Treatment of localized prostate cancer using high-intensity focused ultrasound

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OBJECTIVE

To evaluate the biochemical disease-free survival (DFS), predictors of clinical outcome and morbidity of patients with localized prostate cancer treated with high-intensity focused ultrasound (HIFU), a noninvasive treatment that induces complete coagulative necrosis of a tumour at depth through the intact skin.

PATIENTS AND METHODS

In all, 63 patients with stage T1c-2bN0M0 localized prostate cancer underwent HIFU using the Sonablate™ system (Focus Surgery, Inc., Indianapolis, IN, USA). None of the patients received neoadjuvant and/or adjuvant therapy. Biochemical recurrence was defined according to the criteria recommended by the American Society for Therapeutic Radiology and Oncology consensus definition, i.e. three consecutive increases in prostate-specific antigen (PSA) level after the nadir. The median (range) age, PSA level and follow-up were 71 (45–87) years, 8.5 (3.39–57.0) ng/mL and 22.0 (3–63) months, respectively.

RESULTS

The overall biochemical disease-free rate was 75% (47 patients). The 3-year biochemical DFS rates for patients with a PSA level before HIFU of <10, 10.01–20 and >20 ng/mL were 82%, 62% and 20% ($P < 0.001$), respectively. The 3-year biochemical DFS rates for patients with a PSA nadir of <0.2, 0.21–1 and >1 ng/mL were 100%, 74% and 21% ($P < 0.001$), respectively. Final follow-up sextant biopsies showed that 55 (87%) of the patients were cancer-free. Multivariate analysis showed that the PSA nadir ($P < 0.001$) was a significant independent predictor of relapse.

CONCLUSION

HIFU therapy appears to be a safe, effective and minimally invasive therapy for patients with localized prostate cancer, and the PSA nadir is a useful predictor of clinical outcome.

KEYWORDS

localized prostate cancer, minimally invasive therapy, high-intensity focused ultrasound

INTRODUCTION

Prostate cancer is the most common malignancy in men and the second leading cause of death from cancer in the USA [1]. Radical prostatectomy (RP) has long been regarded as appropriate therapy for patients with organ-confined prostate cancer. Despite excellent 5- and 10-year survival rates after RP, surgery is associated with significant morbidity, e.g. blood loss with transfusion-related complications, erectile dysfunction in 30–70% of men, and stress incontinence in up to 10% [2–5]. In addition, surgical intervention is not typically considered for patients whose life-expectancy is <10 years. Recently, several alternative and less invasive treatments have been developed to treat localized prostate cancer. Brachytherapy, cryosurgical ablation of the prostate, three-dimensional conformal radiotherapy, intensity-modulated external beam radiotherapy and laparoscopic RP have been used [6–10]. However, these alternative treatments, except the conformal radiotherapy and intensity-modulated therapy, require at least percutaneous access.

High-intensity focused ultrasound (HIFU) is a noninvasive technique for the thermal ablation of tissue. HIFU can noninvasively induce complete coagulative necrosis of a target tumour, without requiring surgical exposure or insertion of instruments into the lesion. This advantage makes it one of the most attractive potential options for the localized treatment of tumours. Since January 1999, we have been treating localized prostate cancer with transrectal HIFU [11,12]; we report the efficacy, safety and predictive preoperative values of HIFU ablation for treating patients with localized prostate cancer.

PATIENTS AND METHODS

We used the Sonablate™ (Focus Surgery, Inc., Indianapolis, IN, USA) HIFU machine; the treatment module includes the ultrasound power generator, multiple transrectal probes of different focal depth, the probe-positioning system, and a continuous cooling system (Fig. 1). The transrectal HIFU probes use proprietary transducer technology with low-energy ultrasound (4 MHz) for imaging the prostate and to deliver high-energy ablative pulses (site intensity, 1300–2200 W/cm^2). The single piezoelectric crystal alternates between high-energy power for ablative (3 s) and low-energy for ultrasound imaging (6 s).

