TRANRECTAL HIGH-INTENSITY FOCUSED ULTRASOUND FOR LOCAL TREATMENT OF PROSTATE CANCER: CURRENT ROLE

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Summary.- Attractivity of robotic high intensity focused ultrasound (HIFU) is based largely on the non-invasive, extremely precise nature of this high-tech robotic therapy as well as its clean, radiation free, surgical, but nevertheless, bloodless character. Today, in urological oncology, HIFU is used clinically as a therapeutic tool for the treatment of prostate cancer. Experimentally it is investigated for therapeutic use in kidney and breast cancer.

Transrectal treatment of localized prostate cancer with HIFU has been under investigation since the 1990s and it is meanwhile an actively used therapy for the disease in many urological departments worldwide. Since 2000 HIFU is mostly used in combination with transurethral resection of the prostate in order to reduce prostate gland size, to facilitate effective tissue destruction and to avoid side effects. Palliative and salvage indications as well as focal therapy of prostate cancer are under investigation to extend the spectrum of HIFU indications for non-invasive prostate cancer therapy.

Keywords: High Intensity Focused Ultrasound (HIFU). PCA Therapy. Non-invasive. Focal Therapy. Hormone resistant PCA.

Resumen.- OBJETIVO: El atractivo del HIFU (High intensity focused ultrasound) robotizado se basa ampliamente en la naturaleza no invasiva, extremadamente precisa de este tratamiento robótico de alta tecnología, así como su carácter limpio, sin radiación, quirúrgico y sin embargo sin sangrado. Hoy, en urología oncológica, el HIFU se utiliza clínicamente como una herramienta terapéutica para el tratamiento del cáncer de próstata. Su uso terapéutico en cáncer de riñón y mama se está investigando a nivel experimental.

El tratamiento del cáncer de próstata localizado con HIFU transrectal ha sido investigado desde los años 90, y mientras tanto es una terapia utilizada activamente contra la enfermedad en muchos departamentos de urología en todo el mundo. Desde el 2000 el HIFU se utiliza principalmente en combinación con resección transuretral de próstata para reducir el tamaño de la glándula prostática, facilitar la destrucción efectiva del
INTRODUCTION

Since the 1930s it has been known that tissue can be destroyed from a distance by high intensity focused ultrasound (HIFU). However, clinical implementation of this technology was delayed due to the lack of a reliable control implementation.

Today computers special software, transrectal ultrasound devices and MRI allow real-time therapy control and monitoring of HIFU treatment. Therefore, treatment with HIFU can now be extended to different surgical areas as an extracorporeal method which allows the non-invasive coagulative destruction without an open surgical procedure. Increased experience and literature on HIFU has led to increased acceptance and validation of transrectal HIFU treatment of prostate cancer worldwide. Although mid-term results have been published (1,2) 10 year results have not been published yet.

Physical principle of HIFU

The first use of HIFU for local tissue destruction was reported in 1944 by Lynn and Putnam (3). 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.

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

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 (4). 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 (Figure 2). This can be achieved by mechanically moving the energy source or electronically with a “phased array” (4-9).

Technology

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...
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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 (Figure 3).

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 (7). Current standard urological applications use HIFU transducers with a fixed but adjustable focal point to be moved mechanically (Figure 4A, 4B).

FIGURE 2. A) Multiple lesion application mode and B) Volume coagulation (transducer movement algorithm).

FIGURE 3. Different transrectal HIFU transducers for Sonablate® and Ablatherm®.
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 (10-12). 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 (13,14) and allows for the measurement of temperature changes during HIFU treatment (13). A few studies have used magnetic resonance elastography (MRE) to investigate the effects of temperature-induced tissue ablation by measuring the mechanical changes of the lesion (15,16). It remains unclear whether elastography changes can be correlated to long term tissue destruction and whether they reflect complete tissue coagulation at a cellular level. HIFU-induced lesions are temporarily seen as hyperdense areas in diagnostic ultrasound (17). 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 (18) or different techniques to the acoustic behavior of tissues have been proposed to determine the extent of HIFU-induced lesions (19). During a 14-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 (Figure 5). A “real time” technology compensating the above mentioned individual tissue effects would be favorable and optimize tissue ablation efficacy.

