ORIGINAL ARTICLE

High Intensity Focused Ultrasound (HIFU): a useful alternative choice in prostate cancer treatment. Preliminary results

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Abstract. *Introduction and aims:* High-Intensity Focused Ultrasound (HIFU) represents an alternative choice in mini-invasive treatment of prostate cancer. The technology of the device used to perform the treatment allows to exactly destroy a pre-selected area and to save all the tissues around it. We report our experience on the effectiveness and complications of this tecnique. *Materials and methods:* From May 2006 to April 2007, 25 patients with prostate cancer were treated through Ablatherm® (EDAP France) in spinal anesthesia. In the first six patients HIFU and TUR-P (Trans-Urethral Resection of Prostate) were performed in the same session and a suprapubic catheter was placed. In the other 14 patients HIFU was afterwards performed. In these patients a trans-urethral catheter was placed. All patients were divided into three groups: low risk (17 patients), intermediate risk (6 patients) and high risk (2 patients). The follow-up consisted in PSA evaluation after 1,3,6,9,12 months and in transrectal biopsy after six months. Complications related to the treatment, and symptomatological and sexual life tests were evaluated before and after the treatment. *Results:* HIFU overall success rate was 84% (biochemical relapses in only 4 patients out of 25). Success rate was represented as follows: 94,2 % in the low risk group, 83,4% in the intermediate risk group and 0% in the high risk group. No complications occurred during the treatment nor in the immediately post-operative time. *Conclusions*: We demonstrated that HIFU represents a useful alternative choice in mini-invasive therapy of prostate cancer. Particularly, results are remarkable in localized (low-intermediate risk) and low morbility prostate cancer. The role of this procedure in high risk patients needs to be further evaluated. Transrectal HIFU represents a mini-invasive therapeutic option that makes the treatment of prostate cancer possible in 84 % of cases. Our results agree with the literature data and demonstrate that the success of the procedure depends on the correct indication of treatment and is strictly related to progression risk parameters. (www.actabiomedica.it)

Key words: Prostate cancer, High Intensity Focused Ultrasound, minimally invasive surgical procedure

Introduction

Prostate cancer is considered one of the most important topics in male health with an important social impact on the quality of life. In Europe, 2,6 million new cases of prostate cancer are yearly observed (11% of male cancer diagnosis), responsible for 9% of deaths for male cancer cases over all. Radical surgery represents the treatment of choice in clinically localized prostate cancer and in > 10 year life expectancy prostate cancer. Nevertheless, radical surgery itself may be considered a high morbility treatment (1).

Mini-invasive procedure development, such as three-dimensional external radiotherapy, brachytherapy or cryotherapy, especially in elderly or anesthesiologically high risk patients, represents a useful treatment in prostate cancer.

HIFU (High-Intensity Focused Ultrasound) is a new and alternative choice in localized and low or intermediate-risk prostate cancer treatment (2-4).

We report our preliminary experience in 25 patients and deal with the oncological secondary consequences of the procedure itself.

Materials and methods

Twenty-five patients underwent HIFU between May 2006 and November 2007: every patient was available for a medium oncological follow-up. Inclusion criteria were: first treatment of prostate localized cancer and local relapse after radiotherapy, age over 70. Exclusion criteria were: anal stenosis, previous rectal surgery, high prostatic volume (anteroposterior diameter more than 25 mm) and coxofemoral anchilosis. The oncological follow-up consisted in PSA evaluation after 1,3,6,9,12 months, and in transrectal biopsy after six months. The growth of PSA obtained in three consecutive samples was considered as a failure, according to the ASTRO criteria (American Society for Therapeutic Radiology and Oncology) (5). Urinary symptoms and sexual potency were evaluated by IPSS - International Prostate Symptom Score (0-7 Mildly symptomatic; 8-19 Moderately symptomatic; 20-35 Severely symptomatic) and IIEF5 - International Index of Erectile Function 5 (6-10 High erectile deficit; 11-16 Moderate deficit; 17-25 Low deficit; 26-30 No deficit).

In our statistic elaboration we considered t-student parameter only.