Before starting the treatment the operator uses longitudinal and transverse ultrasonograms 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, which directs each ablative pulse to the targeted region of the prostate. Each discrete HIFU pulse ablates a volume of $3 \times 3 \times 10$ mm of tissue [13]. The total acoustic power is initially set at 24 and 37 W for 3- and 4-cm focal length probes, respectively. The individual focal lesion produces almost instantaneous coagulative

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

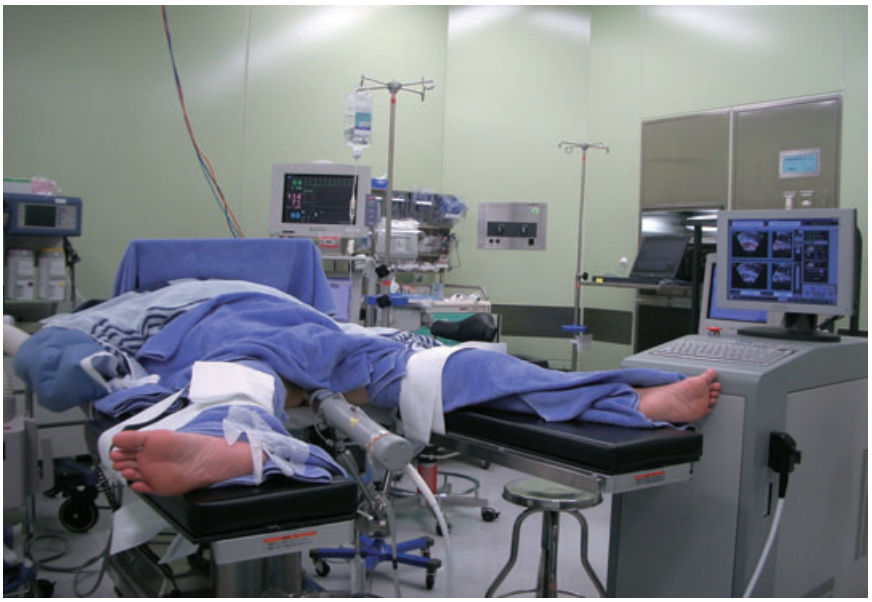
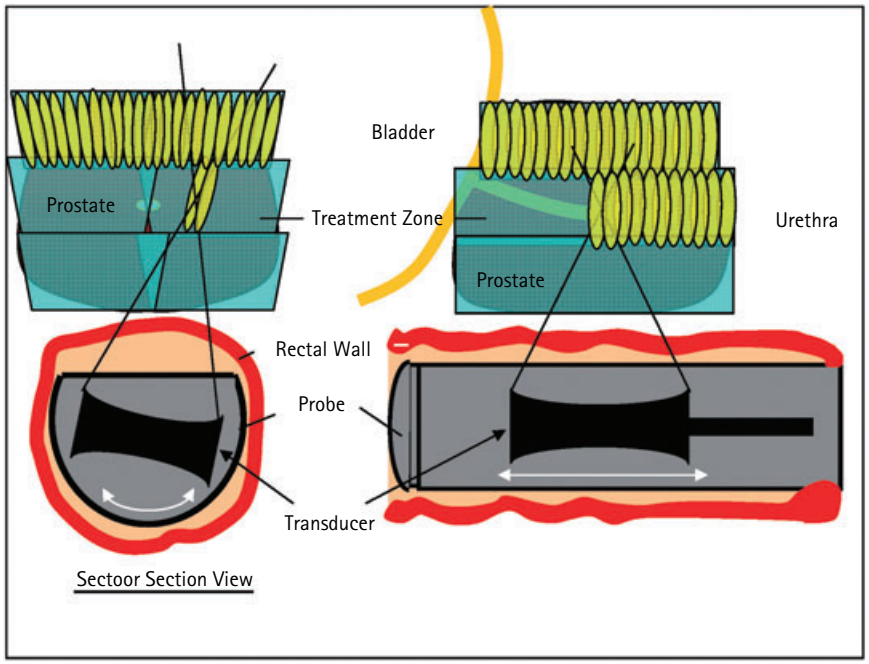


FIG. 2. The computer-controlled transducer ablates the entire prostate tissue. Focal lesions are overlapped in linear rows (left) at each of the lateral sector positions (right), to create a volume lesion.



necrosis of tissue as the temperature increases to 80–98 °C in the focal zone [13,14]. Under computer control, the ultrasound beam is steered mechanically to produce consecutive lesions so that all focal lesions overlap 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 <18 °C in the transrectal probe, which helps to prevent thermal injury of the rectal mucosa.

