Robotic High-intensity Focused Ultrasound for Prostate Cancer: What Have We Learned in 15 Years of Clinical Use?

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Abstract High-intensity focused ultrasound (HIFU) is an emerging, noninvasive, local treatment of prostate cancer with 15 years of clinical experience, during which about 30,000 HIFU treatments have been performed worldwide. In this paper, we review relevant publications regarding the means by which new and old prostate cancer technologies are evaluated, the outcomes of HIFU by Ablatherm (EDAP TMS, Lyon, France), and the evolution currently underway regarding how prostate cancer is diagnosed and treated. We show the potential of HIFU to be used as local therapy for men with any stage of prostate cancer and how this additional therapeutic option can fit within the future armamentarium of a sequential multimodal therapy concept.

Keywords High-intensity focused ultrasound · HIFU · Prostate cancer · Localized prostate cancer · Advanced prostatic cancer · Focal therapy · Immune response · Transurethral resection of the prostate · TURP · Combination therapy

Introduction

Currently, on average, men live almost 4 years longer and prostate cancer is diagnosed 10 years earlier compared to 25 years ago [1, 2]. This means that the therapeutic necessity is more than double the time than it was then. None of the classical therapies is effective enough to cover this time frame as a monotherapy without a significant risk of aggressive recurrence during these years. Therefore, new concepts of multimodal and sequential therapies have to be introduced to cover the time effectively to maintain the patient’s quality of life (QOL). One of these new therapeutic modalities may be the treatment of prostate cancer with high-intensity focused ultrasound (HIFU).

This review evaluates what we have learned in 15 years of clinical development by focusing on significant and relevant publications that have appeared in the past few years. The focus also covers ongoing clinical research and development in all possible indications and tumor stages of prostate cancer.

During the past 15 years, over 30,000 prostate HIFU treatments have been performed, mainly in Europe, but also throughout the world, including the United States (under an investigational device–exemption protocol, approved by the US Food and Drug Administration). In 2010, two transrectal HIFU devices are on the market (Ablatherm [EDAP-TMS, Lyon, France] and Sonablate [Misonix, Inc., Farmingdale, NY]), differing significantly in technology, installed units, number of treatments performed, scientific evaluation, and publications. Data received by one device cannot be pooled with the other. The authors’ personal experiences and data are based on Ablatherm.

Method

HIFU is a single-session therapy in spinal anesthesia with a duration of 2 to 3 h. It is accomplished by placing a probe that contains a curved piezoelectric crystal and a transrectal
ultrasound (TRUS) scanner into the rectum. This probe collects emitted ultrasound beams at a focal point. The applicators’ intrarectal position is controlled and corrected automatically on time according to a treatment plan, ensuring highest intraoperative precision of the applied ultrasound.

Physically, HIFU tissue ablation occurs via two modes of action: thermal and mechanical. The thermal effect is a temperature increase as the ultrasound energy is absorbed into the tissue and converted into heat. The resulting temperature increase and the geometry within this increase depend on the shape and size of the crystal, the amount of energy (ultrasound frequency and intensity) focused on the point, the applicators’ movement algorithm, power settings, and the thermal capacity of the tissue itself. When sufficient temperature increase occurs (> 80°C) over a sufficient duration of time (> 4 s), irreversible tissue damage through coagulative necrosis results. Mechanically, a negative pressure imparted on the tissue by the ultrasound wave causes bubbles to form inside the cells, which increase in size to the point at which resonance is achieved. Sudden collapse of these bubbles results in a very high pressure (20,000–30,000 bars), which damages cells. The primary single lesions are small (1.7×19–26 mm), are applied side-by-side, and produce reproducible volumes of sharply demarcated ablation. During the clinical procedure, due to the steep temperature gradient between the tissue in the focus, the surrounding tissue-sensitive adjacent structures, namely the rectum, external sphincter, and the neurovascular bundles, are not compromised [3, 4].

High-intensity Focused Ultrasound in Localized Prostate Cancer

Diagnosis of prostate cancer is based on the histopathological examination of biopsies in cases of suspicious prostate-specific antigen (PSA), digital rectal examination, magnetic resonance, or transrectal ultrasound (TRUS) or unexpected findings in resected tissue after open adenomectomy, holmium, or transurethral resection. The group of “localized prostate cancers” contains three subgroups of patients: primary localized, incidental, and monofocal prostate cancer.