Experimental background

Destruction of tissue with HIFU has been studied in various experimental tumor models. To study the HIFU effect in vivo, experiments were performed on mouse glioma (20), hamster medulloblastoma (21) and on the rat Morris hepatoma (22,23). DUNNING R3327, as well as AT2 and AT6 carcinomas with high metastatic potential (24,25), implanted in rats, were studied as models of prostate cancer.
In vitro (26,27) ex vivo (26,28) and in vivo (14,27,29) experiments were also performed to study the treatment possibilities with HIFU for kidney tumors. These animal studies provided evidence that cancerous tissue can be destroyed with HIFU without inducing metastasis (25). Transrectal HIFU for treatment of the prostate was confirmed in experimental canine models (30,31).

Transrectal HIFU Devices

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 worldwide. Initial attempts to treat BPH with HIFU proved less successful (32). Meanwhile two devices have been designed and are routinely manufactured for the treatment of prostate cancer. Initial results are available from Sonablate® (Focus Surgery Inc., Indianapolis, IN in 2002) (6).

Efficacy and side effects of Ablatherm® (EDAP TMS SA, Vaulx-en-Velin, France) (Figure 6) in prostate cancer have been studied as well in a European multicenter study as in other prospective studies and described in detail (33,34). 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 both devices there is no FDA approval until now, because of ongoing prospective HIFU trials in US.

Indications and contraindications for HIFU (Ablatherm®) therapy

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 both HIFU devices are a missing or small rectum and a damaged rectal wall caused by previous prostatic/rectal therapies.

**TUR before HIFU**

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 (Figure 7), 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 (35,36) to the extent that a larger gland (> 40 ml) is no longer regarded as a contraindication.
Effect of HIFU on Prostate Tissue

Despite the fact, that biopic controls have a low significance in relation to their random character, they can prove the homogenous intraprostatic ablative effect of the HIFU procedure by the replacement of prostatic with fibrotic tissue. In a clinical study, in which a partial HIFU treatment was performed 1-2 weeks before radical prostatectomy, the efficacy of HIFU was histologically confirmed. The prostate was histologically analyzed after complete removal. HIFU had been applied to the sites where positive tissue biopsies had been found. The histological examination of the samples showed a sharp demarcation between the HIFU-treated and the untreated areas, while in the treated areas complete necrosis was found (37).

The extent of tissue damage caused by HIFU can be determined by gadolinium enhanced MRI. The treated area appears as a hypodense zone surrounded by a strong 3-8 mm peripheral rim. This corresponds to histo-pathological findings characterized by a core of coagulation necrosis surrounded by a peripheral zone of inflammation. The treatment induced MRI changes usually disappear within 3-5 months and the HIFU-induced contraction of the tissue results after about 6 months in small prostates of approximately 5cc (38).

Efficacy of HIFU in localized prostate cancer

The prediction of treatment outcome in patients treated with radical prostatectomy is among other features, based on pathological features such as tumor grade, stage, margin status. Due to the absence of histological specimens following HIFU, it is necessary to consider other predictors of treatment outcome. PSA nadir as a predictor of clinical failure following HIFU has been evaluated and shown to be a strong predictor of treatment failure (39). In a 6-month study involving 115 patients, failure rates following HIFU were 11% (four of 36), in patients with a PSA nadir of 0.0-0.2 ng/ml compared with 46% (17 of 37) in patients with a PSA nadir of 0.21-1 ng/ml and 48% (20 of 42) with a PSA nadir of >1.0 ng/ml. In addition, the PSA nadir was strongly associated with both preoperative PSA level and residual prostate volume. PSA nadir effects in patients with a longer follow-up have been reported by Ganzer et al (40). The median follow-up was 4.9 (3-8.6) years and patients were divided into three PSA nadir subgroups (≤0.2 ng/ml, 0.21-1 ng/ml and > 1 ng/ml). Treatment failure was defined according to ASTRO criteria. It was shown that the PSA nadir after HIFU correlated highly significantly with treatment failure and disease-free survival rate (DFSR). Treatment failure rates during follow-up were 4.5%, 30.4%, and 100%, respectively, for the three PSA nadir groups (P < 0.001). The actuarial disease-free survival rates at 5 years were 95%, 55%, and 0%, respectively, for the 3 groups (P < 0.001). These findings suggest that outcome is improved if a PSA nadir of ≤0.2 ng/ml is reached.

