High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer

Albert Gelet, Sebastien Crouzet, Olivier Rouviere, and Jean-Yves Chapelon

1 Introduction

The incidence of prostate cancer is increasing worldwide. In Europe, the mortality rate declined from 15 per 100,000 in 1995–12.5 per 100,000 in 2006 [1]. This decline of mortality can be attributed to two factors: firstly, since the use of screening with prostate-specific antigen, 70 % of these newly diagnosed prostate cancers are organ confined and therefore suitable for a local, curative therapy; secondly, better control of the disease was secured from a wider adoption of radical prostatectomies and the use of combined androgen deprivation and radiotherapy for patients with locally advanced disease. But the morbidity associated with the radical treatment of both surgery and radiotherapy are significant, suggesting that radical surgery and/or radiation therapy should only be offered to men who are likely to survive more than 10 years. However, the PIVOT trial, started during the PSA era, failed to demonstrate a significant survival advantage in the radical surgery group compared to the observation group [2]. The review of Steyerberg et al. [3] suggests that 49 % of men undergoing radical prostatectomy have pathological features in the RP specimen consistent with an insignificant cancer (organ confined cancer <0.5 ml, no Gleason grade 4 or 5 component). Albertsten et al. reported the impact of comorbidity on survival among men with localized prostate cancer. The results suggest that relatively few men diagnosed with moderately differentiated localized prostate cancer older than

A. Gelet, MD (✉)
Department of Urology, Edouard Herriot Hospital, Lyon, France

Therapeutic Ultrasound Research Laboratory, Inserm U1032, Lyon F-69003, France

Université de Lyon, Lyon F-69003, France

Urology and Transplantation Department, Edouard Herriot Hospital, 5 place d'Arsonval, 69437 Lyon Cedex 03, France
e-mail: albert.gelet@chu-lyon.fr

S. Crouzet
Department of Urology, Edouard Herriot Hospital, Lyon, France

Therapeutic Ultrasound Research Laboratory, Inserm U1032, Lyon F-69003, France

Université de Lyon, Lyon F-69003, France

O. Rouviere
Therapeutic Ultrasound Research Laboratory, Inserm U1032, Lyon F-69003, France

Université de Lyon, Lyon F-69003, France

Department of Radiology, Edouard Herriot Hospital, Lyon, France

J.-Y. Chapelon
Therapeutic Ultrasound Research Laboratory, Inserm U1032, Lyon F-69003, France

Université de Lyon, Lyon F-69003, France

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65 years will die as a result of prostate cancer within 10 years of diagnosis [4]. Most men with either no comorbidity or only one will survive at least 10 years, whereas men with two or more comorbidities have a high risk of dying as a result of a competing medical hazard within this time frame. Thus the quest continues for a reliable alternative to open surgery or radiation therapy and one whose chief objective is to find a procedure as minimally invasive as possible.

Klotz et al. published in 2015 the long term results of a large series of patients treated with active surveillance (watchful-waiting protocol with selective delayed intervention) [5]. Focal therapy is an alternative to active surveillance of low-risk prostate cancer with the aim of achieving local control of the cancer, without the associated morbidity of radical therapies. HIFU is also a very promising technology for focal therapy of prostate cancer.

2 Principles

The first description of HIFU was made in 1942 and the ability to destroy tissue was established in 1944 [6]. HIFU is a nonionizing and nonsurgical physical therapy that produces biological effects by thermal and mechanical means. Heating tissue denatures proteins and leads to cell death, regardless of whether they are normal or abnormal, whereas mechanical effects disrupt cells by the collapse of microbubbles generated by cavitation. In most applications, spherically shaped power transducers are used to focus the ultrasound energy onto a target point deep within the body. This results in thermal tissue coagulation necrosis, cavitation, and heat shock. Each sonication heats only a small focal target, creating an elementary lesion with extreme precision and accuracy (Fig. 1a). Subsequently, multiple sonications, side-by-side and layer after layer, are necessary to create a volume of lesions covering a larger volume of tissue targeted for ablation (Fig. 1b). The main sonication parameters are acoustic intensity, duration of exposure, on/off duty cycle, the distance between two elementary lesions, and the displacement path when multiple lesions are made [7].

3 HIFU in Prostate Cancers Models and First Clinical Trials

In 1992, Chapelon et al. established the ultrasound parameters required to induce irreversible tissue lesions in animals. With the experimental adenocarcinoma of a prostate implanted in rats (R 3327 AT2 Dunning tumor), they demonstrated that HIFU could be used to ablate the tumor and cure cancer without causing metastasis [8]. In 1993, Gelet et al. established that it was possible to induce irreversible coagulation necrosis lesions in dog prostates using transrectal route without damaging the rectal wall [9]. The first in human studies were started in 1993 and included men with benign prostate hypertrophy [10, 11]. Beerlage et al. completed a phase one study of HIFU before prostatectomy demonstrating HIFU being able to deposit a large amount of energy into the tissue, resulting in its destruction through cellular disruption and coagulative necrosis [12]. The results of phase two pilot study were published in 1996 and the preliminary results of the first 50 patients in 1999 [13, 14].

4 Prostate Modern Imaging: A Critical Key for Improving HIFU Ablation Outcome

Imaging is beginning to play a critical role in the management of prostate cancer patients [15]. This role is likely to increase as both imaging and HIFU treatment becomes more precise and evolves towards focal ablation of selected cancer foci. In theory, imaging is useful in four different domains: patient selection, treatment planning, assessment of HIFU ablation, and detection of local recurrences.

4.1 Patient Selection and Treatment Planning: The Need for a Better Prostate Cancer Mapping

The first step of patient selection is to rule out the presence of lymph node and distant metastases.

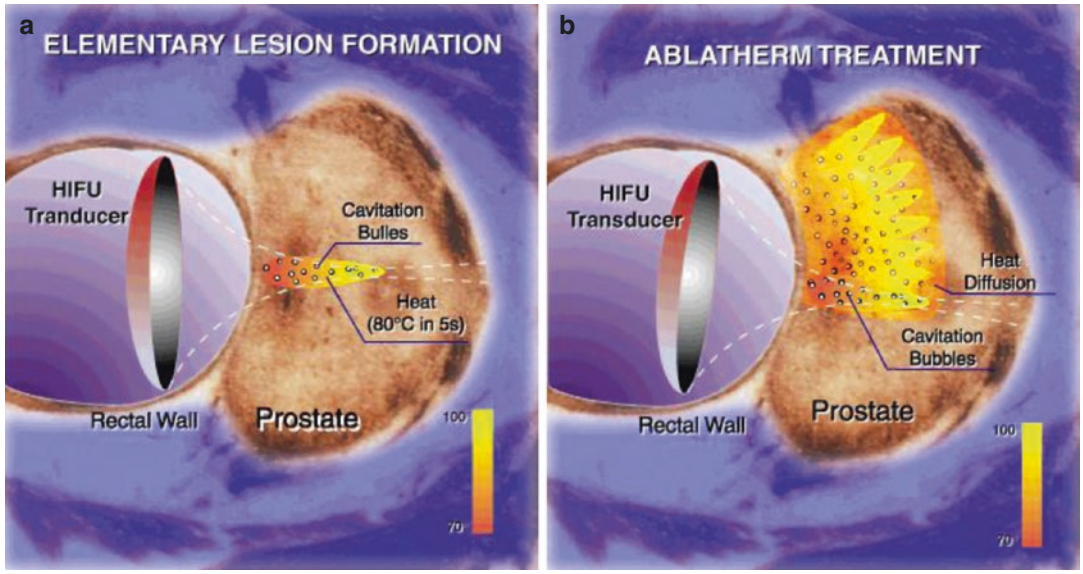

Fig. 1 To treat the prostate, the HIFU transducer is previously covered with a balloon filled with coupling liquid. Then it is inserted into the patient's rectum and positioned close to the rectum wall in such a way that the base of the lesion will stop close to the prostate capsula (**a**). This precise positioning prevents any rectal wall damage. Prostate treatment is performed by the repetition and juxtaposition of several elementary lesions. The sum of these elementary lesions creates a continuous volume where tissue is entire destroyed (**b**)

This step may be optional in low-risk patients, but it is critical in other populations such as the patients with a local recurrence after radiation therapy. The risk of metastases can be assessed by combining clinical and biological data such as the digital rectal examination and biopsy findings, the PSA value, the PSA doubling time or, in case of recurrence, the characteristics of the initial tumor and the delay of the biochemical recurrence. Several nomograms have been shown to predict the onset of metastases and may be useful for clinical decision-making [16]. As detailed in chapters 7 and 8, new MR-based and isotopic techniques can also help in detecting clinically occult metastases.

Once the risk of metastases has been reasonably ruled out, the second step consists of obtaining a precise mapping of the position of cancer foci within the prostate. This is critical for focal ablation candidates, but even in case of whole-gland treatments it helps identify areas where complete tissue destruction is critical. Chapter 7 detailed the progress made in prostate cancer detection and localization, particularly since the advent of multiparametric MRI (mpMRI). MpMRI has a high sensitivity for detecting aggressive cancers [17–19]. At our institution, in 2008 we started a database collecting precise correlation between MR images and prostatectomy specimens. Patients were imaged either at 1.5 T ($n=71$) or 3 T ($n=104$). Images were reviewed by two independent radiologists and compared to histological findings. On a series of 175 consecutive patients, the detection rates for tumors of <0.5 cc, 0.5–2 cc, and >2 cc were 21–29 %, 43–54 %, and 67–75 % for Gleason ≤6 cancers; 63 %, 82–88 %, and 97 % for Gleason 7 cancers; and 80 %, 93 %, and 100 % for Gleason ≥8 cancers, respectively (Fig. 2). Results were not significantly influenced by the field strength [17].

