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Clinical Paper

Noninvasive Surgery of Prostate Tissue by High Intensity Focused Ultrasound: An Updated Report

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Abstract:

Objective: To establish clinical efficacy and safety of High Intensity Focused Ultrasound (HIFU) for the treatment of benign prostatic hyperplasia (BPH) in a multiple site clinical study. *Methods:* Seven clinical sites were set up for the studies, five in the USA, one in Canada and one in Japan respectively. Sixty two patients were enrolled in these three studies. Transrectal ultrasound probes made to produce sufficient acoustic power required for focused ultrasound surgery of the prostate as well as to perform imaging of the prostate, were employed in the study. The probes ware made of 2.5, 3.0, 3.5, 4.0 and 4.5cm focal length transducers to treat varying prostate sizes and shapes and operated at 4 MHz frequency for both imaging and treatment. The employed ultrasound device produced both transverse and longitudinal images of the prostate on the same display. The images were used for selection of tissue volume, treatment planning and monitoring of tissue during the HIFU treatment cycle. The patients in the USA and Canada were followed for two years and those in Japan were followed for one year on a regular interval. The results were evaluated for changes in the peak flow rate (Qmax in ml/s), quality of life (QOL) and International Prostate Symptom Score (IPSS). *Results:* The average pre / post treatment results at 180 days were significantly different for Qmax, QOL and IPSS 8.5/14.2 (ml/s), 4.7/2.1 and 22/10 respectively. *Conclusion*: Under this protocol, HIFU was found safe and efficacious for the treatment of BPH. The HIFU treatment produced statistically significant results for the parameters measured with least complications. Additionally, the HIFU treatment was found to be durable.

Key words: High Intensity; Focused Ultrasound; Prostate; and Non-invasive surgery.

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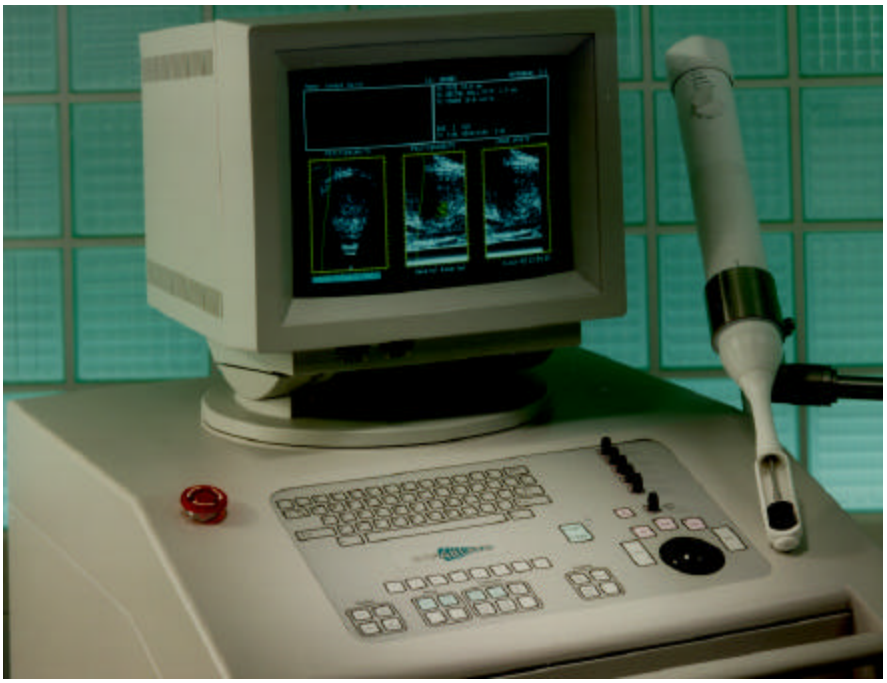

Fig. 1. The SB-200 device with a transrectal ultrasound probe.

1. Introduction

Since the 1940s', High Intensity Focused Ultrasound (HIFU) has been envisioned as a potential energy modality for the noninvasive surgery of diseased tissue located deep in the body (Lynn et al., 1942; Wall et al., 1951). HIFU has many unique capabilities and qualities, some of which are described here. 1) When used with appropriate peak focal *in-situ* intensities, HIFU can elevate tissue temperature in the focal zone up to 80-100^{o}C range in a very short exposure duration (1 - 10 s) while maintaining the intervening tissue temperature at physiologically safe levels. 2) HIFU can be applied externally and contact free to the tissues and organs that are being treated. 3) HIFU can produce sharply demarcated and predictable lesions. The size andshape of each lesion conforms to the ultrasound beam dimensions, site intensity and exposure duration (Fry et al., 1955; Coleman et al., 1985). 4) When individual lesions are combined in a matrix format, one can create a large contiguous lesion of desired size and shape (Maderbacher and Marberger 1995). 5) Since the tissue temperature is raised rapidly, blood perfusion effects are minimized during the HIFU treatment (Robinson and Lele, 1972). 6) The ultrasound energy is non-ionizing and can be applied repeatedly. 7) The HIFU procedure does not require sterile environment therefore it can be performed as an outpatient treatment.

