Role of Focal Therapy with High-Intensity Focused Ultrasound in the Management of Clinically Localized Prostate Cancer

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Introduction

Overtreatment of prostate cancer (PC) remains one of the main burdens in uro-oncology. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) failed to demonstrate a cancer-specific survival benefit in the low-risk group after radical prostatectomy (RP) compared to ‘watchful waiting’ [1]. The Scandinavian Prostate Cancer Group (SPCG)-4 trial found similar results when watchful waiting was compared to RP in men with high-risk prostate cancer [2]. Under this light of evidence, the risks of incontinence and erectile dysfunction associated with definitive treatment strategies like RP or radiotherapy are 15–20% and 30–60%, respectively [3, 4].

Active surveillance (AS) is a reasonable alternative in low- and very-low-risk PC patients [5] but leaves the cancer ‘untreated’. This fact may cause anxiety problems in a subset of men over time [6].

Multiparametric magnetic resonance imaging (mp-MRI) has shown to be capable of visualizing PC foci in the prostate with high sensitivity and specificity [7–9]. This evidence sets the stage for focal ablation of tumor foci by different energy sources like high-intensity focused ultrasound (HIFU), cryotherapy, brachytherapy, or irreversible electroporation (IRE). All focal therapy strategies involve the ablation of tumor foci with a decent safety margin, in theory minimizing the collateral damage to surrounding structures such as the external urinary sphincter, the bladder neck, neurovascular bundles, and the rectum, with consecutive lower side effects [10, 11]. The latest HIFU machines allow the fusion of mp-MRI data into live ultrasound images, allowing more precise treatment planning in theory. This paper gives an overview of the existing evidence on focal HIFU. Today, 3 HIFU devices are approved for the treatment of localized PC: Sonablate™, Ablatherm™ and the FocalOne™ device. In summary, the first published results of focal HIFU are promising. The quality of life and potency of the patients are well preserved. Therefore, HIFU treatment, and especially focal ablation of tumor foci, seems to be a safe alternative to standard treatment, with low side effects. The oncologic results seem satisfactory but need further follow-up to validate this practice of PC control.

Keywords
Prostate cancer · HIFU · Focal therapy · Review

Summary

Overtreatment of prostate cancer (PC) remains one of the main burdens in uro-oncology. Focal therapy may be a reasonable alternative with less side effects and morbidity. Application of high-intensity focused ultrasound (HIFU) induces immediate and irreversible coagulation. The treatment leads to consecutive necrosis with sharply delineated margins, making HIFU a promising tool for the focal therapy of localized PC. Unlike radiation, the treatment leaves no collateral damage outside of the heated tissue, allowing repeated use of HIFU, if necessary. In case of non-organ-confined relapse, additional radical salvage therapy can be performed. This review gives an overview of the existing evidence on focal HIFU. Today, 3 HIFU devices are approved for the treatment of localized PC: Sonablate™, Ablatherm™ and the FocalOne™ device. In summary, the first published results of focal HIFU are promising. The quality of life and potency of the patients are well preserved. Therefore, HIFU treatment, and especially focal ablation of tumor foci, seems to be a safe alternative to standard treatment, with low side effects. The oncologic results seem satisfactory but need further follow-up to validate this practice of PC control.

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Evidence Acquisition

Today, 3 devices are approved for the treatment of localized PC: Sonablate™ (SonaCare Medical, Charlotte, NC, USA), Ablatherm™ and the FocalOne™ device (EDAP-TMS SA, Vaulx en Velin, France). A systematic review of the literature using PubMed was performed to highlight the results of all 3 machines in focal therapy.

Evidence Synthesis

The first treatment results of local HIFU were described in 2008 by Muto et al. [12] in single-lobe confirmed PC. They reported outcomes in 29 patients after zonal ablation of 1 lobe including the peripheral zone and half of the transitional zone. The mean prostate-specific antigen (PSA) level decreased from 5.36 ± 5.89 ng/ml to 1.52 ± 0.92 ng/ml at 36 months. 3 patients (10%) had residual cancer 6 months after treatment. At the 12-month biopsy, this number increased to 4 out of 17 patients (23.5%).