Data about efficacy and side effects are listed in Table 1 and 2. In a series of 120 patients with localized prostate cancer and PSA values of <10ng/ml, cancer free survival rates were examined. These patients were not suitable for radical prostatectomy and had a life expectancy of 10 years (2). The calculated cancer free 5-year survival rate for the average patient population was 76.9%, this was significantly increased to 85.4% in highly differentiated tumors (Gleason score 2-6) compared to 61.3% in low-differentiated tumors (Gleason score 7-10). There was no significant difference in survival rates calculated in terms of prostate volume or the number of positive biopsies. The nadir PSA is seen as the basic prognostic factor with a theoretical 5-year survival rate of 86% in patients with a nadir PSA <0.5 ng / ml. The European multicenter study reported short-term results of 402 patients with localized prostate cancer (T1-2/N0-x/M0) between 1995 and 1999 1 year after HIFU treatment (33). In total, 87.2% of control biopsies were negative. Stratified according to the prognostic risk in the group with low risk (Gleason <7), 92.1% were negative, in the medium risk group (Gleason 7) 86.4% and in the high risk group (Gleason > 7) 82.1% showed negative biopsies. The PSA nadir was found generally 3-4 months after HIFU treatment. PSA after treatment was significantly influenced by the prostate volume in relation to the completeness of the HIFU treatment. PSA remained stable after treatment during the mean follow-up of 407 days.

Blana et al. reported a study of 140 patients with localized prostate cancer (1). These patients had a baseline PSA value of ≤ 15 ng / ml and a Gleason score of ≤ 7. TRUS biopsies 6 months following HIFU treatment were negative in 93.4% of patients. The mean PSA nadir was 0.07 ng / ml and the PSA value remained during a mean observation period of 22 months at 0.16 ng / ml. In 77% and 69% there was no biochemical relapse after 5 or 7 years. Although a satisfactory “cure” rate in patients with low and medium risk disease has been observed with HIFU as monotherapy, combination therapy should be considered for patients with high risk disease.

In this study, no severe incontinence (grade II-III) could be found. Because of a urinary obstruction 12% of the patients needed a transurethral resection during the follow-up period. In 47.3% of patients,
potency could be maintained and there were no reports of significant changes in International Prostate Symptom Scores (IPSS). The 5-year survival rates of this study correspond to the large series of standard treatments of localized prostate cancer (41-47) (Table I).

### Side effects after HIFU

The most common observed side effects of HIFU for prostate cancer include prolonged voiding dysfunction and retention caused by edema, necrosis or bladder outlet obstruction. To reduce the time of

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### TABLE I. ROBOTIC HIGH-INTENSITY FOCUSED ULTRASOUND: EFFICACY SUMMARY.