These attractive qualities of HIFU have inspired us to pursue the application of HIFU for the treatment of benign and malignant tumors. This paper addresses the clinical application of HIFU for the treatment of benign prostatic hyperplasia (BPH) using the SB-200 device. The device was developed after extensive safety studies in the animal models, analytical computer simulations and laboratory measurements. Thereafter, under local and national regulatory approvals, several institutions under-took clinical studies to demonstrate efficacy and safety of the device. This paper summarizes the USA multi-site

clinical study results that have been obtained after 24 months of HIFU treatment. In addition, the long term study results form the Male Health Centere (THMC), Ontario, Canada and Kitasato School of Medicine, Sagamihara, Japan (Kitasato-study), that utilized indwelling uretheral catheter as a source for heat sink are compared and summarized.

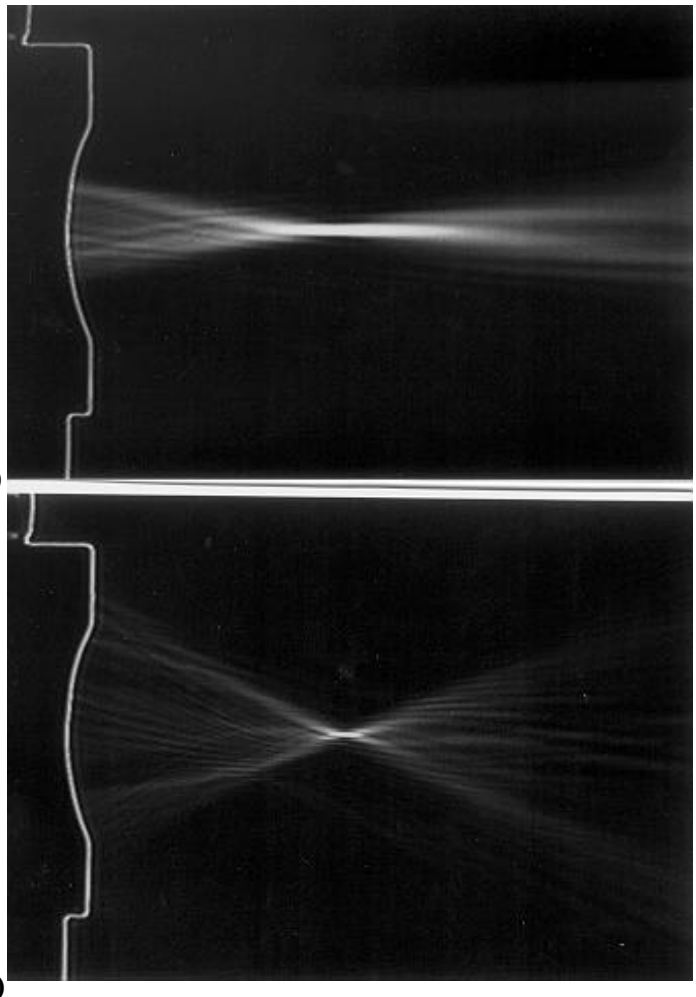

Fig. 2. Schelieren images of the transducer during imaging and HIFU therapy modes. a) The ultrasound transducer uses only the center circular segment of the crystal to generate long and uniform beam during the visualization of tissue. b) During the HIFU mode the entire transducer crystal surface is excited with RF high voltage to generate a sharp and narrow beam for treatment of the tissue.

2. Method and material

2.1. Instrumentation

2.1.1 Transrectal probe

The SB-200 device with a transrectal probe is shown in Fig. 1. The probe has a transducer that incorporates both the ultrasound visualization and HIFU capabilities on the same ceramic crystal operating at 4 MHz. The transducer is fabricated from modified lead titanate material (manufactured by Etalon Inc., Lebanon, IN) with two matching layers of quarter wavelength thickness. The aperture of the transducer is a curved rectangular shape of 30 x 22 mm, which is a cut out piece from a spherical disc of a fixed radius (focal length). The transducer disc is segmented into two electrically separate conducting surfaces. The center circular segment with an 11 mm diameter is used in a pulse-echo mode for imaging of the prostate. While the entire transducer surface is energized with high voltage RF energy during the HIFU treatment. Fig. 2 represents the ultrasound beam configurations during visualization and HIFU modes of operation. The probe tip is protected with a thin latex sheath and is covered with ultrasound gel for acoustic coupling to the rectal wall. The probe tip is filled with degassed circulating coupling water that keeps the rectal wall at a lower desired temperature and also cools the transducer during the treatment mode.