All patients were anaesthetized by epidural or spinal anaesthesia, and placed supine with open legs. A condom was placed over the probe and degassed water was used to inflate the condom, which 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 selecting 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 TRUS, with larger glands requiring longer focal lengths. The treatment continued layer by layer (10 mm thick) 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 completing the treatment, a transurethral balloon catheter or percutaneous cystostomy was inserted into the bladder.

The study included patients with stage T1c-2bN0M0 localized prostate cancer; those with anal stricture were excluded from the study. None of the patients received adjuvant hormonal and/or chemotherapy. All patients were fully informed of the details of this treatment and provided written consent before HIFU. Beginning in January 1999, 63 patients with clinically localized prostate cancer were treated with HIFU. Evaluations before HIFU included a history, physical examinations, including a DRE, initial PSA level and Gleason score on needle biopsy of the prostate. All patients had a negative radionuclide bone scan and CT of the abdomen and pelvis confirmed that there was no metastatic disease. Tumours were staged using the TNM staging system [15]. The characteristics of the 63 patients are listed in Table 1.

Patient status and treatment-related complications were followed using all available means, including periodic patient visits and self-administered questionnaires on urinary continence and erectile function. The serum PSA level was usually assayed every 1–6 months during the follow-up. At 6 months after HIFU a prostate biopsy was taken in all patients. The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition for biochemical failure, i.e. three consecutive increases in PSA level

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after a nadir, was used to define biochemical failure [16]. The time to biochemical failure was defined as midway between the PSA nadir and the first of the three consecutive PSA increases. None of the patients received androgen deprivation after HIFU or other anticancer therapy before documentation of a biochemical failure.

The chi-squared test was used to assess the correlation between variables before and after HIFU. Distributions of biochemical disease-free survival (DFS) times were calculated according to the Kaplan-Meier curves and the log-rank test used to determine the differences between the curves. A multivariate Cox proportional hazards regression model was used to estimate the prognostic relevance of age, clinical stage, Gleason score, volume of the prostate, pretreatment and nadir serum PSA levels on DFS, with $P < 0.05$ taken to indicate statistical significance.

RESULTS

The prostate was treated in one (50 patients) or two (13) HIFU sessions for a total of 76 procedures in 63 patients (1.2 sessions/patient). Reasons for repeating the HIFU treatments were: in five patients because we tried different 'on' and/or 'off' times, e.g. shorter (2 s) and/or longer off (8–12 s) intervals before establishing the standard on (3 s) and off (6 s) interval; in three for residual tumour or PSA increases; two were only treated on the right or left lobe of the prostate; two because they had a large prostate; and one because there was a problem with the HIFU machine. The median (range) operative duration and hospitalization was 149 (55–356) min and 4 (2–20) days, respectively. The gland size decreased from an initial mean volume of 28.6 mL to a final median volume of 14.5 mL ($P < 0.001$) in a mean of 6.5 (3–23) months. The mean (SD, median) PSA nadir levels were 1.38 (2.55, 0.5) ng/mL.

Of the 63 patients, 47 (75%) were biochemically disease-free during the follow-up; the 3-year biochemical DFS rates for those with a PSA level before HIFU of <10, 10.01–20 and >20 ng/mL was 82%, 62% and 20%, respectively ($P < 0.001$). The PSA nadir was 4–8 weeks after treatment; the 3-year biochemical DFS rates for patients with a PSA nadir of <0.2 (20 patients), 0.21–1.0 (25) and >1 (18) were 100%, 74% and 21% (log-rank test, $P < 0.001$), respectively. Risk factors were a PSA level of ≥10 ng/mL, a Gleason score of ≥7, and stage T2b disease, with patients at low-risk having none of these factors, at moderate risk having one and at high risk having two or more [17]. The 3-year biochemical DFS rates in patients at low, moderate and high risk was 84%, 69% and 51% ($P = 0.0295$), respectively (Fig. 3). However, there was no statistically significant difference in patients within stage and Gleason score groups.