All patients were preliminarily disobstructed: 7 underwent TUR-P (Trans-Urethral Resection of Prostate) at the same time of the HIFU-procedure; 11 underwent TUR-P two months before and 7 underwent TUR-P or trans-vesical adenomectomy more than two months before.

They received: a) anti-trombotic prophylaxis with sodic dalteparin 5.000 I.U. the day before the procedure; b) antibiotic therapy; c) careful intestinal toilet. All patients underwent an intraspinal block with Chirocaine®; if Marcaine® is administrated, it is important to begin the procedure from the left lobus prostatae, because this lobe is above due to the left decubitus of the patient on the device. In order to make the procedure more bearable and to obtain the best cooperation from the patient, Midazolam 0,03 mg/kg was administrated during the procedure.

We used Ablatherm® device (EDAP, Lyon, France): it consists of a 3.0 MHz piezoelectric therapeutic applicator and a 7,5 MHz ultrasound scanner for treatment planning.

Ablatherm® is a computerized surgical device equipped with a treatment table, an ultrasound treatment system connected to an endorectal probe, a safety infrared ray detector, a refrigeration system keeping the rectal mucosa temperature below 14 °C and a monitor to set and control the treatment procedure through echographic screening (Fig. 1).

A standard procedure can be personalized in order to obtain ideal treatment settings: ultrasound frequency (standard 3 MHz), shot duration (standard 5 seconds) and waiting-time between shots (standard 5 seconds) may be modified. Elementary lesion volume measures 19-24 mm and its diameter measures 1.7 mm (Fig. 2).

Conceptually, a piezoelectric trasducer generates a high intensity converging ultrasound beam that destroys local tissues through three mechanisms:

1. Coagulative necrosis, due to hyperthermia (85-100°C) generated in the focal point. Elementary lesion is ellipsoidal and the short length of the shot limits heat diffusion around the focal point. Shot by shot, it is possible to generate a

