Evolution and Outcomes of 3 MHz High Intensity Focused Ultrasound Therapy for Localized Prostate Cancer During 15 Years

Stefan Thüroff*,† and Christian Chaussy†

From Harlachinger Krebshilfe e.V. (ST, CC) and Department of Urology, Klinikum Harlaching (ST), Munich, and Department of Urology, University of Regensburg, Regensburg (CC), Germany

Abbreviations and Acronyms

ADT = androgen deprivation therapy

BDFS = biochemical disease-free survival

HIFU = high intensity focused ultrasound

PCa = prostate cancer

PSA = prostate specific antigen

RP = radical prostatectomy

TRUS = transrectal ultrasonography

TUR = transurethral resection

TURP = transurethral prostate resection

Accepted for publication February 6, 2013.

* Correspondence and requests for reprints: Department of Urology, Klinikum Harlaching, Sanatoriumsplatz 2, 81545 München, Germany (telephone: 49-89-6210-0; e-mail: sthueroff@mnet-mail.de).

† Financial interest and/or other relationship with EDAP TMS.

Editor's Note: This article is the fifth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 818 and 819.

Purpose: We describe the long-term cancer control and morbidity of high intensity focused ultrasound with neoadjuvant transurethral resection of the prostate, the risk of metastatic induction by transurethral prostate resection, and the evolution of high intensity focused ultrasound application and technology with time.

Materials and Methods: A prospective Harlaching high intensity focused ultrasound database was searched for patients with primary localized prostate cancer (T1–2, N0, M0, PSA at first diagnosis less than 50 ng/ml) and followup longer than 15 months. Those patients with previous long-term androgen deprivation therapy, locally advanced prostate cancer or any therapy influencing prostate specific antigen were excluded from study. All patients were treated completely with an Ablatherm® high intensity focused ultrasound device. Evaluation was performed in aggregate, and by stratification according to cohort group, risk group (D'Amico criteria), prostate specific antigen nadir and Gleason score. The Phoenix definition was used for biochemical failure. Statistical analysis was performed using the Kaplan-Meier method, and univariate and multivariate analysis was performed using a Cox model.

Results: Of 704 study patients 78.5% had intermediate or high risk disease. Mean followup was 5.3 years (range 1.3 to 14). Cancer specific survival was 99%, metastasis-free survival was 95%, and 10-year salvage treatment-free rates were 98% in low risk, 72% in intermediate risk and 68% in high risk patients. Prostate specific antigen nadir and Gleason score predicted biochemical failure, and side effects were moderate. The high intensity focused ultrasound re-treatment rate has been 15% since 2005.

Conclusions: Long-term followup with high intensity focused ultrasound therapy demonstrated a high overall rate of cancer specific survival and an exceptionally high rate of freedom from salvage therapy requirements in low risk patients. Advances in high intensity focused ultrasound technology and clinical practice as well as the use of neoadjuvant transurethral prostate resection allow the complete treatment of any size prostate without inducing metastasis.

Key Words: prostatic neoplasms; ultrasound, high-intensity focused, transrectal; robotics; ultrasonic therapy; ablation techniques

HIGH intensity focused ultrasound has been used experimentally in urology since the 1930s[1–6] and clinical investigations began in 1996 as a transrectal ablative therapy for localized prostate cancer.[7–9] Since the early 2000s HIFU has been combined with neoadjuvant transurethral resection of the

0022-5347/13/1902-0702/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.02.010
Vol. 190, 702-710, August 2013
Printed in U.S.A.

Table 1. *Reasons for exclusion from study*

	No. (%)
Overall	736 (51)
Followup less than 15 mos	490 (34)
Treatment vol less than 80%	115 (8.0)
Neoadjuvant ADT greater than 12 mos	61 (4.2)
Previous radiation	30 (2.0)
PSA at first diagnosis greater than 50 ng/ml	25 (1.7)
Previous orchiectomy	6 (0.4)
Previous other HIFU	5 (0.3)
Previous chemotherapy	4 (0.2)

prostate.[10,11] The status of HIFU has remained investigational because the body of published evidence has not yet reached sufficient maturity to provide definitive data on long-term cancer control. This is especially true given the followup length of studies evaluating external beam radiotherapy and radical prostatectomy.[12,13]

The current study was designed in 1995, before the first use of HIFU at 3 MHz with the Ablatherm device. Given the typical slowly progressing natural history of PCa and the need to document long-term cancer control and morbidity, patient accrual and followup were planned from the outset in 1996 to run 25 years. The primary objective of the current study was to evaluate the long-term cancer control efficacy and morbidity of HIFU with neoadjuvant TURP. The secondary objective was to evaluate metastasis induction by TUR in prostate cancer. The third objective was to document and evaluate advances in technology and refinement in clinical application during the study period.

