

Focal Therapy with High-Intensity Focused Ultrasound for Prostate Cancer in the Elderly. A Feasibility Study with 10 Years Follow-Up

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ABSTRACT

Purpose: To evaluate the long-term efficacy of prostate cancer control and complication rates, in the elderly, after focal therapy with high-intensity focused ultrasound (HIFU).

Materials and Methods: Between June 1997 and March 2000, patients with localized prostate cancer were included into a focal therapy protocol. Inclusion criteria were: PSA ≤ 10 ng/mL, ≤ 3 positive biopsies with only 1 lobe involved, clinical stage \leq T2a, Gleason score ≤ 7 (3+4), negative CT scan and bone scan. Hemi-ablation of the prostate was performed with the Ablatherm^(R) device. Survival, complication rates and urinary continence were evaluated. Control biopsies were performed at 1 year. Treatment failure was defined as a positive biopsy or need for salvage therapy.

Results: Twelve patients with a mean age 70 years were included. Median follow-up was 10 years. Control prostate biopsies were negative in 11/12 (91%) patients. Overall survival was 83% (10/12) and cancer specific survival was 100% at 10 years. Two patients died from other causes. Recurrence free survival was 90% (95% CI; 0.71-1) at 5 years, and 38% (95% CI; 0.04-0.73) at 10 years. Five patients had salvage therapy with repeat HIFU (n = 1) or hormonal therapy (n = 4) and all salvage patients were alive at 10 years. No patients developed lymph node or bone metastasis. No patients suffered from urinary incontinence. International Prostate Symptom Score was stable at 1 year. Complications included two urinary tract infections and one episode of acute urinary retention.

Conclusions: Hemi-prostate ablation with HIFU can be safely performed in selected elderly patients with adequate long-term cancer control and low complication rates. Results from larger prospective studies using improved imaging techniques and extensive biopsy protocols are awaited.

Key words: prostate neoplasms; ultrasound; high-intensity focused; transrectal
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INTRODUCTION

Radical treatments such as radical prostatectomy (RP) or radiation therapy (RT) offer an excellent cancer cure rate around 85 to 90%, but post-treatment side-effects on urinary control and sexual function are common (1-3). In the elderly, the use of such radical treatments that reduce quality of life is questionable (3). Recently, there has been a demand

to develop ablative therapies that attempt to reduce post-treatment side-effects, to avoid the psychological morbidity associated with active surveillance (AS) and maintain cancer control (4). In the United States, observational studies show that neither patients nor their physicians are enthusiastic about AS, an option chosen by only 10% of men (5). HIFU therapy, is a minimally invasive therapeutic option that has already shown efficacy in long-term cancer control with lim-

ited morbidity when applied to the whole gland (6,7). We hypothesize that applying HIFU on focal lesions could control disease with minimal harm to adjacent tissues, thus limiting post-treatment side effects of more radical therapy. We retrospectively reviewed our population and describe the long-term results of focal therapy with HIFU.

MATERIALS AND METHODS

Patients

Between June 1997 and March 2000, patients with localized prostate cancer were included in a focal therapy protocol. Inclusion criteria were: prostate specific antigen (PSA) ≤ 10 ng/mL, ≤ 3 positive biopsies with only 1 lobe involved, clinical stage \leq T2a, Gleason score ≤ 7 with no predominant pattern 4, and negative staging (absence of lymphadenopathy on CT scan and a negative bone scan). All patients provided written informed consent before entering the study. Patients with a previous history of any definitive treatment for prostate cancer or hormonal therapy were excluded.

Technique

Patients underwent HIFU with the first-generation Ablatherm^(R) device (EDAP-TMS, Vaux-en-Velin France) using a 2.5 and 3 MHz transducer under general anesthesia. At the very beginning of our experience, even positive apical biopsies were considered suitable for HIFU treatment. Nevertheless, in the operative protocol, the sphincter was always avoided. Initially transurethral resection of the prostate (TURP) was offered prior to HIFU in patients with large prostate volumes. It was subsequently done routinely since TURP reduces post-operative bladder outlet obstruction (8). Overall, 5 patients underwent TURP before HIFU.

