

High-Intensity Focused Ultrasound (HIFU) For the Prostate Cancer: 5-year Experience

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Abstract HIFU shows a successful treatment for localized prostate cancer. Here we explored the effectiveness of the HIFU treatment for the prostate cancer, hormone-resistant prostate cancer and failure after external beam radiotherapy and radical prostatectomy. 795 patients were treated in our centre in 2007 – 2012: Kaplan-Meier analyses of the total group indicated that the risk of progression was 23% after 5 years of follow-up. Our experience shows that HIFU ablation is safe, minimally invasive, effective treatment with moderate side effects for the PC, hormone-resistant prostate cancer, HIFU also may be used as a salvage therapy.

Keywords HIFU, High Intensity Focused Ultrasound, Prostate Cancer

1. Introduction

Prostate cancer (PC) in developed countries is the most common malignancy among men and the second leading cause of cancer death after lung cancer[1]. In 2010, PC took the third place in the structure of cancer among male population of Russia (11.0%) - showed 26,268 new cases of the disease[2]. Over the last 10 years the increase was 155,3%. 10,251 patients died from prostate cancer in 2010 (fourth place on the men's deaths from cancer). Radical prostatectomy (RPE) and external beam radiation therapy (EBRT) are the standard treatments for patients with localized prostate cancer with a life expectancy of at least 10 years[3]. Patients presenting with localized prostate cancer are treated with curative intent by surgery or radiation, but up to 30% will relapse. Treatment then involves androgen-ablation therapies and all patients will eventually develop hormone-resistant prostate cancer (HRPC). In the past, systemic treatments for HRPC, such as second line hormone therapy, chemotherapy, mitoxantrone and prednisone, offered palliative benefit, but no survival advantage[4]. Newer treatments with docetaxel and prednisone have shown to offer both palliative and survival benefits[5, 6].

During the last decade new minimally invasive therapeutic modalities for prostate cancer have developed, such as brachytherapy, HIFU and cryotherapy. HIFU is an alternative choice in localized and low or intermediate-risk prostate cancer treatment[7].

Rising PSA in nonmetastatic prostate cancer indicates

failure of initial local therapy and the onset of early HRPC cancer prior to documented clinical metastases. The ideal salvage therapy for these patients is not clear and includes salvage local therapies and systemic approaches, of which the mainstay is hormonal therapy. Treatment needs to be individualized, based upon the patient's risk of progression, the likelihood of success and the risks involved with the therapy. Therefore attention of scientists is focused on the developed and implemented into clinical practice new effective, minimally invasive treatments for prostate cancer, HRPC and failure after EBRT and RPE[6]. However, due to the fact that studies analysing the effectiveness of HIFU-therapy for prostate cancer HRPC and failure after EBRT and RPE with a cohort of sufficient size and statistical power is few, the real work done. The main aim of this study is to evaluate the results of HIFU treatment of PC with low and high risk progression, and local recurrence after EBRT and RPE.

2. Main principles of HIFU

The first therapeutic trial of high intensity ultrasound beams was carried out in 1942[8]. The Fry brothers were credited with the first application of HIFU for neurologic disorders in humans[9]. High-energy ultrasound, parabolic focused on tissue leads to mechanical alteration of the cells and causes changes in biological structures (Figure 1). During application of focused ultrasound three different physical mechanisms can be observed: mechanical, thermal and cavitation effects[10].

Mechanical effects are induced by sudden pressure increase within the tissue by the HIFU beam being highly energetic.