Characteristic	Value
Mean (SD), median (range):	
Age, years	70.5 (1.3), 71 (45–87)
PSA, ng/mL	11.2 (8.7), 8.5 (3.39–57.0)
Prostate volume, mL	28.5 (11.9), 25.9 (13.2–68.8)
Follow-up, months	23.3 (12.7), 22.0 (3–63)
N (%):	
PSA level (ng/mL) before HIFU	
≤ 10	34 (54)
10.1–20	24 (38)
>20	5 (8)
Clinical stage	
T1c	39 (62)
T2a	18 (29)
T2b	6 (9)
Gleason score	
2–4	13 (21)
5–7	46 (73)
8–10	4 (6)
Risk group	
Low	22 (35)
Intermediate	26 (41)
High	15 (24)
PSA nadir (ng/mL)	
0–0.2	20 (32)
0.21–1.0	25 (40)
>1.0	18 (28)

TABLE 1
The clinicopathological data of 63 patients with localized prostate cancer

In the Cox regression analysis, the PSA nadir was a statistically significant variable for prognosis but age, stage, Gleason grading, serum PSA level and prostate volume were not (Table 2). The final follow-up prostate biopsies showed that 55 (87%) of the 63 patients were cancer-free. The main pathological findings of the prostate biopsy at 6 months after HIFU showed a coagulation necrosis and fibrosis.

All patients reported urinary symptoms, e.g. frequency, urgency and difficulty in urination, during the first 2 months after HIFU treatment. The symptoms were transitory and easily managed by medical treatment. Urethral catheters in all patients were removed 1–2 days after HIFU, but were reinserted in those who could not urinate spontaneously, and removal was attempted every 1–2 weeks thereafter. The median (range) urinary catheterization period after HIFU was 14 (0–31) days. Fifteen (24%) patients developed a urethral stricture, two (3%) complained of retrograde ejaculation and two (3%) other patients of epididymitis. One (2%) patient had a TURP for prolonged urinary retention, one (2%) had grade 1 transient incontinence for a month, and one (2%) developed a recto-urethral fistula (Table 3). Eight of the 34 patients who were sexually active complained of erectile dysfunction after HIFU; two of these eight who desired treatment were treated with sildenafil citrate, and recovered.

DISCUSSION

In 1995, Madersbacher *et al.* [14] reported the effect of HIFU (using the older Sonablate 200 system) in an experimental study of 10 patients with histologically confirmed hypoechoic and palpable localized prostate