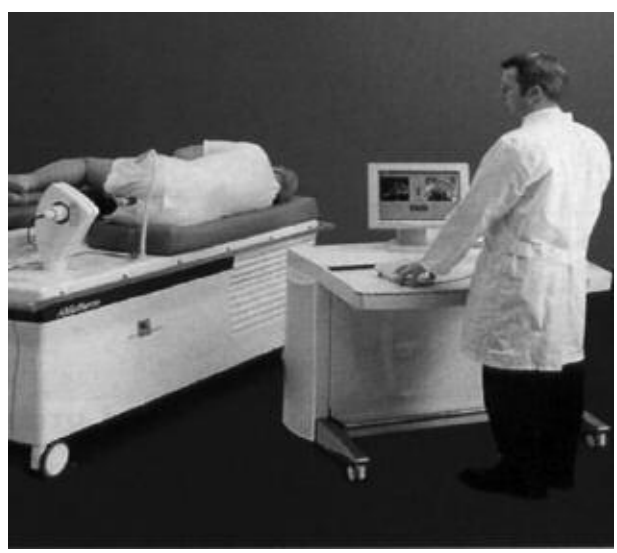

Figure 1. HIFU device at work

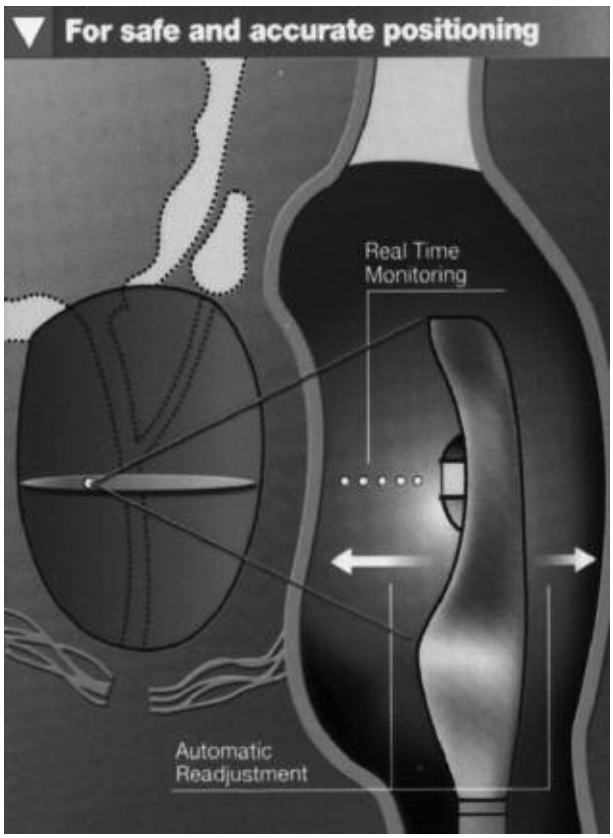

Figure 2. The probe correctly positioned in rectum

Figure 3. High intensity focused ultrasounds completely destroy prostatic tissue

plethora of elementary lesions until all prostate tissue is destroyed (Fig. 3);

2. Cavitation, due to the gas microbubble vibration dissolved in prostate tissue;
3. Heat growth, maximal in the middle of the treated volume and minimal in the external area of the treated volume. This difference allows to surely set the treatment outlines and save the prostate apex (and the striated sphincter) and vasculo-nervous bundles.

HIFU is a transrectal treatment; the patient lays on a bed with a special antidecubital pillow: the correct position is on the left side, thighs and legs flexed 90°on the trunk.

After introducing the rectal probe, anatomic limits must be echographically set (apex, bladder neck, rectal side, prostate capsule), in order to make the computer able to determine the correct subdivision in different prostate portions (generally four). Then, the procedure begins, and the probe (equipped with the trasducer) gives out a beam of high-focused convergent ultrasounds. In the ultrasound converging point (focal point), the ultrasound beam absorption generates an immediate growth of temperature (85-100°C), destroying prostate cells in the circumscribed area. Adequately translating the focal point with a robotic and automatic device, the successive ultrasound emissions may destroy all prostate cells.

Results

Twenty-five patients were considered. Mean age was 71.6 years (range 56-78). The initial PSA average was 9,7 ng/mL (range 0.78-54.9).

All patients were divided into three different groups according to the cancer progression risk: low risk group (T1-T2a, Gs ≤6, PSA ≤10 ng/mL) (17 pa-

tients), intermediate risk group (T2b, Gs = 7, PSA 11-20 ng/mL) (6 patients), high risk group (T2c, Gs ≥8, PSA ≥20 ng/mL) (2 patients).

Cancer clinical stadiation was T1 in 19 patients, T2 in 5 patients and T3 in 1 patient. Histological Gleason score was 3 in 2 patients, 4 in 2 patients, 5 in 1 patient, 6 in 14 patients, 7 in 5 pateints, and 8 in 1 patient. One patient belonging to the Intermediate Risk Group underwent treatment for relapse after radiotherapy* (Table 1).

In 10 patients (5 low risk, 4 intermediate risk, 1 high risk) a neoadjuvant hormonal therapy (bicalutamide) was administered.

Weight average of treated prostate tissue was 25,2 gr (range 5-38,4).

High-intensity focused ultrasound treatment had a mean duration of 90,5 minutes (range 50-127).

The number of lesions caused by the treatment was 399 (235-574); no intraoperative complication occurred.

The mean hospital stay was 2,1 days (range 1-5).

Seven patients underwent TUR-P+HIFU in the same session. At the end of the procedure a suprapubic catheter and a bladder Foley catheter were placed.

With regards to the other 18 patients, who underwent TUR-P before HIFU-treatment, in 5 patients either suprapubic or transurethral catheter was placed and in 13 a transurethral catheter was placed only.

In the patients who underwent TUR-P+HIFU, the suprapubic catheter was removed after a mean of 10,4 days (range 1-45 days) and the bladder catheter was removed after 8,8 days (range 2-45). In the patients who underwent only HIFU-treatment, the mean time of indwelling catheter was 10 days (when only bladder catheter was placed). When both catheters were necessary, the bladder catheter was removed after 3,4 days (range 2-9) and the suprapubic catheter was removed after 9,2 days (range 1-14).