2.1.2 *Imaging and therapy planning*

The SB-200 provides transverse and longitudinal imaging of the prostate and displays both planes simultaneously on the video monitor as shown in Fig. 3. The mechanical scanning, (as depicted in Fig. 4) of the transducer steers the ultrasound beam during the imaging and treatment modes. The SB-200 software links these two images as shown in Fig. 3 by the trackball and cursors displayed on the images. Thus, positioning the cursor on the longitudinal image can produce a transverse image at that position; similarly, longitudinal image plane position is controlled by the cursor location on the transverse image. A 5 cm^3 balloon silicon catheter (16 or 18 French, Dow Corning) is used to localize and

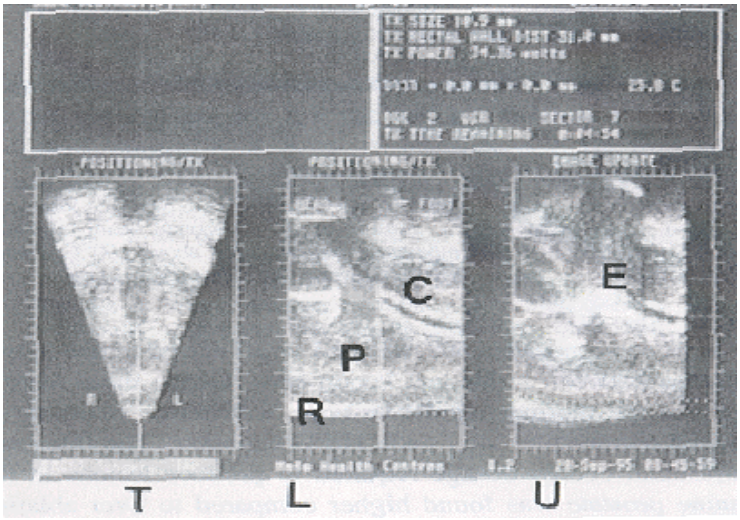

Fig. 3. The transverse (T) and longitudinal (L) images with a balloon catheter (C) of the prostate (P) are displayed for prostate treatment localization. These images are displayed simultaneously on the TV monitor. The operator can move the cursor, shown as a vertical line, on the images to select the position of a scanning plane. Thus multiple parallel transverse or longitudinal planes can be viewed quickly during the scanning procedure. During the treatment OFF time an update image (U) of the treated tissue is displayed on the right panel. The treated tissue region is hyperechoic (E) in the focal zone.

position the bladder neck and urethra in the focal zone. The coupling water in the probe tip is used to inflate or deflate the latex rubber sheath. This water standoff aids in positioning the urethra in the focal zone and keeps the rectal wall at a fixed predetermined position from the transducer. The operator uses both transverse and longitudinal images to localize and describe the prostate tissue treatment volume. Generally, the treatment volume is selected from the verumontanum extended to 5 mm above the bladder neck. The selected treatment volume is based on the size of the prostate. This is accomplished by outlining areas in the transverse and longitudinal planes by using the computer controlled cursor of the device.

2.1.3 *Treatment and treatment monitoring*

The HIFU treatment of BPH is primarily based on thermal ablation of the prostate tissue. The ultrasound treatment dosage is based on the tissue depth (i.e. distance from rectal wall to the desired site in the prostate). The focal peak acoustic intensity, ultrasound absorption coefficient and duration of ultrasound exposure calculate the temperature rise in tissue. The required site intensity is calculated for each patient by measuring the tissue depth from the rectal wall to the focal distance and using the absorption coefficient of 0.7 dB/cm MHz. The site intensity in the range of 1260 W/cm^2 to 2000 W/cm^2 is used for 4.0 cm and 3.0 cm focal length transducers respectively. Initially, the HIFU treatment was performed with an ultrasound exposure cycle of 4 seconds ON followed by a 12 seconds OFF period. However, the recent treatment uses 4 s ON followed by a 12 s OFF duty cycle. Thus reducing the overall treatment time. During the OFF period treated tissue is imaged. This provides a feed back to the user on the position of the prostate and any changes to the tissue caused by the treatment.

2.1.4 *Indwelling balloon catheter*

A 5 cm^3 balloon silicon catheter (18 French, Dow Corning) is kept in the urethra during the treatment.

