TRANSRECTAL HIGH-INTENSITY FOCUSED ULTRASOUND IN THE TREATMENT OF LOCALIZED PROSTATE CANCER : A MULTICENTER STUDY

Toyoaki UCHIDA[1], Shiro BABA[2], Akira IRIE[2], Shigehiro SOH[2], Naoya MASUMORI[3], Taiji TSUKAMOTO[3], Hiroomi NAKATSU[4], Hiroyuki FUJIMOTO[5], Tadao KAKIZOE[5], Takeshi UEDA[6], Tomohiko ICHIKAWA[6], Nobutaka OHTA[7], Tadaichi KITAMURA[7], Makoto SUMITOMO[8], Masamichi HAYAKAWA[8], Teiichiro AOYAGI[9], Masaaki TACHIBANA[9], Ryusuke IKEDA[10], Kohji SUZUKI[10], Nobuo TSURU[11], Kazuo SUZUKI[11], Seiichiro OZONO[11], Kiyohide FUJIMOTO[12], Yoshihiko HIRAO[12], Kohichi MONDEN[13], Yasutomo NASU[13], Hiromi KUMON[13], Kazuhiko NISHI[14], Shoichi UEDA[14], Hirofumi KOGA[15] and Seiji NAITOH[15]

[1]*The Department of Urology, Tokai University Hachioji Hospital*
[2]*The Department of Urology, Kitasato University*
[3]*The Department of Urology, Sapporo Medical University*
[4]*The Department of Urology, Asahi General Hospital*
[5]*The Department of Urology, National Cancer Center*
[6]*The Department of Urology, Chiba University*
[7]*The Department of Urology, Tokyo University*
[8]*The Department of Urology, National Defense Medical College*
[9]*The Department of Urology, Tokyo Medical University*
[10]*The Department of Urology, Kanazawa Medical University*
[11]*The Department of Urology, Hamamatsu University School of Medicine*
[12]*The Department of Urology, Nara Medical University*
[13]*The Department of Urology, Okayama University*
[14]*The Department of Urology, Kumamoto University*
[15]*The Department of Urology, Kyusyu University*

We report a multicenter trial with transrectal high-intensity focused ultrasound (HIFU) in the treatment of localized prostate cancer. A total of 72 consecutive patients with stage T1c-2N0M0 prostate cancer were treated using the Sonablate 500^{TM} HIFU device (Focus Surgery, Indianapolis, USA). Biochemical recurrence was defined according to the criteria recommended by the American Society for Therapeutic Radiology and Oncology Consensus Panel. The median age and prostate specific antigen (PSA) level were 72 years and 8.10 ng/ml, respectively. The median follow-up period for all patients was 14.0 months. Biochemical disease-free survival rates in all patients at 1 and 2 years were 78% and 76%, respectively. Biochemical disease-free survival rates in patients with stage T1c, T2a and T2b groups at 2 years were 89, 67% and 40% ($p=0.0817$). Biochemical disease-free survival rates in patients with Gleason scores of 2-4, 5-7 and 8-10 at 2 years were 88, 72% and 80% ($p=0.6539$). Biochemical disease-free survival rates in patients with serum PSA of less than 10 ng/ml and 10-20 ng/ml were 75% and 78% ($p=0.6152$). No viable tumor cells were noted in 68% of patients by postoperative prostate needle biopsy. Prostatic volume was decreased from 24.2 ml to 14.0 ml at 6 months after HIFU ($p<0.01$). No statistically significant differences were noted in International Prostate Symptom Score, maximum urinary flow rate and quality of life analysis with Functional Assessment of Cancer Therapy. HIFU therapy appears to be minimally invasive, efficacious and safe for patients with localized prostate cancer with pretreatment PSA levels less than 20 ng/ml.