These results underline a limitation of mpMRI: a substantial part of Gleason 6 tumors may be undetected. Another limitation lies in the evaluation of the tumor volume. Accurate assessment of tumor volume is critical for focal ablation. There is a consensus that mpMRI underestimates the histological tumor volume [20–22]. However, some authors found that the volume underestimation was more marked in case of Gleason ≥7 cancers or in case of lesions with a Likert score of 4–5 [19], while others found the opposite [21].

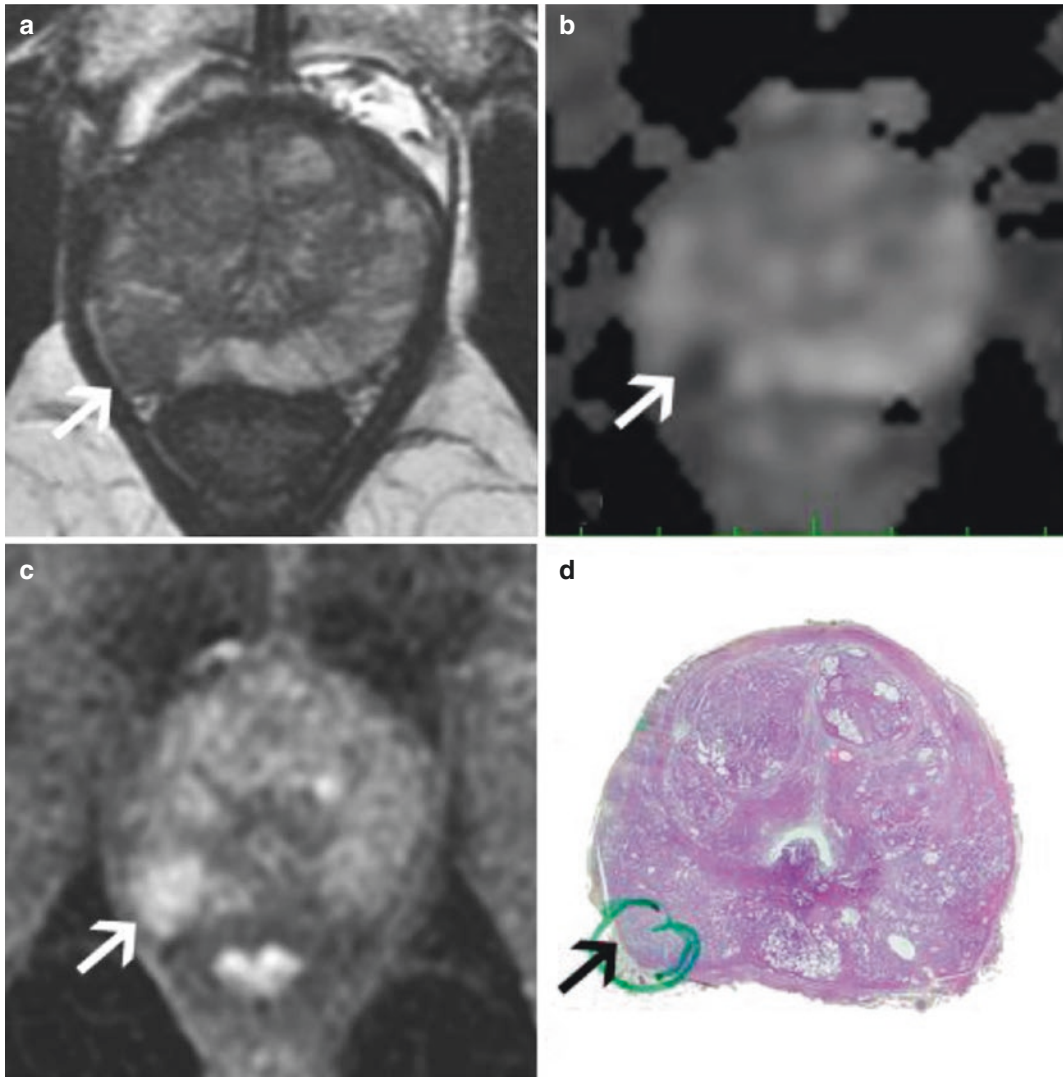

Fig. 2 Multiparametric axial MR images (**a**): T2-weighted image; (**b**): apparent diffusion coefficient (ADC) map computed from diffusion-weighted images (b values: 0 and 2000 s/mm^2); (**c**): dynamic contrast-enhanced image and axial section of the prostatectomy specimen obtained in a 66 year-old patient with a Gleason 8 prostate cancer of the right mid-gland and base at biopsy. MRI images showed a highly suspicious lesion located in the posterolateral part of the peripheral zone of the right midgland, with hyposignal on T2-weighted image (**a**, *arrow*), decreased ADC values (**b**, *arrow*), and early and intense enhancement (**c**, *arrow*). The analysis of the prostatectomy specimen (**d**, *arrow*) was confirmative and showed in that area a Gleason 8 cancer. The rest of the gland did not contain cancer

Thus, further research is needed to better evaluate the safety margin that needs to be used around lesions seen on mpMRI in case of focal ablation.

It is of note that mpMRI seems much more accurate in delineating intraprostatic local recurrences after radiotherapy. Several independent groups reported a strong agreement between mpMRI and biopsy findings in patients with rising PSA after radiotherapy, at the patient, lobe, and even sextant level [23–25]. The contrast between recurrent cancer and post-radiation fibrosis seems high, both on diffusion-weighted imaging and on dynamic contrast-enhanced imaging (Fig. 3). As a result, mpMRI interpretation is easier and interreader agreement is good, even with junior readers

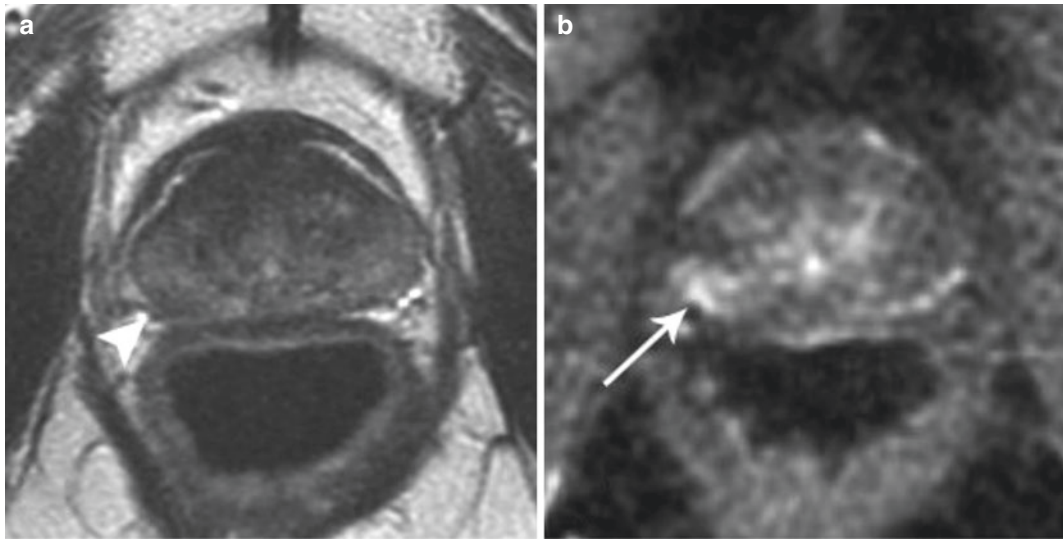

Fig. 3 Multiparametric MR images (**a**): T2-weighted image; (**b**): dynamic contrast-enhanced image) obtained in a 69-year-old patient with history of radiation therapy for prostate cancer 10 years before. The nadir of the PSA level after radiation therapy was 0.8 ng/ml. The PSA level had slowly increased to 3.21 ng/ml at the time of MRI. MR images showed a suspicious lesion of the right midgland, with mild hyposignal on T2-weighted imaging (**a**, *arrowhead*) and marked enhancement on dynamic imaging (**b**, *arrow*). Biopsy showed Gleason 6 recurrent cancer in the right midgland

[25]. In the postradiation setting, mpMRI also provides prognostic information: in a series of 46 patients with postradiotherapy local recurrences treated with HIFU at our institution, the position of the recurrence anterior to the urethra (as determined by DCE MRI) was shown to be an independent negative predictive factor along with the pre-HIFU PSA value [26].

4.2 Postoperative Evaluation of the Ablated Area

Ideally, imaging could show the prostate volume destroyed at the end of the HIFU ablation session so that in case of unsatisfactory results, a new HIFU ablation could be immediately performed. Unfortunately, transrectal ultrasound, used to guide HIFU treatment, cannot accurately show the ablated area [27].

Gadolinium-enhanced (nondynamic) MRI clearly reveals the treated volume as a devascularized zone (corresponding to the central core of the coagulation necrosis) surrounded by a peripheral rim of enhancement (corresponding to edema), but MRI cannot be obtained in the operating room [28, 29].

We have recently shown that contrast-enhanced ultrasound (CEUS), using Sonovue™ as contrast agent, can show the ablated volume immediately at the end of the treatment with an excellent correlation with MR and biopsy findings. All prostate sectors showing no enhancement at CEUS at the end of HIFU ablation can be considered entirely destroyed. In contrast, prostate sectors showing any degree of enhancement can be considered containing living (benign or malignant) tissue [30] (Fig. 4). These results should allow immediate re-treatment of the parts of the gland showing residual enhancement and that are within the range of the transducer.