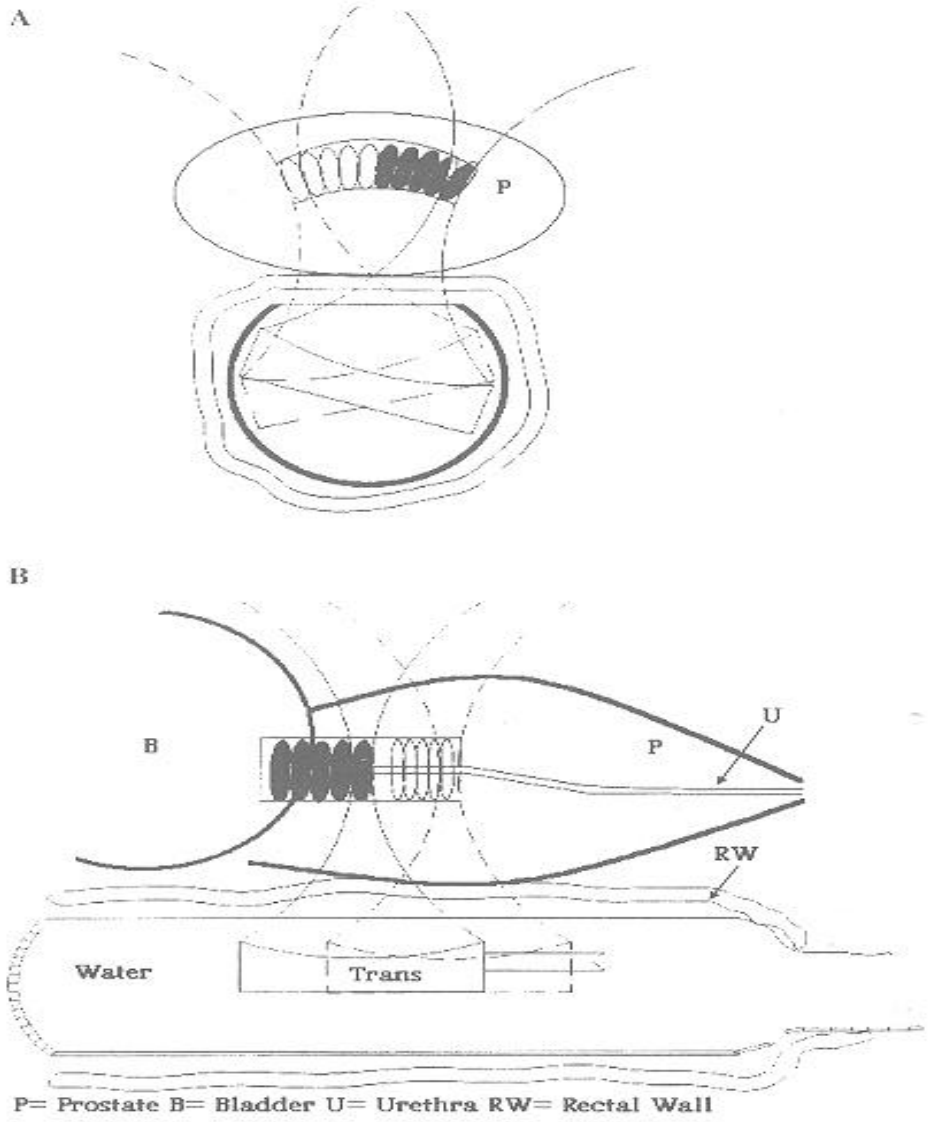

Fig. 4. The mechanical scanning of the transducer provides images of the prostate in transverse and longitudinal planes as shown in A and B frames. The operator selects the treatment zones as shown by the shaded areas in the focal zone of the transducer. Like a TURP procedure, the appropriate treatment volume is selected based on the size of the prostate. More tissue can be treated using multiple focal zone probes.

2.2 Patient treatment protocol

The United States Pilot Study (USPS, n=25) was conducted at five sites under the Investigational Device Exemption (IDE # 9110188) from the Food and Drug Administration of the USA, The Male Health Centre Study (TMHC, n=14) was conducted in Oakville, Canada under approved Investigational Review Board (IRB). The Kitasato study (Uchida et al., 1998) (n=22) was performed at the Kitasato University School of Medicine, Sagamihara, Japan under the approval of Japan Ministry of Health and Welfare. Briefly Table 1describes patient inclusion criteria for these studies. Patients were excluded if

they had a history of prostate surgery,clinical or pathological evidence of carcinoma of the prostate or rectum or anal disease.

There were major Differences among the three protocols: For the USPS study, patients had their bladder neck and proximal urethra treated with a minimum focal intensity of 1640 Watts / cm^2. The treatment protocol consisted of nine lesions in the transverse plane. The treatment extended from the bladder neck to the verumontanum. The catheter used for treatment alignment was removed before treatment. In the TMHC and Kitasato studies, patients were treated with the same intensity but had the balloon catheter *in-situ* during the treatment. Additionally, the treatment consisted of ten lesions in the region of the bladder neck and 17 lesions in the region of the prostate tissue to increase the tissue treatment volume. In the Kitasato study more anterior portion of the prostate tissue volume was treated using two or more focal length probes. All the TMHC patients were treated as outpatients, under IV sedation and intra-prostatic injection of Lidocaine. It the Kitasato study, all patients were given epidural anesthesia.

Table 1

Patient inclusion criteria

Inclusion criteria	Parameter
Patients having symptomatic bladder outlet obstruction	
Age	50 and above
Prostate volume	<80 cm^3
Peak urinary flow rate	≤12 ml/s
Post-void residual urine volume	≤300 cm^3
Voided urine volume	≥125 m
American Urology Association (AUA) symptom scores	≥12

3. Results

Three relevant quantitative (peak urine flow rate, ml/s) and qualitative (Symptoms and Quality of life scores) parameters to the BPH conditions were studied for the evaluation of outcome of the HIFU treatment. The patients were followed on a regular interval basis as listed in the Tables 3-5. The outcomes are also presented in the graphical forms in Fig. 5 for comparison purpose. The improvement in the symptoms and quality of life scores were statistically significant ($P<0.0001$) in all the three studies. The mean peak urinary flow rate improvements were statistically significant in the range of $P<0.01$ to $P<0.001$ post twelve months treatment. The complications resulting from the HIFU treatment are listed in Table 2. All complications were found to be transient and were resolved within 30 days. A total of three patients (two from USPS and one from Kitasato) were treated by TURP procedure because of insufficient improvements post HIFU treatment. There were no injuries or side effects due to HIFU treatment.