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Key words : Prostate cancer, High-intensity focused ultrasound, Minimally invasive surgery

INTRODUCTION

Prostate cancer is the most common malignancy in men and the second leading cause of death due to cancer in the United States[1]. Prostate cancer has been treated in various ways, depending on the severity of the condition, age of the patient, staging, Gleason score and serum prostate-specific antigen (PSA) level. Radical prostatectomy has long been regarded as appropriate therapy for patients with organ-confined prostate cancer. Despite excellent 5- to 10-year survival rates after radical prostatectomy for organ-confined disease, surgery is

associated with significant morbidity, including blood loss due to transfusion-related complications, erectile dysfunction in 30% to 70% of cases, and stress incontinence in up to 10% of patients[2,3]. In addition, surgical intervention is not typically considered for patients whose life expectancy is less than 10 years. Recently, a number of alternative less invasive treatments have been developed for patients with localized prostate cancer, either not appropriate for surgery or who do not want to risk the potential side effects of surgery. Three-dimensional conformal radiotherapy (3D-CRT), brachytherapy, intensity-modulated external beam radiotherapy, cryosurgical ablation of the prostate and laparoscopic radical prostatectomy have all been applied for the treatment of this group of patients[4–6] However, in the event of treatment failure, these cannot be repeated and salvage radical prostatectomy is associated with a high morbidity rate[7].

High-intensity focused ultrasound (HIFU) delivers intense ultrasound energy with consequent heat destruction of tissue at a specific focal distance from the probe without damage to tissue in the path of the ultrasound beam[8] HIFU non-invasively induces complete coagulative necrosis of a tumor without surgical exposure or insertion of instruments into the lesion. This advantage makes it one of the most attractive options for the localized treatment of tumors[9,10]. We report here a multicenter trial with 72 consecutive patients treated with HIFU for clinical stage T1c-2N0M0 localized prostate cancer.

PATIENTS AND METHODS

Inclusion and Exclusion Criteria

As a rule, the inclusion criteria for treatment were patients with biopsy proven and untreated stage T1c-2N0M0 localized prostate cancer[11] Age, serum PSA levels, prostatic volume and WHO performance status should be less than 80 yrs, 20 ng/ml, treatable with a 4.0 focal length probe which means a prostatic volume less than 50 ml and 0–1. Patients with urethral stricture, anal stricture, bleeding tendency, renal dysfunction with serum Cr more than 2.0 mg/dl, hydronephrosis, larger than 5 mm calcifications in the prostate, uncontrolled diabetes mellitus, hypertension, angina, history of cardiac infarction or other malignant diseases were excluded from the study. None of the patients were receiving neoadjuvant hormonal and/or chemotherapy before HIFU. All patients were fully informed of the details of this treatment and gave written consent preoperatively.

HIFU Eqipment

For this study, we used the Sonablate 500™ (Focus Surgery, Indianapolis, IN, USA) HIFU machine. This treatment module includes the ultrasound power generator, transrectal probes, the probe positioning system, and a continuous cooling system (Fig. 1). The

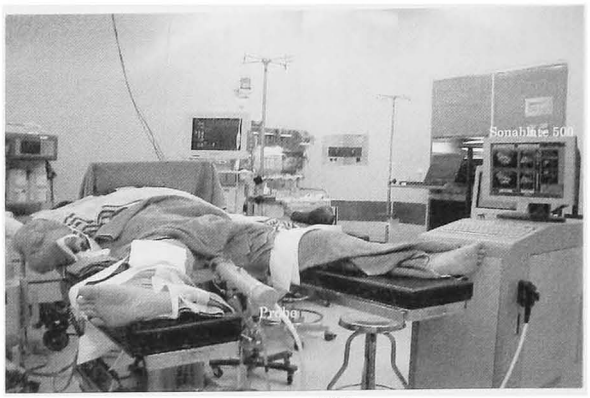

Fig. 1. The Sonablate-500™ type device consists of an operator's console, imaging monitor, transrectal probe and an automatic continuous cooling system.

transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging of the prostate and for the delivery of high-energy ablative pulses (site intensity, 1,300–2,200 W/cm^2). The single piezoelectric crystal alternates between high-energy power for ablative (3 sec) and low-energy for ultrasound imaging (6 sec)[10]

Prior to beginning the treatment, the operator uses longitudinal and transverse sonograms to obtain an image of the prostate and selects the prostate tissue volume to be ablated by a set of cursors on these images. The probe houses a computer-controlled positioning system that directs each ablative pulse to the targeted region of the prostate. Each discrete high-energy focused ultrasonic pulse ablates a volume of $3 \times 3 \times 10$ mm^3 of tissue[10] The total acoustic power is initially set at 24 W and 37 W for 3.0 and 4.0 cm focal length probes, respectively. The individual focal lesion produces almost instantaneous coagulative necrosis of the tissue due to a temperature rise of 80° to 98°C in the focal zone[8] Under computer control, the ultrasound beam is steered mechanically to produce consecutive lesions in a manner such that all focal lesions overlap