Primary Localized Prostate Cancer

Several reports of HIFU as a primary treatment of localized prostate cancer have emerged (Table 1). Blana et al. [12] reported multicenter results from 140 patients (T1-2, PSA < 15 ng/mL, Gleason ≤7) treated in Germany and France with HIFU and followed for a minimum of 5 years. The negative biopsy rate was 86.4% and the biochemical disease-free rates were 77% at 5 years and 69% at 7 years. Blana et al. [13] also reported an 8-year experience of 163 patients in Germany (T1-2, N0M0, PSA ≤20 ng/mL, Gleason ≤7) followed for 4.8±1.2 years and observed a 5-year biochemical survival rate of 75%. More recently, Crouzet et al. [14] reported a multicenter analysis consisting of 803 patients from six French centers followed for 42±33 months. They observed 5- and 7-year biochemical survivals according to the Phoenix definition of 83% and 75%, respectively, for the low-risk group and 72% and 63%, respectively, for the intermediate-risk group. The negative biopsy rate for the low- and intermediate-risk groups were 84.9% and 73.5%, respectively. They also observed 8-year overall, metastasis-free, and cancer-specific survivals of 89%, 97%, and 99%, respectively. Comparing to radiation therapy outcomes, Crouzet et al. [14] concluded that primary HIFU outcomes are at least equivalent to radiation therapy. This is a very reasonable conclusion. It also is reasonable to extend this conclusion to the outcomes of radical prostatectomy as well when one considers the 2008 report of 5277 men who underwent prostate cancer treatment in the United States and were tracked in the CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor) database [15]. Recurrence occurred in 587 of the 935 men (63%) who underwent external-beam radiation therapy (XRT) at a mean time of 38 months after treatment. Of the 4342 men who underwent prostatectomy, 1590 (30%) failed at a mean of 34 months.

Incidental Prostate Cancer

Histological examination shows prostate cancer in up to 8% of the patients who undergo adenomectomy/holmium-laser enucleation or transurethral resection of the prostate (TURP) because of symptomatic benign prostatic hyperplasia. Consequently, these patients need a therapeutic approach for their prostate cancer. We offered these patients HIFU as a local therapy and analyzed efficacy and side effects since 2000 [16].

Overall, 65 patients with incidental prostate cancer at an age of 70 years (57–87 y) have been treated. Initial PSA was 4.9 ng/mL (1–32 ng/mL) and prostate volume was 39 mL (16–130 mL), and 20 g (1–95 g) had been resected. Histology showed 5% (5%–50%) positive chips and a Gleason of 5 (3–9). Patients were treated completely with transrectal HIFU (robotic Ablatherm-integrated imaging) in spinal anesthesia in a single session. In follow-up, PSA nadir of 0.07 ng/mL (0–3.67 ng/mL) was measured after 1.8 months (0.7–5.9 mo), including 62% with PSA less than 0.1 ng/mL and 81% with PSA less than 0.5 ng/mL. A median PSA of 0.13 ng/mL (0–8.3 ng/mL) equivalent to a median PSA velocity of 0.01 ng/mL/y was found after a mean follow-up of 48 months (3–110 mo). Intraoperative
and postoperative side effects were minimal (Clavien classification: < 15% I–III). Long-term follow-up showed 45% of secondary obstructions caused by necrotic tissue or bladder neck stenosis. Other long-term side effects were mild: intermediate grade I urinary stress incontinence was found in 11% (no Grade II or III stress incontinence), and UTI in 14%. There was no cancer-specific mortality.

The PSA nadir of 0.07 ng/mL and the PSA velocity of 0.01 ng/mL/y indicate that HIFU can be used as a curative therapy for patients with incidental prostate cancer. These results show that the psychological burden of these patients, who are confronted either with untreated cancer disease in cases of "wait and see" or with fear of side effects in cases of radical surgery or radiation, can be avoided by this noninvasive therapy.

### Focal High-intensity Focused Ultrasound

The overtreatment of prostate cancer is recognized and the need for less-aggressive minimally sufficient treatments is paramount [17, 18]. Focal therapy for prostate cancer is in the same vein as the progress that has been made for the treatment of breast cancer, where lumpectomy is suggested as a first-line treatment of patients with lesions of limited size. In the same way, for moderate-sized kidney cancers (less than 40 mm), it actually has been shown that conservative treatment (lumpectomy or partial nephrectomy) is as effective as extensive nephrectomy in terms of oncology while preserving a maximum of renal functioning. For superficial TCC bladder cancer, focal resection has been "gold standard" for decades.