4.3 Detection of Post-HIFU Local Recurrences

After HIFU ablation, residual prostate is composed of scarring fibrosis and benign prostate hyperplastic (BPH) tissue that has not been destroyed because of its anterior location.

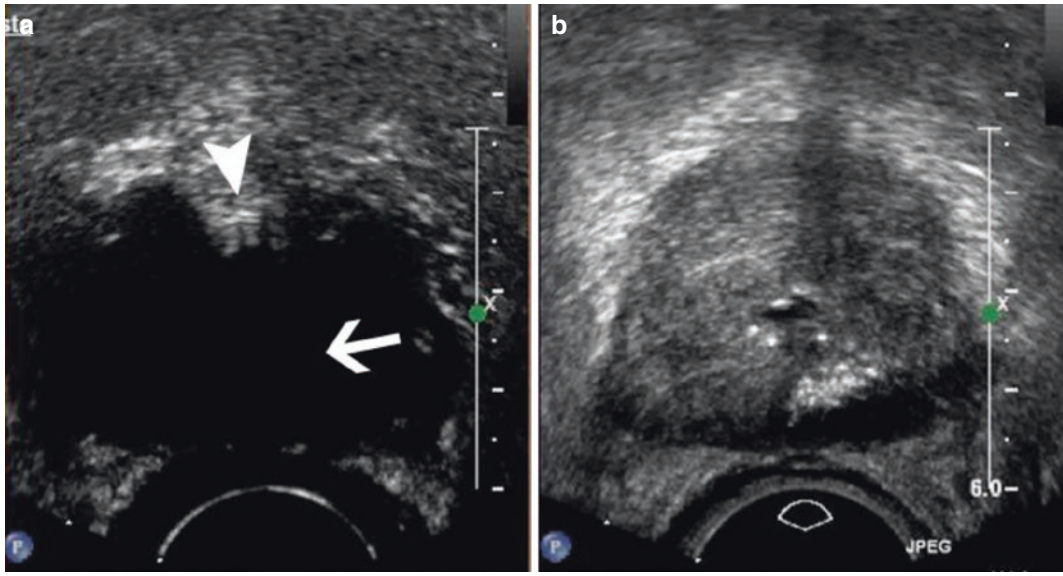

Fig. 4 Contrast-enhanced ultrasound (CEUS) axial image (**a**) with corresponding low mechanical index gray-scale image (dual mode; **b**), obtained after HIFU ablation of a local recurrence of prostate cancer after radiation therapy in a 68-year-old patient. CEUS image showed the nearly complete devascularization of the gland (*large arrow*), with a small strip of anterior and median residual parenchyma that still enhanced (*arrowhead*). Note that tissue destruction is not visible on the gray-scale image

Because local recurrences (or residual cancers) can be treated with a second session of HIFU ablation or by radiation therapy [31], it is important to detect them early. The precise location of these recurrences can also help in selecting an appropriate salvage treatment (e.g., anterior recurrences may be better treated by radiation therapy).

Even if color Doppler can sensitize TRUS [32], US-based techniques are not accurate enough to detect local recurrences early and guide biopsy.

MRI, and particularly DCE MRI, seems to provide early detection and accurate localization of recurrent cancers that enhance earlier and more than post-HIFU fibrosis [33, 34] (Fig. 5). However, DCE MRI lacks specificity. It is indeed difficult to distinguish recurrent cancer from residual BPH tissue. In a retrospective study of 65 patients with biochemical recurrence after HIFU ablation performed at our institution, neither the enhancement pattern nor the apparent diffusion coefficient (ADC) was able to significantly distinguish BPH nodules from recurrent cancers, even if the latter had, on average, higher wash-in rates, lower wash-out rates, and lower ADCs (unpublished results).

Thus, to date, all patients with rising PSA after HIFU ablation should undergo prostate MRI, and all areas with early and intense enhancement should be biopsied to distinguish cancers from BPH residual tissue.

4.4 Towards an Increased Integration of Imaging and Therapy

Imaging is so essential for patient selection, treatment planning and guidance, assessment of tissue destruction, and detection of local recurrences that it is likely that imaging and therapy will become increasingly intertwined in the future.

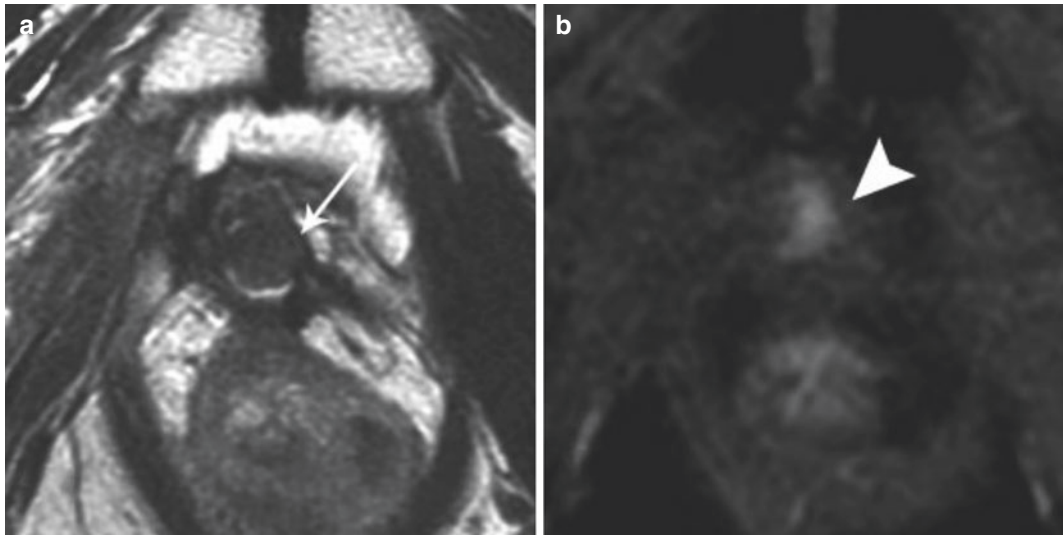

Fig. 5 Multiparametric MR images (**a**): T2-weighted image; (**b**): dynamic contrast-enhanced image) obtained in a 76-year-old patient with history of HIFU ablation for prostate cancer 5 years before. The nadir of the PSA level after HIFU ablation was 0.03 ng/ml. The PSA level had slowly increased to 1.47 ng/ml at the time of MRI. MR images showed an atrophic residual prostate (approximately 4 cc; **a**, *arrow*) with a marked enhancement of its anterior and central part (**b**, *arrowhead*). Targeted biopsy showed recurrent Gleason 6 cancer in this area

Two possible technological strategies can be foreseen.

The first one is the development of prostate cancer HIFU ablation under MR guidance. This approach would directly benefit of MR cancer detection/location capabilities. It can also provide real-time temperature monitoring during treatment [35]. The volume of tissue ablated could be immediately assessed by contrast-enhanced MRI and re-treatment would be easily possible in case of incomplete tissue destruction. This MR-guided integrated approach is probably the ideal solution, but will be expensive and will necessitate dedicated scanners.

Another approach, much less expensive, will consist in keeping the traditional US guidance, but after taking into account preoperative MR cancer mapping by using US/MR fusion software. The assessment of the ablated volume at the end of the treatment will be obtained using CEUS, and thus immediate re-treatment will be possible.

It is too soon to know which approach will prevail in the future.

5 HIFU Devices and Techniques

Three commercially available devices are currently used for the treatment of prostate cancer: Sonablate® (Focus surgery Inc., Indianapolis IN, USA), Ablatherm®, and Focal One® (EDAP-TMS SA, Vaulx en Velin, France).

The Sonablate uses a single transducer (4 MHz) for both imaging and treatment (Fig. 6). Several probes are available with many focal lengths (from 25 to 45 mm). The size of elementary lesion is 10 mm in length and 2 mm in diameter. The Sonablate procedure is conducted in a dorsal position with a patient lying on a regular operating table. Sonablate uses a single treatment protocol in which the power has to be adapted manually by the operator. The treatment is usually made in three consecutive coronal layers, starting from the anterior part of the prostate and moving to the posterior part, with at least one probe switch during the procedure [36]. The probe chosen depends on the prostate size, with

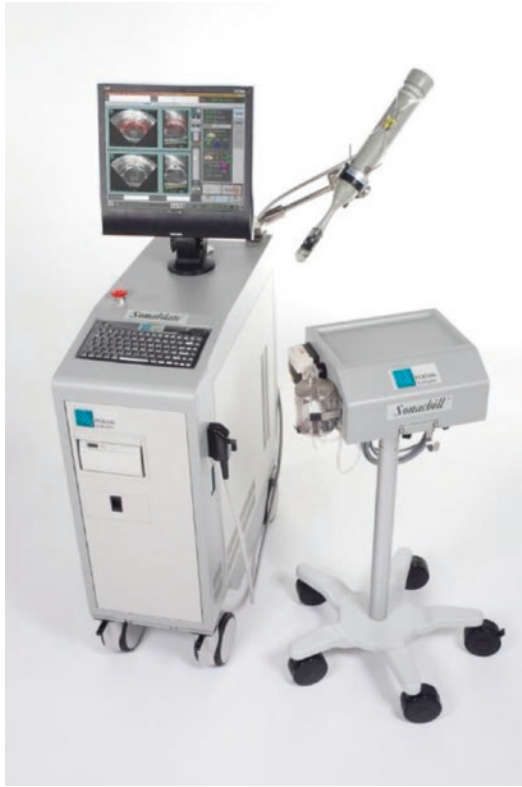

Fig. 6 Sonablate 500

larger glands requiring longer focal length probes.