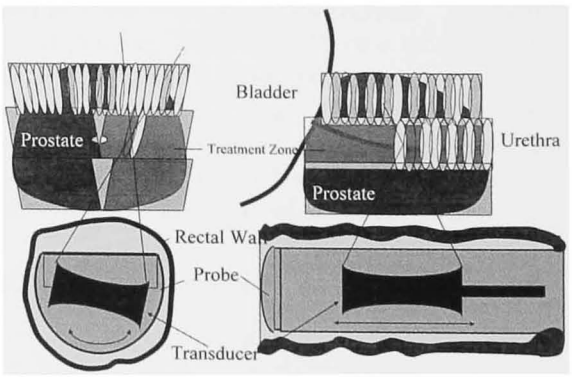

Fig. 2. The computer-controlled transducer ablates the entire prostate tissue. Focal lesions are overlapped in linear rows (left) at each of the lateral sector positions (right) to create a volume lesion.

laterally and longitudinally to ensure necrosis of the entire targeted prostate volume (Fig. 2). An automatic cooling device is used during treatment to maintain a constant baseline temperature of less than 18°C in the transrectal probe that helps to prevent thermal injury of the rectal mucosa.

HIFU Procedure

All patients were anesthetized by general, epidural, spinal or intravenous anesthesia, and were placed in a supine and open leg position. A condom was placed over the probe and degassed water was used to inflate the condom that was covered with ultrasound gel for close coupling of the ultrasound probe to the rectal wall, and the probe was inserted manually into the rectum. The probe was fixed in position by an articulating arm attached to the operating table. After selection of the treatment region of the prostate from the verumontanum to the bladder neck, the treatment was started. Transrectal probes with focal lengths of 3.0 and 4.0 cm were used according to the size of the prostate as determined by transrectal ultrasound (TRUS), with larger glands requiring longer focal lengths. The treatment continued layer by layer (10 mm thickness) from the apex to the base (Fig. 2). Usually, three successive target areas (anterior, mid-part and base) were defined to treat the whole prostate. After treatment was completed, a transurethral balloon catheter was inserted into the bladder[10].

Clinical Follow-up and Definition of Outcome

Patient status and treatment-related complications were followed up by all available means, including periodic patient visits and self-administered questionnaires dealing with urinary continence and erectile function using Functional Assessment of Cancer Therapy (FACT) questionnaire. Urinary symptoms and urinary flow rate analysis were performed using International Prostate Symptom Score (I-PSS) index and urowflowmetry[12,13] Serum PSA was assayed every 1 to 6 months during follow-up. A postoperative prostate needle biopsy under TRUS was performed on all patients at 6 months. The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition, i.e., three consecutive increases in post treatment PSA after a nadir has been achieved, was used to define biochemical failure[14] The time to biochemical failure was defined as midway between the post treatment PSA nadir and the first of three consecutive PSA increases. None of the patients received androgen deprivation after HIFU or other anticancer therapy before documentation of a biochemical recurrence. HIFU related complications were defined by Japanese version of National Cancer Institute-Common Toxicity Criteria version 2.0[15].

Statistical Analyses

All statistical analyses were performed by the Department Statistics in Indiana University. The chi-square test was used to assess the correlation between preoperative and postoperative parameters. The distributions of biochemical disease-free survival times were calculated according to the Kaplan-Meier curves and the logrank test was used to compare curves for groups. All p values less than 0.05 reflected statistically significant differences.