Therefore, it seems logical to propose a strategy of this type to a patient who has a multifocal prostatic tumor with a good prognosis. The objective is to propose a partial treatment that is limited to the tumor and a safety margin for the patient with noninvasive, multifocal, localized prostate cancer. This type of treatment should enable treatment to be "totalled up" in the event of failure or recurrence. Thus, the object is twofold: preserve normal sphincter function, sexual performance, and fertility on one hand, and on the other, treat the disease with sufficient efficacy. This would achieve the same morbidity goal of active surveillance but lower the psychological burden resulting from the definitive treatment of the known disease for the patient [19, 20].

The primary idea of carrying out a focal treatment goes back to Onik et al. [21], who were the first to use cryoaolation to offer patients "a prostate lumpectomy." This concept paper was followed by the first outcomes of focal cryoaolation in 2007 [22–24] and a report of focal ablation with HIFU [25]. Bahn et al. [22] followed 31 men treated with hemispherical cryoaolation using stage as the primary

### Table 1 High-intensity focused ultrasound: efficacy summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Pretreatment PSA, ng/mL</th>
<th>Gleason score</th>
<th>Stage</th>
<th>Median follow-up, mo</th>
<th>Negative biopsy rate, %</th>
<th>Biochemical survival</th>
<th>Retreatment rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaussy and Thieroff [5]</td>
<td>184</td>
<td>12</td>
<td>–</td>
<td>T1–2 N0 M0</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>Gelet et al. [6]</td>
<td>102</td>
<td>8.38 (mean)</td>
<td>54% 2–6; 46% 7–10</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. [7]</td>
<td>120</td>
<td>5.67 (mean)</td>
<td>64% 2–6; 36% 7–10</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. [8]</td>
<td>402</td>
<td>10.9 (mean)</td>
<td>13.2% 2–4; 9.3% 8–10</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. [9]</td>
<td>146</td>
<td>7.6 (mean)</td>
<td>5±1.2</td>
<td>T1–2 N0M0</td>
<td>30% T2b; 70% T3; 70% T3</td>
<td>6</td>
<td>77</td>
<td>90% at 1 year (PSA &gt;0.3)</td>
</tr>
<tr>
<td>Ficarra et al. [10]</td>
<td>30</td>
<td>18 (median)</td>
<td>17% 7; 33% 8; 37% 9; 13% 10</td>
<td>T1–2</td>
<td>20.5</td>
<td>86</td>
<td>NR</td>
<td>42.7</td>
</tr>
<tr>
<td>Poissonnier et al. [11]</td>
<td>227</td>
<td>7.0 (mean)</td>
<td>67% 2–6; 33% 7</td>
<td>T1–2</td>
<td>7</td>
<td>96.4</td>
<td>77% at 5 years (Phoenix)</td>
<td>29.3</td>
</tr>
<tr>
<td>Blana et al. [12]</td>
<td>140</td>
<td>7.0 (mean)</td>
<td>5.2±1.4</td>
<td>T1–2 N0M0</td>
<td>76.8%</td>
<td>92.7</td>
<td>75% at 5 years (Phoenix)</td>
<td>20.8</td>
</tr>
<tr>
<td>Blana et al. [13]</td>
<td>163</td>
<td>5 (median)</td>
<td>7.9±3.7</td>
<td>T1–2 N0M0</td>
<td>57.6%</td>
<td>92.7</td>
<td>75% at 5 years (Phoenix)</td>
<td>20.8</td>
</tr>
</tbody>
</table>

*a Mean

ASTRO American Society for Therapeutic Radiology and Oncology, NR not reported; Nx lymph nodes not tested, PSA prostate-specific antigen, Tx T grading unknown
selection criteria (26.6% of men had a Gleason of 7 and 9.7% had a PSA >10 ng/mL). With a median follow-up of 70 months, 92.8% of men had a stable PSA (American Society for Therapeutic Radiology and Oncology [ASTRO] definition) and 96% had negative biopsies. In the Ellis et al. [24] series, 60 patients were selected for hemispherical cryoablation via a 12-core biopsy. The average follow-up was 15 months and the biological progression-free survival rate was 80.4%, the incontinence rate was 3.6%, and erectile function was preserved in 70.6% of patients. It should be noted that 33% of patients included in this series were of intermediate risk or higher. In the Onik et al. [23] series (55 patients with a follow-up of more than 1 year), a stable PSA was obtained in 95% of the patients and sexual function was preserved in 86% of the patients. Not all patients in these two series were reevaluated by biopsy after the focal treatment and, under these conditions, the rate of negative biopsies is therefore subject to caution (100% in the Onik et al. [23] series and 77% in the Ellis et al. [24] series).