4. Discussion

Our group proposed the HIFU treatment of BPH in early 1986 (Sanghvi et al., 1996). The first clinical protocol for the BPH treatment was developed based on the assumption that debulking of prostatic tissue surrounding the urethra would be sufficient to relieve the patients from BPH condition. Based on that hypothesis, the Sonablate-1 (later replaced by the SB-200) system was developed and human clinical studies were performed at several sites (Bihrle et al., 1993a,b; Maderbacher et al., 1994; Ebert et al., 1997; Uchida et al., 1998). These studies provided early safety and efficacy data and significant insight on HIFU interactions with prostate and the surrounding tissues. These early studies also revealed that the peak urinary flow improvements were not adequate after the HIFU treatment. Therefore it was required to debulk large volume of periurethral and central zone tissue and include the bladder neck in the treatment. To improve

Table 2

Complications post HIFU treatment

PRIVATE Complication list	USPS (n = 26)	TMHC[a] (N = 14)	Kitasato (n = 22)
Hematospermia	3[b]	1[b]	0
Epididymitis	1	0	1
Gross hemauria	5[b]	0	0
Post operative urinary retention (> 1 day)	7	4	13
Post operative balloon catheter (days)	NA[b]	4	4.8 +/- 5.4
TURP# within 2 years	2	0	1
Dysuria	2	0	0
Urinary Tract Infections (UTI)	1	0	0

[a] All TMHC patients had a post operative balloon catheter and transient hematospermia.

[b] * Resolved within 30 days, ** Resolved in 1 week, NA= Not available. # TURP = Transurethral resection of the prostate.

Table 3

The US PILOT STUDY (USPS)- Summary Statistics[a]

PRIVATE Parameter	Base line(n)	1 Month(n)	3 Months (n)	6 Months(n)	12 Months(n)	24 Months(n)
Qmax(ml/s)						
Mean	8.7(24)	13.3(24)	13.1(23)	13.6(22)	12.6(23)	11.7(12)
SD	2.3	5.9	4.0	5.9	4.6	3.5
P Value#		P<0.0012	P<0.0003	P<0.0006	P<0.0006	P<0.06
AUA S.S.						
Mean	23.5(24)	11.5(24	9.3 (23)	8.4 (22)	10.7 (22)	10.6 (13)
SD	5.7	7.5	5.6	6.2	7.4	7.3
P Value[#]		P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001
Q of L						
Mean	4.6 (24)	2.6 (24)	2.1 (22)	1.8 (19)	2.2 (18)	2.2 (13)
SD	1.1	1.7	1.3	1.1	1.5	1.3
P Value[#]		P<0.0001	P<0.0001	P<0.0001	P<0.0001	P<0.0001

[a] n = number of patients, SD = Standard Deviation, Qmax = Peak flow rate, AUA S. S. = American Urology Association Symptoms Score.

#P values are calculated using confident interval of 0.05 and unpaired 2 tailed t-test.

the efficiency of the treatment, it was necessary to remove the necrotic tissue faster from the prostate. That meant to deliver more power and mechanically disintegrate the urethra to mimic a TURP like procedure. Based on this information the treatment protocols were revised. First, more transverse lesions were placed in the prostate and the bladder neck tissues were included in the treatment (USPS). Later HIFU studies were performed by keeping the silicon catheter in the urethra during the treatment (TMHC). The catheter has higher acoustic impedance compared to tissue and reflects partial energy into the posterior part of the prostate. Thus, providing higher localized acoustic intensity at the urethra and raising tissue temperature near to vaporization. The vapor gas bubbles are trapped on the surface of the catheter. These micro gas bubbles are hyperechogenic and provide a brighter image at the site of treated tissue. In addition, the ultrasound energy absorbed by the catheter is converted into heat. The silicon material is a good thermal insulator. It retains the heat at the treatment site for a longer time thus maintaining higher base temperature of the prostate during the entire treatment. This was confirmed during in-vivo

Table 4

THE MALE HEALTH CENTRE (MHC) -Summary Statistics[a]

PRIVATE Parameter	Base line (n)	3 Months (n)	12 Months (n)	24 Months (n)
Qmax (ml/s)				
Mean	9.1 (14)	13.6 (14)	14.5 (11)	13.9 (11)
SD	3.2	4.5	5.5	3.0
P value[#]		P<0.004	P<0.0012	P<0.0007
AUA S. S.				
Mean	22.6 (14)	6.8 (14)	8.8 (12)	6.5 (11)
SD	7.5	4.6	6.2	6.9
P value[#]		P<0.0001	P<0.0001	P<0.0001
Q of Life				
Mean	4.5 (14)	1.5 (14)	1.8 (12)	1.0 (11)
SD	1.5	1.1	1.5	1.1
P value[#]		P<0.0001	P<0.0001	P<0.0001

[a] n = number of patients, SD = Standard Deviation, Qmax = Peak flow rate, AUA S. S. = American Urology Association Symptoms Score. #P values are calculated using confident interval of 0.05 and unpaired 2 tailed t-test.

experiments in a canine model (n=20) prior to human trials. The temerpatre between the catheter surface and tissue were measured. To measure temperature in the focal zone, a bare wire 50 micrometer diameter bead tehrmocouple was attached to the catheter. The catheter was inserted in the dog prostate and imaged with SB-200. The HIFU therapy zone was selected to cover the thermocouple. Fig. 6 shows the temperature profile for the entire treatment. The tissue site near the thermocouple reached above 100^{o} C while maintaining approximately 60^{o} C temperature at the tissue interface during the entire treatment time. The temperature profile shows peaks and valleys as a function of sound ON/OFF cycle and the location of HIFU beam relative to the thermocouple. The highest temperature is recorded when the ultrasound beam is closest to the thermocouple.