RESULTS

A total of 75 patients were entered in the trial. The prostate was treated in 1 (75) or 2 (14) HIFU sessions in a total of 89 procedures (1.2 sessions/patient). One patient with stage T1b, 1 patient with a serum PSA of 20.60 ng/ml and 1 patient on whom treatment was stopped during the procedure because of appearance with large microbubbles in the prostate were excluded. The median age, serum PSA level and prostatic volume of the 72 patients analysed were 72 yrs (range 45 to 79), 8.10 ng/ml (range 2.10 to 19.80) and 22.1 ml (range 8.5 to 52.8), respectively. The TNM stage was T1c in 40 patients, T2a in 18 patients and T2b in 14 patients. All patients had a histological diagnosis of prostatic adenocarcinoma according to the Gleason grading system. The Gleason score was 2 to 4 in 9 patients, 5 to 7 in 55 patients, 8 to 10 in 6 patients and unknown in 2 patients (Table 1).

The median time of HIFU treatment and hospitalization was 169 min (range 65 to 485 min) and 5.0 days (range 2 to 55), respectively. The gland size decreased from an initial volume of 24.2 ml to a final median volume of 14.0 ml ($p < 0.01$) in 45 patients. Totally, 49 out of 72 (68%) had negative follow-up biopsies at 6 months after HIFU. Biochemical disease-free survival rates were analyzed in 60 patients. Twelve patients were excluded from the analysis for unsatisfactory followup. The median follow-up period for all patients was 14.0 months (range 2 to 24). Biochemical disease-free survival rates in all patients at 1

Table 1. Characteristics in 72 patients with localized prostate cancer

Median age (range)	72 (45-79)
Median PSA (range)	8.10 ng/ml (2.10-19.80)
Prostate volume (range)	22.1 (8.5-52.8)
Pretreatment PSA (%):	
10 or less	44 (61)
10.1-20	28 (39)
Clinical stage (%):	
T1c	40 (56)
T2a	18 (25)
T2b	14 (19)
Gleason score (%):	
2-4	9 (13)
5-7	55 (76)
8-10	6 (8)
Unknown	2 (3)
Median mos followup (range)	14.0 (2-24)

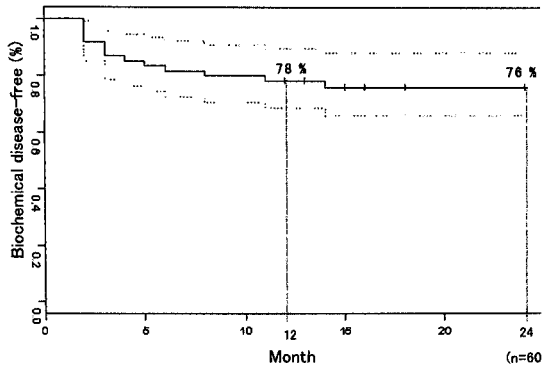

Fig. 3. Kaplan-Meier biochemical disease-free survival curves in all patients.

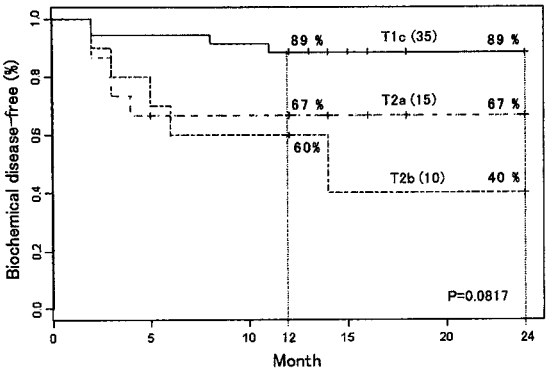

Fig. 4. Kaplan-Meier biochemical disease-free survival curves according to clinical stage.

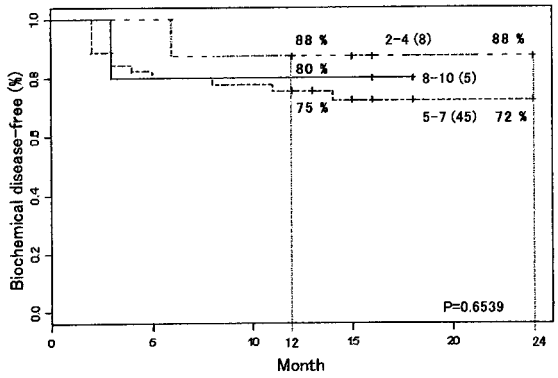

Fig. 5. Kaplan-Meier biochemical disease-free survival curves according to Gleason score.

and 2 years were 78% and 76%, respectively (Fig. 3). Biochemical disease-free survival rates in patients with stage T1c, T2a and T2b groups at 2 years were 89%, 67% and 40% ($p = 0.0817$, Fig. 4). Biochemical disease-free survival rates in patients with Gleason 2-4, 5-7 and 8-10 groups at 2 years were 88, 72% and 80% ($p = 0.6539$, Fig. 5). The biochemical disease-free survival rate in patients whose serum PSA less than 10 ng/ml and 10 - 20 ng/ml were 75% and 78% ($p = 0.6152$).