Endpoints

Cancer control: treatment failure was defined as any positive control biopsy (irrespective of the side) and/or salvage therapy. Prostate biopsies were

performed at 1 year after treatment and if there was a rising PSA. Salvage therapy was introduced on treatment failure, that is, when a control biopsy was positive or when PSA increased to above pre-treatment levels. In case of treatment failure, patients were offered HIFU if the recurrence was considered local (one positive biopsy in the same lobe); if more diffuse, they were offered androgen deprivation therapy. Adverse events, death and cause of death were recorded. Overall survival was calculated at the time of death, regardless of cause. Prostate cancer specific survival was calculated at the time of death from prostate cancer.

Quality of Life

Treatment related morbidity was recorded. Continence was evaluated as the number of pads used per day at 1, 6 and 12 months. Lower urinary tract symptoms (LUTS) were assessed with the International Prostate Symptom Score (IPSS), before treatment, and at 1, 6, and 12 months. Sexual function was not assessed in this study because 7/12 patients were not interested in sexual activity or had pre-existing erectile dysfunction. The International Index of Erectile Function-5 questionnaires were unavailable for the remaining patients. Subjective information related to sexual function was available in the charts, but because of the lack of objective data, sexual function was not assessed in this analysis.

Follow-up

PSA measurements were performed in all patients at 3 months from initial HIFU treatment, and then every 6 months thereafter. Clinical assessment was performed every 6 months during the first 5 years and then annually thereafter. A six-core control biopsy involving both prostatic lobes was performed 1 year after treatment and/or in case of rising PSA. The data was analyzed retrospectively.

RESULTS

A total of 12 patients met the inclusion criteria and were enrolled in this protocol. Pre-treat-

Table 1 – Patient demographics.

Patient Number	Age (yrs)	Pre-op PSA (ng/ml)	Pre-op IPSS	Prostate Volume (cc)	Number of Positive Biopsies	Number of Apical Biopsies	Gleason Score	Clinical Stage
1	80	10.0	10	30	2	0	3+4	T1c
2	73	9.4	2	25	3	1	3+3	T1c
3	72	5.4	2	62	1	0	3+3	T1c
4	72	7.9	6	26	3	1	3+2	T1c
5	66	4.8	12	40	1	1	3+3	T1c
6	76	6.7	22	40	2	1	3+3	T1c
7	68	6.6	10	42	2	0	3+2	T1c
8	65	10.0	8	38	1	1	3+2	T1c
9	66	10.0	1	51	1	0	3+3	T2a
10	67	9.8	1	23	2	0	3+3	T1c
11	65	6.7	11	30	2	1	3+4	T2a
12	72	2.6	-----	40	1	0	3+3	T2a

PSA = prostate-specific antigen; IPSS = International prostate symptom score.

ment patient characteristics are shown in Table-1. Long-term oncologic and functional outcomes are shown in Table-2. Data on patients with recurrence

is shown in Table-3. The mean age was 70 years (\pm 4.8) and median procedure time was 69 minutes. Median number of shots was 374 (161-533), median

Table 2 – Focal therapy with HIFU: oncological and functional results.

Patient Number	Post-op IPSS	Nadir PSA (ng/mL)	PSA value at the Time of Salvage Therapy (ng/mL)	Time to Introduction of Salvage Therapy (years)	Type of Salvage Therapy	Last PSA (ng/mL)	Total Follow-up (years)
1	12	2.4	8.6	9.0	ADT	1.3	11.0
2	1	2.0	14.5	10.0	ADT	0.1	11.1
3	7	2.8	26.0	10.0	ADT	1.0	10.5
4	4	1.9	9.9	9.0	ADT	3.2	10.6
5	8	2.2	NST	NST	NST	6.8	10.8
6	12	2.3	NST	NST	NST	3.8	10.5
7	12	1.1	NST	NST	NST	1.5	10.6
8	6	1.1	NST	NST	NST	1.2	Dead
9	4	1.1	NST	NST	NST	1.5	7.5
10	5	0.4	NST	NST	NST	0.4	Dead
11	6	0.3	1.6	5.0	HIFU	4.6	9.5
12	--	1.0	NST	NST	NST	1.7	8.0

ADT = androgen deprivation therapy; HIFU = high-intensity focused ultrasound; IPSS = international prostate symptom score; NST = no secondary treatment; PSA = prostate-specific antigen.

Table 3 – Status of recurrent patients.