PATIENTS AND METHODS

Data from all patients treated with HIFU in Munich-Harlaching were prospectively entered into a database. All patients were treated completely with Ablatherm HIFU devices. At the time of analysis the database consisted of 2,079 cases including 1,440 treated for localized disease (T1–2, N0, M0). The remaining cases received HIFU as primary therapy for advanced stage PCa or as salvage therapy for recurrence after nonHIFU primary therapy. Of the 1,440 patients treated for localized disease 736 were excluded from analysis as they did not meet the inclusion criteria (see Appendix, table 1). This yielded a study population of 704 patients treated from 1996 to the end of 2009. These patients were stratified into 3 cohort groups based on year of therapy and treatment device. During the study period 3 generations of HIFU devices were used because patients were treated with the then most recent HIFU device available. These included the prototype device from 1996 to 1999 (cohort 1), the first commercially available device, the Ablatherm Maxis®, from 2000 to 2005 (cohort 2), and the second device, Ablatherm Integrated Imaging, beginning in 2005 (cohort 3). Data collection and evaluation were performed by a third party (Harlachinger Krebshilfe e.V.), and did not involve individuals with a commercial interest in the study outcomes.

Localized PCa was diagnosed by transrectal ultrasound guided biopsy of the prostate and seminal vesicles. The combined results of digital rectal examination, transrectal ultrasound, radiological staging, TRUS guided rectal biopsies, TUR chips and PSA were used in clinical tumor staging. Specific transitional zone biopsies were not performed as the ventral area of the prostate was resected and histopathologically analyzed. The integration, characteristics and histopathological outcome of neoadjuvant TURP before HIFU are displayed in table 2. The operational procedure of the Ablatherm HIFU device has been previously described in detail.[14–16]

Before 2000 most patients received HIFU therapy without TURP. In the absence of pre-HIFU TURP, prostates larger than 30 cc could only be partially ablated due to limited rectal movement space for the transrectal applicator, and limited HIFU penetration into the ventral areas and middle lobes. During the 15-year study period the majority of HIFU/TURP treatments at our institution (more than 75%) were performed by 2 surgeons, while the remaining treatments were supervised by these surgeons.

Neoadjuvant TURP has undergone substantial refinement since its introduction. Several characteristics now distinguish neoadjuvant TURP from conventional TURP performed for adenoma resection. HIFU induces substantial shrinkage of the residual prostatic capsule and bladder neck. TURP compensates for this effect with resection of a large bladder neck and the entire middle lobe.

The penetration depth of HIFU is limited to approximately 30 mm. Therefore, ventral prostatic tissue in larger prostate glands cannot be completely coagulated and requires TURP. Because HIFU induces the formation of fibrotic scar tissue, apical tissue should not be left in place but should instead be resected in a radical manner as when TURP is used for adenoma resection.

Monopolar resection of the prostate was performed from 2000 to 2005 and bipolar resection has been performed since 2005. Few patients underwent previous open

Table 2. *Transurethral resection data*

	All	Prototype	Maxis	Integrated Imaging
Yrs study period	1996–2009	1996–1999	2000–2004	2005–2009
No. pts	704	170	358	176
No. TUR before HIFU (%)	528 (75)	6 (3.5)	346 (96.6)	176 (100)
TUR (%) of prostate vol:				
Median	43	36	39	52
Mean	44	38	39	51
Max	93	55	93	86
Min	2	25	4	2
No. no TUR histology (%)	55 (10.4)	0	36 (10.1)	19 (10.8)
No. no PCa (%):	220 (41.7)	3 (50)	150 (43.4)	67 (38.1)
Less than 10%	143 (27.1)	2 (33.3)	91 (28.9)	50 (28.4)
10%–30%	83 (15.7)	0	49 (14.2)	34 (19.3)
Greater than 30%	27 (5.1)	1 (16.7)	20 (5.8)	6 (3.3)
No. TUR combined (%)*	422 (79.9)	1 (16.7)	311 (89.9)	110 (62.5)
No. TUR split (%)†	106 (20.1)	5 (83.3)	35 (10.1)	66 (37.5)

* TUR and HIFU in 1 session.

† TUR 1 month before HIFU.