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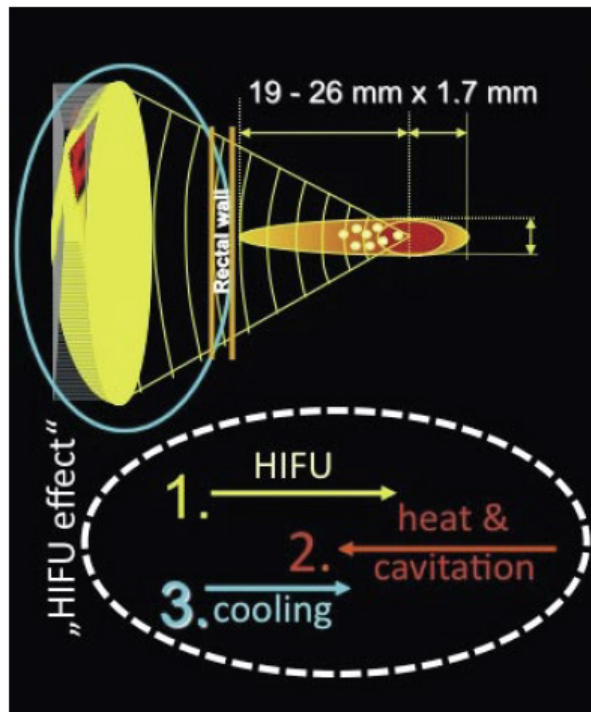


Figure 1. Physical principle of focused energy application

This energy input into the tissue induces formation of cavitation bubbles within the tissue. This mechanical cavitation effect damages cell membranes. A thermal effect is caused by the absorption of ultrasonic energy within the tissue. The temperature increase in tissues depends on the absorption coefficient of the tissue, and the size, shape and temperature sensitivity of the heated area. Biological changes caused by the heating depend on the temperature level and duration of exposure. A “thermal dose”, which exceeds a certain threshold, causes tissue coagulation and leads to irreversible tissue damage[11]. High intensive focused ultrasound generates a very high intensity in the focal area, causes high temperatures within a few seconds (up to 85° C) and destroys the tissue in a circumscribed area while surrounding areas remain unharmed. The defined small tissue volume which is destroyed by one single ultrasonic beam is a “primary” lesion. In order to coagulate larger areas, multiple lesions have to be added in a certain algorithm. This can be achieved by mechanically moving the energy source or electronically with a “phased array”[12-16].

HIFU’s most important parameters are: 1) the Ultrasound frequency (MHz), 2) the acoustic intensity (Watts), 3) the duration of application (shot-time), 4) the intervals of the pulses (delay-time), 5) the lateral distance between elementary lesions as well as 6) the longitudinal displacement of the energy source when applying multiple lesions and 7) the penetration depth (focal point) dependent on the applicator design.

These multiple technical parameters are essential in the assembly of a HIFU system for specific tissue and a dedicated application. The most difficult technical decisions concern the selection and design of the piezoelectric energy

applicator, the parameters of ultrasound treatment (MHz, Watts), the application algorithm (impulse-delay relation), the imaging system, the intraoperative target and safety features, target localization during treatment (TRUS or MRI) and controls.

The therapeutic ultrasonic energy transducer is characterized mainly by the operating frequency, and the geometric and physical design.

Piezoelectric systems can be operated with sufficient energy density, reproducibility and long-term stability in accordance with the requirements of the therapy which allow the production of geometric shapes in order to adapt them to the different anatomical needs[13]. Current standard urological applications use HIFU transducers with a fixed but adjustable focal point to be moved mechanically (Figure 2A, 2B).