The Ablatherm has both the imaging (7.5 MHz) and therapeutic (3 MHz) transducers included in a unique endorectal probe focused at 40 mm (Fig. 7a, b). Ablatherm requires a specific bed with a patient on a lateral position. Lateral position treatment allows gas bubbles produced through the heating of the prostate tissue to rise with gravity to a position lateral to the prostate, which will reduce the risk of acoustic interference with the HIFU waves. The Ablatherm includes three treatment protocols with specifically designed treatment parameters depending on the clinical use (standard, HIFU re-treatment, and radiation failure). The size of the HFU induced lesion can be precisely controlled by adjusting the power and the duration of the ultrasound pulse. The size of the elementary lesion may vary from 19 to 26 mm in length (1.7 mm in diameter). HIFU efficacy was mathematically modeled [37]. This allows the calculation of the optimal acoustic intensity necessary to achieve an irreversible necrosis lesion in several clinical situations, particularly for an irradiated prostate. The Ablatherm integrated imaging offers a real-time ultrasonic monitoring of the treatment. The HIFU probe is robotically adjusted with a permanent control of the distance between the transducer and the rectal wall. By repeating the shots and moving the transducer a precise volume can be treated, defined by the operator (planning phase). The treatment is made in transversal layers. The prostate is usually divided into four to six volume boundaries and treated from the apex to the base, slice by slice, by an entirely computer-driven probe. The risk of urethrorectal fistula has been reduced to almost zero thanks to the refinement of the acoustic parameters and many safety features (control of the distance transducer/rectal wall, cooling system, patient motion detector). The standard treatment parameters used 100 % of the acoustic power with a 6-s pulse of energy to create each discrete HIFU lesion with a 4-s delay between each shots. For HIFU re-treatment, the shot duration was reduced to 5 s with the acoustic power of 100 % and a 4-s delay between each shot. Starting in March 2002, specific postradiation treatment parameters were adopted (5-s pulse, 5-s waiting period, 90 % of the acoustic power). These were developed because of the decreased vascularity of the previously irradiated tissue. The goal was to optimize the thermal dose delivered within the gland while minimizing the damage probability to the surrounding tissues, and particularly the rectal wall, caused by the conductive heat transfer. Finally, postbrachytherapy parameters have been developed with 85 % of the acoustic powers with 4-s of energy and 5-s waiting period. In contemporary series, the incidence of urethrorectal fistula was reported between 0 and 0.6 % for primary procedures.

Focal One is a new device specifically designed for focal therapy of prostate cancer, combining the necessary tools to visualize, target, treat, and validate the focal treatment (Fig. 8a). MR images are imported through the hospital's network or USB drive. The operator defines the contours of the prostate and the

Fig. 7 Ablatherm integrated imaging (device and probe)

regions of interests that have been confirmed as prostate tumors. The same contouring of the prostate is performed on the live ultrasound volume acquired by the transrectal probe. The software proceeds to an "elastic fusion": the live ultrasound volume is considered as the reference volume and the MR volume is smoothly deformed so the 3D contour of the prostate on the MR volume matches perfectly the contours of the prostate on the ultrasound volume. The same 3D elastic transformation is applied to the ROIs initially indicated on the MR image so they appear at the adequate position on the live ultrasound image, guiding the planning process (Fig. 9).

Focal One is equipped with a new generation of HIFU probe able to electronically vary the focal point along the acoustic axis using a HIFU multielement transducer (Fig. 8b). The

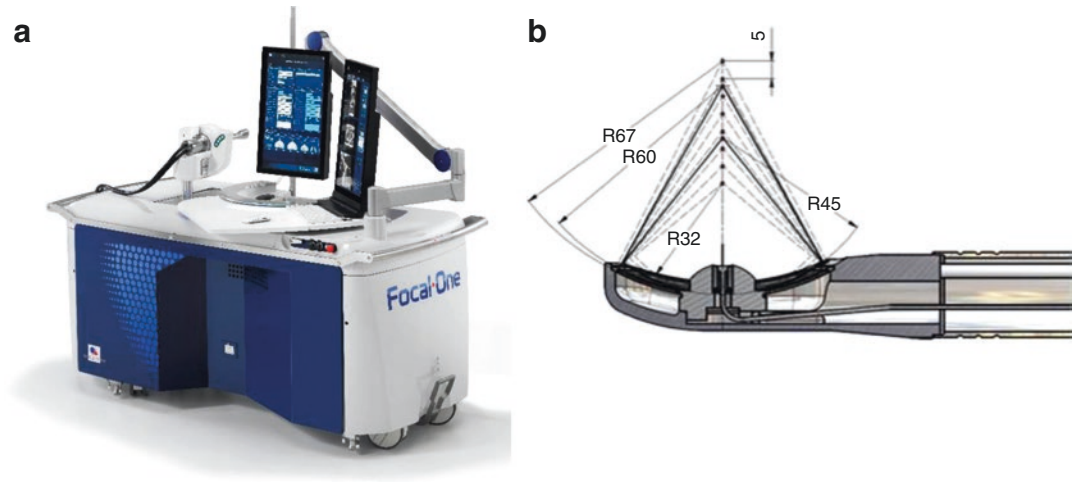

Fig. 8 (**a**, **b**) Focal one (device and phase array transducer)

Dynamic Focusing transducer is made of 16 isocentric rings that allowed an electronic displacement of the focal point to a maximum of 8 different points 32–67 mm from the transducer. The Dynamic Focusing treatment consists in stacking several unitary HIFU lesions (Fig. 9a–c). The unitary HIFU lesion height is 5 mm and stacking two to eight unitary lesions leads to necrotic lesion of 10–40 mm height. The shooting process is 1 s fire at foci and no OFF between different foci. Compare to Fixed Focusing treatment the Dynamic Focusing allow the treatment of bigger prostates with maximum lesion height of 40 mm instead of 26 mm. The wide range of lesion heights (10–40 mm) allows to a better contouring of the prostate. The HIFU treatment of prostate cancer should be faster due to the shooting process with no time OFF between firings. The last advantages of Dynamic Focusing HIFU treatment could be a more homogeneous necrotic zone due to a better energy distribution. During the HIFU energy delivery process, the operator sees a live ultrasound image of what is being treated and, if necessary, can readjust the treatment planning. At the end of the treatment process, a contrast-enhanced ultrasound volume is acquired showing the devascularized areas. This CEUS volume can be fused with the treatment planning as well as the initial MR image showing immediate concordance between targeted and treated areas.

MRgFUS Devices: Magnetic resonance guided focused ultrasound surgery (MRgFUS) was recently presented as a method for ablation with focused ultrasound under magnetic resonance imaging guidance. This approach has the advantage of improved targeting and real-time temperature monitoring. To date, two different approaches have been used for MRgFUS of the prostate: one with a transrectal probe compatible with the ExAblate ® system (InSightec, Haifa, Israel) under a 1.5 T GE MRI, and another with an MRI-compatible ultrasound applicator to deliver controlled thermal therapy to the regions of the prostate gland via a transurethral approach (Profound Medical Inc., Toronto, Canada). The potential of both technologies is currently being demonstrated in Phase I clinical trials, but only a few studies have been conducted in therapy of PCa with human patients [38, 39].

6 HIFU Contraindications

All HIFU devices are size limited and it is not yet possible to treat a prostate gland greater than 60 cc. In order to reduce the size of the prostate, and in particular the distance between the rectal