Patient	Initial PSA	Initial Positive Biopsy Location	Nadir PSA (ng/mL)	PSA Value at the Time of Salvage Therapy (ng/mL)	Post-op Positive Biopsy Location	Time to Introduction of Salvage Therapy (yrs)	Type of Salvage Therapy	Last PSA (ng/mL)
1	10.0	Lb,Lm	2.4	8.6	Lb, Lm	9.0	ADT	1.3
2	9.4	Lb,Lm,La	2.0	14.5	Lb,Lm,La Rb,Rm,Ra	10.0	ADT	0.1
3	5.4	Rb	2.8	26.0		10.0	ADT	1.0
4	7.9		1.9	9.9	Rb,Ra, Lb,La	9.0	ADT	3.2
11	6.7	Rb,Ra	0.3	1.6	Ra	5.0	HIFU	4.6

R = right; L = left; b = base; m = mid; a = apex; PSA = prostate-specific antigen.

catheterization time was 2.5 days (range, 2-13). Mean prostate volume was 37 g (23-62), mean pre-operative PSA level was 7.3 ng/mL (2.6-10), mean number of positive biopsies was 2 (1-3) and median follow-up was 10.6 years (7.5-11.1). Six of the twelve patients had an initial apical positive biopsy. For two of these patients, this biopsy was the only positive biopsy. Control biopsies at one year were negative in 11/12 patients (91%). One of twelve patients harbored a residual Gleason 4 (2+2) cancer. This one patient with low grade, low volume disease was monitored with serial PSA, and was treated 4 years later with a second HIFU procedure on PSA increase. Treatment failure was observed in 5 patients. These patients had a salvage therapy with either HIFU (n = 1) or androgen deprivation therapy (ADT) (n = 4) and survival rate for recurrent patients was 100% at 9.5 to 11 years of follow-up. Three of the six patients with an initial apical positive biopsy recurred. None of the recurrences had subsequent lymphadenopathy or bone metastasis on staging. The last median PSA in the recurrence-free group was 1.63 ng/mL (range, 0.42-6.82). The patient re-treated with HIFU had a stable PSA at 4.6 ng/mL, 4.5 years after salvage HIFU treatment alone. The group treated with salvage ADT has a stable median PSA at 1.15 ng/mL (range, 0.13-3.2).

Two patients died during the follow-up period from non-cancer related causes (both from heart failure), they were free of disease when they died 2 and 3 years, respectively, with a PSA at 1.18 ng/mL

and 0.42 ng/mL on the last follow-up. Each also had a negative control biopsy. Recurrence free survival was 90% (95% CI; 0.71-1) at 5 years, and 38% (95% CI; 0.04-0.73) at 10 years (Figure-1). Overall survival was 83% (10/12 still alive) and cancer specific survival was 100%. No urinary incontinence was observed. Two of twelve patients experienced urinary tract infection post-operatively: one episode of epididymo-orchitis, and one asymptomatic urinary tract infection. One patient experienced acute urinary retention post-operatively and had a supra-pubic catheter placed for 13 days. No urethral strictures were recorded. One patient did not have an IPSS score recorded. Eight of eleven patients (75%) had a similar IPSS 1 year after treatment. Two of eleven patients had a lower IPSS and one of eleven patients had a higher IPSS. Of the two patients with lower IPSS scores one year after HIFU treatment; one did not receive further therapy for lower urinary tract symptoms, while the other patient underwent a TURP before HIFU to prevent post-treatment urinary retention.

COMMENTS

In the PSA era, low-risk disease represents a growing proportion of newly diagnosed prostate cancer. Recent data from Cancer of the Prostate Strategic Urological Research Endeavor demonstrates the number of patients with low-risk tumor characteristics