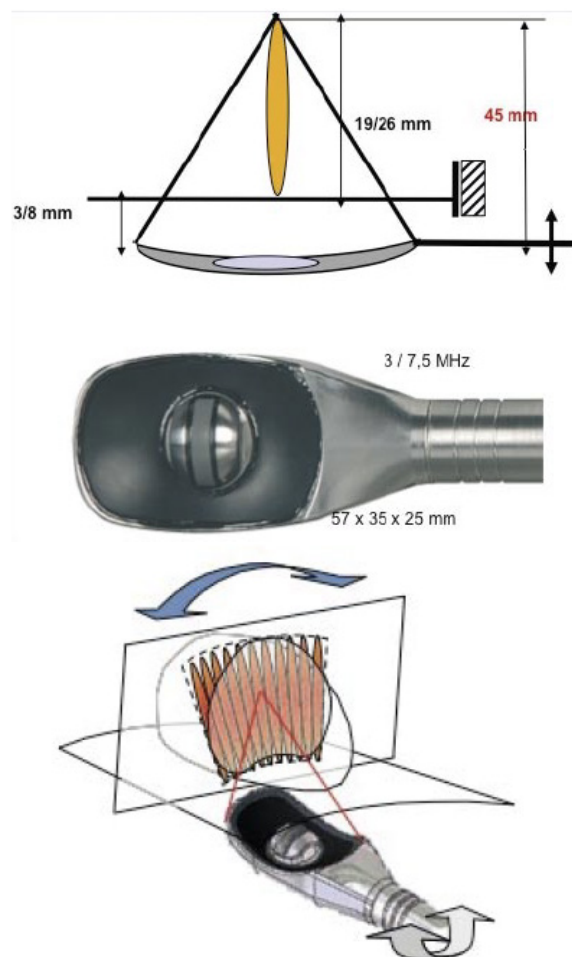


Figure 2. Focal point adjustment: A) Penetration depth (19-26 mm); B) Latero-longitudinally (1.7 mm steps)

To find the ultrasound parameters that are required for the treatment of prostatic tissue, in vitro and in vivo experiments have been performed, as well as computer simulations[17, 18]. MRI is one technique to assess the effectiveness of HIFU treatment and the only one to perform real-time temperature measurements. MRI is used in extracorporeal HIFU treatments for localization and monitoring effectiveness[19, 20] and allows for the measurement of

temperature changes during HIFU treatment[19]. HIFU-induced lesions are temporarily seen as hyper dense areas in diagnostic ultrasound[21]. However, the real extent of a primary lesion cannot be defined precisely because effects such as HIFU reflection (prostatic capsule, calcifications, catheters) absorption (untreated or pretreated tissue) and cooling (blood vessels, intraprostatic TUR cavity liquid) are individually different. Further characterization techniques based on ultrasound, contrast-enhanced Doppler[22] or different techniques to the acoustic behavior of tissues have been proposed to determine the extent of HIFU-induced lesions[23]. During a 15-year clinical experience with HIFU in prostate cancer, it has been proven that transrectal ultrasound is safe for reproducible application even without “real time” temperature measurement. A “real time” technology compensating the above mentioned individual tissue effects would be favorable and would optimize tissue ablation efficacy.

During the last decades transrectal HIFU for prostate cancer has found its way into routine clinical practice with approximately over 30,000 patients having been treated world wide. Efficacy and side effects of Ablatherm® (EDAP TMS SA, Vaulx-en-Velin, France) (Figure 3) in prostate cancer have been studied as well in a European multicenter study as in other prospective studies and described in detail[24,25]. The authors reported separately about their experiences in well-defined patient groups and established - on the basis of these results - standardized procedures and protocols for patient management. For device there is no FDA approval until now, because of ongoing prospective HIFU trials in US.



Figure 3. HIFU devices: Ablatherm®

In the beginning the only indication for HIFU were patients with localized prostate cancer who were not candidates for surgery due to their age, general health status, co-morbidity or patients who decided against radical prostatectomy.

However, the indications have been expanded based on clinical experience to: partial and focal therapy in unilateral low volume, low Gleason tumors, to incidental prostate cancer after TUR, as salvage therapy in recurrent prostate

cancer after radical prostatectomy, radiotherapy, or hormone ablation, for locally advanced prostate cancer as adjuvant local tumor debulking therapy, for non metastatic as well as metastatic stages and for hormonal resistant prostate cancer (HRPCa). It is well accepted that – besides with TURP – the gland can also be downsized by 30% within 3 months of androgen deprivation therapy (ADT). Still remaining contraindications for HIFU device are a missing or a small rectum and a damaged rectal wall, caused by previous prostatic/rectal therapies.