Table 3. *Prognostic factors for biochemical progression (Phoenix) and need for salvage treatment using univariate analysis and Cox model*

	Univariate p Value	Univariate Risk Ratio	Univariate 95% CI	Multivariate p Value	Multivariate Risk Ratio	Multivariate 95% CI
			Biochemical progression (Phoenix)			
Age	0.653	1.01	0.97–1.04	0.706	1.00	0.98–1.04
PSA (ng/ml):						
4 or Less	—	1	—	—	1	—
4–10	0.695	0.87	0.42–1.79	0.613	0.83	0.40–1.72
10 or Greater	0.016	2.40	1.18–4.88	0.044	2.11	1.01–4.35
Gleason:						
6 or Less	—	1	—	—	1	—
7	0.215	1.32	0.85–2.04	0.896	1.03	0.65–1.65
8 or Greater	0.077	2.29	0.91–5.74	0.221	1.80	0.70–4.61
Stage:						
T1	—	1	—	—	1	—
T2	0.607	1.19	0.62–2.29	0.601	0.83	0.42–1.66
Biopsies:						
2 or Less	—	1	—	—	1	—
3–4	0.124	1.40	0.91–2.15	0.120	1.43	0.91–2.25
5 or Greater	0.350	1.40	0.69–2.85	0.281	1.51	0.72–3.17
Prostate vol (cc):						
25 or Less	—	1	—	—	1	—
Greater than 25	0.224	0.75	0.47–1.20	0.188	0.73	0.45–1.17
TURP:						
No	—	1	—	—	1	—
Yes	0.050	0.65	0.43–1.00	0.713	0.80	0.24–2.63
Neoadjuvant ADT:						
No	—	1	—	—	1	—
Yes	0.022	1.61	1.07–2.41	0.177	1.34	0.88–2.05
			Need for salvage treatment			
Age	0.049	0.97	0.95–1.00	0.075	0.98	0.95–1.00
PSA (ng/ml):						
4 or Less	—	1	—	—	1	—
4–10	0.554	0.82	0.42–1.60	0.364	0.73	0.37–1.44
10 or Greater	0.055	1.90	0.99–3.66	0.473	1.28	0.65–2.53
Gleason:						
6 or Less	—	1	—	—	1	—
7	0.001	1.98	1.30–3.00	0.196	1.35	0.96–2.12
8 or Greater	0.001	3.20	1.57–6.54	0.021	2.49	1.15–5.39
Stage:						
T1	—	1	—	—	1	—
T2	0.006	7.05	1.74–28.58	0.041	4.39	1.06–18.2
Biopsies:						
2 or Less	—	1	—	—	1	—
3–4	0.001	2.10	1.37–3.22	0.003	1.99	1.27–3.12
5 or Greater	0.002	2.55	1.39–4.68	0.210	1.56	0.78–3.15
Prostate vol (cc):						
25 or Less	—	1	—	—	1	—
Greater than 25	0.229	0.75	0.47–1.20	0.360	0.80	0.49–1.29
TURP:						
No	—	1	—	—	1	—
Yes	0.001	0.41	0.27–0.61	0.961	0.97	0.26–3.64
Neoadjuvant ADT:						
No	—	1	—	—	1	—
Yes	0.002	1.87	1.26–2.77	0.485	1.17	0.75–1.82

adenectomy or green light laser ablation of the prostate. Those who did were endoscopically re-resected to achieve a standardized anatomy before HIFU. During the consent process, patients were informed of a 20% probability that they would be offered a second HIFU treatment during followup and a 20% probability of secondary endoscopic necrosis/scar tissue removal within postoperative year 1. HIFU re-treatment was suggested to patients with PSA relapse and biopsy proven locally residual or recurrent PCa at followup. Followup data were obtained by patient survey, medical records, mail and telephone contact. For perioperative complications the Clavien classification was used.[17]

In addition to device/year cohort groupings, patients were also stratified by risk group for tumor recurrence including low risk (T1–T2a and PSA 10 ng/ml or less and Gleason 6 or less), intermediate risk (T2b or PSA 11 to 20 ng/ml or Gleason 7) and high risk (stage T2c or PSA 21 to

50 ng/ml or Gleason 8 or greater), and by Gleason score and by PSA nadir.[18]

To determine BDFS rates, biochemical failure was defined using the Phoenix definition (PSA nadir + 2 ng/ml). The Kaplan-Meier method was used to construct survival curves which were compared using the log rank test. A Cox regression model was used in univariate and multivariate analysis of variables with possible prognostic relevance (table 3). Patients undergoing second HIFU were not censored from evaluation. A $p < 0.05$ was chosen as the level of statistical significance.

RESULTS

A total of 704 patients were included in this analysis. Staging biopsy per patient (range 6 to 24) was correlated to 8 target areas of the prostate (right, left, apex, mid, base) and seminal vesicles, and an average of 2.23 (range 1 to 6) prostatic areas were positive for malignancy. Unilateral PCa was found in 66%, 68% and 69% of patients in cohorts 1, 2 and 3, respectively. HIFU was performed with the patient under spinal anesthesia and sedation (89.6%). Full anesthesia (10.4%) was used per to patient preference or when spinal anesthesia was not feasible. The average HIFU treatment session lasted 119 minutes with 626 lesions. This did not change significantly during the study period because the delivery approach of alternating shots and delays (5 seconds/5 seconds) and prostate size at HIFU remained constant (table 4). The overall re-treatment rate was 22.3% and decreased with time (56%/25%/15%).

