ELSEVIER

Urologic Oncology: Seminars and Original Investigations xx (2011) xxx

UROLOGIC ONCOLOGY

Original article

HIFU as salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven locally recurrent prostate cancer after radical prostatectomy: A pilot study

Anastasios D. Asimakopoulos, M.D., Roberto Miano, M.D., Guido Virgili, M.D., Giuseppe Vespasiani, M.D., Enrico Finazzi Agrò, M.D.*

Division of Urology, Department of Surgery, Fondazione Policlinico Tor Vergata, University of Tor Vergata, Rome, Italy

Received 4 May 2010; received in revised form 29 July 2010; accepted 19 August 2010

Abstract

Objective: To test high-intensity focused ultrasound (HIFU) as salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven locally recurrent prostate cancer (CaP) after radical prostatectomy (RP).

Materials and methods: Nineteen patients with palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP after RP, unwilling to undergo salvage radiotherapy (SRT), underwent HIFU as a single-session procedure. Pre-, intra-, and postoperative data including early and late complications, and oncologic outcomes (PSA nadir, biochemical recurrence (BCR)-free survival, and need of secondary adjuvant treatment) were prospectively evaluated. Success was defined as PSA nadir $\leq$0.1 ng/ml obtained within 3 months from HIFU. In case of PSA nadir $>$0.1 ng/ml or PSA increase $\geq$1 ng/ml above the PSA nadir, a biopsy of the treated lesion was performed, and if negative, maximum androgen blockade (MAB) was adopted. In case of positive biopsy, RT was performed. Failure was defined as use of secondary adjuvant treatment (MAB or RT).

Results: Median follow-up was 48 months. All cases were performed as overnight procedure. No case of urethrorectal fistula or anastomotic stricture was observed. Two cases of acute urinary retention were resolved with prolonged urethral catheterization. Four cases of stress urinary incontinence were observed; 2 (mild incontinence) were resolved after pelvic floor exercises within 6 months, while 2 cases of severe incontinence required surgical minimally invasive treatment;17/19 patients (89,5%) were classified as success. Two patients failed to show a PSA nadir $<$0.1 ng/ml. During follow-up, 8/17 patients (47%) were classified as failure, with consequent total rate of failures 10/19 (52.6%). A statistically significant difference was observed in pre-HIFU median PSA (2 vs. 5.45 ng/ml, respectively, $P = 0.013$) and Gleason score of the RP specimen ($P = 0.01$) between the success and failure group.

Conclusions: Salvage first-line HIFU for palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP is a feasible, minimally invasive day-case procedure, with an acceptable morbidity profile. It seems to have a good cancer control in the short- and mid-term. Patients with lower pre-HIFU PSA level and favorable pathologic Gleason score presented better oncologic outcomes. A prospective randomized trial with an adequate recruitment and follow-up is necessary to confirm our preliminary oncologic results.

Keywords: High-intensity focused ultrasound; Prostate; Prostate cancer; Radical prostatectomy; Local recurrence

1. Introduction

Prostate cancer (CaP) is the most commonly diagnosed malignancy and the second leading cancer-related cause of death in men in the United States [1]. Although radical prostatectomy (RP) is an effective treatment for many patients with clinically localized CaP [2], treatment fails in up to one-third of patients. Without salvage therapy, 65% of men will develop distant metastasis within 10 years of biochemical recurrence (BCR) [3].

For patients with biopsy-proven or radiographically identified local recurrence after RP and in absence of identifiable metastatic disease, salvage radiotherapy (SRT) is the standard treatment [4–7]. However, it is a time-consuming therapy (it takes several weeks to complete); moreover, the additional gastrointestinal and genitourinary toxicity could

* Corresponding author. Tel.: +39 06 20902835 or +39 340 6054387; fax: +39 06 20902975.

E-mail address: tasospao2003@yahoo.com (A.D. Asimakopoulos).

1078-1439/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.urolonc.2010.08.019

be physically challenging, especially for elderly patients with co-morbidities and lower performance status [8].