Use of TURP prior to HIFU allows the instant removal of any reflecting/deviating calcifications, abscesses, intravesical middle lobes and large (> 40 ml) adenomas. The generation of a cavity and its subsequent compression by the rectal balloon increases the accessibility of the HIFU waves to the remaining gland, fixes the residual prostate behind the symphysis and avoids movement artefacts. The beneficial effect in regard to higher effectiveness and lower side effects could be proven in different studies. Furthermore, it expanded the indication range for HIFU to the extent that a larger gland (> 40 ml) is no longer regarded as a contraindication.

3. Materials and Methods

Seven hundred ninety five patients with PC underwent HIFU in the period between September 2007 and August 2012. Every patient was available for oncological follow-up. Inclusion criteria were: patients with prostate localized and locally advanced PC, patients after EBRT or RPE failure. Exclusion criteria were: anal stenosis, metastatic PC. The oncology follow-up consisted of PSA evaluation, MRI and transrectal biopsy in the case of rising PSA. 139 patients were hormone-resistance (median time before hormone-resistance 25 months), 297 – received neoadjuvant hormone therapy 6 months, 320 – no treatment before HIFU, 39 – after the EBRT and RPE failure. 706 patients underwent trans-urethral resection of prostate (TURP) and HIFU-procedure; 89 underwent only HIFU ablation (prostate volume <40cc). All patients underwent spinal anaesthesia. We used the Ablatherm® device (EDAP, Lyon, France).

4. Results

In this paper, we analyse our 5 year experience with HIFU treatment of 795 patients with PC. The patients were divided into three groups according to the cancer progression risk: low risk group - 465 patients, Gleason ≤ 7 , stage T1-2N0M0, age 69 (60-89) years PSA before treatment 40,0 (5,8-92,9) ng/ml, mean prostate volume - 39,3 (28-92) cc; high risk progression group – 291 patients, Gleason ≤ 9 , stage T2-3N0M0, age 72 (52-83) years, PSA before treatment 30,3 (20,1-60) ng/ml, mean prostate volume - 41,2 (25-198) cc, the third group - patients after EBRT and RPE failure – 39 patients.

Cancer clinical staging in the whole group was T1 in 149 patients, T2 in 321 patients and T3 in 325 patients. Histological Gleason score was 2 in 42 patients, 3 in 87 patients, 4 in 113 patients, 5 in 136 patient, 6 in 189 patients, 7 in 158 patients, and 8 in 62 patients, 9 in 8 patients.

The average volume of treated prostate tissue was 30 cc (range 5-38.4). High-intensity focused ultrasound treatment had a mean duration of 120 minutes (range 60-245).

The average hospital stay was 7 days. 251 patients underwent TURP+HIFU in the same session. 455 patients with prostate volume larger than 60 cc. first underwent TURP and then HIFU after one month. 89 patients with small prostate volume underwent only HIFU. At the end of the procedure a Foley catheter was placed.

Table 1. Groups of patients

| Group description | Number of patients | Age (mean value) | Prostate volume, cc | PSA before treatment, ng/mL |
|---|--------------------|------------------|---------------------|-----------------------------|
| Gleason score ≤ 7 , stage T1-2N0M0 | 465 | 69 | 39,3 (28-92) | 40,0 (5,8-92,9) |
| Gleason score ≤ 9 , stage T2-3N0M0 | 291 | 72 | 41,2 (25-198) | 30,3 (20,1-60) |
| Failure after EBRT and RPE | 39 | 69,5 | 21,3 (5,5-64,8) | 21,0 (5,2-76) |

In the patients who underwent TURP+HIFU, the catheter was removed after a mean of 7 (3-21) days. In the patients who underwent HIFU, the catheter was removed after a mean of 14 (10-28) days. PSA values after treatment are presented in Table 2.