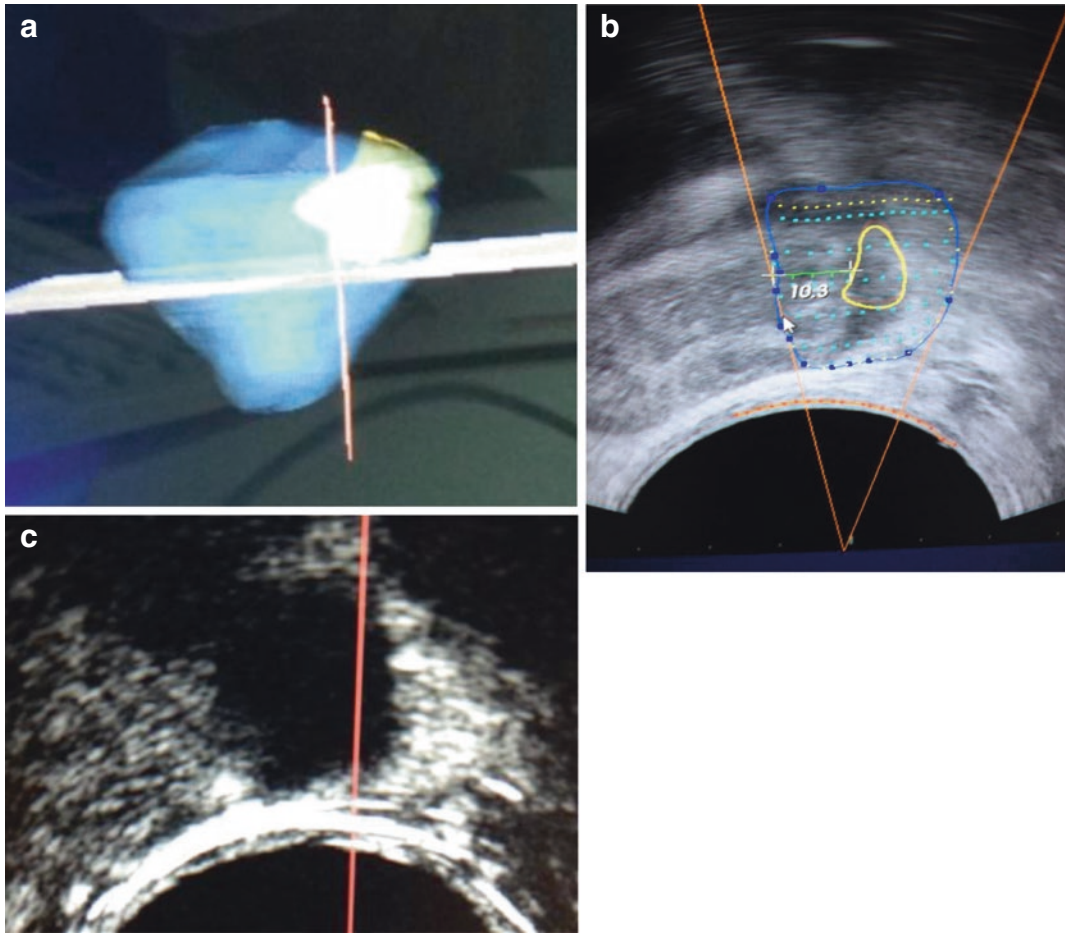

Fig. 9 The live ultrasound volume is considered as the reference volume and the MR volume is smoothly deformed so the 3D contour of the prostate on the MR volume matches perfectly the contours of the prostate on the ultrasound volume (**a**) The same 3D elastic transformation is applied to the ROIs initially indicated on the MR image so they appear at the adequate position on the live ultrasound image, guiding the planning process (**b**). At the end of the treatment process, a contrast-enhanced ultrasound volume is acquired showing the devascularized areas (**c**)

wall and the prostate's anterior, a TURP could be carried out at the time of HIFU or 2 months before the session. TURP dramatically reduces the catheter duration after the HIFU [40–44] and also reduces the risk of bladder outlet obstruction, which is one of the main side effects observed after HIFU.

The HIFU contraindications included a rectal wall thickness >6 mm (Ablatherm device) or >10 mm (Focal One device), a rectal stenosis, chronic inflammatory disease of the intestines, or intense prostate calcifications not removed by the TURP.

7 HIFU as Primary Care Treatment

The usual recommendations on the choice of HIFU for prostate cancer as a primary treatment concern patients with localized prostate cancer (clinical stage T1–T2, NX/0 MX/0) for whom radical prostatectomies are not an option for one the following reasons: age >70 year old, life expectancy ≤10 years, major comorbidities which preclude surgery, or the simple refusal on the part of the patient to undergo one [45, 46]. Among publications on HIFU as a primary

therapy for prostate cancer, 18 studies report a series of at least 50 patients [47–64], while the five most recent studies report a series of at least 500 patients [65–69]. In most cases, the PSA nadir was reached 3–4 months after the HIFU treatment. Many studies have demonstrated that the PSA nadir was a significant predictor of HIFU failure. Patients with a PSA nadir over 0.5 ng/ml must be carefully monitored [56, 62]. A PSA nadir >0.2 ng/ml after HIFU has been associated with a four times greater risk of treatment failure (as defined by cancer on biopsy after HIFU) [65].

Articles published from three European urology departments confirmed the long-term efficacy (mean follow-up 76–97 months) of HIFU treatment with Ablatherm device [65–67].

Crouzet et al. reported results of 1002 patients treated for localized PCa from 1997 to 2009 [65]. At 10 years, the PCa-specific survival rates (PCSSR) and metastasis-free survival rates (MFSR) were 97 % and 94 %, respectively. Salvage therapies included external beam radiation therapy (EBRT) (13.8 %), EBRT+ androgen deprivation (ADT) (9.7 %), and ADT alone (12.1 %). Thuroff et al. published outcomes of 709 patients with primary localized prostate cancer [66]. Mean follow-up was 5.3 years (1.3–14 years). Cancer specific survival was 99 %, metastasis-free survival was 95 %, and 10-year salvage treatment-free rates were 98 % in low-risk, 72 % in intermediate-risk, and 68 % in high-risk patients respectively. The HIFU re-treatment rate has been 15 % since 2005. Ganzer et al. reported results of a prospective study on 538 consecutive patients who underwent primary HIFU for clinically localized PCa [67]. The mean follow-up was 8.1 years. Metastatic disease was reported in 0.4, 5.7, and 15.4 % of low-, intermediate-, and high-risk patients, respectively. The salvage treatment rate was 18 %. PCa-specific death was registered in 18 (3.3 %) patients.

Two recent articles confirm the efficacy of whole-gland HIFU treatment (median follow-up 46–78 months) with Sonablate device. Uchida et al. included 918 patients treated with Sonablate™ devices during 1999–2012 and followed-up for >2 years [68]. The 10-year overall and cancer-specific survival rates were 89.6 % and 97.4 %, respectively. The 5-year biochemical disease-free survival rates in the SB200/500, SB500 version 4, and SB500 tissue change monitor groups were 48.3 %, 62.3 %, and 82.0 %, respectively ($p<0.0001$). Dickinson et al. reported medium-term outcomes in 569 men receiving primary whole-gland HIFU [69]. Of the 569, 163 (29 %) required a total of 185 redo-HIFU procedures. Median follow-up was 46 months. Failure-free survival at 5 years after first HIFU was 70 %; it was 87 %, 63 %, and 58 % for low-, intermediate-, and high-risk groups, respectively.

Complication rates are low with sloughing occurring in 0.3–8.6 %. Urethrorectal fistula occurs in 0.23–0.7 % in the large studies treated with Ablatherm device [65–67]. Erectile dysfunction (ED) occurs in 35–45 % of previous potent patients and bladder outlet obstruction in 24–28 % [66, 67]. Incontinence rates reported in recent studies were: 4–5.5 % grade I and 1.5–3.1 % grade II/III [66, 67]. In the largest study published [65], severe incontinence and bladder outlet obstruction (BOO) decreased with refinement in technology, from 5.7 % and 10.2 % to 3.1 % and 5.9 %, respectively.

In a study from a prospective database, Shoji et al. included 326 patients who filled out self-administered questionnaires on urinary function, QOL, and sexual assessment [70]. Maximum flow rate and residual urine volume were significantly impaired at 6 months ($P=0.010$) after HIFU, even if they returned to baseline values at 12 or 24 months after HIFU. At 6, 12, and 24 months after HIFU, 52 %, 63 %, and 78 %, respectively, of the patients who hadn't received neoadjuvant hormonal therapy were potent.

In a prospective study, Li et al. compared the IIEF score, penile color Doppler ultrasound, penile length, and circumference on patients

treated for prostate cancer with HIFU or cryoablation [71]. At 36 months, cryoablation patients experienced a lower erectile function recovery rate compared to HIFU patients (cryoablation = 46.8 %; HIFU = 65.5 %; $P = 0.021$).

Finally, the oncologic outcomes achieved in large HIFU studies are remarkably consistent across series.

8 HIFU Re-treatment

In case of incomplete treatment or treatment failure, HIFU does not result in a therapeutic impasse. Unlike radiation, there is no dose limitation and no limited number of sessions. In large series, the re-treatment rate is estimated to be between 15 % and 42 % [65–67]. The morbidity related to repeat HIFU treatment for localized prostate cancer has been studied on 223 patients with a re-treatment rate of 22 %. While urinary infection, bladder outlet obstruction and chronic pelvic pain did not significantly differ after one or more sessions, a significant increase was observed for urinary incontinence and impotence in the group which required retreatment [72].

9 Salvage EBRT After HIFU Failure

In a retrospective study, Pasticier et al. presented results of salvage radiation after HIFU [73]. A total of 100 patients were included with a median follow-up of 33 months. Mean doses of radiation were 71.9 ± 2.38Gys. The mean delay between HIFU and ERBT was 14.9 ± 11.8 months. Mean PSA before salvage ERBT was 2.1 ± 1.8 ng/ml and the nadir PSA after ERBT was 0.28 ± 0.76 ng/ml with 17.4 ± 10.8 months to reach nadir. The incontinence rate was the same before and 1 year after salvage ERBT. The progression-free survival rate was 76.6 % at 5 years, and was 93, 70, and 57.5 % for low-, intermediate-, and high-risk group respectively. The predicting factors of failure were the PSA nadir after salvage ERBT and the time to reach this nadir. Recently, Munoz et al. reported the outcomes of 24 patients treated by salvage EBRT after HIFU [74]. The median follow-up was 40.3 months. The 3-years biochemical disease-free rate (bDFS) was 77.8 % (Phoenix definition). Patients achieving nadir PSA ≤ 0.35 ng/ml had a significantly higher bDFS (87.7 % at 3-years).

SRT provides satisfactory oncologic control after HIFU failure with little (or mild) additional toxicity.

10 Salvage Surgery After HIFU Failure

Salvage surgery is feasible after HIFU but with a higher morbidity than after primary surgery. Lawrentschuk et al. reported the results in 15 men with a rising PSA and biopsy-verified prostate cancer after HIFU treatment [75]. Perioperative morbidity was limited to one transfusion in a patient with a rectal injury. Pathological extensive periprostatic fibrosis was found in all patients. Postoperative PSA value was undetectable in 14 patients (93.3 %). Six of ten patients experienced no postoperative incontinence at 12 months, but with uniformly poor erectile function.