<table>
<thead>
<tr>
<th>Study (year) [ref.]</th>
<th>n</th>
<th>Pretreatment PSA (ng/ml)</th>
<th>Gleason score</th>
<th>Stage</th>
<th>Median follow up (months)</th>
<th>Negative biopsy rate (%)</th>
<th>Biochemical survival</th>
<th>Retreatment rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaussy et al. (2001) [43]</td>
<td>184</td>
<td>12</td>
<td></td>
<td>T1–2 Nx</td>
<td>80</td>
<td>NR</td>
<td>26,1</td>
<td></td>
</tr>
<tr>
<td>Gelet et al. (2001) [44]</td>
<td>102</td>
<td>8.38 (mean)</td>
<td>54% 2–6</td>
<td>T1–2</td>
<td>19</td>
<td>75</td>
<td>66% at 5 years (ASTRO)</td>
<td>78.4</td>
</tr>
<tr>
<td>Poissonnier et al. (2003) [2]</td>
<td>120</td>
<td>5.67 (mean)</td>
<td>64% 2–6</td>
<td>T1–2</td>
<td>27</td>
<td>86</td>
<td>76.9% at 5 years (ASTRO)</td>
<td>1,4 Tx per patient</td>
</tr>
<tr>
<td>Thüroff et al. (2003) [37]</td>
<td>402</td>
<td>10.9 (mean)</td>
<td>13.2% 2–4</td>
<td>T1–2</td>
<td>13</td>
<td>87.2</td>
<td>NR</td>
<td>36.7</td>
</tr>
<tr>
<td>Blana et al. (2004) [45]</td>
<td>146</td>
<td>7.6 (mean)</td>
<td>5 ± 1.2</td>
<td>T1–2 N0M0</td>
<td>22</td>
<td>93.4</td>
<td>84% at 22 months (PSA &lt; 1.0)</td>
<td>18.7</td>
</tr>
<tr>
<td>Ficarra et al. (2006) [46]</td>
<td>30</td>
<td>18 (median)</td>
<td>17% 7; 33% 8; 30% T2b; 70% T3; 70% T3</td>
<td>6</td>
<td>77</td>
<td>90% at 1 year (PSA &gt; 0.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Poissonnier et al. (2007) [47]</td>
<td>227</td>
<td>7.0 (mean)</td>
<td>67% 2–6</td>
<td>T1–2</td>
<td>20.5</td>
<td>86</td>
<td>NR</td>
<td>42.7</td>
</tr>
<tr>
<td>Blana et al. (2008) [48]</td>
<td>140</td>
<td>7.0 (mean)</td>
<td>5.2 ± 1.4</td>
<td>T1–2 N0M0</td>
<td>76.8 (mean)</td>
<td>96.4</td>
<td>77% at 5 years (Phoenix)</td>
<td>29.3</td>
</tr>
<tr>
<td>Blana et al. (2008) [49]</td>
<td>163</td>
<td>5 (median)</td>
<td>7.9 ± 3.7</td>
<td>T1–2 N0M0</td>
<td>57.6 (mean)</td>
<td>92.7</td>
<td>75% at 5 years (Phoenix)</td>
<td>20.8</td>
</tr>
</tbody>
</table>

**Notes:**
- ASTRO: American Society for Therapeutic Radiology and Oncology;
- Nx: Lymph nodes not tested;
- PSA: Prostate-specific antigen;
- Tx: T grading unknown.
urinary diversion and the postoperative morbidity (sludging, obstruction, infection) studies were undertaken to observe the effect of a combination therapy (HIFU and TUR). In 30 patients with localized prostate cancer a one-stage (in the same anesthesia) combination therapy with TUR and HIFU was performed. The mean treatment duration was 2 h 48 min. The transurethral catheter time was 2 days and the mean hospitalization 3 days. After 6 months, control biopsies were negative in 80% of patients, and the median PSA was 0.9 ng / ml. The mean PIPSS (Post-treatment International Prostate Symptom Score) was 6.7, compared with a pre-treatment score of 7.5. Potency was preserved in 73% of patients who had reported no erectile dysfunction before treatment [35].