Table 2. PSA values during the follow-up

| Group description | PSA 12 months after HIFU treatment, ng/mL | PSA 48 months after HIFU treatment, ng/mL | Recurrence 5 years of follow-up, % |
|---|---|---|------------------------------------|
| Gleason score ≤ 7 , stage T1-2N0M0 | 0,04 (0-2,24) | 0,5 (0,0-3,6) | 4,5 |
| Gleason score ≤ 9 , stage T2-3N0M0 | 0,05 (0-48,4) | 3,2 (0,0-21,3) | 25 |
| Failure after EBRT and RPE | 0,05 (0-3,2) | 1,7 (0,0-9,8) | 19,6 |

At 12 month follow-up in the low risk group, the PSA median was 0,04 (0-2,24) ng/mL; in the high risk group it was 0,05 (0-48,4) ng/mL, with failure after EBRT and prostatectomy - 0,5 (0-3,2) ng/mL. At 48 months follow-up in the low risk group, PSA median was 0,5 (0,0-3,6) ng/mL; in the high risk group it was 3,2 (0-21,3) ng/mL, with failure after EBRT and RPE - 1,7 (0-9,8) ng/mL.

During 12 months of follow-up after the treatment, we noticed the following complications: incontinence I - 17,5%, incontinence II - 7,7%, stricture - 18,2%, fistula - 0,3%. The

incontinence was due to the TURP. Patients who had only HIFU did not face such problems. These complications resolved during three-six months after treatment. (Table 3).

Table 3. Complications values after treatment

| Group description | Incont. rate I, % | Incont. rate II, % | Stricture, % | Fistula, % |
|---|-------------------|--------------------|--------------|------------|
| Gleason score ≤ 7 , stage T1-2N0M0 | 4,2 | 5,0 | 8,0 | 0 |
| Gleason score ≤ 9 , stage T2-3N0M0 | 9,0 | 6,7 | 8,7 | 0 |
| Failure after EBRT and RPE | 11,2 | 5,3 | 11,0 | 0,3 |

Six months after the treatment prostatic volume (measured by transrectal ultrasonography) was in average 9,3 cc (range 2-18 cc). It was statistically reduced in comparison with the initial volume ($p < 0,01$).

HIFU is a repeatable procedure, 7 patients needed to undergo a second treatment due to a local recurrence.

70% of the patients reported an improvement in the quality of life six months after treatment in comparison with their quality of life six months before the treatment and 30% reported no change. These percentages are statistically significant.

Finally, we confirmed that HIFU has been generally successful in 77,0% of treated patients (182 biochemical relapses in 795 patients). The success rate was represented as follows: 95,5 % in the low risk group, 75% in the high risk group, 80,4% in the group with failure after EBRT and RPE (Figure 4).

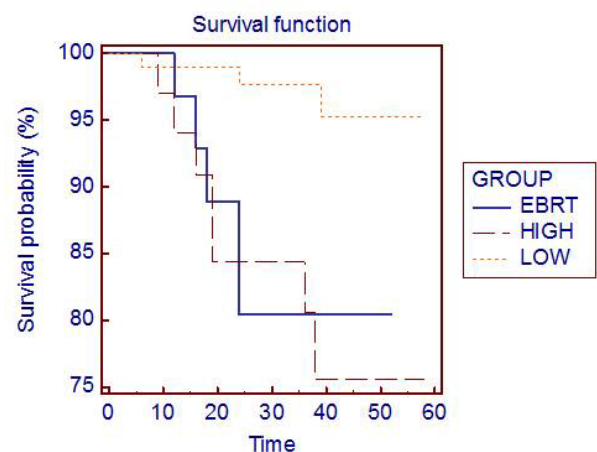


Figure 4. Kaplan–Meier disease-free survival (DFS) curves according to risk group after HIFU

