for radical prostatectomy.

PATIENTS AND METHODS

Equipment

The equipment consists of a treatment table, a diagnostic ultrasound device, which is connected to the treatment table, and equipment for patient fixation (Fig. 1). Integrated into the treatment table are a power generator for the piezoapplicator, watt meter, computer, computer screen, printer, Zip drive, high-precision distance measurement unit, cooling device, temperature control unit, roller pump, power supply, etc. Mounted on the table is a motorized and computer-driven treatment head (Fig. 2). It is three-dimensionally movable and is able to integrate two high-precision driving motors (1/1000 mm/step), piezoelectric therapeutic applicator (2.25–3.0 MHz), and a conventional diagnostic ultrasound scanner for treatment planning at 7.5 MHz. The therapeutic applicator has the shape and size of a tablespoon (55 × 40 × 10 mm) and can twist in the rectal ampulla as much as 45° laterally to allow the isocentric mo-

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FIG. 1. New HIFU device and patient positioning for treatment.

torized insertion of the transrectal ultrasound (TRUS) scanner. On the applicator's concave surface, three concave piezoelectric ceramics are placed. Two of them fire at preselected MHz and with a preselected shot duration and delay between two shots in accordance with the software.

The HIFU is applied in one session as day surgery or an outpatient procedure. The HIFU device used is ABLATHERM® (EDAP-TMS, Lyon, France).[6–9] The evaluation of the patient consists of TRUS at 7.5 MHz, TRUS-guided sextant prostate biopsies, and total PSA (tPSA) measurement. A CT scan, MRI, and a bone scan are obligatory before HIFU as preoperative staging. Efficacy was monitored by PSA at day 1, 14, 30 and every additional 3 months. Follow-up TRUS-guided sextant biopsies were performed routinely at month 3 and 12 and in cases of significant PSA elevations during follow-up.[10–12]

FIG. 2. Transrectal treatment head.

HIFU Application

Treatment is performed with the patient lying on his right side (see Fig. 1) under spinal anesthesia with a suprapubic tube in place. Therapy planning starts in transversal TRUS mode, to define the anatomic apex of the prostate gland. It changes to the longitudinal mode and defines the apical treatment start point, which is 5 mm distant to the anatomic apex. The next step is to identify the bladder neck as the therapeutic endpoint. A "security distance" is defined consisting 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 will be treated in sequential slices from the apex to bladder neck.

As many as 1000 individual HIFU lesions coagulate the prostate at 2.25 MHz (before November 1997) or 3.0 MHz (beginning in November 1997) with the therapeutic piezoelectric transducer. In 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. These treatments were given at a fixed 18-mm focus with 4.5-second shots and a 12-second delay between shots. There was a fixed 3-mm distance between the capsule and the rectum, and no security features. The HIFU technique, application mode, and treatment strategy have been standardized since November 1997. In the 94 patients treated during this time, there was a flexible focus of 13 to 18 mm with autofocusing. The shots were of 5.0 seconds with a 5-second delay. The distance between the capsule and the rectum was 3 to 6 mm, and there was a 5-mm apex distance. The rectum was cooled during the treatment with a 5°C inflow and 13°C outflow. The equipment detected and compensated for patient movement.

Inclusion Criteria

Patients in this study were not candidates for surgery but had a life expectancy of at least 5 years. Elderly men with localized biopsy-confirmed CaP were selected in order to postpone by HIFU the first application of hormonal ablation as a systemic palliative time-limited therapy. There were 184 patients aged 59 to 81 years (mean 72 years). The tumor stage was $T_{1-2}N_xM_0$ in all patients. Gleason scores were available for all of them, being 2–4 in 9.5%, 5–7 in 80%, and 8–10 in 10.5%. By TRUS, the prostate volume ($H \times L \times W \times 0.5$) averaged 26 cc and was <30 cc in all patients. There were no prostatic calcifications >5 mm. The tPSA was <20 ng/mL in all cases.

TABLE 1. PERCENT OF PATIENTS HAVING RESIDUAL CANCER IN SUBCAPSULAR (P) OR CENTRAL (Z) REGION AFTER HIFU

MHz	*P*	*P + Z*	*Z*
2.25	30	7	23
3.0	1	2	17

TABLE 2. EFFECT OF HIFU ON MEAN SERUM PSA (NG/ML)

	Day 0	*After 24 hours*	*Nadir*	*Last value*
Min	0.1	0	0	0
Max	20	100	8.2	14.3
Median	9.8	20.7	1.3	1.3
Mean	12	30.9	1.8	2.6
Mean after 3.0 MHz	2.2	8.7	0	0.2

They all had normal rectal anatomy. All patients gave informed consent to participation in the trial.

RESULTS

From November 1996 to April 1999, 315 HIFU treatments in three study arms have been performed, with 80% of the patients being treated for local disease, 10% for local recurrence, and 10% for local adjuvant debulking. In this article, the side effects of all 315 treatments are reported, while the efficiency of treatment is analyzed only in patients with local disease (N = 184).