In the Muto et al. [25] article, 29 patients underwent focal HIFU with a biochemical progression-free survival rate at 2 years of 83.3% for patients at low risk (TA-T2A, and Gleason 6 and PSA <10 ng/mL) and of 53.6% for patients at intermediate risk (T2B or Gleason 7 or PSA > 10). The rate of negative biopsies was 76.5% at 12 months in 17 patients who were rebiopsied. It should be noted that the focal treatment in this series consisted of treating the entire peripheral zone of the two prostate lobes and the transitional area of the diseased lobe (in the end, only the transitional area of the lobe presumed to be healthy was saved). Focal therapy for prostate cancer is a noninvasive answer to the question of overtreatment. Studies in the United States, France, and Germany are on the way.

**Side Effects after Primary High-intensity Focused Ultrasound in Localized Prostate Cancer**

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 urinary diversion and the postoperative morbidity (sludging, obstruction, infection), studies were undertaken to observe the effect of a combination therapy (HIFU and TURP). In 30 patients with localized prostate cancer, a one-stage (in the same anesthesia) combination therapy with TURP and HIFU was performed. The mean treatment duration was 2 h and 48 min. The transurethral catheter time was 2 days and the mean hospitalization period was 3 days. After 6 months, control biopsies were negative in 80% of patients, and the median PSA was 0.9 ng/mL. The mean 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 [26].

The beneficial effect of a combination of TURP and HIFU was demonstrated in a series of 271 patients with prostate cancer and an initial median PSA less than 15 ng/mL. Of these 271 patients, 96 received HIFU monotherapy, while 175 were treated with combination therapy. The mean resection weight was 15.7 g (2–110 g; 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 was 10.9±6.2 months for the combination-therapy group. 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. The benefits of a combination therapy have been demonstrated with this study [27].

The rate of adverse events among patients with primary therapy is low (Table 2). Grade I stress incontinence was observed in 4% to 6% of patients, grade II in up to 2%, and secondary infravesical obstruction in 5% to 10%. Severe incontinence (grade III) and rectourethral fistulae are rare (< 1%). Preservation of erectile function is directly dependent on the position of the primary lesion in relation to the neurovascular bundle. Although sparing the contralateral side for neurovascular preservation can improve potency, this results in a higher retreatment rate [29–32].

Results from a prospective QOL study from Japan recently have been reported [33]. They evaluated QOL impact using standard questionnaires, including the Functional Assessment of Cancer Therapy-Prostate and the Sexual Health Inventory for Men administered to 326 men before HIFU and then at follow-up months 6, 12, and 24. Their primary conclusion was that functional and QOL outcomes after HIFU for localized prostate cancer are better than those after other treatment modalities. Based on these results, HIFU as therapy for localized prostate cancer has definitively emerged from the experimental stage, and is, since 2000, in the investigational stage for this indication.

**Salvage High-intensity Focused Ultrasound Therapy after Failed Primary Therapy**

HIFU can be used as local salvage therapy after almost any previous primary prostate cancer therapy: for patients with recurrent cancer after external radiation, after low–dose rate and high–dose rate brachytherapy after cryoablation or biochemically progressing PSA, after failed primary HIFU,
and after combined pretreatments, including radical prostatectomy. This is due to the poor treatment options for recurrent disease. According to CaPSURE data, 63% of the patients who underwent XRT had disease recurrence. The salvage therapy employed for this population almost always was androgen deprivation, which was applied in 93.5%. Definitive local therapy was employed only in 3.9% (salvage radical prostatectomy: 0.9% and cryoablation: 3.0%). It has been well recognized that salvage radical prostatectomy and cryoablation are more theoretical options with high morbidity rates. The cause of this may be due to the complexity of the procedure, the high rates of side effects, and/or the procedure costs.