The high safety level of HIFU has allowed users of the SB-200 device to treat larger volume of the prostatic tissue. Dr. Uchida et al. (Kitasato) treated BPH patients with two focal length probes. Initially, all patients were treated with the silicon catheter in the urethra. The appropriate focal length probe was selected to place the urethra and the bladder neck tissue in the prescribed treatment focal zone. Later the catheter was removed and a longer focal length probe was used to treat the anterior fibromuscular stroma. The Kitasato-study resulted in higher urine peak flow rates. The average peak flow rate was improved by 7 ml/s compared to about 4-5 ml/s from the other two studies. The significant aspect of the study showed that the flow rate continued to improve over time and at the end of twelve months the improvement was close to 95% compared to the base line. In addition, the average prostate volume decreased by 29% (9.4 + / - 9.4 ml, n = 12). This was due to the fact that treated prostates continued to shrink as necrotic tissues were sloughed and absorbed by the body's scavenging system. In ten out of 12 patients, cavities were formed with new urethra in the treated prostates. These two factors, i.e. more tissue treatment and the higher temperatures generated by the in-dwelling catheter resulted in the desired urine flow rate improvements. All patients also attained the desired improvement in Symptoms score and Quality of life.

5. Conclusion

Over the last six years the non-invasive HIFU treatment of BPH has improved as more experience and knowledge