Kane reported short term results of 13 men with locally recurrent prostate cancer after HIFU undergoing salvage radical laparoscopic surgery [76]. There was no perioperative mortality and no conversion to open surgery was necessary. None of the patients received any transfusion. On histopathologic evaluation, eight patients had extracapsular extension (pT3a). Positive surgical margins (PSMs) were detected in two patients in the pT3a group. Four patients showed mild incontinence and used two pads per day. None of the patients were potent.

This study confirms that salvage surgery is feasible for men in whom whole-gland HIFU ablation has failed but has a higher morbidity rate than primary surgery. Salvage surgery after whole-gland HIFU is feasible but difficult to perform due to fibrotic reaction.

11 Salvage HIFU After EBRT or Brachytherapy

11.1 EBRT Failure

The rate of positive biopsy after external beam radiotherapy (ERBT) for prostate cancer in the literature is between 25 and 32 % [77, 78].

There appears to be a role for salvage HIFU therapy with curative intents for patients with a locally proven recurrence after external-beam radiation therapy and no metastasis that are usually treated with androgen deprivation [79]. Crouzet et al. examined the outcomes of salvage HIFU in 290 consecutive patients with biopsy-confirmed locally radiorecurrent PCa, without evidence of metastasis [80]. Progression was defined using Phoenix biochemical failure criteria or androgen deprivation (AD) introduction. Local cancer control with negative biopsy results was obtained in 169 patients out of 208 who underwent post-HIFU biopsies (81 %). The median PSA nadir was 0.14 ng/ml. The cancer-specific and metastasis-free survival rates at 7 years were 80 % and 79.6 % respectively. The PFSR was significantly influenced by three factors: the pre-HIFU PSA level, the Gleason score and a previous AD treatment. With the use of dedicated acoustic parameters, the rate of severe side effects decreased significantly from standard parameters: rectourethral fistula (0.4 %), grade II/III incontinence (19.5 %), and bladder outlet obstruction (14 %). Rouvière et al. demonstrated [81] that the MRI localization of cancer recurrence anterior to the urethra is an independent significant predictor of salvage HIFU failure after EBRT. Therefore, MRI may be useful for patient selection before post-EBRT salvage HIFU ablation. Similar outcomes were reported by Berge et al. [82].

Two articles reported outcome of salvage HIFU performed with the Sonablate, the biochemical survival rate was 71 % at 9 months and 52 % at 5 years [83, 84].

Nevertheless, the risk–benefit ratio of salvage HIFU compares favorably with those of the other available techniques and with less morbidity and similar oncological outcomes. In this context, HIFU appears to be an effective curative treatment option for local recurrence after radiation failure.

11.2 Salvage High-Intensity Focused Ultrasound for Patients with Recurrent Prostate Cancer After Brachytherapy

Sylvester et al. reported 15-year biochemical relapse-free survival rate and cause-specific survival following I^{125} prostate brachytherapy in 215 patients: 15-year BRFS for the entire cohort was 80.4 % and the cancer specific survival rate was 84 % [85]. There was no significant difference between the low- and intermediate-risk group. Salvage surgery is a challenging procedure after brachytherapy [86]. Forty-seven patients treated with salvage HIFU for biopsy-proven recurrence after brachytherapy are under evaluation in an ongoing clinical trial in Lyon (unpublished data); 38 patients underwent 1 HIFU session and 9 underwent 2 HIFU sessions. The mean follow-up is 28 months. The mean PSA before HIFU was 4.97 ± 2.9 ng/ml and the median nadir PSA is 0.35 ng/ml. The overall survival rate is 89 %. Cancer specific, metastases-free, and the additional treatment-free survival rates were 94 %, 87 %, and 50 %, respectively. For the first patients, we used post-EBRT treatment parameters. Because of the high rates of side effects, new treatment parameters for brachytherapy failure were developed with a decrease in the acoustic dose according to the intense prostate fibrosis. Main complications were urethrorectal fistula in two patients (4 %) and pubic osteitis in one patient (2 %). Incontinence grade 2/3 and bladder neck stenosis occurred in 17 % and 8.5 % of the cases, respectively. Yutkin reported the outcomes of 19 patients with locally recurrent prostate cancer after brachytherapy treated with whole-gland HIFU [87]. Thirteen men had grade 3a or 3b complications by the Clavien system; there were

no grade 4 or 5 complications. The most common postoperative complication was dysuria, which was self-limited. Three men developed rectourethral fistulae. The overall continence rate was 68.4 %. At a mean follow-up of 51.6 months, all men were alive. The overall biochemical recurrence-free survival rate was 73.3 % using the Astro-Phoenix criteria.

The oncologic outcomes of salvage HIFU after brachytherapy is similar to the outcomes achieved with salvage HIFU after EBRT, but the risk of rectal injury seems higher.

12 Focal Therapy

HIFU focal therapy is another pathway that must be explored when considering the accuracy and reliability for PCa mapping techniques. HIFU would be particularly suitable for such a therapy since it is clear that HIFU results and toxicity are relative to treated prostate volume.

12.1 Focal Therapy as Primary Care Treatment

Active surveillance has been adopted as an option for men who have a low-risk prostate cancer. The advantages of active surveillance must be weighed against the very real possibility of missing the "window" to cure some cancers because of delayed treatment. In the Canadian trial, overall, 30 % of patients have been reclassified as higher risk and have been offered definitive therapy [88]. Of 117 patients treated radically, the PSA failure rate was 50 %, which was 13 % of the total cohort. Focal therapy is emerging as an alternative to active surveillance in the management of low-intermediate risk, selected patients. In patient candidates for active surveillance, the risk of extracapsular extension was found to range from 7 to 19 % and seminal vesicle invasion ranged from 2 to 9 %, depending on the inclusion of patients with Gleason 7 disease [89]. Mouraviev et al. identified unilateral cancers in 19.2 % of 1184 radical prostatectomy specimens [90]. This study suggests, without taking into account cancer significance, that almost a fifth of the patients who are candidates for radical surgery could be amenable to hemiablation using thermal therapy targeting one lobe of prostate. The literature showed a direct correlation between the Gleason score and the outcomes after radical surgery [91]. Stamey et al. demonstrated that tumor volume was associated with biochemical relapse: recurrence occurs in only 14 % of men with a tumor volume of less than 2.0 ml [92]. Focal therapy must be used only in carefully selected patients (Gleason 6 or Gleason 7 3+4, small solitary cancer foci) included in prospective trials. As discussed above, mp-MRI may be useful in the evaluation of patients considering active surveillance or focal therapy [93]. The concept of a index tumor does, however, potentially allow for the use of focal therapy on patients with bilateral tumors. Some evidence exists which shows the largest tumor (the index lesion) is the main driver of progression, outcome, and prognosis; small secondary cancers might be clinically irrelevant [94, 95]. HIFU might be one of the best techniques for focal therapy because it is performed under real time control using ultrasound or MRI. An immediate control of the boundaries of the necrosis area is possible using contrast agents (either with ultrasound and MRI). HIFU procedures can also be repeated if necessary. Finally, salvage standard curative therapies are feasible after HIFU (EBRT, surgery or cryoablation).

In 2008, Muto et al. reported the outcomes of 29 patients treated with Sonablate™ device [96]. In selected patients whose cancer was confined to only one lobe by multiregional biopsies, the total peripheral zone and a half portion of the transitional zone were ablated. The PSA level decreased from 5.36 ± 5.89 ng/ml to 1.52 ± 0.92 at 36 months. Twenty-eight patients underwent control biopsies 6 months after the procedure: a residual cancer foci was found in three patients (10.7 %). Seventeen patients underwent control biopsies 12 months after the procedure: a residual cancer foci was found in four patients (23.5 %). No significant change was found on

IPSS score and maximal flow rate before and 12 months after the procedure.

The first study (20 patients) of prostate hemiablation with HIFU was published in 2011 [97]. Inclusion criteria were men with low-moderate risk (Gleason = 7, PSA = 15 μg/ml), unilateral PCa on TRUS biopsy underwent MRI and 5 mm-spaced trans-perineal template biopsies to localize disease. Of the men, 25 % had low-risk and 75 % intermediate-risk cancer. The mean PSA pre-HIFU was 7.3 ng/ml. Mean PSA decreased to 1.5 ng/ml ± 1.3 at 12 months. A total of 89 % of the patients had no histological evidence of any cancer. Two patients (11.1 %) had positive protocol biopsy at 6 months with residual 1 mm Gleason 3 + 3: one elected for retreatment and the other active surveillance. An erection sufficient for penetrative sex occurred in 95 % of the patients and 95 % of patients were pad free after focal HIFU.

Ahmed et al. reported in 2015, the outcomes of 56 patients with multifocal localized prostate cancer treated with HIFU focal ablation targeted to the index lesion [98]. The mean age was 63.9 years and median prostate-specific antigen (PSA) was 7.4 ng/ml. There were 7 (12.5 %) low-risk, 47 (83.9 %) intermediate-risk, and 2 (3.6 %) high-risk cancers. The median PSA nadir was 2.4 ng/ml. At 12 months, 42/52 (80.8 %) patients had histological absence of clinically significant cancer (Gleason <7, <2 positive cores, and no cancer core length > 3 mm regardless of grade) and 85.7 % (48/56) had no measurable prostate cancer (biopsy and/or mpMRI). Two (3.6 %) patients had clinically significant disease in untreated areas not detected at baseline. Pad-free and leak-free plus pad-free continence was preserved in 92.3% and 92.0% of patients, respectively. Erections sufficient for intercourse were preserved in 76.9 % of patients.