Two significant publications regarding salvage HIFU recently appeared. Murat et al. [34] updated the Lyon series of patients and reported outcomes of 167 men who underwent salvage HIFU, observing a 73% negative-biopsy rate and a 5-year overall survival rate of 84%. Surprisingly, they did not present a biochemical disease–free survival rate. No rectal complications were observed, but the urinary incontinence rate was 49.5%, which is similar to rates reported in salvage radical prostatectomy series. Berge et al. [35] reported early results from a prospective study of salvage HIFU and observed a biochemical failure rate of 39.1%. Significantly, the urinary incontinence rate was much lower in their cohort than in the Lyon group, with 17.3% developing either grade II or grade III incontinence. One patient developed a rectourethral fistula.

Salvage HIFU remains an attractive treatment option for those men who have had a recurrence after radiation therapy, although the postoperative course does have an associated higher morbidity due to the alterations of the tissue after radiation therapy. It is a curative option that should be discussed with any patient who is thought to have a localized recurrence after radiation therapy.

### High-intensity Focused Ultrasound in Locally Advanced (T3-4) or Non-metastatic Hormone-resistant Prostate Cancer

Although not yet published as full manuscripts, a few important abstracts regarding the use of HIFU for the treatment of more aggressive disease were presented in 2010 and need to be mentioned because the results are compelling and encouraging. Most HIFU outcome reports are limited to T1-2 or radiation failures. The first report of T3-4 disease came recently, with 113 patients followed for a median of 4.6 years [36]. The median PSA velocity of this cohort was 0.19 ng/mL/y and the cancer-specific survival was 96.4%. A series of 55 men with PSA progression during their definitive hormonal ablation with a local biopsy-proven tumor recurrence were reported [37]. With a mean follow-up of 21 months, the prostate-specific survival was 87.3%. This is impressive and encouraging because this is a group of patients with a very poor prognosis and a short median survival.

### Immune Induction: More than Just a High-intensity Focused Ultrasound “Side Effect”?

Recent progress has been made in developing an effective immune strategy for treating prostate cancer. A number of immunotherapy regimens are being studied, including immunomodulatory cytokines/effectors, peptide and cellu...

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### Table 2 Summary of morbidity results following high-intensity focused ultrasound

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>INC, %</th>
<th>ED, %</th>
<th>FIS, %</th>
<th>S&amp;S, %</th>
<th>PR, %</th>
<th>UTI, %</th>
<th>CA, d</th>
<th>Pain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blana et al. [9]</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>Thürroff et al. [8]</td>
<td>402</td>
<td>GI 10.6</td>
<td>GI 2.5</td>
<td>GI 1.5</td>
<td>13</td>
<td>1.2</td>
<td>3.6</td>
<td>8.6</td>
<td>13.8</td>
</tr>
<tr>
<td>Gelet et al. [6]</td>
<td>102</td>
<td>GI 8.8</td>
<td>GI 9.8</td>
<td>GI 3.9</td>
<td>61</td>
<td>1</td>
<td>17</td>
<td>NR</td>
<td>9.1</td>
</tr>
<tr>
<td>Chaussy et al. [27]</td>
<td>96</td>
<td>GI 9.1</td>
<td>GI 4.6</td>
<td>GI 1.7</td>
<td>40</td>
<td>NR</td>
<td>27.1</td>
<td>NR</td>
<td>47.9</td>
</tr>
<tr>
<td>Chaussy et al. [27]</td>
<td>175</td>
<td>GI 4.6</td>
<td>GI 2.3</td>
<td></td>
<td>31.8</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>11.4</td>
</tr>
<tr>
<td>Ficarra et al. [10]</td>
<td>30</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>0</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Lee et al. [28]</td>
<td>58</td>
<td>GI 16</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>3.4</td>
</tr>
<tr>
<td>Poissonnier et al. [11]</td>
<td>227</td>
<td>GI 9.0</td>
<td>GI 3.0</td>
<td>GI 1.0</td>
<td>39</td>
<td>0</td>
<td>12</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Blana et al. [12]</td>
<td>140</td>
<td>GI 5.0</td>
<td>GI 0.7</td>
<td></td>
<td>43.2</td>
<td>0</td>
<td>13.6</td>
<td>–</td>
<td>7.1</td>
</tr>
<tr>
<td>Blana et al. [13]</td>
<td>163</td>
<td>GI 6.1</td>
<td>GI 1.8</td>
<td></td>
<td>44.7</td>
<td>0</td>
<td>24.5</td>
<td>–</td>
<td>7.8</td>
</tr>
</tbody>
</table>

a No TURP. b TURP

CA postoperative catheter duration, ED erectile dysfunction, F Foley catheter, FIS fistula, GI incontinence grade I (loss of urine under heavy exercise requiring 0–1 pad/d), GII incontinence grade II (loss of urine under light exercise requiring >1 pad/d), GIII incontinence grade III (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
lar immunization, viral vaccines, dendritic cell vaccines, and antibody therapies. Immunomodulatory agents, such as granulocyte-macrophage colony-stimulating factor, Flt3 ligand, and interleukin 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. [38] examined the effect of HIFU on systemic antitumor immunity, particularly T lymphocyte-mediated immunity in patients with cancer.