To avoid the limits of the SRT, increasing interest is being focused on the minimally invasive forms of CaP treatment. Recently, Siddiqui et al. [9] reported their experience on the use of cryotherapy for patients with local recurrence after RP, demonstrating that it could be an effective alternative to SRT.

Transrectal high-intensity focused ultrasound (HIFU) has demonstrated an effective long-term cancer control in patients with low- or intermediate-risk localized CaP [10]. Its role as a salvage treatment after RT for CaP has also been evaluated [11]. However, there is only one study (case-series, Level of evidence 4) regarding the use of salvage HIFU in the post-RP setting [8].

We designed a pilot study, with no control arm, to test HIFU as first-line salvage treatment in patients with palpable, transrectal ultrasound (TRUS)-evidenced, biopsy-proven local recurrence of CaP after RP.

2. Materials and methods

2.1. Patients' enrollment and ethics

In our center, the first-line treatment for the local recurrence of CaP after RP is the SRT. However, in the period June 2003–June 2008, 19 patients with palpable, TRUS-evidenced, biopsy-proven CaP local recurrence post-RP were unwilling to undergo SRT for several reasons: distance from the reference center of RT, long waiting list, fear/apprehension of the potential collateral effects of RT, duration of treatment. These patients were enrolled in the HIFU protocol, after obtaining institutional review board approval and written informed consent of patients. The study was conducted in accordance with the Good Clinical Practice rules and with the ethical principles contained in the Declaration of Helsinki as amended in Hong Kong.

2.2. Inclusion and exclusion criteria

Inclusion criteria for first-line salvage HIFU were: palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP, independently of PSA level and pathologic Gleason score; no evidence of distant metastasis assessed by means of bone scan and total body CT scan or 18F PET/CT scan. DRE findings were considered abnormal if any mass, nodule, induration, or irregularity was noted in the prostatic fossa. A gray-scale TRUS was performed by a single operator with a linear 7.5 MHz biplane probe (Technos; Esaote SpA, Rome, Italy). The TRUS findings were considered to be suggestive of local recurrence if any suspected lesion was identified at or around the area of the anastomosis, at the bladder neck, in the retrovesical space, or if any asymmetry or obvious distortion of the urethrovesical anastomosis was noted [12]. The size of the local recurrence was determined by its greatest diameter.

The subsequent biopsies, all performed by the same operator through the transperineal route and under TRUS guide, were positive for local recurrence of CaP. The grading of the lesion was assigned according to the Gleason system.

Exclusion criteria were: evidence of distant metastasis, not TRUS-evidenced local recurrence, adjuvant external radiation or hormonal treatment, if administered after RP but before the time of the evaluation, anal stenosis or any other condition that does not permit the introduction of the HIFU probe in the rectum.

2.3. Study end-points and methodology

Primary end-point was the evaluation of the feasibility of the procedure in terms of safety and early and late morbidity. All medical and surgical complications occurring in both in-patient and out-patient setting were recorded. They were classified as early onset ($<$30 days) and late onset ($>$30 days), and graded according to the modified Clavien classification [13].

Secondary end-point was the preliminary evaluation of the oncologic efficacy of salvage HIFU in terms of PSA nadir, biochemical disease free survival (bDFS), and need of secondary adjuvant treatment (ormonotherapy or SRT).

Success was defined as PSA nadir $\leq$0.1 ng/ml, obtained within 3 months [14]. In case of PSA nadir $>$0.1 ng/ml or PSA increase $\geq$1 ng/ml above the PSA nadir, a biopsy of the treated lesion was performed, and if negative, hormonal therapy [maximum androgen blockade (MAB)] was adopted. In case of positive biopsy, secondary SRT was performed. Failure was defined as use of MAB or RT after first-line HIFU.

2.4. Treatment protocol and postoperative care

All patients underwent HIFU using the "re-treatment" protocol of the Ablatherm device (EDAP TMS, Vaux-en-Velin, France). Antiplatelet agents were stopped 10 days prior to HIFU treatment. HIFU was performed under spinal anesthesia, with the exception of the cases where it was not technically feasible or it was refused by the patient. A urethral catheter was inserted in all cases before surgery, removed during the procedure to permit the treatment of periurethral tissue, and replaced at the end of the treatment.