Prostatic volume was decreased from 24.2 ml to 14.0 ml at 6 months after HIFU ($p < 0.01$, Fig. 6). No statistically significant difference was noted in I-PSS, Q-max and FACT quality of life analysis (Fig. 7, 8 and 9).

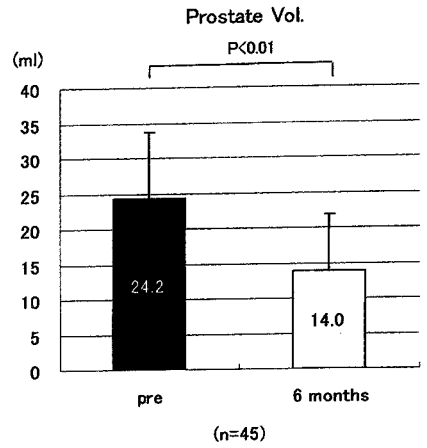

Fig. 6. Changes of prostatic volume.

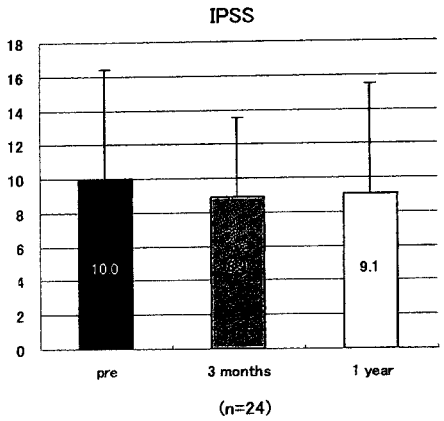

Fig. 7. Changes of International Prostatic Symptom Score.

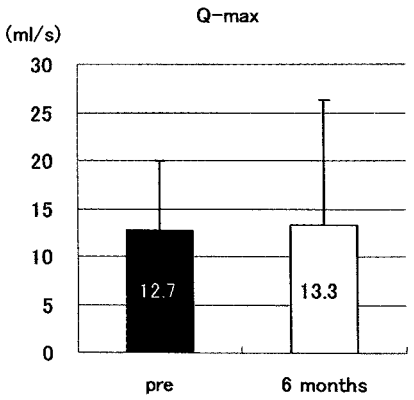

Fig. 8. Changes of maximum flow rate.

Thirteen out of 72 patients developed a urethral stricture, 6 and 4 patients developed epididymitis and prostatitis. Postoperative erectile dysfunction was noted in 12 out of 31 (39%) patients who were potent preoperatively. Nephrotic syndrome, transient urinary incontinence, transit stooly incontinence, balanoposthitis or retrograde ejaculation was observed in 1 patient each (Table 2).

For analysis of HIFU treatment using Sonablate 500^{TM}, ultrasound imaging for identifying prostate and quality levels were categorized more than good in patients with 92%. A transrectal probe was easily

Table 2. Complications

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Total
Urethral stricture	0	0	13	0	13
Erectile dysfunction (31 potent patients)	0	0	12	0	12
Epididymitis	2	2	2	0	6
Prostatitis	2	0	2	0	4
Nephrotic syndrome	0	0	1	0	1
Balanoposthitis	1	0	0	0	1
Uninary incontinence (grade 1)	1	0	0	0	1
Stooly incontinence	1	0	0	0	1
Retograde ejaculation	1	0	0	0	1