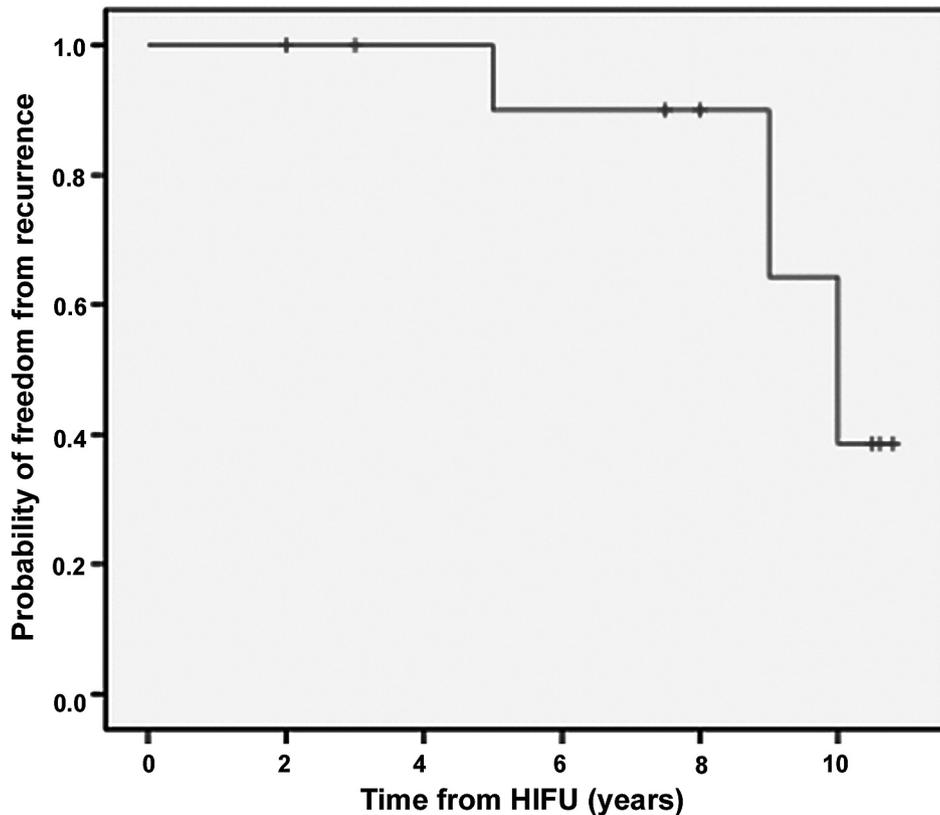


Figure 1 – Probability of freedom from recurrence after initial hemi-ablation of the prostate.

(defined as serum PSA ≤ 10 ng/mL, Gleason score ≤ 6 and clinical stage $\leq T2a$) rose from 27.5% from 1990 to 1994, to 46.4% from 2000 to 2001 (5). Focal therapy has been suggested as an alternative to radical treatment (4).

In our study, focal therapy with HIFU provided a 5 and 10 years recurrence free survival of 90% and 38%, an overall survival of 83% (10/12), and a cancer specific survival of 100% (12/12). Besides the very large 95% CI resulting from the small sample size, these results are comparable to HIFU treatment of the whole gland. In a multicenter analysis including 140 patients treated with HIFU for the whole gland (7), the overall survival was 90% at 5 years and 83% at 8 years. Prostate cancer specific-survival rate was 98%. Treatment failure was defined as presence of at least one positive biopsy, PSA $>$ nadir PSA + 2 ng/mL or salvage therapy. In this analysis, disease free survival was 66% at 5 years, and 59% at 7 years.

When stratified for risk-group, disease free survival at 5 years was 68% for low risk patients and 58% for the intermediate risk patients ($p = 0.021$).

General limitations of whole-gland HIFU also apply to focal therapy. The major limitation is apical cancer. In the beginning of our experience, apical cancers were considered suitable for HIFU and six of twelve patients had apical cancers in this study, including 2 patients with exclusively apical lesions. Half of these patients recurred in our series (2 patients in both lobes and 1 patient at the apex). Increased incontinence risk has been described with treating apical lesions (9). Even at the beginning of our experience special attention was given to the sphincter and no urinary incontinence was observed in this study. Improvement in real-time magnetic resonance imaging (MRI) thermometry for monitoring the treatment effect can further reduce the risk of treating apical lesions (10). Re-treatment with HIFU is also

a relatively safe option since there is no cumulative effect of ultrasound. In a cohort of 223 patients with a retreatment rate of 22%, Blana et al. reported there was no significant difference in urinary infection, outlet obstruction, and chronic pelvic pain after one or several HIFU sessions. However, they observed a significant increase in urinary incontinence and impotence rates in this retreatment group (11). Salvage radiotherapy (RT) has recently been described as an option after HIFU failure with reasonable results (12). Even if most of our patients were treated with ADT, focal therapy with HIFU allows many options for salvage therapy such as repeat HIFU (9,11,13), RT (12), and radical prostatectomy (RP) (14) in case of recurrence.