Table 4. *Included patients*

	All	Prototype	Maxis	Integrated Imaging
No. pts	704	170	358	176
Cohort yrs	1996–2009	1996–1999	2000–2004	2005–2009
Mean pt age	68.4	67	68.6	69.2
Mean ng/ml PSA at first diagnosis	9.9	9.9	11.5	9.6
% (No.) Gleason score:				
Less than 7	67 (472)	53	73	68
7	27.9 (196)	44	20	28
Greater than 7	5.1 (36)	3	7	4
% (No.) Risk (D'Amico):				
Low	21.6 (153)	14.7	23.5	24.4
Intermediate	38.4 (270)	42.9	36.6	37.5
High	40.0 (281)	42.4	39.9	38.1
% (No.) neoadjuvant ADT less than 6 mos	25.3 (178)	31.8	23.7	22.2
% (No.) neoadjuvant ADT 6–12 mos:	4.4 (31)	7.1	3.6	3.4
T1	11.5 (81)	11	12	10.2
T2	88.5 (623)	89	88	89.8
Mean cc prostate vol diagnosis	36	23.00	37.70	45.4
Mean cc prostate vol at HIFU	21.5	21.6	21.6	21.2

Table 5. *Biochemical efficacy*

	Mean PSA Nadir	Median PSA Nadir	Median Mos to PSA Nadir	Median ng/ml/yr PSA Velocity
All	1.7	0.1	2.1	0.02
Prototype	1.5	0.2	2.3	0.02
Maxis	2.5	0.1	1.9	0.03
Integrated Imaging	0.1	0.1	2.3	<0.01

Efficacy

PSA nadir occurred at a mean of 2.1 months (range 0.2 to 12.0) at a median of 0.10 ng/ml (range 0.0 to 21.0). Median PSA nadir values differed among cohorts 1, 2 and 3 less than the mean values (table 5). After PSA nadir, the median PSA velocity of the sample was 0.02 ng/ml per year (mean 0.44).

The overall survival of the patient population was identical to current local Bavarian population survival statistics (fig. 1, *A*). Through 10 years of followup a correlation between overall survival and patient risk group was not found (fig. 1, *B*). The 10-year cancer specific survival rate was 99%, which remained constant through to 14 years of followup (fig. 1, *C*) The 10-year metastasis-free survival rate was 95% in patients who received neoadjuvant TURP (fig. 2, *A*). BDFS rates varied by risk group, with 5-year rates of 92% to 84% and 10-year rates of 68% to 60% (fig. 2, *B*).

A correlation was found between PSA nadir group and biochemical failure (fig. 2, *C*), as was a correlation between risk group and salvage treatment-free survival (fig. 3, *A*). After TURP and HIFU, few low risk patients required salvage therapy at 12-year followup. The salvage therapy-free rates for intermediate and high risk patients at 5 years were 87% and 82%, and at 10 years were 72% and 68%, respectively. D'Amico risk groups were correlated with salvage treatment-free survival. At 10-year followup salvage therapy was initiated in less than 2% of low risk patients and in 27% to 36% of intermediate/high risk patients.

Morbidity

Perioperative complications (Clavien classification) occurred in 16% of the entire sample, and a decrease with time was found among cohorts 1, 2 and 3 (29%/10%/14%).[17] No perioperative complications were severe, all were of short duration and no Clavien IV or V complications were observed.

The rates of short to intermediate-term morbidity included incontinence (4%), obstruction (4.6%), infection (2.1%), rectourethral fistula formation (0.23%), perineal pain (0.7%) and other morbidity (4.4%). There were no cases of fistula since the introduction of robotic HIFU in 2005 (table 6). The morbidity profile but not the overall rate changed significantly in subsequent cohorts. The overall rate of urinary incontinence for