Ahmed et al. [10] published the first series of hemiablation in 2011. Patients with low- and intermediate-risk PC underwent multiparametric MRI and consecutive transperineal saturation biopsy. The entire lobe positive on biopsy excluding the urethra was ablated. At the 12-month follow-up, the mean PSA level decreased to 1.5 ± 1.3 ng/ml and 89% of patients had no histological evidence of cancer. 2 patients (11.1%) had a positive biopsy at 6 months, with a marginal residual of 1 mm Gleason grade 3 + 3.

Another hemiablation study was published by El Fegoun et al. in 2011 [13]. They treated 12 patients with a mean preoperative PSA level of 7.3 ng/ml. Patients were included if a 12-core transrectal ultrasound (TRUS) biopsy showed Gleason score ≤ 4 + 3 PC.

The control biopsy 1 year after treatment showed residual PC in 1 of 12 patients (8%).

The first real focal therapy study was published in 2012 also from the Emberton group in London [14]. 41 patients were included with low-, intermediate-, and high-risk PC. All patients underwent focal ablation of mp-MRI-visible lesions confirmed by transperineal saturation biopsy. A maximum of 60% of the prostate was ablated using the Sonablate device. Of the 41 patients included, 49% received unilateral single-area, 37% received bilateral 2-area, and 15% received a urethra-near 1-area ablation. All patients were able to void via naturalis on the first postoperative day. PSA levels decreased with a median baseline PSA level of 6.6–1.9 ng/ml at the 12-month follow-up (p = 0.0001). At the 6-month biopsy, 30 of 39 (77%) patients were negative for PC; 2 patients refused re-biopsy. Out of 9 patients with evidence of tumor, 3 (8%) had evidence of clinically significant tumor according to the Epstein criteria. All 38 men were pad free at baseline and remained pad free at 12 months. The International Prostate Symptom Score (IPSS) improved, with a decrease between baseline and 12 months (p = 0.026). Of the 35 men with erection sufficient for penetration, 31 (89%) preserved this function 12 months after focal therapy.

Barret et al. [15] presented the largest series (106 patients) of focal therapy. The median PSA levels at baseline and at 3, 6, and 12 months were 6.0, 2.7, 3.1, and 3.1 ng/ml, respectively. The median IPSS at baseline and at 12 months were 6.0 and 3.1, respectively. The median International Index of Erectile Function (IIEF)-5 score decreased from 20 at baseline to 14 at the 12-month follow-up. The overall complication rate was 13% with 5 urinary retractions after focal HIFU.

A summary of the available literature is given in table 1.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ablative treatment</th>
<th>Patients, n</th>
<th>Mean preoperative PSA level</th>
<th>Gleason score included</th>
<th>Biopsy modality</th>
<th>Biopsy-proven recurrence</th>
<th>Potency</th>
<th>Continence</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muto et al. [12]</td>
<td>zonal ablation</td>
<td>29</td>
<td>5.36</td>
<td>5–10</td>
<td>TRUS biopsy</td>
<td>6-month: 3/28 (10%); 12-month: 4/17 (23.5%)</td>
<td>NA</td>
<td>29/29 (100%)</td>
<td>none</td>
</tr>
<tr>
<td>Ahmed et al. [10]</td>
<td>hemiablation</td>
<td>20</td>
<td>7.3</td>
<td>≤ 4 + 3</td>
<td>MRI and saturation transperineal biopsy</td>
<td>6-month: 2/19 (11%) in the treated lobe</td>
<td>19/20 (95%)</td>
<td>18/20 (90%)</td>
<td>urethral stricture in 1 patient</td>
</tr>
<tr>
<td>Ahmed et al. [14]</td>
<td>focal ablation or bilateral 2-area ablation</td>
<td>41</td>
<td>6.6</td>
<td>≤ 4 + 3</td>
<td>MRI and saturation transperineal biopsy</td>
<td>6-month: 9/39 (23%), 3 (8%) with significant cancer</td>
<td>31/35 (89%)</td>
<td>38/38 (100%)</td>
<td>urinary retention and stricture in 1 patient each</td>
</tr>
<tr>
<td>Barret et al. [15]</td>
<td>hemiablation</td>
<td>106</td>
<td>6</td>
<td>6</td>
<td>transperineal saturation biopsy</td>
<td>NA</td>
<td>IIEF 14 at 12 months</td>
<td>100%</td>
<td>urinary retention in 5 patients (24%)</td>
</tr>
<tr>
<td>El Fegoun et al. [13]</td>
<td>hemiablation</td>
<td>12</td>
<td>7.3</td>
<td>≤ 4 + 3</td>
<td>TRUS biopsy</td>
<td>12-month: 1/12 (8%)</td>
<td>NA</td>
<td>12/12 (100%)</td>
<td>urinary retention in 1 patient</td>
</tr>
</tbody>
</table>