Surgical time, intra- and postoperative complications, and hospital stay were recorded. Patients were all discharged with the Foley catheter still in place; the catheter was then electively removed on an outpatient basis.

2.5. Follow-up

Follow-up visits were scheduled every 3 months during the first year and every 6 months afterwards. They included: total serum PSA, assessment of continence status (number

Table 1
Clinical and pathologic baseline characteristics of the patient cohort

Mean age at HIFU (years)	70 (60–77, SD 4.84)
Median interval RRP to HIFU (month)	40 (8–103)
RRP pathological stage (*n*)	
T2a	6
T2b	6
T2c	5
T3a	1
T3b	1
RRP Gleason score (*n*)	
≤6	4
3+4	4
4+3	5
>7	2
Missing	4
Median PSA before HIFU (ng/ml)	3.81 (0.5–8)
Pre-HIFU continent patients (%)	16/19 (84%)
Mean lesion size (mm)	23.7 (20–40)
Biopsy Gleason score of local recurrence (*n*)	
≤6	7
3+4	3
4+3	3
>7	3
Scarcely differentiated	1
Not specified	2
Median follow-up (month)	48 (13–77)

of pads/d), and radiologic imaging at the discretion of the treating physician. Erectile function was not evaluated.

2.6. Statistical analysis

Baseline characteristics and follow-up data of success and failure patients were compared by means of *t*-test (parametric) or Fisher's exact test (nonparametric data). *P* values <0.05 were considered significant. All statistics were performed with Statistica Base (software for Windows, StatSoft Italia srl, Vigonza, Padova, Italy).

3. Results

The clinical and pathologic baseline characteristics of the patient cohort are outlined in the Table 1.

The procedure was feasible in all cases and it was carried out within a mean of 32 minutes (15–43). No serious intra- or postoperative complications were observed. All patients were discharged within 24 hours with the Foley catheter still in place.

Catheter was routinely removed within 7 days and post-void residual evaluation was performed. Two cases of acute urinary retention after catheter removal required prolonged catheterization for 14 and 15 days, respectively (early complication, Grade IIIa according to the Clavien classification).

Sixteen of 19 (84%) patients achieved continence (no pad) before HIFU. Four cases of newly diagnosed stress urinary incontinence (early onset) were observed after the treatment; 2/4 patients presented a mild to moderate incontinence, resolved after pelvic-floor muscle exercises within 6 months (Grade I); 2 cases of severe incontinence required a minimally invasive day-case procedure with the placement of adjustable continence therapy (ProACT, Uromedica, Plymouth, MN) (Grade IIIb). Two opposing balloons were successfully implanted via a transperineal approach, under TRUS-guidance, paraurethrally at the level of bladder neck without complications. Three patients who were incontinent before HIFU did not report any worsening of their incontinence status. No case of urethrorectal fistula, anastomotic stricture, or persistent storage symptoms was observed.

Table 2 summarizes the early and late complications, providing a comparison with the published series of minimally invasive surgical treatment for local recurrence after RP.

Seventeen of 19 patients (89,5%) were classified as success 3 months after HIFU, showing a PSA nadir ≤0.1 ng/ml; 8/17 patients (47%) were classified as failure during follow-up (median follow-up: 48 months); 7/8 had negative biopsy of the treated lesion and showed an increase of PSA ≥1 ng/ml above PSA nadir; consequently MAB was administered; 1/8 had positive biopsy and was treated with SRT. At a median follow-up of 48 months, 9/17 (52, 9%) patients continue to be considered as "success" according to

Table 2
Complications of the published series of minimally invasive surgical treatment for local recurrence of CaP after RP

	Siddiqui et al. [9]	Murota-Kawano et al. [8]	Current study
Patients (*n*)	15	4	19
Treatment modality	Cryoablation	HIFU*	HIFU
Mean or median follow-up (months)	20	18	48
Recto-urethral fistula (*n*)	0	0	0
De novo incontinence (treatment)	2 (1 security pad 1 artificial urinary sphincter)	0	4 (2 PFME**; 2 Pro-ACT)
Worsening of pre-existing incontinence	1	0	0
Acute urinary retention	NR	0	2
Storage symptoms	1	0	0
Anastomotic stricture	NR	0	0

* 3/4 patients received first-line SRT before HIFU.
** PFME = pelvic-floor muscle exercises.