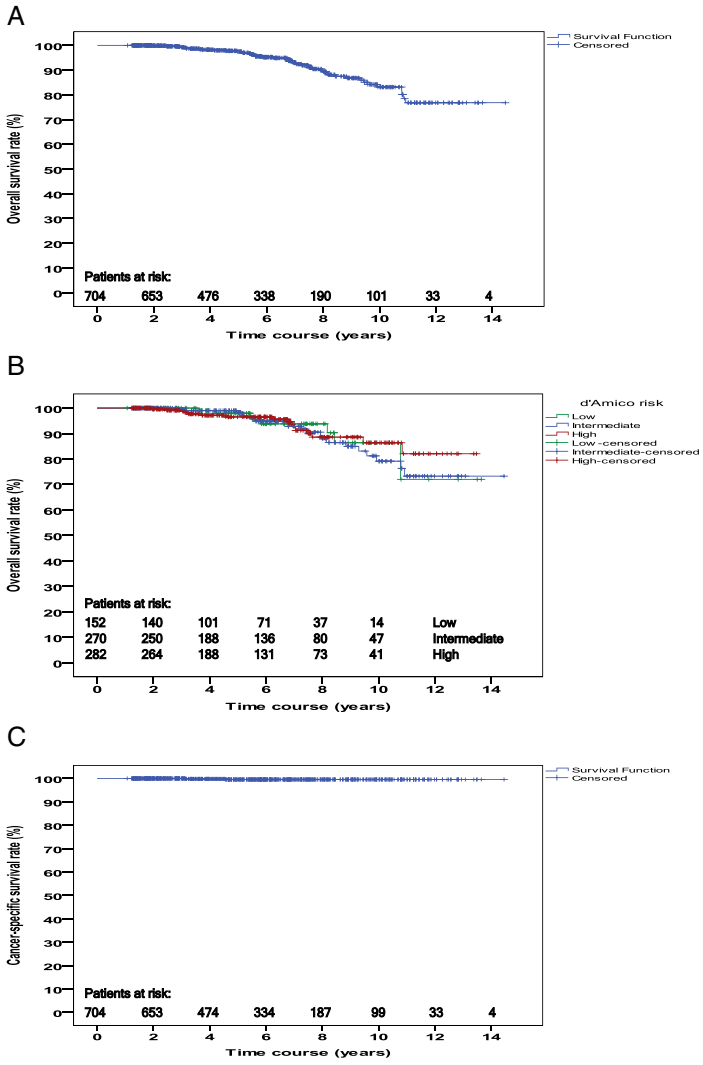

Figure 1. Overall (*A*), D'Amico risk (*B*) and cancer specific (*C*) survival rates

more than 3 months was 3.26%, with rates of 5.1%, 3.1% and 1.5% in cohorts 1, 2 and 3, respectively. The overall rate of secondary obstruction (from necrotic or scar tissue that resulted in bladder neck or intraprostatic stenosis) was 24%, 19% and 24% in cohorts 1, 2 and 3, respectively. Urinary tract infection recurred in 2.56%, 1.87% and 3.08% of the sample. Although comprehensive data on erectile function with validated questionnaires were not available, the post-HIFU clinical potency rate in previously potent patients was about 55%. Of these patients approximately two-thirds were taking phosphodiesterase type 5 inhibitors.

It should be mentioned that there were no cases of late onset impotence and no cases of any other late onset (greater than 1 year) morbidity. Morbidity with the longest delay in onset was a 5Fr bladder neck stenosis from circular scar tissue occurring 6 to 12 months after HIFU. As a result, a significant rate of secondary endourological interventions of 24% was registered.

DISCUSSION

Biopsy and radiological imaging in preoperative PCa tumor staging are limited because of restricted digital resolution and visual analysis. In this study we established tumor stage clinically with the combined use of digital rectal examination, transrectal ultrasound, radiological staging, TRUS guided rectal biopsies, TUR chips and PSA.

The extent of PSA decrease within 3 months after localized therapy produces the PSA nadir value, which we found was a significant predictive factor in biochemical failure. After the PSA nadir is reached, PSA velocity can be used to trigger the need for the timing of salvage therapy. Several studies have shown that a PSA nadir less than 0.3 ng/ml is asso-