Pre-operative IPSS test score was 8,4 (range 2-23). Post-operative score presented positive results: in fact the score was 5,2 (range 1-14) after six months.

With regards to sexual potency, only 3 patients were potent at IIEF-5 test before the treatment (score 11,25): unfortunately, they were impotent after the treatment (score 2,75).

Pre-operative Quality of Life (QoL) index average was 2,2 (0-4), while six months later post-operative QoL index was 1,7 (range 0-4).

With regards to our preliminary follow-up results, we noticed the following PSA values (Table 2).

Nineteen patients underwent transrectal prostatic mapping (generally 4-6 bioptic samples) 6 months after the treatment. In 3 patients (1 low risk, 1 intemediate risk and 1 high risk) an area of adenocarcinoma was found. At the moment of the biopsy, in the low risk group, PSA was 0,4 ng/mL; in the intermediate risk group, it was 1,48 ng/mL; in the high risk group it was 10,1 ng/mL.

Histopathologic interpretation was not clear because of the wide fibrotic degeneration of the prostatic tissue. In fact, an eosinophil necrotic tissue, with coagulative necrosis, rich in *corpora amilacea*, with the presence of granulation tissue and haemosiderinic macrophages was often found (Fig. 4).

During six months of follow-up after the treatment, we noticed the following less important complications: urinary tract infections in 3 patients, treated with antibiotic therapy; transitory dysuria in 3 patients; perineal pain in 1 patient, resolved a few days after the procedure; acute retention of urine by clot in 2 patients. They were treated with bladder catheterism for two days: after catheter removal, dysuria continued for ten days; 1 patient referred left leg pain, due to intra-operative decubitus; 3 patients referred urgency: one of them presented a previous diagnosis of urge incontinence due to detrusorial overcontractility and was treated with anticolinergic drugs; one patient had

Table 1. Groups of patients according to the progression risk

Risk	Patients	Age (mean value)	Basal PSA
Low	17	70.6	4.8
Medium	6*	70.5	10.4
High	2	75.5	34.7

Table 2. PSA values during the follow-up

Risk	PSA I	PSA III	PSA VI
Low	0.5	0.49	0.62
Medium	0.2	0.32	0.52
High	5.55	7	1,32

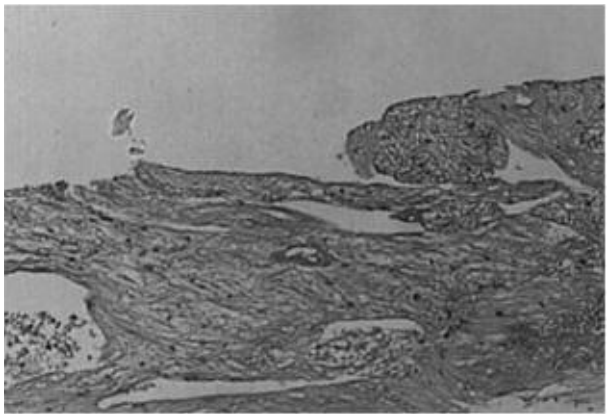

Figure 4. Prostatic tissue after the treatment. See the fibrotic degeneration, coagulative necrosis, granulation tissue and *corpora amilacea*

a haemorroidal crisis and one referred painful tenesmus and diarrhea for 3 weeks: it was caused by a pseudo-actinic rectosigmoiditis, therefore treated with mesalazine. Three patients referred transitory haematuria, without a significant haemocrome alteration. Two weeks after the treatment, two patients discharged necrotic eschars, without dysuria or pain.

We observed only one important complication: a rectovesical fistula. It was found 15 days after catheter removal: the patient reported previous major surgery, which consisted in hemycistectomy for confined bladder cancer and subsequently TUR-P for BPH. The rectovesical fistula was diagnosed by urethrocystography. Although it was a low-flow fistula, it was not completely healed after two months of catheterism. The patient is now catheterized and is waiting for a therapeutic decision (Table 3).

All patients are now continent, including the three patients with urgency in the first two months after the treatment.