<table>
<thead>
<tr>
<th>Study (year) (ref.)</th>
<th>Number</th>
<th>INC (%)</th>
<th>ED (%)</th>
<th>FIS (%)</th>
<th>S&amp;S (%)</th>
<th>PR (%)</th>
<th>UTI (%)</th>
<th>CA (days)</th>
<th>Pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blana et al. (2004) [45]</td>
<td>146</td>
<td>5.8</td>
<td>57.2</td>
<td>0.7</td>
<td>11.7</td>
<td>NR</td>
<td>4.1</td>
<td>SP: 12.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Thüroff et al. (2003) [37]</td>
<td>402</td>
<td>GI 10.6; GII 2.5; GIII 1.5</td>
<td>13</td>
<td>1.2</td>
<td>3.6</td>
<td>8.6</td>
<td>13.8</td>
<td>F: 5; SP: 34</td>
<td>NR</td>
</tr>
<tr>
<td>Gelet et al. (2001) [44]</td>
<td>102</td>
<td>GI 8.8; GII 9.8; GIII 3.9</td>
<td>61</td>
<td>1</td>
<td>17</td>
<td>5</td>
<td>NR</td>
<td>9.1</td>
<td>2</td>
</tr>
<tr>
<td>Chaussy et al. (2003) no TURP [40]</td>
<td>96</td>
<td>GI 9.1; GII 4.6; GIII 1.7</td>
<td>40</td>
<td>NR</td>
<td>27.1</td>
<td>NR</td>
<td>47.9</td>
<td>SP: 45.1</td>
<td>NR</td>
</tr>
<tr>
<td>Chaussy et al. (2003) TURP [40]</td>
<td>175</td>
<td>GI 4.6; GII 2.3</td>
<td>31.8</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>11.4</td>
<td>SP: 13.7</td>
<td>NR</td>
</tr>
<tr>
<td>Ficarra et al. (2006) [46]</td>
<td>30</td>
<td>7</td>
<td>NR</td>
<td>0</td>
<td>10</td>
<td>13</td>
<td>16</td>
<td>SP: 12</td>
<td>NR</td>
</tr>
<tr>
<td>Lee et al. (2006) [50]</td>
<td>58</td>
<td>GI 16</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>3.4</td>
<td>NR</td>
<td>SP: 15</td>
<td>NR</td>
</tr>
<tr>
<td>Poissonnier et al. (2007) [47]</td>
<td>227</td>
<td>GI 9.0; GII 3.0; GIII 1.0</td>
<td>39</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Blana et al. (2008) Multi [48]</td>
<td>140</td>
<td>GI 5.0; GII 0.7</td>
<td>43.2</td>
<td>0</td>
<td>13.6</td>
<td>7.1</td>
<td>NR</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Blana et al. (2008) Single [49]</td>
<td>163</td>
<td>GI 6.1; GII 1.8</td>
<td>44.7</td>
<td>0</td>
<td>24.5</td>
<td>7.8</td>
<td>NR</td>
<td>3.7</td>
<td></td>
</tr>
</tbody>
</table>

CA requiring >1 pad/day; GII: Incontinence grade II, that is loss of urine under any exercise requiring >2 pads/day; INC: Incontinence; NR: Not reported; PR: Postoperative retention; SP: Suprapubic catheter; S&S: Stricture and stenosis; TURP: Transurethral resection of the prostate; UTI: Urinary tract infection.
The beneficial effect of a combination of TUR and HIFU was demonstrated in a series of 271 patients with prostate cancer and an initial PSA of <15 ng / ml. 96 of 271 patients received HIFU monotherapy, while 175 were treated with combination therapy. The mean resection weight was 15.7 g (2-110g), median 12.5 g. In 51.6% of the patients, carcinoma was found in the resection material. The mean follow-up time in the monotherapy group was 18.7 ± 12.1 months, and for the combination therapy group was 10.9 ± 6.2 months. The histological results in both groups were similar after treatment, with negative biopsies in 87.7% versus 81.6%. The mean follow-up time in the monotherapy group was 18.7 ± 12.1 months, and for the combination therapy group was 10.9 ± 6.2 months. The histological results in both groups were similar after treatment, with negative biopsies in 87.7% versus 81.6%. The median PSA Nadir was 0.0 ng / ml in both groups. The monotherapy group required a suprapubic catheter for 40 days, while in the combination group it was removed after 7 days. With this study, the benefits of a combination therapy could be demonstrated (36).

The rate of adverse events among patients with primary therapy is low (Table II): Grade I stress incontinence was observed in 4-6% of patients, Grade II in 0-2%, and secondary infravesical obstruction seen in 5-10%. Severe incontinence (Grade III) and urethra-rectal fistulae are rare (<1%). Preservation of erectile function is directly dependent on the position of the primary lesion in relation to the neuro-vascular bundle. Although sparing the contralateral side for neurovascular preservation can improve potency, this results in a higher re-treatment rate (49-52).

**Radical prostatectomy after HIFU**

Before introduction of the combination therapy (TUR + HIFU) we performed 7 radical prostatectomies after HIFU between 1996 and 2000. This was due to incomplete HIFU treatments of larger size prostates. Since the application of HIFU causes severe fibrotic adhesions between the rectum and Denovillier’s fascia radical prostatectomy after HIFU is surgically more demanding, however, in our experience not associated with higher morbidity compared to a standard prostatectomy.