Although radical treatment offers excellent cancer cure rates, post treatment side effects on urinary, sexual and bowel function are common (15). In the low-risk patient, RP offers a probability of freedom from progression of 79% to 91% and a cancer specific survival rate of 97% and 89% at 10 and 15 years (1,2). RT provides a 10-year progression-free survival rate for low risk patients treated with 75.6 Gy of 85% (16). For RP, urinary incontinence and impaired sexual function rates were 14% and 79%, respectively, 5 years after treatment. For RT, these values were 4% and 64%, respectively, 5 years after treatment (17). Gastrointestinal problems occur in 59% of patients undergoing RT compared to 14% of age-matched controls (18). Compared with radical treatment, focal therapy could provide a way to control low-risk cancers with minimal morbidity. In our population, the only side-effects were urinary tract infection in 2 cases and acute urinary retention in 1 case. With the routine use of pre-operative TURP, the rate of urinary retention can be reduced (8). Nevertheless, we do not perform pre-HIFU TURPs for our focal therapy patients, since this is not in agreement with our definition of focal therapy. Furthermore, LUTS were not significantly changed by HIFU 12 months after treatment and no urethral strictures were recorded. As expected, our data demonstrates focal therapy with HIFU minimizes side-effects. Our findings are also better than the results for the whole gland HIFU protocols reported in the literature. In a multicenter trial conducted on 402 patients, urinary retention was present in 9% of patients, urethral strictures developed

in 4%, and epididymitis in 6% (9). In another study 94% of patients recovered normal urinary continence, 14% had urinary obstruction associated with strictures, 6% complained of pelvic pain for less than 6 months and 26% previously potent patients developed severe erectile dysfunction (7). In a phase II trial assessing feasibility, safety and early efficacy of hemiprostate ablation with HIFU, Emberton et al. found that the probability of men being free of significant genito-urinary toxicity was 95% at 3 months. Patients were 100% pad-free immediately following treatment. Erectile function sufficient for intercourse occurred in 70% by 2 weeks, and at 3 months, 95% had erections sufficient for penetration (19). In a prospective study, comparing whole gland and focal therapy with HIFU, these two options were equivalent for short-term cancer control. No significant differences were observed in the 2 year biochemical disease free survival for patients in the low and intermediate risk groups. Complications tended to be lower in the focal therapy group (20).

Despite reasonable short-term evidence supporting the safety and feasibility of AS in men with low-risk prostate cancer (21), few patients accept this approach. Active surveillance among patients older than 75 years has fallen by half in the PSA era, with less than one-quarter of low-risk patients electing initial observation (22). Moreover, due to anxiety, 50% of these patients usually exit the surveillance protocols during follow-up (21). Compared with AS, focal therapy offers a method to treat the index foci of cancer, relieving anxiety associated with waiting for the disease to progress. Focal HIFU is an attractive option with the advantage of delaying definitive therapy and minimizing its associated adverse effects on patients' quality of life (23).

Despite obvious limitations of a non-randomized retrospective study, including a small sample size, our results are interesting with regards to the long-term oncologic and functional outcomes after hemi-ablation of the prostate with HIFU. One of the weaknesses of our study is the use of a sextant biopsy protocol as recommended in the 1990's. Standard transrectal prostate biopsy strategies have been developed to improve cancer detection but not to accurately locate or stage prostate tumors. To better characterize cancer location, many different

techniques such as image guidance with color Doppler ultrasonography or MRI, transrectal saturation biopsies and perineal mapping biopsies are under evaluation (24-27). Sextant biopsy protocols are insufficient to correctly characterize the cancer and some tumors may have been underestimated (28). It is not clear to what extent this under sampling can explain the recurrence rate observed in our study. One can argue that prostate cancer multifocality explains the high level of recurrence when the whole gland is not treated, and that focal therapy may be of limited efficacy. More than 80% of the patients have multifocal prostate cancer (29) with 80% of secondary tumor foci $< 0.5 \text{ cm}^3$ (30). Volume distribution of the secondary cancers, however, is almost identical to the cancers found incidentally in men undergoing cystoprostatectomy for bladder cancer (29). There is a growing body of evidence to support that the prognosis of the disease is driven by the index tumor foci. Our results are concordant with this assertion and it is encouraging to observe that the 10 year cancer specific and disease free survival of this small sample feasibility study are comparable to the whole gland treatment with HIFU.