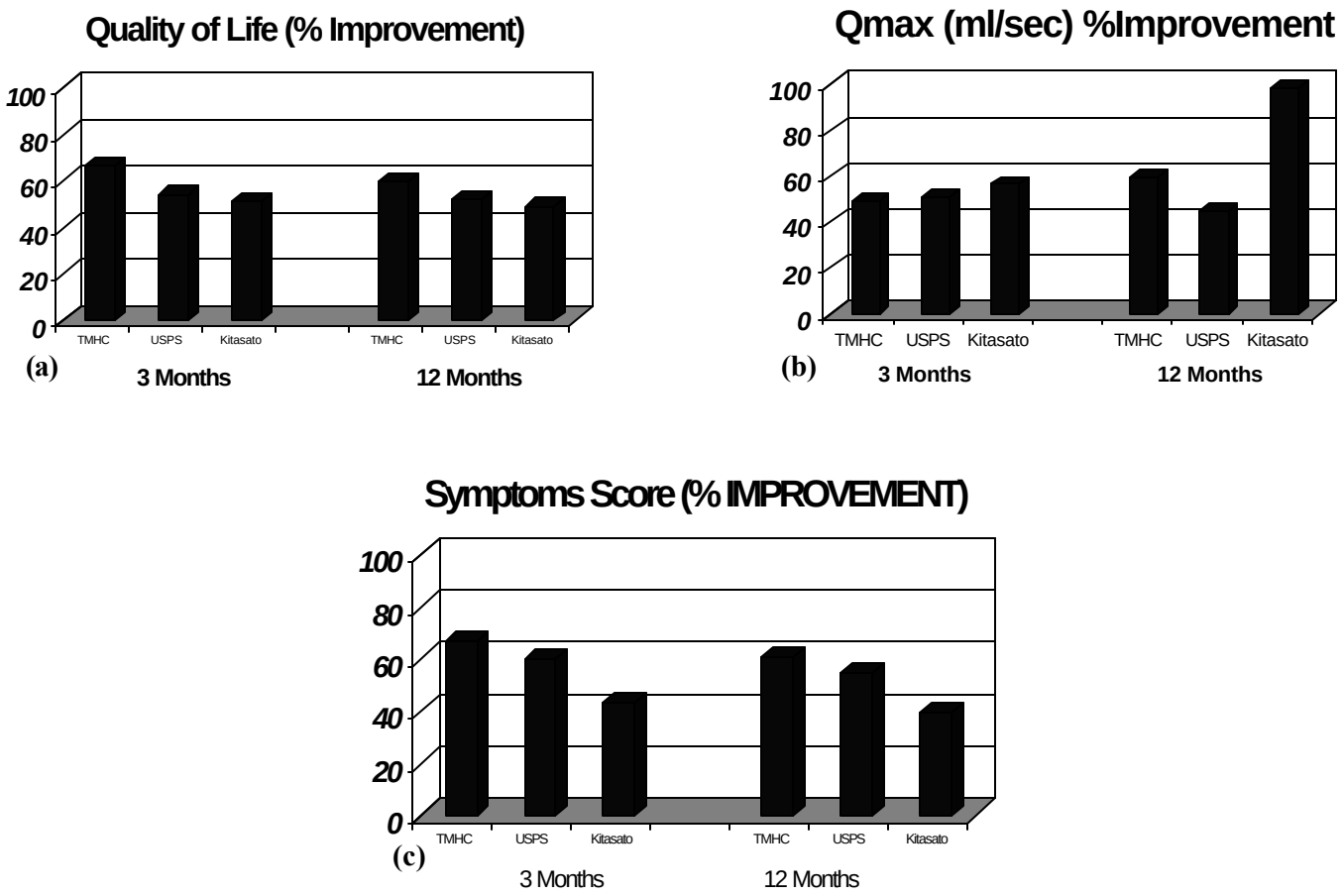

Fig. 5. Quality of life improvement scores at three and 12 months post HIFU treatment. As shown, this parameter is stable and maintained over time, (b) Peak urinary flow (Qmax in ml/s) rate after three and 12 months post HIFU treatment. The improvement appears within a month post HIFU treatment and continues to improve as the treated tissue is removed from the prostate. In the case of Kitasato study larger volume of prostate tissue was treated. This was also evident as the overall prostate gland volume decreased over time and created cavities at the treatment site, (c) Symptoms score improvements at three and 12 months post HIFU treatment. The symptoms score appears to improve within a month and continues to be stable over time.

has been gained from various clinical studies and continuned life science studies. The improvements in the technology have allowed us to treatpatients more aggressively and remove larger volume of prostatic tissue in shorter treatment time. The bi-plane software linkage between transverse and longitudinal planes makes the treatment planning easier and allows more accurate targeting of the tissue. The circulating cooling water keeps the rectal temperature lower than body temperature and shortens the treatment time by reducing the OFF time. The BPH patients with prostate from 30ml to 40 ml are treated in less than 45 minutes. These clinical studies prove the reliability and durability of HIFU treatment of the BPH condition. The technological changes are under way to make the HIFU device more user friendly and more effective by means of electronic beam steering and control. High-resolution ultrasound imaging and HIFU beam steering techniques will tremendously enhance in the treatment of both BPH and localized prostatic carcinoma.

Table 5 The Kitasato (Japan)-Summary Statistics[a]

PRIVATE Parameter	Base line (n)	3 Months (n)	6 Months (n)	12 Months (n)
Qmax (ml/s)				
Mean	7.8 (17)	12.2 (17)	15.2 (14)	15.5 (12)
SD	3.2	5.2	6.5	5.7
P value[#]		P<0.01	P<0.001	P<0.001
I.P.S. S.				
Mean	19.7 (18)	11.2 (18)	11.9 (14)	11.4 (12)
SD	6.9	7.2	5.9	7.2
Q of Life				
Mean	4.9 (18)	2.4 (18)	2.5 (14)	2.9 (12)
SD	0.8	1.6	1.6	1.5

[a] n = number of patients, SD = Standard Deviation, Qmax = Peak flow rate, I.P.S.S. = International Prostatic Symptoms Score.
[#] P values are calculated using confident interval of 0.05 and unpaired 2-tailed t-test.