Table 1. Focal therapy study results
Discussion

The complication rates differ between the treatment strategies. Looking into the literature, urinary retention after HIFU requiring intervention seems to be more common if hemiablation is performed [13, 15–17]. Depending on the amount of ablated tissue and the system used, urinary retention rates of up to 20% have been reported [17]. Newer systems like the FocalOne™ are able to ablate smaller volumes and therefore spare structures at risk like the bladder neck or the urethra from thermal damage (fig. 1).

The necessity of hospitalization and catheterization seems also lower in focal therapy compared to earlier systems. Murat et al. [18] in 2009 reported a catheterization time of 5.8 days after whole-gland treatment with the Ablatherm™ device. The Embertron group was also able to report such results [14] as all their patients were able to void normally on the first postinterventional day. This may be the result of preserving risk structures like the bladder neck or the prostatic urethra from thermal damage (fig. 1).

The function of the lower urinary tract seems very much preserved by focal HIFU. Ahmed et al. [14] and Feijoo et al. [21] did not observe a significant change in IPSSs between baseline and the 12-month follow-up. Therefore, the functional results of focal HIFU seem very promising, especially if the urethra can be preserved during ablation.

The influence of HIFU on erectile function seems also very low. In the literature, potency rates between 89 and 95% after focal therapy have been reported [10, 14]. As erectile function is influenced by age and comorbidities, larger prospective studies are necessary to evaluate the impact of focal HIFU.

One of the problems occurring when ablation of peripheral tumors is performed by HIFU may be the thermal damage due to heat convection. IRE has been promoted by different groups as a non-thermal treatment option where ablation only occurs between the inserted electrodes [22–24]. The latest publication by van Gemert et al. [25] showed a thermal effect in tissues between 67 and 92 °C by IRE. This may cause significant damage outside the planned boundaries. Such significant extra-boundary damage was also observed in vivo by the group of de la Rosette [26], which questions the precision of this new focal therapy option. Prospective trials on IRE are recruiting and may add evidence to these preliminary observations [27, 28].

Conclusions

In conclusion, focal HIFU treatment of tumor foci seems to be a safe alternative to standard treatment, with low side effects. Next-generation devices like the FocalOne™ allow precise ablation and the preservation of risk structures like the external sphincter, the urethra, or neurovascular bundles. The impact of mp-MRI on the

Fig. 1. One example of a treatment effect and b postoperative correlating perfusion deficit in contrast-enhanced TRUS of 1 in-house HIFU patient.
treatment by ablative procedures is still under investigation, but it seems very useful if the user is aware of its limitations and the necessary safety margins. The oncologic results seem satisfactory but need further follow-up to validate this practice of PC control. Prospective trials like the PRO-FOCUS trial may provide more evidence to help integrate focal HIFU therapy into clinical guidelines. IRE as a promoted alternative to focal HIFU seems not to be precise enough for focal therapy at the moment.

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Disclosure Statement
The authors declare no conflict of interest.