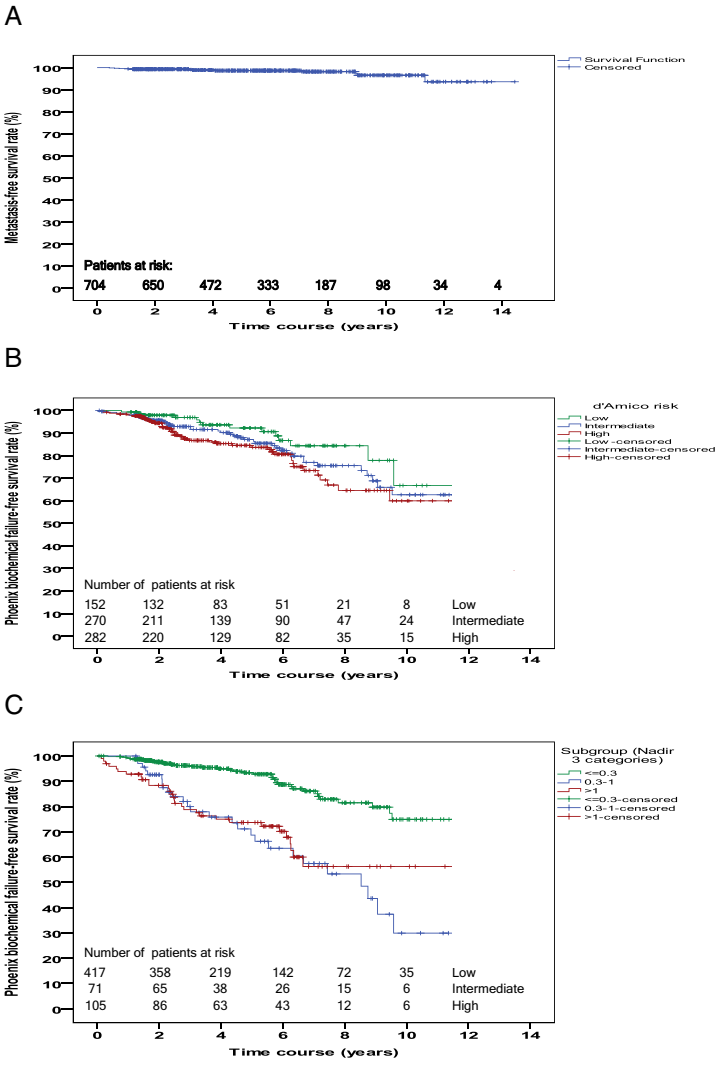

Figure 2. Metastasis-free (*A*), BDFS (*B*), and PSA nadir and biochemical failure (*C*) survival rates.

ciated with a salvage treatment-free survival rate at 10 years of more than 80%.[19] Biochemical disease-free survival rates of 94% at 5 years and 74% at 10 years, after a PSA nadir of less than 0.3 ng/ml, and greater than 80% (according to D'Amico risk groups) at 5 years and greater than 60% at 10 years, are promising.

The overall survival of the study population was equal to the general Bavarian survival rate and did not differ between risk groups. The 10-year cancer specific survival was 99%, a finding typical of most long-term PCa studies, and reflects the slowly progressing nature of the malignancy. The 10-year metastasis-free survival rate of 95% in patients who underwent TURP addresses the concern of metastatic induction by TURP in patients with prostate cancer, and shows no relationship between TURP and metastatic spread. The BDFS rate was correlated with risk group. The 5-year BDFS rates of 92% to 84% and the 10-year BDFS rates of 68% to 60% showed a parallel decrease in all risk groups with time (fig. 2, *B*). PSA nadir reflects the completeness of tumor ablation with HIFU and a difference in BDFS was shown among the 3 nadir subgroups (table 5, fig. 2, *C*). Among patients with a PSA nadir less than 0.3 ng/ml, the BDFS rate was 94% at 5 years and 74% at 10 years. In patients with a PSA nadir of 0.3 ng/ml or greater the BDFS rate was 73% to 70% at 5 years and 56% to 30% at 10 years (depending on risk group, fig. 2, *C*).

Although efficacy associated with the different generations of HIFU technology did not change significantly during the study period, neoadjuvant TURP contributed to efficacy by decreasing the average PSA nadir values as the result of reducing prostate size to less than 25 cc to make the prostate gland more amenable to complete HIFU ablation.

The point at which salvage therapy is required (excluding a second HIFU session) represents an important variable in the setting of clinical practice

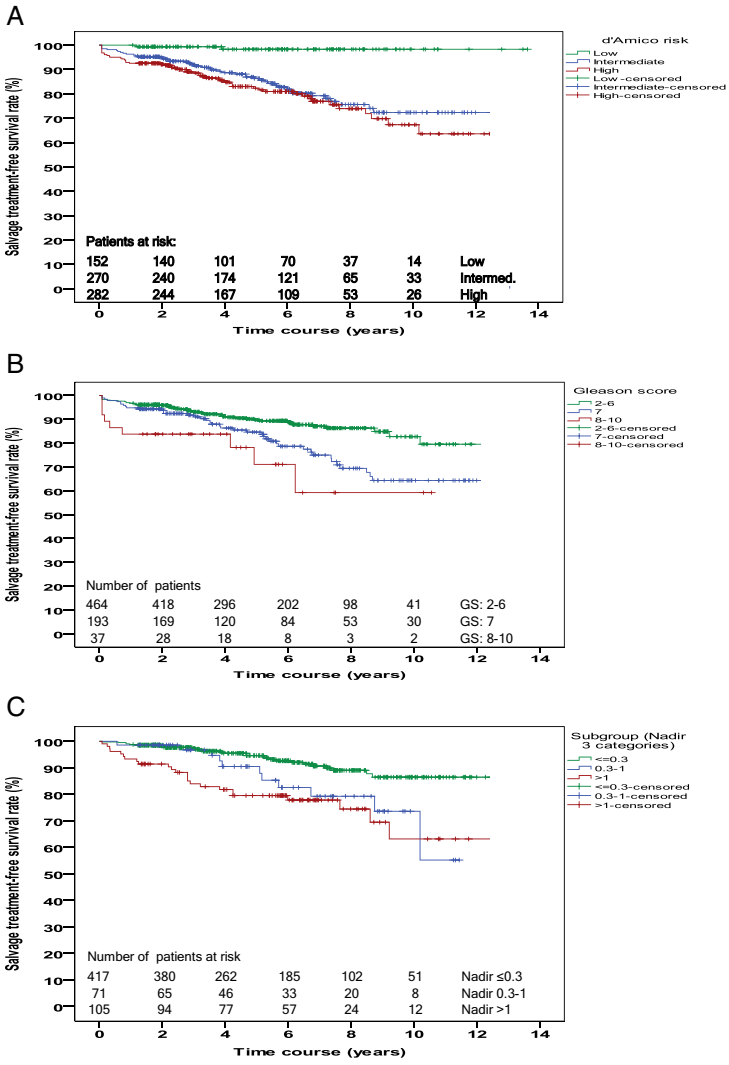

Figure 3. D'Amico risk (*A*), Gleason score (*B*) and PSA nadir (*C*) salvage treatment-free survival.