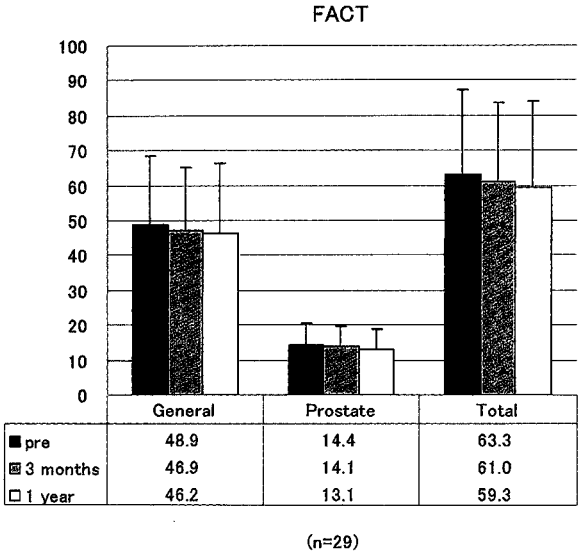

Fig. 9. Quality of life change by FACT general and prostate.

inserted into the rectum in 97% of the patients. Totally, 96% of the HIFU treatment was categorized as an easy procedure.

DISCUSSION

In 1995, Madersbacher et al. reported the effectiveness of HIFU in 10 cases of localized prostate cancer[8] Histologically, HIFU-treated lesions of the prostate demonstrated a coagulation necrosis with sharp boundaries. In 1996, Gelet et al. reported preliminary experiences with HIFU using the Ablatherm device (EDAP-Technomed, Lyon, France) for treating localized prostate cancer[16] Beerlage et al. reported the results of HIFU treatments in 111 patients with clinical stage T1-3N0M0 prostate cancer and a PSA level less than 25 ng/ml. The treatment for the first 49 patients was performed selectively (i.e. unilateral or bilateral treatment in one or two sessions depending on findings from TRUS and biopsies) and the whole prostate was treated in the remaining 62 patients. A complete response (defined as a PSA level < 4.0 ng/ml and a negative biopsy) was achieved in 60% of the whole prostate treated patients with and in 25% of selectively treated patients[17]

In 2001, Gelet et al. reported their long-term follow-up data in which a complete response was obtained in 66% of patients with no residual cancer (regardless of PSA levels) or no increases in PSA levels in three consecutive examinations with a PSA velocity < 0.75 ng/ml/year for patients with negative biopsies[18]. More recently, Chaussy and Thuroff summarized clinical outcomes by the ASTRO definition as 84.2% stability rate in the HIFU group and 80% rate in the combination with transurethral resection of the prostate (TURP) and HIFU group in 1 year[19] In summarizing our clinical outcome using the ASTRO definition, the biochemically disease-free survival rate was 76% at 2 years follow-up. Patients with stage T1c, T2a and T2b showed resectively 89, 67% and 40% biochemical disease-free survival rates at 2 years follow-up ($p=0.0817$). The clinical outcome in our series of patients with preoperative PSA less than 20 ng/ml were comparable to the outcome of patients treated with radical prostatectomy[2,3].

In our series, postoperative urethral strictures at near verumontanum in the prostatic urethra occurred in 21% of the patients. Recently, TURP or bladder neck incision immediately before or after HIFU was found to reduce the treatment-related morbidity such as postoperative prolonged urinary retention, urinary catheterization time and urinary infection[20,21] Neoadjuvant hormonal therapy also might be useful to reduce the volume of the prostate which can reduce the time of treatment and rate of morbidity. However, the upper limit of the gland volume is 50 ml even after reducing the size of the prostate with neoadjuvant androgen deprivation or TURP in our series. Generally, radicalism of prostate cancer and preservation of sexual function are always controversial because postoperative impotence depends on preservation of neuro-vascular bundles that sometimes includes tumor invasion. In our study, 39% of the patients exhibited erectile dysfunction after the HIFU therapy. One out of 12 patients who desired treatment for postoperative erectile dysfunction recovered with sildenafil citrate. We considered this rate to be lower than that compared to radical prostatectomy[2,3] Further experience is required to confirm this important conclusion.