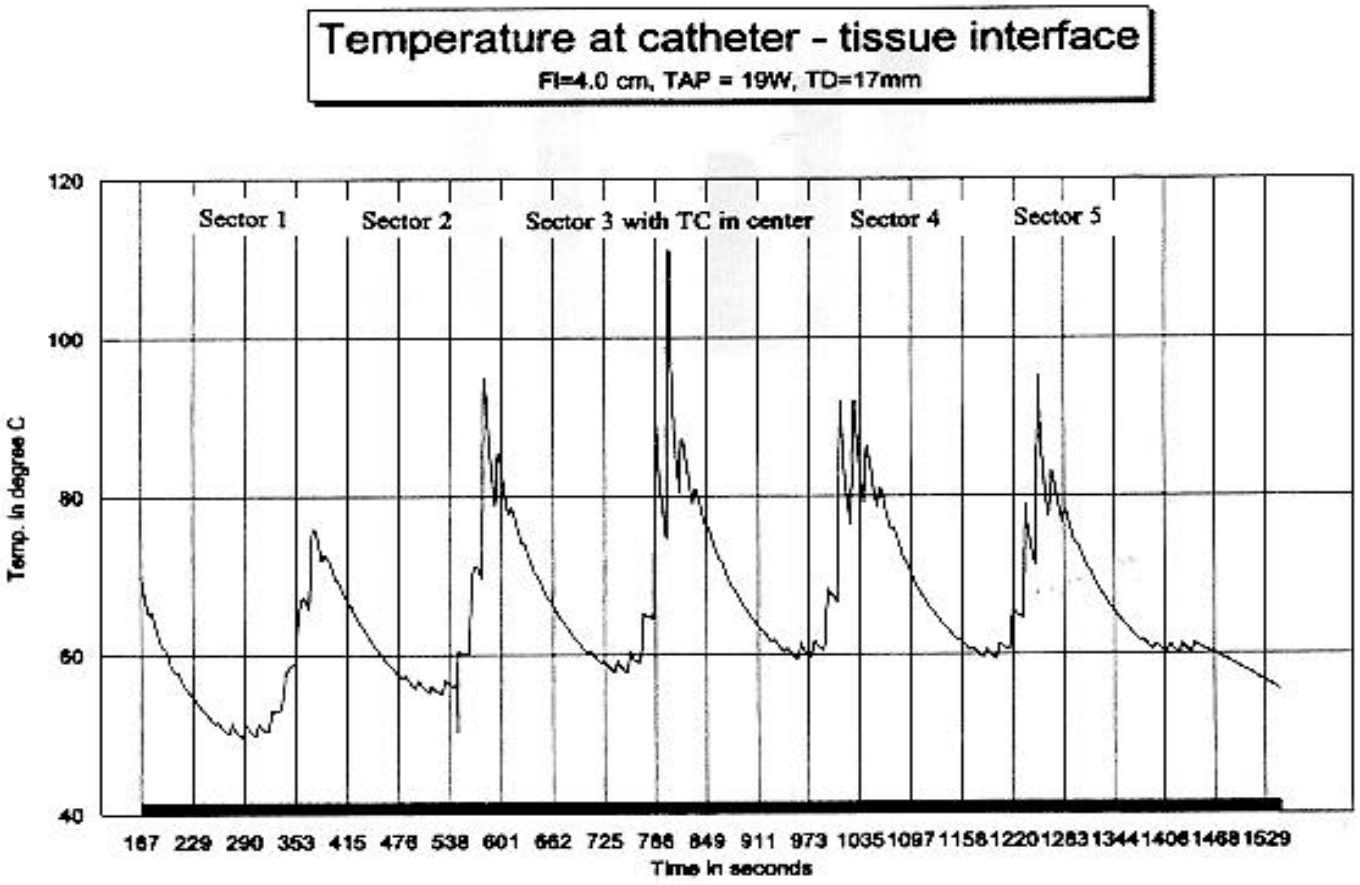

Figure 6. The temperature profile of tissue treatment with the silicon catheter. The temperature was measured during the in-vivo experiment by placing a 50-μm diameter thermocouple bead between the urethra and the catheter. The tissue site near the thermocouple reached above 100° C when the HIFU beam was nearest to the thermocouple while maintained approximately 60°C temperature for the entire treatment duration.

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References

Bihrle R, Foster RS, Sanghvi NT, Donohue JP, Hood PJ High intensity focused ultrasaound for the treatment of BPH: Early U.S. clinical experience. J. Urology 151;1993:1271-5**.**

Bihrle R, Foster RS, Sanghvi NT, Fry, Donohue JP. High intensity focused ultrasaound in the treatment of prostatic tissue. Urology 1993;43:21–6.

Coleman DJ, Lizzi FL, Driller J, Rosado AL, Burgess SEP, Torpey JH, Smith ME, Silverman RH , Yobolonski ME, Chang S, Rondeau MJ. Therapeutic ultrasound in the treatment of glaucumo II. Clinical applications. Opthalmology, 1985;92:347-53.

Ebert T, Miller S, Anastasiadis A, Ackermann R. High intensity focused ultrasound for the treatment of benign prostatic hyperplasia (BPH). In: Chaussy C, Eisenberger F, Jocham D, and Wilbert D, editors. High Energy Shock Waves in Medicine, 1997:171-4 ISBN 3-13-104831-x.

Fry WJ, Barnard JW, Fry FJ, Bernnan JF. Ultrasonically produced localized lesions in the central nervous system. Am J Phys Med. 1955; 34:413-23.

Lynn GR, Zwemer RL, Chick AJ, Miller AF. A new method for the generation and use of focused ultrasound in experimental biology. J Gen Physiol 1942; 26:179-193.

Maderbacher S, Marberger M. Therapeutic applications of ultrasound in urology. In: Marberger M, ed. Application of Newer Forms of Therapeutic Energy in Urology. Oxford: ISIS Medical Media Ltd.,1995: 115-136.

Maderbacher S, Kratzik C, Susani M, Marberger M. Tissue ablation in benign prostatic hyperplasia with high intensity focused ultrasound. J Urol 1994; 152: 1956-61.

Robinson TC, Lele PP. An analysis of lesion development in the brain and in plastics by high-intensity focused ultrasound at low-megahertz frequencies. J Acoust. Soc Amer 1972; 51:1333-1.

Sanghvi NT, Fry FJ, Bihrle R, Foster RS, Phillips MH, Syrus J, Hennige C. Non-invasive surgery of prostate tissue by high intensity focused ultrasound. IEEE Trans Ultrasonics, Ferroel Freq Contr 1996; 43:1099-110.

Uchida T, Muramoto M, Kyunou H, Iwamura M, Egawa S, Koshiba K. Clinical outcome of high-intesity focused ultrasound for treating benign prostatic hyperplasia: Preliminary report. Urology 1998; 52:66-71.

Wall PD, Fry WJ, Stephens R, Tucker D, Lettvin JY. Changes produced in the central nervous system by ultrasound. Science 1951,114:686-7.