**Salvage HIFU after Brachytherapy**

Very limited experience exists with HIFU following brachytherapy, but it appears that this approach is not associated with a significant increase in complications compared to primary HIFU. It is definitely advisable to monitor the position of the seeds precisely before HIFU (MR). There should no seeds be outside the prostate capsule, especially not between rectum and prostate. In these areas they would interfere with the direct entry path of the ultrasound.

**Salvage HIFU after radical Prostatectomy**

Therapeutic options for local recurrence following radical prostatectomy are limited. HIFU offers a treatment option when local recurrence can be identified through transrectal ultrasound and verified by biopsies. After treatment with HIFU, the treated areas showed negative biopsies in 77%. The PSA Nadir averaged 0.2 ng/ml and 66% of the patients achieved PSA Nadir values <0.5 ng/ml. During follow-up of 5 years, 91% of the patients showed no biochemical progress (53,54).

**Salvage HIFU after Radiation therapy**

HIFU treatments have been performed as salvage therapy following external radiotherapy failures. Gelet reported results of 71 patients (55). All patients were diagnosed with a biochemical recurrence and local disease confirmed by biopsies. In one third of patients androgen deprivation was employed either as a measure to auxiliary radiotherapy or early biochemical relapse, prior to HIFU treatment. After HIFU, 80% of treated patients showed negative biopsies during follow-up (median follow-up period of 14.8, 6-86 months). The median PSA nadir was 0.2 ng / ml. In patients with HIFU as salvage therapy after external radiotherapy a significantly higher rate of side effects is observed, compared with patients who undergo primary HIFU therapy. Nevertheless, there is a favourable risk-benefit ratio after HIFU treatment as compared to the alternatives (56).

**Adjuvant palliative PCA therapy in advanced PCA**

Preliminary results for the palliative treatment of advanced prostate cancer with HIFU show promising results in terms of reduction in local morbidity (rectal compression, infravesical obstruction, hydronephrosis, hematuria, pelvic pain-syndromes). Still unpublished data in several large patient groups (n > 70) in T3 and HRPCa cases with follow-up of 10 years show a post-HIFU PSA velocity of 0.19 ng/ml/ year in T3 disease (without additional hormone ablation). Local tumor ablation with HIFU also resulted in a PSA reduction of 80% in HRPCa cases. There was also evidence of a synergistic effect in hormone ablative therapies, with delays seen in the onset of hormone resistance (53,57).

**Immunological response**

Recent progress has been made in developing an effective immune strategy for treating prostate cancer with HIFU. Preliminary studies have shown promising results in terms of immune response and tumor regression. HIFU-induced immunological responses include the activation of immune cells, the release of cytokines, and the modification of the tumor microenvironment. These responses may contribute to the therapeutic efficacy of HIFU in prostate cancer treatment. Further research is needed to better understand the mechanisms underlying these responses and to optimize the use of HIFU as an immunomodulating therapy.
cancer. A number of immunotherapy regimens are being studied including immunomodulatory cytokines/effectors, peptide and cellular immunization, viral vaccines, dendritic cell vaccines, and antibody therapies. Immunomodulatory agents, such as granulocyte–macrophage colony-stimulating factor (GM-CSF), Flt3 ligand, and IL-2, have been used to stimulate the immune system to generate an antitumor response against prostate cancer.

Several recent studies have looked at the potential of HIFU to initiate an immune response. Wu et al. examined the effect of HIFU on systemic antitumor immunity, particularly T lymphocyte-mediated immunity in cancer patients (58).

The same group investigated whether the tumor antigens expressed on breast cancer cells may be preserved after HIFU treatment (59). Primary lesions in 23 patients with biopsy-proven breast cancer were treated with HIFU, then submitted to modified radical mastectomy. Breast cancer specimens were then stained for a variety of cellular molecules, including tumor antigens and heat-shock protein 70 (HSP-70). A number of tumor antigens were identified and these could provide a potential antigen source to stimulate antitumor immune response.

It has been suggested that endogenous signals from HIFU-damaged tumor cells may trigger the activation of dendritic cells and that this may play a critical role in a HIFU-elicited antitumor immune response (60).