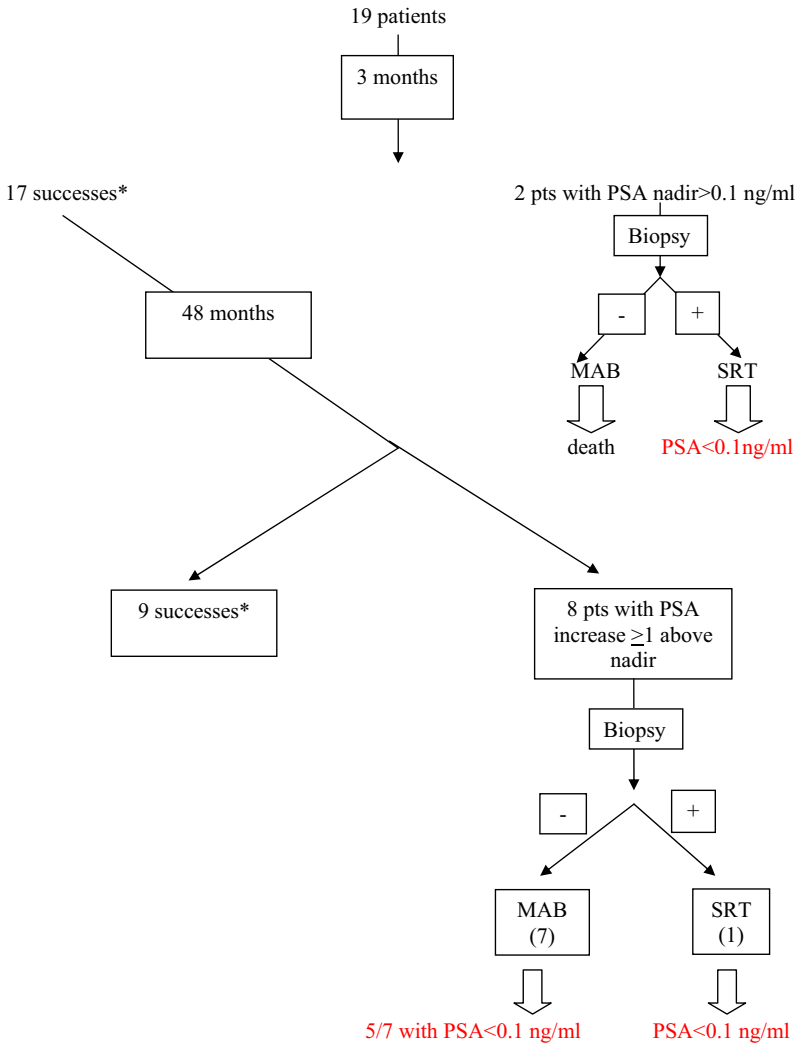

Fig. 1. Oncologic efficacy of salvage HIFU after RP palpable local failure. * PSA nadir ≤0.1 ng/ml. (Color version of figure is available online.)

the previous definition. Overall, the 4-year bDFS was 47.4% (9/19 patients).

Two of 19 patients failed to show a PSA nadir ≤0.1 ng/ml: 1 of them had positive biopsy and was treated with SRT, while the other, having negative biopsy, received MAB. The latter died during the follow-up period after development of hormone refractory CaP. Currently, 7/9 patients classified as failure present a PSA level ≤0.1 ng/ml, while 2/9 have a PSA >0.1 ng/ml (1.39 and 1.74 ng/ml, respectively, after adjuvant MAB). These results are summarized in the Fig. 1.