The results for local CaP are encouraging: 80% of patients have cancer-free biopsies and 97% had a PSA nadir <4 ng/mL and 61% a PSA nadir <0.5 ng/mL (Tables 1 and 2). Proctoscopic pathological findings such as rectal burns occurred in 15% of the men treated at 2.25 MHz but only 0.7% of those treated at 3.0 MHz. All rectal burns were asymptomatic. Rectourethral fistulas decreased from 3.1% to 0.5% in primary treatment of local disease at 3.0 MHz. Prostate volume decreased an average of 50%, and the QoL did not change significantly (from 1.8 to 2.1 on a 6-point scale). The IPSS for micturition changed from 5 to 4, probably because a third of the patients had significant obstructive symptoms before HIFU and had to undergo TUR of necrotic debris within 6 to 8 weeks after HIFU. All patients were discharged <24 hours after HIFU treatment or were treated as outpatients. Urinary tract infections occurred in 58% of the first 96 cases, but this figure decreased to 17% in the 3.0 MHz cases because of low-dose antibiotic prophylaxis. Potency was preserved in one third of the men when the entire prostate was treated. If potency was important to the patient and the cancer was unilateral, on the contralateral side near the neurovascular bundle, 5 mm of tissue was excluded from the treatment, accepting a 15% higher rate of recurrence. This practice resulted in two thirds of these men preserving their potency.

Mild stress incontinence was seen in 24% of the men treated 2.25 MHz because in the beginning, we did not start the treatment with an apical security margin of 5 mm. Using this security margin, the stress incontinence rate decreased to 3.9% with no increase of apical residual cancer (Table 3). The necessity for auxiliary procedures (Table 4) for the treatment of complications decreased in men with stress incontinence (collagen injection from 2.5% to 0.5%) and fistula (fibrin injection from 1.3 % to 0), but not in patients with obstruction. Obstruction rates and the period of necessary drainage increased after November 1997 because of the increase in the HIFU dosage per treatment. Consequently, the rate of transurethral resection after HIFU rose from <10% to 30%.

DISCUSSION

High-intensity focused ultrasound is a therapeutic alternative for minimally invasive local treatment of CaP. In local disease, HIFU treatment should postpone the use of hormonal ablation and reduce progression of the disease to hormone insensitivity. Transrectal HIFU might be curative, is a single-session treatment, and can be performed on an outpatient basis. Radiation as a competitive treatment is performed in 25 to 30 sessions and obligates a patient for nearly 6 weeks to complete his therapy. The complications, side effects, and disease recurrence rates of radiation therapy resulted in the development of brachytherapy as single-session treatment, external conformal radiation, or a combination. The possibility of local ablation of CaP in the given set up creates interesting new indications for HIFU besides local disease (80% of the cases). These include treatment for local recurrence after radiation or surgery or early hormonal ablation (10%) and adjuvant local debulking in combination with hormonal ablation (10%). These additional uses are now under investigation. Local symptoms and local progression of disease should be postponed. Better quality of life and longer survival should result.

TABLE 3. SIDE EFFECTS OF HIFU AT 2.25 *v* 3.0 MHz (% OF PATIENTS)

	Treatment No.		
	1–96	*97–315*	*Last 100*
UTI	58	15	8
Stress incont.	24	0.9	1
Rectal burn	15	0	0
Fistula	3.1	0.5	0

TABLE 4. AUXILLARY TREATMENTS AFTER HIFU

	All 315	*Last 100*
TURP	40	30
Collagen	8	0
Fibrin	4	0
Turner/Warwick	6	1
Urethrotome	2	0
Bougie	6	2
Other	4	1

Transrectal HIFU is a urologic treatment, which needs surgical three-dimensional anatomic knowledge, diagnostic TRUS experience, and SWL-based application experience to perform a proper treatment. Today, only 10 treatments are needed to learn the technique of HIFU therapy using the ABLATHERM®. The efficacy of transrectal HIFU (3.0 MHz) for local CaP is demonstrated by an 80% negative follow-up biopsy rate and the large number of patients with PSA nadirs <4 ng/mL or even <0.5 ng/mL. No other treatment is excluded by HIFU. Treatment is possible as day surgery or on an outpatient basis. Side effects have diminished by improvement of the technique and application strategy. Auxillary procedures are TURP in a third of the patients and antibiotic treatment one third for urinary infection. Under this regimen, all patients have returned to normal micturition, and the IPSS remains stable. Potency is preserved in as many as two thirds of the patients who were potent before HIFU depending on treatment strategy

Long-term follow-up will let us learn more about PSA elevations after nadir, rates of recurrence, and side effects by tissue shrinkage. To date, HIFU is a local palliative treatment of CaP with a curative potential.

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