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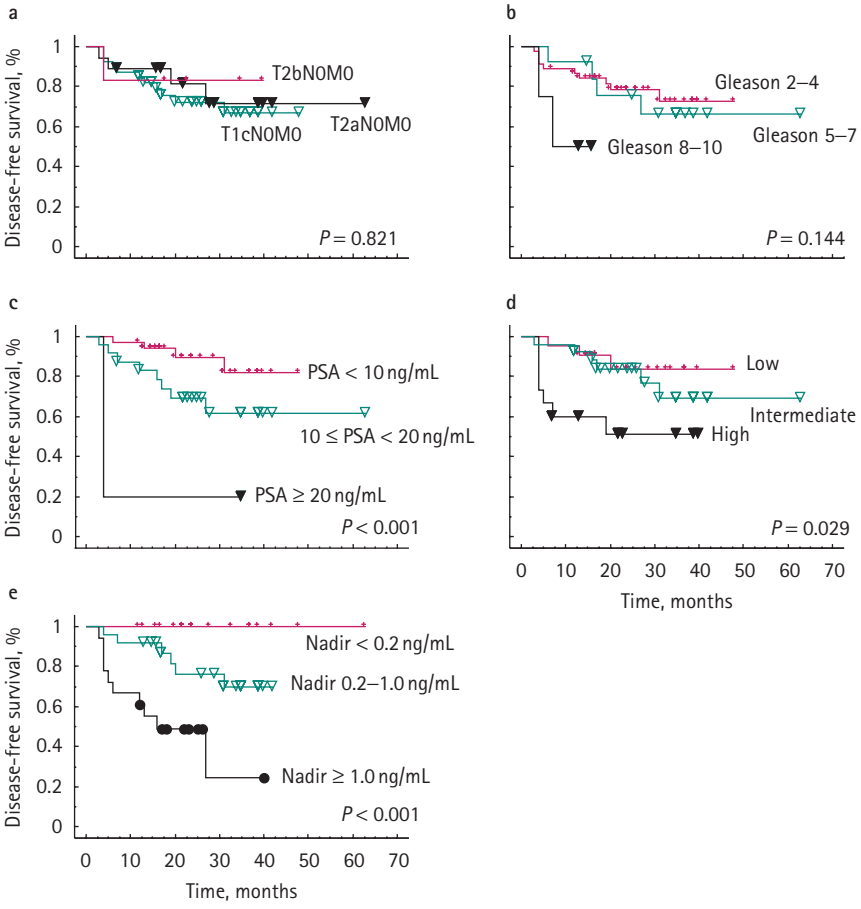
FIG. 3. Kaplan-Meier biochemical disease-free survival curves according to: a, stage; b, Gleason score; c, serum PSA level; d, risk group; and e, PSA nadir level.



cancer. In 1996, Gelet *et al.* [18,19] reported a preliminary experience of HIFU using Ablatherm prototype 1.0 (EDAP-Technomed, Lyon, France) for treating localized prostate cancer. They later summarized their clinical outcome, in which there was a complete response in two-thirds of the patients, with no residual cancer and no three consecutive increases in PSA level. More recently, Chaussy and Thuroff [20] reported that the combination of TURP immediately before HIFU reduced the treatment-related morbidity, e.g. catheter time, incontinence, urinary infection and the IPPS. In addition, they summarized the clinical outcome using the ASTRO definition, an 84% stability rate in the HIFU group and an 80% rate in the TURP and HIFU group. In 1999, Beerlage *et al.* [21] reported results of 143 HIFU treatments using the Ablatherm prototype 1.0 and 1.1 in 111 patients with clinical stage T1–3N0M0 prostate cancer and a PSA level of <25 ng/mL. The first 65 treatments in 49 patients were selective (i.e. a unilateral or bilateral treatment in one or two sessions, depending on the findings from TRUS and biopsies) and the second 78 treatments in 62 patients treated the whole prostate. There was a complete response (defined as a PSA level of <4.0 ng/mL and a negative biopsy) in 60% of the group with the whole prostate treated, and in 25% of the selectively treated patients. In the present study, two patients who were treated selectively in the right lobe of the prostate for adenocarcinoma, identified by a prostate biopsy, showed a gradual increase in PSA level and viable cancer cells in the untreated lobe on prostate biopsy after HIFU. A second HIFU treatment of the whole prostate maintained the PSA at a low level, with a negative biopsy. Recently, many methods of imaging have been analysed for detecting prostate cancer, including TRUS, CT, endorectal coil MRI and multiple biopsies of the prostate under TRUS guidance. However, prostate cancer is a multifocal disease and it is not yet possible to determine the sites of microscopic foci of cancer cells by imaging analysis alone. Therefore, the whole prostate must be treated, as corroborated by the results of the present study and others.

When summarising the present clinical outcome by the ASTRO definition, 75% of the patients were biochemically disease-free. Particularly those patients whose PSA level before HIFU was <10 ng/mL and with a PSA nadir of <0.2 ng/mL had an 82% and 100% biochemical DFS rate at 3 years after HIFU treatment. In addition, the PSA nadir ($P < 0.001$) was a significant independent predictor of time to biochemical recurrence in the multivariate analysis.