The clinical and pathologic comparisons between the HIFU success and failure groups are outlined in Table 3. The comparison of the Gleason score was obtained after their subdivision in 2 subgroups: A (≤ 3+4) and B (≥ 4+3).

Age, median pre-RP PSA, size of lesion, local recurrence biopsy Gleason score (pre-HIFU), and mean time from RP to HIFU did not differ significantly between success and failure group. A statistically significant difference was observed between the 2 groups for pre-HIFU median PSA (2 vs. 5.45 ng/ml; $P = 0.013$) and Gleason score of the RP specimen ($P = 0.01$).

4. Discussion

Primary curative procedures, such as RP and radiotherapy, are well-established therapeutic options in the management of localized CaP. Despite the improvements in both fields, there is still a significant risk of cancer recurrence after therapy and up to 27%–53% of all patients undergoing radiation therapy or RP will develop local or distant recurrences within 10 years after initial therapy, and 16%–35% of patients will receive second-line treatment within 5 years of initial therapy [15].

CaP recurrence after RP is defined as only a BCR if a detectable serum PSA value is noted in the absence of clinical evidence of local recurrence or of metastatic disease. Local recurrence has been defined to occur with ab-

Table 3
Clinical and pathologic data of HIFU success and failure groups

	Success group (n = 9)	Failure group (n = 10)	P value
Age (years)	71.1	68.7	0.3
Pre-RP PSA (ng/ml)	7.45	9.76	0.62
Pre-HIFU PSA (ng/ml)	2	5.45	0.013*
Size of lesion (mm)	25.6	20.75	0.16
RP Gleason score			P = 0.01*
Missing	1	3	
≤6	4	0	
3+4	3	1	
4+3	1	4	
>7	0	2	
Local recurrence biopsy Gleason score pre-HIFU			P = 0.62
≤6	4	3	
3+4	1	2	
4+3	1	2	
>7	1	2	
Scarcely differentiated	0	1	
Not specified	2	0	
Follow-up, median (month)	42	62	
RRP to HIFU			
Mean	47.3	32	0.40

* P <0.05.

normal results at DRE of the prostatic fossa in the presence of a detectable PSA value, regardless of the results of prostatic fossa biopsy [16].

For patients with biopsy-proven or radiographically identified local recurrence after RP and in absence of identifiable metastatic disease, SRT is the standard treatment. However, it is a time-consuming therapy (it takes several weeks to complete); moreover, the potential gastrointestinal and genitourinary toxicity could be physically challenging for elderly patients with co-morbidities or lower performance status [8]. Furthermore, SRT has been found to be less successful in palpable than nonpalpable local recurrence [17].

Recently, Siddiqui et al. [9] published their study on the salvage cryotherapy for biopsy-proven local recurrence of CaP after RP, reporting a success rate of 40% (6/15) and a failure rate of 60% (9/15), defined as a PSA increase greater than 0.1 ng/ml from the PSA nadir or the addition of EBRT or ADT. They also found that pre-RP and RP Gleason scores as well as lesion size were significantly lower in the success group than in the failure one. They concluded that salvage cryotherapy can be an effective and safe treatment modality, especially for patients with favorable biopsy and pathologic Gleason scores, before cryotherapy.

HIFU, a minimally invasive procedure, has been shown to provide good outcomes with limited morbidity in the treatment of CaP [18–21]. HIFU acts through coagulative necrosis of the tissue to destroy prostate cells without damaging the intervening structures [22,23]. It can be used as primary therapy with effective long-term cancer control in patients with low- or intermediate-risk localized CaP [10]. It has also demonstrated its efficacy as a salvage treatment after primary HIFU or external beam radiation therapy (EBRT) [11].

Murota-Kawano et al. [8] published their preliminary experience on the role of salvage HIFU after RP. In their small study, 3/4 enrolled patients had RT+ADT as primary salvage treatment after RP. At 24-month of follow-up, 2/4 patients were BCR-free (defined as an increase in PSA level >0.2 ng/ml). No complications were observed.

To our knowledge, we present the largest series of salvage first-line HIFU after RP published till now.