D'Amico et al. compared the outcome of a cohort

treated with 3D-CRT versus a matched cohort treated with brachytherapy plus external radiation therapy. The 5-year estimate of PSA failure-free survival rate after 3D-CRT alone was 45% and 67% when both radiation treatments were combined[22] More recently, Kupelian et al. compared the biochemical disease-free survival rate after permanent seed brachytherapy, external beam radiation therapy (EBRT), combined seeds and EBRT, or radical prostatectomy for clinical stage T1-2 localized prostate cancer[23] The 5-year biochemical disease-free survival rate for radical prostatectomy, EBRT <72 Gy, EBRT ≥ 72 Gy, permanent seed brachytherapy and combined seeds and EBRT were 81, 51, 81, 83% and 77%, respectively. Although not directly comparable, the results after treatment with HIFU appear to be similar to those after radiotherapy, even when both brachytherapy and EBRT are combined.

For many reasons, transrectal HIFU appears to be highly attractive as a minimally invasive treatment for localized prostate cancer. HIFU treatment requires no incision or puncture, with no bleeding, can be performed on an outpatient basis and is repeatable even when patients with local recurrence have already been treated with radiation therapy[24] In addition, radiation therapy including brachytherapy and even surgery can be performed after HIFU.

Transrectal HIFU has considerable potential as a noninvasive treatment modality for patients with localized prostate cancer especially whose PSA less than 20 ng/ml.

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和文抄録

限局性前立腺癌に対する高密度焦点式超音波療法：多施設共同研究

内田 豊昭[1]，馬場 志郎[2]，入江 啓[2]，宋 成浩[2]
舛森 直哉[3]，塚本 泰司[3]，中津 裕臣[4]，藤元 博行[5]
垣添 忠生[5]，植田 健[6]，市川 智彦[6]，太田 信隆[7]
北村 唯一[7]，住友 誠[8]，早川 正道[8]，青柳貞一郎[9]
橘 政昭[9]，池田 龍介[10]，鈴木 孝治[10]，鶴 信雄[11]
鈴木 和雄[11]，大園誠一郎[11]，藤本 清秀[12]，平尾 佳彦[12]
門田 晃一[13]，那須 保友[13]，公文 裕巳[13]，西 一彦[14]
上田 昭一[14]，古賀 寛史[15]，内藤 誠二[15]

[1]東海大学八王子病院泌尿器科，[2]北里大学医学部泌尿器科
[3]札幌医科大学泌尿器科，[4]旭中央病院泌尿器科
[5]国立がんセンター泌尿器科，[6]千葉大学医学部泌尿器科
[7]東京大学医学部泌尿器科，[8]防衛医科大学泌尿器科
[9]東京医科大学泌尿器科，[10]金沢医科大学医学部泌尿器科
[11]浜松医科大学医学部泌尿器科，[12]奈良県立医科大学医学部泌尿器科
[13]岡山大学医学部泌尿器科，[14]熊本大学医学部泌尿器科
[15]九州大学医学部泌尿器科

限局性前立腺癌に対する高密度焦点式超音波療法の多施設共同研究の成績について報告する．対象は，stageT1-2N0M0 の72例の限局性前立腺癌で，治療にはソナブレート500 (Focus Surgery, IN, USA) を用いた．効果判定には，American Society for Therapeutics Radiology and Oncology の効果判定基準を用いた．症例の年齢中央値は72歳，血清 PSA 中央値は 8.10 n/ml であった．また，術後観察期間中央値は14.0カ月間であった．治療効果は，全体では1年78%，2年76%が非再発生存であった．浸潤度別に2年目の生化学的非再発生存率を集計したところ，stage T1c が89%，stage T2a 67%，stage T2b は40% (p=0.0817) であった．悪性度別では，Gleason 2～4群は88%，Gleason 5～7群は72%，Gleason 8～10群は80% (p=0.6539) であった．術前の血清 PSA 値別2年非再発生存率は，PSA が10 ng/ml 以下群は75%，10～20 ng/ml 群は78% (p=0.6152) であった．術後6カ月目の前立腺生検では68%において癌細胞は認められなかった．前立腺体積は，術前 24.2 ml から術後6カ月目 14.0 ml と縮小していた (p<0.01)．IPSS，最大尿流量率，Functional Assessment of Cancer Therapy (FACT) を用いた生活の質項目は術前後に有意な変化は認められなかった．高密度焦点式超音波療法は，術前血清 PSA 値が 20 ng/ml 以下の限局性前立腺癌に対して低侵襲性でかつ有用な治療法と思われる．

(泌尿紀要 **51**：651-658，2005)