The French Urological Association (AFU) has started a multi-institutional study to evaluate hemiablation with HIFU as a primary treatment for patients >50 years, T1C or T2A, PSA < 10 ng/ml, Gleason 6 or 7 (3 + 4), in no more than one lobe after MRI, random, and targeted biopsies. To be included, the tumor must be >6 mm from apex and >5 mm from the midline. Only one prostatic lobe is treated. The primary outcome was the absence of clinically significant cancer (CSC) on control biopsy (Gleason <7, <2 positive cores, and no cancer core length >3 mm regardless of grade). Secondary outcomes were the presence of any cancer on biopsy, biochemical response, or radical treatment-free survival (RTFS). A total of 111 patients were treated (mean age 64.8 ± 6.2 years; mean PSA 6.2 ± 2.6 ng/ml; 74 % Gleason ≤6; 26 % Gleason 7). On control biopsy, 12 patients (11.9 %) had a CSC (5 ipsilateral; 7 contralateral). Secondary treatments were technically uneventful and the radical treatment-free survival rate at 2 years was 89 %. The mean PSA decrease at 2 years was 62.8 %. The rate of adverse events was 12.6 % Clavien III. At 12 months, urinary and erectile functions were preserved in 97.2 and 78.4 % of patients. No significant decrease in QOL score was observed at 12 months. Similar results were reported by Cordeiro Feijoo et al. [99].

Van Velthoven published the first long term results of a prospective clinical trial of HIFU hemiablation for clinically localized prostate cancer [100]. Hemiablation HIFU was primarily performed in 50 selected patients with biopsy-proven clinically localized unilateral, low-intermediate risk prostate cancer in complete concordance with the prostate cancer lesions identified by magnetic resonance. The median follow-up was 39.5 months. The mean nadir PSA value was 1.6 ng/ml, which represents 72 % reduction compared with initial PSA pre-treatment value ($P < 0.001$). Biochemical recurrence, according to Phoenix definition, occurred in 28 % of patients, respectively. The 5-year actuarial metastases-free survival, cancer-specific survival, and overall survival rates were 93, 100, and 87 %, respectively. Out of the eight patients undergoing biopsy, six patients had a positive biopsy for cancer occurring in the untreated contralateral ($n = 3$) or treated ipsilateral lobe ($n = 1$) or bilaterally ($n = 2$). A Clavien-Dindo grade 3b complication occurred in two patients. Complete continence (no pads) and

erection sufficient for intercourse were documented in 94 or 80 % of patients, respectively.

After hemiablation HIFU, the rate of clinically significant disease was low and associated with low morbidity and preservation of quality of life. This treatment strategy does not preclude future definitive therapies.

New devices (i.e., Focal One) will make HIFU an even more effective treatment option for focal therapy. Preliminary results compare favorably with those of hemiablation studies [101].

12.2 Focal Therapy as Salvage Treatment (Focal Salvage HIFU)

Early identification of a local relapse after radiation therapy failure is feasible using MRI and targeted biopsies performed soon after the biochemical failure (Phoenix criteria). Focal Salvage HIFU is a new therapeutic option. The aim of focal salvage HIFU (FSH) is to destroy the recurrent cancer with a minimal risk of severe side effects.

The study of Ahmed et al. demonstrated that, focal therapy with HIFU can achieve a local control of the disease with minimal morbidity in patients with unilateral relapse after EBRT [102]. Baco and Gelet reported outcomes of 48 men with unilateral radio-recurrent prostate cancer prospectively enrolled in two European centers and treated with hemisalvage HIFU [103]. After HSH, the mean PSA nadir was 0.69 ng/mL at a median follow-up of 16.3 months. Disease progression occurred in 16 patients. Of these, four had local recurrence in the untreated lobe and four bilaterally, six developed metastases, and two had rising PSA levels without local recurrence or radiological confirmed metastasis. Progression-free survival rates at 12, 18, and 24 months were 83, 64, and 52 %. Severe incontinence occurred in 4 of the 48 patients (8 %), 8 (17 %) required one pad a day, and 36/48 (75 %) were pad-free. The mean IPSS and erectile function (IIEF-5) scores decreased from a mean of 7.01–8.6 and from 11.2 to 7.0, respectively.

13 Androgen Deprivation and Chemotherapy Associated with HIFU for High-Risk Prostate Cancer

13.1 Androgen Deprivation

Promising preliminary results on HIFU and hormonal deprivation in patients with locally advanced disease and/or high-risk PCa have been published [61]. At 12 months after the procedure, 28 patients (93 %) were continent. Seven of the 30 men (23 %) had a positive prostate biopsy. At the 1-year follow-up, only three of the 30 patients with high-risk prostate cancer had a PSA level of >0.3 ng/m. Long term outcome was unknown.

13.2 Chemotherapy

Experimental studies have demonstrated the potential of chemotherapy associated with HIFU. In a rat model, Paparel et al. evaluated the therapeutic effect of HIFU combined with Docetaxel on AT2 Dunning adenocarcinoma [104, 105]. They showed a synergistic inhibitory effect of the HIFU + Docetaxel association.

In an ethical committee approved study, 27 high-risk patients (Gleason ≥ 4 + 3 and/or PSA >15 ng/ml and/or >2/3 of positive biopsy) underwent HIFU associated with Docetaxel. Chemotherapy was delivered 30 min before the HIFU treatment. The protocol included a dose escalation starting at 30 mg/ml. Fifteen patients received 30 mg/m^2 of Docetaxel with no adverse effects, two patients received 50 mg/m2 with 1 febrile neutropenia and 1 transient alopecia grade 1 and the next seven patients received 40 ml/m2 without adverse effects. A PSA nadir ≤0.30 ng was achieved in 15 patients (55.5 %). At 7 years, the cancer-specific survival rate and the metastasis-free survival rate were estimated at 90 % (CI:47–98) and 77 % (CI:48–91), respectively. An additional therapy was used in 13 cases: salvage EBRT alone in five patients, salvage EBRT + AD in two patients, and palliative

AD was started in six patients. At 5 years, the progression-free survival rate was 48 % (95 %CI: 27–66). Randomized studies with long term follow-up are required to evaluate the potential role of chemotherapy associated with HIFU in high-risk patients.

Conclusion

The outcomes achieved for primary care patients seem close to those obtained by standard definitive therapies. HIFU does not represent a therapeutic impasse: EBRT is a safe salvage option after HIFU failure and salvage surgery is possible in young and motivated patients. On the other hand, HIFU has a considerable potential for local recurrence after radiation failure. Recently, some early experiences on focal therapy suggest that HIFU provides an excellent opportunity to achieved local control of the disease in low-intermediate risk prostate cancer and in early identified local relapse after EBRT.

References

1. Bosetti C, Bertuccio P, Chatenoud L, Negri E, La Vecchia C, Levi F. Trends in mortality from urologic cancers in Europe, 1970–2008. Eur Urol. 2011;60(1):1–15.
2. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367(3):203–13.
3. Steyerberg EW, Roobol MJ, Kattan MW, van der Kwast TH, de Koning HJ, Schröder FH. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. J Urol. 2007;177(1):107–12.
4. Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. J Clin Oncol. 2011;29(10):1335–41.
5. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, Yamamoto T, Mamedov A, Loblaw A. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33(3):272–7.
6. Lynn JG, Putnam TJ. Histology of cerebral lesions produced by focused ultrasound. Am J Pathol. 1944;20(3):637–49.
7. Chapelon JY, Ribault M, Birer A, Vernier F, Souchon R, Gelet A. Treatment of localised prostate cancer with transrectal high intensity focused ultrasound. Eur J Ultrasound. 1999;9:31–8.
8. Chapelon JY, Margonari J, Vernier F, Gorry F, Ecochard R, Gelet A. In vivo effects of high-intensity ultrasound on prostatic adenocarcinoma Dunning R3327. Cancer Res. 1992;52(22):6353–7.
9. Gelet A, Chapelon JY, Margonari J, Theillere Y, Gorry F, Cathignol D, et al. Prostatic tissue destruction by high-intensity focused ultrasound: experimentation on canine prostate. J Endourol. 1993;7(3):249–53.
10. Gelet A, Chapelon JY, Margonari J, Theillere Y, Gorry F, Souchon R, et al. High-intensity focused ultrasound experimentation on human benign prostatic hypertrophy. Eur Urol. 1993;23 Suppl 1:44–7.
11. Madersbacher S, Kratzik C, Szabo N, Susani M, Vingers L, Marberger M. Tissue ablation in benign prostatic hyperplasia with high-intensity focused ultrasound. Eur Urol. 1993;23 Suppl 1:39–43.
12. Beerlage HP, van Leenders GJ, Oosterhof GO, Witjes JA, Ruijter ET, van de Kaa CA, et al. High-intensity focused ultrasound (HIFU) followed after one to two weeks by radical retropubic prostatectomy: results of a prospective study. Prostate. 1999;39(1):41–6.
13. Gelet A, Chapelon JY, Bouvier R, Souchon R, Pangaud C, Abdelrahim AF, et al. Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. Eur Urol. 1996;29(2):174–83.
14. Gelet A, Chapelon JY, Bouvier R, Pangaud C, Lasne Y. Local control of prostate cancer by transrectal high intensity focused ultrasound therapy: preliminary results. J Urol. 1999;161(1):156–62.
15. Rouviere O, Gelet A, Crouzet S, Chapelon JY. Prostate focused ultrasound focal therapy – imaging for the future. Nat Rev. 2012;9(12):721–7.
16. Sartor O, Eisenberger M, Kattan MW, Tombal B, Lecouvet F. Unmet needs in the prediction and detection of metastases in prostate cancer. Oncologist. 2013;18(5):549–57.
17. Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol. 2013;23(7):2019–29.
18. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol. 2011;186(5):1818–24.
19. Turkbey B, Pinto PA, Mani H, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection – histopathologic correlation. Radiology. 2010;255(1):89–99.
20. Le Nobin J, Orczyk C, Deng FM, et al. Prostate tumour volumes: evaluation of the agreement between magnetic resonance imaging and histology