and efficacy research. Several factors influence the decision to undergo salvage therapy, including post-treatment PSA, treatment guidelines, comorbidity, psychological factors and concern over potential morbidity associated with the salvage therapy.

The correlation of D'Amico risk group with salvage treatment-free survival involves 2 interesting issues. 1) With 99% of patients with low risk disease not requiring salvage therapy during a 10-year followup, the extent of cancer control is obvious. This finding might encourage the use of focal therapy in these patients, especially given the finding during staging that nearly 67% of these patients had unilateral cancer. 2) The intermediate and high risk groups still exhibited reasonable BDFS rates of 87% to 82% at 5 years and 72% to 68% at 10 years.

Recently Wilt et al published their data regarding the effectiveness of surgery vs observation for men with localized prostate cancer.[20] The authors showed that among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all cause or prostate cancer mortality compared with observation through at least 12 years of followup. Although their data should be taken with caution considering the relatively small study population

Table 6. *Side effects*

	Prototype (%)	Maxis (%)	Integrated Imaging (%)
Incontinence (less than 3 mos)*	4.2	4.2	3.1
Incontinence (more than 3 mos)*	5.1	3.1	1.5
Rectourethral fistula	0.59	0.28	0.0
Recurrent urinary tract infections	2.56	1.87	3.08
Perineal discomfort	1.26	0.23	0.51
Others periop	11.7	1.17	2.56
Secondary obstruction	24	19	24

* Defined as more than 1 pad per day.

and the short followup, their study clearly shows that minimally invasive therapies for prostate cancer will become even more important in the future.

There are several important limitations to our study. The presented data are based on a single arm study without comparison groups. Furthermore, changes in technology and surgical protocol during the course of the study may have confounded some of the outcome analyses.

CONCLUSIONS

The results in 704 patients show that HIFU offers men with localized PCa a standardized reliable therapy with a low rate of perioperative comorbidity, an absence of serious morbidity and sufficient cancer control such that salvage therapy was not required at 10-year followup by 99%, 72% and 68% of low, intermediate and high risk patients, respectively, which is particularly important from a patient centered perspective. PSA nadir was demonstrated to be the greatest predictor of biochemical failure and the median PSA nadir has been 0.1 ng/ml or less since 2000. PSA velocity was less than 0.1 ng/ml but not zero, resulting in a slow increase to a PSA of 0.29 ng/ml at 5 years. The 95% metastasis-free survival rate at 10 years excludes TURP as a factor in metastatic spread in patients with localized prostate cancer and represents the first published data to our knowledge that empirically refute this long held assumption. Combined with TUR, HIFU can provide low invasive complete local tumor ablation, substituting surgery/cryotherapy or postponing radiation therapy or/and long-term ADT in elderly patients. The presented data of 10-year outcomes may warrant the possible closing of the investigational phase of HIFU.

ACKNOWLEDGMENTS

Regina Nanieva and Dr. Derya Tilki contributed to this work.

APPENDIX

Inclusion criteria

- Biopsy proven, T1–T2c prostate cancer
- No visible lymph node infiltration or metastasis (N0, M0)
- PSA at first diagnosis less than 50 ng/ml
- Any Gleason stage
- Neoadjuvant androgen deprivation less than 12 months
- HIFU as primary definitive PCa therapy
- Complete HIFU therapy (with/without TURP)
- Informed consent
- Followup greater than 15 months