The same group investigated whether the tumor antigens expressed on breast cancer cells may be preserved after HIFU treatment [39]. Primary lesions in 23 patients with biopsy-proven breast cancer were treated with HIFU, then submitted to modified radical mastectomy. Breast cancer specimens then were stained for a variety of cellular molecules, including tumor antigens and heat-shock protein 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 [40].

Status of tumor-infiltrating lymphocytes (TILs) after HIFU ablation of human breast cancer has been investigated [41]. 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.

The “Randomized Trial” Pipe Dream

One of the biggest lessons of 2010 is that it still appears to be impossible to objectively compare two definitive local therapies for localized prostate cancer. Donnelly et al. [42] made the best attempt in the past 25 years to accrue patients to a cryoablation versus XRT trial in Calgary, but it still fell short of the accrual target. This is the most recent in a string of randomized clinical trials that fall short of their accrual target. Importantly, it is noted that the Calgary trial was done in Canada in the early 2000s, when the treatment options were not as extensive or as confusing as they are today. The two standard options at that time were prostatectomy and XRT. Those not interested in or not indicated for prostatectomy would have only one option: XRT. If they wished to have cryoablation, they could do so only by entering the trial. If they were not randomized to the cryoablation arm, they would get the treatment they would have had anyway. Today, with so many options, this environment is essentially impossible to recreate. Another randomized clinical trial comparing different definitive local therapies is not underway nor on the horizon. As such, it should finally be admitted that accruing patients to a randomized trial comparing two different definitive therapies for localized prostate cancer is a pipe dream.

It is important to distinguish between two phases of development and evaluation of a technology. “Experimental” indicates that the effect of the treatment in terms of both morbidity and efficacy is essentially unknown. An “investigational” procedure is one for which the efficacy and morbidity have been established, but the long-term (>10 years) durability remains to be established. Prostate cancer, being a slowly progressing disease in most cases, necessitates its treatments to be followed for a very long time (>15 years) to completely determine efficacy. In fact, the foundation procedures for management of localized prostate cancer have become “standards,” not due to rigorous research that long ago, but more due to the simple fact that they have been the longest practiced treatments. The only successful randomized trial comparing prostatectomy to active surveillance; however, it is not a comparison of two definitive treatment options, and only yielded meaningful results in 2008 [43]. This is more than 100 years after Young [44] first defined the radical prostatectomy in 1905. Demanding that a new treatment be vetted via a randomized clinical trial is not feasible and demanding one simply is blocking innovation and ignoring reality. Today, everyone wants to be treated with the newest technology, and at the same time, on a highest possible evidence level. This is a dilemma that cannot be solved by a randomized trial.

Conclusions

Since 2000, HIFU by Ablatherm is a nonexperimental therapy under long-term investigation for primary treatment of local prostate cancer as well as salvage therapy after radiation failure. It appears to have a high potential to treat on either side of this spectrum in focal and in incidental prostate cancer as well as adjuvant in T3/T4 disease or in nonmetastatic hormone-resistant prostate cancer. The versatility of HIFU appears to be unique in the treatment of the entire spectrum of prostate cancer, which is a multifaceted increasing and long-lasting disease. HIFU does not substitute or is not competitive to only one classical therapy, but its indications overlap in a certain range with all therapies. As additional local one-session tumor debulking therapy
option with low perioperative morbidity, it is feasible for patients in any age and health status. HIFU helps to delay surgery, radiation, or hormonal ablation to a point in patients’ life when they are really unavoidable and most effective. An eventual HIFU-provoked induction of the immune response as supportive therapeutic effect is under investigation.

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References

Papers of particular interest, published recently, have been highlighted as:

* Of importance


44. Young HH. The early diagnosis and radical cure of carcinoma of the prostate: Being a study of 40 cases and presentation of a radical operation which was carried out in four cases. Bull Johns Hopkins Hosp. 1905;16:315–21.