Status of tumor-infiltrating lymphocytes (TILs) after HIFU ablation of human breast cancer has been investigated (61). Results show that TILs infiltrated along the margins of the ablated region in all HIFU-treated neoplasms, and the numbers of tumor-infiltrating CD3, CD4, CD8, CD4/CD8, B lymphocytes, and NK cells was increased significantly with HIFU treatment. The number of FasL(+) , granzyme (+)+, and perforin(+) TILs was significantly greater in the HIFU group than in the control group.

**Focal and partial therapy**

Future treatment options for prostate cancer, which are being considered and already studied include the development of a precise focal therapy (max. 25% treatment volume without TUR) as well as partial therapy (<90% treatment volume, contralateral nerve sparing with TUR).

Partial HIFU excludes the contralateral lobe/capsule and neurovascular bundle. Ideally this would be achieved, by excluding 5 mm of tissue on the contralateral lobe and treating up to 90% of the prostate. Patients choosing one of these approaches should be advised of the risk of tumor recurrence in the untreated area. A close follow-up of these patients is indispensable. There are several critical issues that need to be addressed regarding focal therapy of prostate cancer. The first of these is the accurate identification and localization of the so-called “index lesion” within the prostate on which to target therapy. There are also issues relating to the effectiveness of focal treatments and how patients should be monitored following treatment, whether this is with PSA monitoring, biopsy, or perhaps imaging in the future (62).

The localization of tumor within the gland both before and after treatment is another important issue. The application and the continued development of a variety of imaging and 3D biopsy techniques are likely to provide improvements in the visualization and assessment of HIFU lesions in the near future (63). With regard to localising disease, variable sensitivity of magnetic resonance imaging (MRI) has been reported (64). Functional imaging techniques such as dynamic contrast enhanced (DCE) MRI, diffusion-weighted imaging (DWI) and magnetic resonance spectroscopic imaging (MRSI) have been evaluated in an attempt to improve the detection and localization of prostate cancer (65,66,67). Results suggest that vascular information from DCE-MRI or DWI MRI combined with metabolic data from MRSI have extremely good potential for improving the accuracy of defining and staging prostate cancer.

In terms of assessing the efficacy of HIFU treatment, MRI is the gold-standard technique and the extent of necrosis can be clearly visualized on gadolinium-enhanced T1-weighted images (38,68). MRE might also provide a means of assessing the effects of thermal tissue ablation by measuring the mechanical properties of the lesion (69). HIFU-induced lesions are visible using standard ultrasound (17), although there are limitations to the accuracy of this approach. Other ultrasound-based techniques that might prove useful for assessing the extent of HIFU-induced lesions include contrast-enhanced power Doppler (18) and other techniques that characterize the acoustic properties of tissues.

Focal therapy has been compared with whole gland ablation in a series of 70 patients (70). Of the 29 patients with unilateral disease focal therapy involved ablation of the total peripheral zone and a half portion of transitional zone and resulted in a 77% negative biopsy rate at 12 months. Of the remaining 41 patients with bilateral disease whole
gland ablation resulted in an 84% negative biopsy rate at 12 months. Two-year biochemical recurrence free survival rates were 91% and 50% for low and intermediate risk groups undergoing whole gland ablation compared with 83% and 54%, respectively for the focal therapy equivalents. Morbidity with the two forms of HIFU were comparable.

**CONCLUSION**

Today, PCa is usually diagnosed earlier, patient’s life expectancy is longer and therefore the therapeutic period is extended. Besides this, resources for medical therapy are decreasing and new cost effective non invasive therapies have to be developed. PCa therapy has already changed from a singular to a multimodal, sequential therapy which leaves a large space for minimal invasive therapies. Transrectal HIFU for prostate cancer therapy is a precise, robotic, evolving and effective treatment with a complete spectrum of indications in all tumor stages (57,71). While most other treatment options for localized prostate cancer (e.g. cryotherapy or brachytherapy) cannot be repeated in cases of local PCa recurrence, HIFU can be repeated. Transrectal HIFU should be taken under consideration as a curative therapy in localized disease as well as a palliative adjuvant therapy in all other tumor stages.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)

44. Ficarra V et al. (2006) Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU Int. 98: 1193-1198