5. Discussion

Treatment for PC may include: active surveillance, interstitial prostate brachytherapy, EBRT and RPE. There is still ongoing debate on the efficiency of focal treatment, but at the same time different focal options emerge. Brachytherapy and radiation external beam therapy are the

most used as minimally invasive techniques, not only for the therapy of localized PC but also for the palliation of high-grade tumours. Some medical associations recommend HIFU for treatment of PC, but its accuracy is still not clear. Prostate cancer is dependent on the presence of androgens. Patients that are not suitable for radical surgery and with metastatic disease are typically first treated with hormonal ablation: strategies include testicular androgen deprivation by either bilateral orchidectomy or administration of a luteinizing hormone releasing hormone (LHRH) agonist, and treatment with anti-androgens such as flutamide to compete with testosterone for the androgen receptor binding site. Unfortunately, resistance to androgen suppression invariably develops: cells accumulate further genetic abnormalities and proliferate despite low testosterone levels at a median interval of 12-16 months after initiation of endocrine treatment. Subsequent lines of hormonal therapy act through related pathways and include the use of the synthetic oestrogen, the reduction of adrenal androgen production by administration of glucocorticoids. There are limited treatment options once recurrent prostate cancer develops androgen independence. Palliative chemotherapy with docetaxel has been shown to improve survival and is commonly instituted for metastatic disease following failure of maximal androgen blockade but is not suitable for all patients, particularly those with poor performance status. Those patients with no metastatic disease may receive local salvage treatment such as brachytherapy or HIFU.

In Russia, localized prostate cancer, when possible to conduct RPE, detected only 35% of patients[1]. In this case, among patients with stage I-II after radical prostatectomy or radiation therapy in 25-50% of cases prostate cancer recurrent is developed[32]. Therefore, patients are not suitable for surgery or radiation therapy, and with recurrent prostate cancer assigned to hormone therapy: bilateral orchidectomy or maximum androgen blockade. It is noted that the rate of relapse-free and overall survival of patients with prostate cancer have remained unchanged for several decades (12-24 and 24-36 months respectively)[33]. The second and the third lines of hormone therapy, chemotherapy are effective only in 15-20% of cases and do not lead to a significant increase life expectancy of patients, while possessing significant side effects[4, 27, 28, 30].

It should be noted that at present tactics and strategies of prostate cancer treatment has not been developed in accordance with the implemented in the practice minimally invasive new technologies, there are no clinically based recommendations. Publications of focal prostate cancer therapy are few, they are based on small clinical material, have a short period of observation, and do not define the role and the place of HIFU-therapy in the treatment of prostate cancer. To date, long-term[31] and the medium-term results published[32, 33] about HIFU-therapy of prostate cancer. According to a European multicenter study that included 559 patients with prostate cancer in low-and moderate-risk, Thuroff *et al.*[30] reported a negative biopsy result after the HIFU-therapy in 87.2%. Blana *et al.* evaluated the results of

HIFU in 146 patients with a mean follow-up of 22.5 months median preoperative PSA was 7.6 ng / mL, while the median PSA level at 3 months after therapy was 0.07 ng / mL[29].

We analysed the results of HIFU treatment of 795 patients with prostate cancer. The estimated 5-year disease-free survival Kaplan-Meier had 95.5% efficiency of HIFU therapy in the group with low risk of progression and 75% in the group with high risk of progression. Treatment results showed that, in general HIFU-therapy was successful in 90.9% of patients. At the same time there were moderate short-term side effects. However, it was obvious that a more long-term monitoring of the effectiveness of HIFU therapy in patients with prostate cancer were necessary.

6. Conclusions

The most recent publications concluded that the use of HIFU is an effective standard treatment for prostate cancer with a broad range of indications in all tumour stages: in the primary treatment of local prostate cancer, in patients with local recurrence after failure of any primary treatment, and as an adjuvant therapy in the palliation of systemic prostate cancer. Our experience shows that HIFU is safe, minimally invasive, effective in treatment for localized and locally advanced prostate cancer, after EBRT and prostatectomy.

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