REFERENCES

1. Burov AK: High-intensity ultrasonic vibrations for action on animal and human malignant tumours. Dokl Akad Nauk SSSR 1956; **106:** 239.
2. Fry FJ and Johnson LK: Tumor irradiation with intense ultrasound. Ultrasound Med Biol 1978; **4:** 337.
3. Fry WJ, Barnard JW, Fry EJ et al: Ultrasonic lesions in the mammalian central nervous system. Science 1955; **122:** 517.
4. Fry WJ, Mosberg WH Jr, Barnard JW et al: Production of focal destructive lesions in the central nervous system with ultrasound. J Neurosurg 1954; **11:** 471.
5. Goss SA and Fry WJ: The effects of high-intensity ultrasonic irradiation on tumour growth. IEEE Trans Sonics Ultrasonics 1984; **SU-31:** 491.
6. Lizzi FL, Coleman DJ, Driller J et al: A therapeutic ultrasound system incorporating real time ultrasonics scanning. In: Proceedings of the 1986 Ultrasonics Symposium, Institute of Electrical and Electronic Engineers. Edited by BR MacAvoy. New York: IEEE 1987; pp 981–984.
7. Gelet A, Chapelon JY, Bouvier R et al: Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. Eur Urol 1996; **29:** 174.
8. Uchida T, Sanghvi NT, Gardner TA et al: Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b-2n0m0 localized prostate cancer: a preliminary report. Urology 2002; **59:** 394.
9. Vallancien G, Chartier-Kastler E, Chopin D et al: Focussed extracorporeal pyrotherapy: experimental results. Eur Urol 1991; **20:** 211.
10. Chaussy C and Thüroff S: The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. Curr Urol Rep 2003; **4:** 248.
11. Vallancien G, Prapotnich D, Cathelineau X et al: Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. J Urol 2004; **171:** 2265.
12. Bill-Axelson A, Holmberg L, Filen F et al: Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian Prostate Cancer Group-4 randomized trial. J Natl Cancer Inst 2008; **100:** 1144.
13. Zelefsky MJ, Reuter VE, Fuks Z et al: Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. J Urol 2008; **179:** 1368.
14. Chaussy CG and Thüroff S: High intensity focused ultrasound for the treatment of prostate cancer. In: Minimally Invasive Uro-oncologic Surgery. Edited by RG Moore and JT Bishoff. Oxford: Taylor and Francis 2005; pp 327–35.
15. Chaussy C, Thuroff S, Rebillard X et al: Technology insight: high-intensity focused ultrasound for urologic cancers. Nat Clin Pract Urol 2005; **2:** 191.
16. Thuroff S and Chaussy C: Status of high intensity focused ultrasound (HIFU) in urology in 2005. In: Therapeutic Energy Application in Urology: Standards and Recent Developments. Edited by C Chaussy, G Haupt, D Jocham et al. Stuttgart: Thieme Vlg 2005; pp 92–102.
17. Dindo D, Demartines N and Clavien PA: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; **240:** 205.
18. D'Amico AV, Whittington R, Malkowicz SB et al: Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; **280:** 969.
19. Crouzet S, Rebillard X, Chevallier D et al: Multicentric oncologic outcomes of high-intensity focused ultrasound for localized prostate cancer in 803 patients. Eur Urol 2010; **58:** 559.
20. Wilt TJ, Brawer MK, Jones KM et al: Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012; **367:** 203.

EDITORIAL COMMENTS

This is the world's largest experience on the HIFU procedure with meaningful 10-year survival figures providing new information beyond the existing literature. Several methodological concerns, eg retrospective analysis on a single arm study, compromise the quality of the evidence. Understandably, however, identifying a comparison group would be a challenge. The population is unavoidably inhomogeneous and the study spans a long period. In addition, there were different treatment philosophies as well as different equipment and surgical protocols (eg extensive vs limited vs no TURP, bipolar vs unipolar etc).

A laudable secondary objective stated by the authors, "to evaluate metastasis induction by TUR," unfortunately was not adequately addressed. In the absence of any form of data analysis, multivariate or otherwise, the observation by the authors that neoadjuvant TURP did not promote metastatic disease is speculative. It should also be noted that neoadjuvant TURP is a feature specific to Ablatherm and not all HIFU devices.

These limitations aside, the authors have meticulously chronicled the development of this technology, demonstrating long-term safety and satisfactory prostate cancer control.

Joseph L. Chin
University of Western Ontario
London, Ontario, Canada

The clinical application of HIFU was initiated at Indiana University in 1953 (references 3 and 4 in article) and has been used since 1993 to treat prostate disorders.[1] Thüroff and Chaussy have demonstrated the ability of the Ablatherm device to effectively treat localized prostate cancer. Uchida et al (reference 8 in article) and our group[2] have demonstrated similar findings in localized and locally recurrent prostate cancer with the Sonablate® device. This study demonstrates that whole gland ablation with or without TURP can be effective, but can be associated with a 10% to 20% risk of bladder neck contracture. The authors add long-term Gleason score dependent cancer control rates to the growing body of literature on HIFU prostatectomy.

Thomas A. Gardner
Department of Urology
VA Medical Center
Indiana University Health
Indianapolis, Indiana

REFERENCES

1. Gardner TA and Koch MO: Prostate cancer therapy with high-intensity focused ultrasound. Clin Genitourin Cancer 2005; **4:** 187.

2. Koch MO, Gardner T, Cheng L et al: Phase I/II trial of high intensity focused ultrasound for the treatment of previously untreated localized prostate cancer. J Urol 2007; **178:** 2366.