The treatment were feasible in all cases with no major complications (Grades IV and V, according to the Clavien classification) and an acceptable morbidity profile. Four Grade III (2 Grade IIIa and 2 Grade IIIb) early complications were recorded. Cases of acute urinary retention could be explained by the local tissue inflammation/edema, usually resolved by a prolonged catheterization. Urinary incontinence is the result of thermal damage to the structures involved in the distal continence mechanism. In our series, 2 cases of mild to moderate incontinence were resolved after pelvic-floor muscle exercises, while 2 patients needed surgery.

It has to be underlined that HIFU was performed in the "re-treatment" modality: it means that a smaller quantity of focused energy is applied for less time (4 instead of 5 seconds for each shot) to recurrent cancer tissue (with regard to standard HIFU treatment). Consequently, the damage to the surrounding structures (including rectal wall and external urethral sphincter) is lower, minimizing the risk of complications, such as urethro-rectal fistula, anastomotic strictures, and incontinence. Considering also the acquired experience with HIFU as a primary treatment of CaP (almost 400 cases treated since 2003 in our center), the low morbidity rate observed in our study appears reasonable.

According to our definition, 9/19 patients (47.4%) were classified as success at our median follow-up of 48 months. Failure cases with positive biopsy of the treated lesion were treated with SRT, while MAB was applied in case of negative biopsy. In an intention-to-treat analysis, among the failure cases, 7 are currently free of BCR, increasing the percentage of bDFS patients to 16/19 (84%). Even though our results seem promising, the low number of patients treated and the absence of a control arm do not allow definitive conclusions on the oncologic efficacy of the procedure. The study population was not planned in advance, since this was a pilot study aiming to evaluate primarily the feasibility, safety, and morbidity profile of the technique. Moreover, the absence of an extended follow-up could be considered another limit since significant disease recurrence may occur with extended follow-up [24]. However, our outcomes could be used to design a prospective randomized trial, with adequate statistical power, comparing HIFU vs. SRT in the treatment of the palpable, local recurrence of CaP after RP.

The analysis of the factors that potentially influence the oncologic efficacy of the procedure revealed that a higher

pre-HIFU total PSA and/or a not-favorable Gleason score of the RP specimen could be associated with higher failure rate. As observed in previous studies for SRT [25], our study seems to confirm that lower serum PSA level prior to salvage HIFU is a predictor of favorable response. Similarly, an increased percentage of high-grade RP Gleason scores (4+3 or greater) was observed in the HIFU failure group compared with the success group (12.5% vs. 86%; $P = 0.01$), suggesting that favorable Gleason Score could be associated with better outcomes.

In our study, salvage first-line HIFU for palpable and biopsy-proven local recurrence after RP failure presented better results compared with salvage RT in the same setting. MacDonald et al. [17] reported a limited efficacy of SRT in the treatment of locally palpable recurrence after RP (42 patients) with a 5-year bDFS of 27% at 5-year follow-up. A much lower bDFS (11% at 5-year follow-up) was reported by Choo et al. [26] in 44 patients with palpable recurrence after RP. The difference in the median follow-up (4 vs. 5 years) and in the number of patients recruited could partially justify the observed bDFS in our study compared with the aforementioned ones.

Moreover, it should be underlined that in both salvage HIFU and in SRT, failure rate could be influenced by staging problems due to poorly sensitive methods being used to distinguish between local and distant recurrence [12], such as digital rectal examination (DRE), nuclear bone scanning, transrectal ultrasonography of the prostatic fossa, computed tomography (CT), magnetic resonance (MR) imaging, monoclonal antibody scanning, and positron emission tomography (PET), as well as clinical parameters such as interval from RP to PSA recurrence, postoperative PSA velocity [27], or postoperative PSA level doubling time [28]. Thus the final oncologic outcomes may be hindered since many patients who receive definitive local salvage therapy harbor micrometastases, suggesting the need of careful patient selection in order to achieve better outcomes.

Lastly, the absence of a cost analysis could represent another limitation of our study and should be part of a larger prospective trial.