Prostate cancer treatments have dramatically evolved towards a more selective approach in order to reduce treatment burden whilst retaining cancer control. Over 10 years ago, our team has embraced HIFU for the treatment of prostate cancer and for the first time we have described the long-term efficacy of focal therapy with HIFU and the limited morbidity of this procedure. Our results are encouraging and we plan to include more patients and eventually younger patients with very strict selection criteria. The main limitation of this non-randomized retrospective study is the small sample size, which precludes statistical analysis; thus, our findings must be interpreted according to this limitation. The ongoing evolution of imaging is also an exciting and important variable in the development of focal therapy (31). As previously defined for open radical prostatectomy, the trifecta remains the essential group of variables to evaluate for any focal therapy approach (1,32). At the beginning of the HIFU experience, we neither had a definition of risk of recurrence, nor a definition for focal therapy. The definition of focal therapy for prostate cancer

describes the treatment of men with organ-confined, low to moderate risk prostate cancer. In these cases, the patient undergoes ablation of only the malignant tumor foci in order to provide acceptable freedom from disease progression and also a high probability of preserving genitourinary and bowel function.

According to the literature, HIFU is a treatment of proven efficacy for localized prostate cancer with limited side-effects. It offers the opportunity to treat elderly patients with a minimally invasive technique that can be repeated and in our initial series could be combined with TURP to offer better urinary outcome (33-36).

A focal approach for prostate cancer performed ten years ago and based on a sextant biopsy diagnosis allowed patients to have similar outcomes as patients treated in the same period with a whole gland approach. This cohort should further expand the discussion on focal therapy, because selected elderly patients were offered ablation of only a half of their prostates and were conferred an acceptable freedom from disease progression and cancer-specific survival.

CONCLUSIONS

This retrospective feasibility study shows that hemi-prostate ablation with HIFU is a reasonable treatment strategy for a selected population of low or intermediate risk prostate cancer in elderly men. The long-term cancer control rate is adequate, recurrences can be treated with a second HIFU session or other techniques. In the elderly, the concept of cancer control instead of cancer cure with HIFU has to be discussed, as it seems to provide an effective long-term disease control with minimal treatment-related morbidity. More extensive biopsy protocols and more accurate imaging techniques will certainly improve patients' selection. Larger prospective studies with a long follow-up are awaited to confirm our small size preliminary results.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

During the last decade developments showed that in most oncologic therapies invasiveness has been reduced. Instead of removing the entire organ radically and surgically the focus is now on the treatment of cancer affected areas only.

Focal therapy in prostate cancer had first been introduced for “male lumpectomy” in 2004 by G. Onic using Cryotherapy.

Statistics show that all local therapies have a high cancer-specific long-term survival rate.

Therefore, the time seems to be right for “NOTES” (Natural Orifice Therapeutic Endoscopic Surgery) - as it is provided by HIFU (High Intensity Focused Ultrasound).

The Montsouris group has used transrectal pulsed focused HIFU since 1996 when it was introduced into clinical practice. They participated in multicenter studies and registered their data in a database ready to be stratified according to specific patient or indication groups. In past years “focal” HIFU has been restricted to few specific cases based on individual medical decision. Thirteen patients have been treated based on current focal HIFU criteria in 12 years (unilateral, low risk PCa treated by hemi-ablation only). Their results have been collected and retrospectively analyzed. The data underline the feasibility of the focal HIFU concept as a realistic balance between low invasiveness, sufficient radicality and low side-effect rate. Even though recurrence free survival of 90% after 5 years decreased to 38% after 10 years, cancer-specific survival still remained 100%.

However, it proves, that this collection of individual indications confirms the feasibility of the focal concept and the validity of “focal HIFU therapy” as well as the rationality of using the NOTES approach for this indication.

It is not possible to draw more statements from a study with such a small number of patients treated by different devices, with different technical settings and a changing application mode.

Other minimal invasive therapies such as Brachy-, Cryo- or Photodynamic therapy are technically able to perform partial treatments as well, but the disadvantage of perineal, tissue and cancer perforating approaches cannot compete with the non invasive NOTES approach by transrectal HIFU.

Patients who decide for focal therapy want to avoid side-effects without major loss of cancer treatment efficacy. Even though this publication is just a feasibility study with 13 patients it proves that this desire of the patient can be met by the focal treatment of PCa with High Intensity Focused Ultrasound.

Focal HIFU may be the first step to postpone more invasive therapies, to preserve functional and sexual prostatic integrity without the psychological burden of “watchful waiting” in prostate cancer therapy.

Once better diagnostic technologies visualize PCa affected areas, focal HIFU with its NOTES approach will have an even higher acceptance within the urological armamentarium to treat prostate cancer.

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