HIFU treatment with the Sonablate machine is limited to a prostate size of 50 mL with the present device, even when using a longer focal-length probe. It is necessary to develop a longer focal-length probe for treating prostates of >50 mL. Neoadjuvant androgen-deprivation therapy may be useful in larger prostates to reduce the volume of the prostate before HIFU.

After HIFU there were urethral strictures at or near the verumontanum in the prostatic urethra in a quarter of the present patients, treated by internal urethrotomy and/or periodic dilatation with metal sounds. Using TURP after HIFU treatment may be useful to prevent urethral stricture or urinary retention [22,23]. A recto-urethral fistula occurred in one patient after the second HIFU treatment. More precise HIFU power control during repeat treatment is needed. A continuous cooling device was applied to keep the rectal mucosa at <18 °C during the procedure, and there was no recto-urethral fistula in any of the patients after using the automatic cooling system.

Generally, the radicality of prostate cancer and preservation of sexual function are always controversial because erectile dysfunction after treatment depends on preserving the neurovascular bundles that are sometimes invaded by the tumour. In the present study, 25% of the patients had erectile dysfunction after HIFU therapy; interestingly, two of the eight affected and who desired treatment recovered with sildenafil citrate. We consider that this rate is lower than after RP [2–5]; obviously, further experience is required to confirm this important consideration.

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Variable	Hazard ratio (95% CI)	P
Age	1.009 (0.933–1.091)	0.825
Preoperative PSA	1.025 (0.961–1.093)	0.459
Stage	0.537 (0.218–1.320)	0.175
Gleason score	1.037 (0.635–1.641)	0.877
Prostate volume	0.968 (0.916–1.032)	0.256
PSA nadir	1.543 (1.208–1.973)	<0.001

TABLE 2
The Cox proportional hazards analysis predicting the time to biochemical failure after HIFU

Complications	N patients (%)	Treatment
Urethral stricture	15 (24)	Bougie or urethrotomy
Retrograde ejaculation	2 (3)	No treatment
Epididymitis	2 (3)	Antibiotics
Retention for 3 weeks	1 (2)	TURP
Stress incontinence (grade 1)	1 (2)	1 pad/day
Recto-urethral fistula	1 (2)	Colostomy and closure
Erectile dysfunction	8/34 (25)	Medical treatment

TABLE 3
The complications after HIFU

The median hospital stay in the present series was 4 days; this was related to local socio-economic conditions rather then clinical or technical factors. There is a significant difference in the national insurance systems between Japan and other countries. Usually, 20–30 days of hospitalization is recommended after RP in Japan. However, recent HIFU treatments at our hospital have involved only an overnight stay.