Table 3. Treatment complications and their therapy

Complications	HIFU	Therapy
LUTS	12%	Antibiotic therapy
Urge-incontinence	12%	Anticolinergic therapy
Stress-incontinence	0%	
Urethral stenosis	0%	
Perineal Pain	20%	
Recto-vesical fistula	1 patient (4%)	catheterism
Acute retention of urine	8%	

Six months after the treatment, prostatic volume (measured by transrectal ultrasonography in course of prostate bioptic mapping) was in average 12,7 cc. (range 6-23): it was statistically reduced in comparison with the initial volume ($p > 0,001$).

Unlike radiotherapy, HIFU is a repeatable procedure in selected patients. Nevertheless, no patient needed to undergo a second treatment.

During the procedure, we did not focus on saving the vasculo-nervous bundle in our patients, because of the their elderly age: this is the reason why the sexual consequences of the procedure have been considered less important.

50% of the patients referred an improvement in the quality of life six months after the treatment in comparison with the quality of life six months before the treatment; 20% referred a worsening and 30% referred no change. These percentages are not statistically significant.

Four patients (two belonging to the high-risk group) underwent hormone-deprivation therapy because they presented three consecutive PSA growths according to ASTRO guidelines. Three of these patients also presented a positive biopsy. The fourth (high risk) did not accepted to undergo prostatic biopsy. One of the mentioned patients could not bear pharmacologic therapy, and thus successfully underwent radiotherapic treatment,.

Finally, we confirmed that HIFU has been generally successful in 84% of treated patients (only 4 biochemical relapses in 25 patients). The success rate was represented as follows: 94,2 % in the low risk group, 83,4% in the intermediate risk group and 0% in the high risk group.

Discussion

The efficacy of the HIFU procedure is demonstrated according to two main parameters: PSA stability and prostate bioptic mapping. According to ASTRO guidelines, the relapse is diagnosed by means of three consecutive PSA growths.

Gelet et al. in a review of 227 patients with confined prostate cancer noticed that the nadir PSA at six months was <0,5 ng/ml in 84%, between 0,5 and 1

ng/ml in 8%, and >1 ng/ml in 8% of patients. The disease-free survival rate (DFSR) at 5 years, judged from combined pathologic and biochemical results, was 66% for the whole population. The use of combined criteria (biopsy and PSA stability) is certainly the best adapted method for evaluating the efficacy of HIFU treatment. No significant difference in the DFSR was observed with reference to previous hormonal deprivation: hormonal deprivation was able to reduce the size of the gland, but no synergistic effect with the HIFU treatment was observed (6).

Blana et al. recently reported a 5 year DFSR of 71% in a similar population. In this study, 93% of the patients had a negative control biopsy and the median nadir PSA was 0,07 ng/ml (7).

In order to describe the safety and effectiveness of HIFU, Thuroff et al. reported a phase 3 prospective european multicentric clinical trial of 402 patients with a mean follow-up duration of 407 days. The negative biopsy rate observed was 87,2% (with 92,1% in low-risk); nadir PSA results correlated with prostate size and clinical procedure (8). In order to reduce post-treatment retention Thuroff combined a transurethral resection (TURP) immediately before the HIFU treatment under the same spinal anesthesia with a significant reduction of catheter time, and less urinary tract infections and retention (9-10-11). Following this multicenter experience, HIFU treatments may be performed as a minimally invasive option, with low related morbility and simple post-treatment management. The day after the HIFU session the patient may be discharged with a catheter or may be discharged a few days later without a catheter, according to the country and cultural context.

Based on these results we should consider patients who are not candidated for surgery because of their age or comorbidities, patients who are poor candidates for surgery because of local conditions or are at high risk for positive margin, and patients refusing surgery as good candidated for HIFU-treatment.

Conclusion

Transrectal HIFU represents a mini-invasive therapeutic option that makes the treatment of prostate cancer possible in 84 % of cases. Our results agree with the literature data and demonstrate that the success of the procedure depends on the correct indication for treatment and is strictly related to progression risk parameters.

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