5. Conclusions

HIFU as salvage first-line treatment for palpable, TRUS-evidenced, biopsy-proven local recurrence of CaP is a feasible, minimally invasive day-case procedure, with an acceptable morbidity profile. It seems to have good cancer control in the short- and mid-term. Patients with lower pre-HIFU PSA level and favorable pathologic Gleason score seem to present better oncologic outcomes. A prospective randomized trial with an adequate recruitment and follow-up is necessary to confirm our preliminary oncologic results.

References

[1] Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–31.
[2] Gerber GS, Thisted RA, Scardino PT, et al. Results of radical prostatectomy in men with clinically localized prostate cancer. JAMA 1996;276:615–9.
[3] Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591–7.
[4] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[5] Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004; 291:1325–32.
[6] Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035–41.
[7] Chalasani V, Iansavichene AE, Lock M, et al. Salvage radiotherapy following radical prostatectomy. Int J Urol 2009;16:31–6.
[8] Murota-Kawano A, Nakano M, Hongo S, et al. Salvage high-intensity focused ultrasound for biopsy-confirmed local recurrence of prostate cancer after radical prostatectomy. BJU Int 2010;105:1642–5.
[9] Siddiqui SA, Mynderse LA, Zincke H, et al. Treatment of prostate cancer local recurrence after radical retropubic prostatectomy with 17-Gauge interstitial transperineal cryoablation: Initial experience. Urology 2007;70:80–5.
[10] Blana A, Murat FJ, Walter B, et al. First analysis of the long-term results with transrectal HIFU in patients with localized prostate cancer. Eur Urol 2008;53:1194–201.
[11] Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol 2009;55:640–9.
[12] Leventis AK, Shariat AF, Slawin KM. Local recurrence after radical prostatectomy: Correlation of US features with prostatic fossa biopsy findings. Radiology 2001;219:432–9.
[13] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg 2004;240:205–13.
[14] Blana A, Brown SC, Chaussy C, et al. High-intensity focused ultrasound for prostate cancer: Comparative definitions of biochemical failure. BJU Int 2009;104:1058–62.
[15] Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68–80.
[16] Pound CR, Partin AW, Epstein JI, et al. Prostate-specific antigen after anatomic radical retropubic prostatectomy: Patterns of recurrence and cancer control. Urol Clin North Am 1997;24:395–406.
[17] MacDonald OK, Schild SE, Vora S, et al. Salvage radiotherapy for men with isolated rising PSA or local palpable recurrence after radical prostatectomy: Do outcomes differ? Urology 2004;64: 760–4.
[18] Rebillard X, Gelet A, Davin JL, et al. Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer. J Endourol 2005;19:693–701.
[19] Blana A, Walter B, Rogenhofer S, et al. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-Year experience. Urology 2004;63:297–300.
[20] Chaussy C, Thuroff S, Rebillard X, et al. Technology insight: High-intensity focused ultrasound for urologic cancers. Nat Clin Pract Urol 2005;2:191–8.
[21] Thuroff S, Chaussy C, Vallancien G, et al. High-intensity focused ultrasound and localized prostate cancer: Efficacy results from the European multicentric study. J Endourol 2003;17:673–7.

[22] Chapelon JY, Margonari J, Vernier F, et al. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. Cancer Res 1992;52:6353–7.

[23] Oosterhof GO, Cornel EB, Smits GA, et al. Influence of high-intensity focused ultrasound on the development of metastases. Eur Urol 1997;32: 91–5.

[24] Ward JF, Blute ML, Slezak J, et al. The long-term clinical impact of biochemical recurrence of prostate cancer 5 or more years after radical prostatectomy. J Urol 2003;170:1872–6.

[25] Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035–41.

[26] Choo R, Morton G, Danjoux C, et al. Limited efficacy of salvage radiotherapy for biopsy confirmed or clinically palpable local recurrence of prostate carcinoma after surgery. Radiother Oncol 2005;74: 163–7.

[27] Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology 1994;43: 649–59.

[28] Patel A, Dorey F, Franklin J, et al. Recurrence patterns after radical retropubic prostatectomy: Clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol 1997;158:1441–5.