For many reasons, transrectal HIFU appears to be highly attractive as a minimally invasive treatment for localized prostate cancer. With HIFU treatment there is no incision or puncture, it is bloodless, can be delivered on an outpatient basis and is repeatable. It can also be used on patients with local recurrences who have already been treated with RP, cryoablation of the prostate and radiation therapy. In addition, the option of HIFU may be more attractive to the patient who wants to avoid incontinence and erectile dysfunction afterward, to maintain their quality of life. These features, combined with the optional curative effect, provide an ideal treatment for patients with localized prostate cancer. The few patients and the relatively short follow-up in the present series limit any definitive conclusions. We think that the present data suggest that HIFU has considerable potential as a noninvasive treatment for patients with localized prostate cancer.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1 **Landis SH, Murray T, Bolden S, Wingo PA.** Cancer statistics, 1999. *CA Cancer J Clin* 1999; **49**: 8–31
2 **Arai Y, Egawa S, Tobisu K *et al.*** Radical retropubic prostatectomy: time trends, morbidity and mortality in Japan. *BJU Int* 2000; **85**: 287–94
3 **Catalona WJ, Smith DS.** Cancer recurrence and survival rate after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. *J Urol* 1998; **160**: 2428–34
4 **Han M, Walsh PC, Partin AW, Rodriguez R.** Ability of the 1992 and 1997 American Joint Committee on Cancer Staging for prostate cancer to predict progression-free survival after radical prostatectomy for stage T2 disease. *J Urol* 2000; **164**: 89–92
5 **Hull GW, Rabbani F, Abbas F, Wheeler TM, Kattan MW, Scardino PT.** Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol* 2002; **167**: 528–34
6 **Vicini FA, Kini VR, Edmundson G, Gustafson GS, Stromberg J, Martinez A.** A comprehensive review of prostate cancer brachytherapy: defining an optional technique. *Int J Radiat Oncol Biol Phys* 1999; **44**: 483–91
7 **Han KR, Cohen JK, Miller RJ *et al.*** Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *J Urol* 2003; **170**: 1126–30
8 **Zelefsky MJ, Wallner KE, Ling CC *et al.*** Comparison of the 5-year outcome and morbidity of three-dimensional conformal radiotherapy versus transperineal permanent iodine-125 implantation for early stage prostate cancer. *J Clin Oncol* 1999; **17**: 517–22
9 **Beerlage HP, Thuroff S, Madersbacher S *et al.*** Current status of minimally invasive treatment options for localized prostate carcinoma. *Eur Urol* 2000; **37**: 2–13
10 **Guillonneau B, el-Fettouh H, Baumert H *et al.*** Laparoscopic radical prostatectomy: oncological evaluation after 1,000 cases a Montsouris experience. *J Urol* 2003; **169**: 1261–6
11 **Uchida T, Sanghvi NT, Gardner TA *et al.*** Transrectal high-intensity focused ultrasound for treatment of patients with stageT1b-2N0M0 localized prostate cancer: a preliminary report. *Urology* 2002; **59**: 394–9
12 **Uchida T, Tsumura H, Yamashita H *et al.*** Transrectal high-intensity focused ultrasound for treatment of patients with stageT1b-2N0M0 localized prostate cancer: a preliminary report. *Jpn J Endourol ESWL* 2003; **16**: 108–14
13 **Wu JS, Sanghvi NT, Phillips MH *et al.*** Experimental studies using a split beam transducer for prostate cancer therapy in comparison to a single beam transducer. *IEEE Ultrasonics Symp Proc* 1999; **2**: 1443–6
14 **Madersbacher S, Pedevilla M, Vingers L, Susani M, Merberger M.** Effect of high-intensity focused ultrasound on human prostate cancer *in vivo*. *Cancer Res* 1995; **55**: 3346–51
15 **International Union Against Cancer: Sobin LH, Witterkind CH eds,** *TNM Classification of Malignant Tumors*, 5th

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edn. New York: John Wiley and Sons, Inc. 1997: 170–3
16 **ASTRO.** Consensus statement. Guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 1997; **37**: 1035–41
17 **Zelefsky MJ, Hollister T, Raben A *et al.*** Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phy* 2000; **47**: 1261–6
18 **Gelet A, Chaperon JY, Bouvier R *et al.*** Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. *Eur Urol* 1996; **29**: 174–83
19 **Gelet A, Chapelon JY, Bouvier R, Rouviere O, Lyonnet D, Dubernard JM.** Transrectal high-intensity focused ultrasound for the treatment of localized prostate cancer: factors influencing the outcome. *Eur Urol* 2001; **40**: 124–9
20 **Chaussy CG, 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**: 248–25
21 **Beerlage HP, Thuroff S, Debruyne FM, Chaussy C, de la Rosette JJ.** Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. *Urology* 1999; **54**: 273–7
22 **Blana A, Walter B, Rogenhofer S, Wieland WF.** High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology* 2004; **63**: 297–300
23 **Vallancien G, Prapotnich D, Cathelineau X, Baumert H, Rozet F.** Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. *J Urol* 2004; **171**: 2265–7

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Abbreviations: **HIFU**, high-intensity focused ultrasound; **RP**, radical prostatectomy; **DFS**, disease-free survival; **ASTRO**, American Society for Therapeutic Radiology and Oncology.

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