using novel co-registration software. BJU Int. 2014;114(6b):E105–12.
21. Bratan F, Melodelima C, Souchon R, et al. How accurate is multiparametric MR imaging in evaluation of prostate cancer volume? Radiology. 2015;275(1):144–54.
22. Cornud F, Khoury G, Bouazza N, et al. Tumor target volume for focal therapy of prostate cancer-does multiparametric magnetic resonance imaging allow for a reliable estimation? J Urol. 2014;191(5):1272–9.
23. Donati OF, Jung SI, Vargas HA, et al. Multiparametric prostate MR imaging with T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences: are all pulse sequences necessary to detect locally recurrent prostate cancer after radiation therapy? Radiology. 2013;268(2):440–50.
24. Abd-Alazeez M, Ramachandran N, Dikaios N, et al. Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. Prostate Cancer Prostatic Dis. 2015;18(2):128–36.
25. Alonzo F, Melodelima C, Bratan F, et al. Detection of locally radio-recurrent prostate cancer at multiparametric MRI: can dynamic contrast-enhanced imaging be omitted? Diagn Interv Imaging. 2016;97(4):433–41.
26. Rouviere O, Sbihi L, Gelet A, Chapelon JY. Salvage high-intensity focused ultrasound ablation for prostate cancer local recurrence after external-beam radiation therapy: prognostic value of prostate MRI. Clin Radiol. 2013;68(7):661–7.
27. Rouviere O, Souchon R, Salomir R, Gelet A, Chapelon JY, Lyonnet D. Transrectal high-intensity focused ultrasound ablation of prostate cancer: effective treatment requiring accurate imaging. Eur J Radiol. 2007;63(3):317–27.
28. Rouviere O, Lyonnet D, Raudrant A, et al. MRI appearance of prostate following transrectal HIFU ablation of localized cancer. Eur Urol. 2001;40(3):265–74.
29. Kirkham AP, Emberton M, Hoh IM, Illing RO, Freeman AA, Allen C. MR imaging of prostate after treatment with high-intensity focused ultrasound. Radiology. 2008;246(3):833–44.
30. Rouvière O, Glas L, Girouin N, et al. Transrectal HIFU ablation of prostate cancer: assessment of tissue destruction with contrast-enhanced ultrasound. Radiology. 2011;259(2):583–91.
31. Pasticier G, Chapet O, Badet L, et al. Salvage radiotherapy after high-intensity focused ultrasound for localized prostate cancer: early clinical results. Urology. 2008;72(6):1305–9.
32. Rouviere O, Mege-Lechevallier F, Chapelon JY, et al. Evaluation of color Doppler in guiding prostate biopsy after HIFU ablation. Eur Urol. 2006;50(3):490–7.
33. Ben Cheikh A, Girouin N, Ryon-Taponnier P, et al. MR detection of local prostate cancer recurrence after transrectal high-intensity focused US treatment: preliminary results. J Radiol. 2008;89(5 Pt 1):571–7.
34. Rouviere O, Girouin N, Glas L, et al. Prostate cancer transrectal HIFU ablation: detection of local recurrences using T2-weighted and dynamic contrast-enhanced MRI. Eur Radiol. 2010;20(1):48–55.
35. Salomir R, Delemazure AS, Palussiere J, Rouviere O, Cotton F, Chapelon JY. Image-based control of the magnetic resonance imaging-guided focused ultrasound thermotherapy. Top Magn Reson Imaging. 2006;17(3):139–51.
36. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int. 2006;97(1):56–61.
37. Chavrier F, Chapelon JY, Gelet A, Cathignol D. Modeling of high-intensity focused ultrasound-induced lesions in the presence of cavitation bubbles. J Acoust Soc Am. 2000;108(1):432–40.
38. Chopra R, Colquhoun A, Burtnyk M, N'djin WA, Kobelevskiy I, Boyes A, Siddiqui L, Foster H, Sugar L, Haider MA, Bronskill M, Klotz L. MR imaging-controlled transurethral ultrasound therapy for conformal treatment of prostate tissue: initial feasibility in humans. Radiology. 2012;265:303–13.
39. Zini C, Hipp E, Thomas S, Napoli A, Catalano C, Oto A. Ultrasound- and MR-guided focused ultrasound surgery for prostate cancer. World J Radiol. 2012;4:247–52.
40. Vallancien G, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. J Urol. 2004;171(6 Pt 1):2265–7.
41. Chaussy C, Thuroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. Curr Urol Rep. 2003;4(3):248–52.
42. Thuroff S, Chaussy C. High-intensity focused ultrasound: complications and adverse events. Mol Urol. 2000;4(3):183–7;discussion 9.
43. Netsch C, Pfeiffer D, Gross AJ. Development of bladder outlet obstruction after a single treatment of prostate cancer with high-intensity focused ultrasound: experience with 226 patients. J Endourol. 2010;24(9):1399–403.
44. Sumitomo M, Asakuma J, Sato A, Ito K, Nagakura K, Asano T. Transurethral resection of the prostate immediately after high-intensity focused ultrasound treatment for prostate cancer. Int J Urol. 2010;17(11):924–30.
45. Rebillard X, Davin JL, Soulie M. Treatment by HIFU of prostate cancer: survey of literature and treatment indications. Prog Urol. 2003;13(6):1428–56. Epub 2004/03/06. Traitement par HIFU du cancer de la prostate: revue de la litterature et indications de traitement.
46. Rebillard X, Soulié M, Chartier-Kastler, et al. High-intensity focused ultrasound in prostate cancer; a

systematic literature review of the French Association of Urology. BJU Int. 2008;101(10): 1205–13.
47. Lee HM, Hong JH, Choi HY. High-intensity focused ultrasound therapy for clinically localized prostate cancer. Prostate Cancer Prostatic Dis. 2006;9(4):439–43.
48. Poissonnier L, Chapelon JY, Rouviere O, Curiel L, Bouvier R, Martin X, et al. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol. 2007;51(2):381–7.
49. Uchidaa T, Nakanoa M, Shojia S, Omataa T, Haranoa Y, Nagataa Y, Usuib Y, Terachib T, et al. Ten year biochemical disease free survival after high intensity focused ultrasound (HIFU) for localised prostate cancer: comparison with three different generation devices. J Urol. 2009;181(4):228.
50. Ahmed HU, Zacharakis E, Dudderidge T, Armitage JN, Scott R, Calleary J, et al. High-intensity-focused ultrasound in the treatment of primary prostate cancer: the first UK series. Br J Cancer. 2009;101(1):19–26.
51. Blana A, Brown SCW, Chaussy C, Conti GN, Eastham JA, Ganzer R, et al. Primary prostate HIFU without pretreatment hormone therapy: biochemical survival of 468 patients tracked with the @-registry. J Urol. 2009;181(4):227.
52. Mearini L, D'Urso L, Collura D, Zucchi A, Costantini E, Formiconi A, et al. Visually directed transrectal high intensity focused ultrasound for the treatment of prostate cancer: a preliminary report on the Italian experience. J Urol. 2009;181(1):105–11; discussion 11–2.
53. Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, et al. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. Eur Urol. 2008;53(6):1194–201. Epub 2007/11/13.
54. Misrai V, Roupret M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, et al. Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. World J Urol. 2008;26(5):481–5.
55. Blana A, Rogenhofer S, Ganzer R, Lunz JC, Schostak M, Wieland WF, et al. Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology. 2008;72(6):1329–33; discussion 33–4.
56. Ganzer R, Rogenhofer S, Walter B, Lunz JC, Schostak M, Wieland WF, et al. PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. Eur Urol. 2008;53(3):547–53.
57. Uchida T, Ohkusa H, Yamashita H, Shoji S, Nagata Y, Hyodo T, et al. Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. Int J Urol. 2006;13(3):228–33.
58. Thuroff S, Chaussy C, Vallancien G, Wieland W, Kiel HJ, Le Duc A, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol. 2003;17(8):673–7.
59. Chaussy C, Thuroff S. Results and side effects of high-intensity focused ultrasound in localized prostate cancer. J Endourol. 2001;15(4):437–40; discussion 47–8.
60. Gelet A, Chapelon JY, Bouvier R, Rouviere O, Lasne Y, Lyonnet D, et al. Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. J Endourol. 2000;14(6):519–28.
61. Ficarra V, Antoniolli SZ, Novara G, Parisi A, Fracalanza S, Martignoni G, et al. Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU Int. 2006;98(6):1193–8.
62. Uchida T, Illing RO, Cathcart PJ, Emberton M. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? BJU Int. 2006;98(3):537–9.
63. Chaussy C, Thuroff S, Rebillard X, Gelet A. Technology insight: high-intensity focused ultrasound for urologic cancers. Nat Clin Pract Urol. 2005;2(4):191–8.
64. Crouzet S, Poissonnier L, Murat FJ, Pasticier G, Rouviere O, Mege-Lechevallier F, et al. Outcomes of HIFU for localised prostate cancer using the Ablatherm Integrate Imaging(R) device. Prog Urol. 2011;21(3):191–7.
65. Crouzet S, Chapelon JY, Rouvière O, Mege-Lechevallier F, Colombel M, Tonoli-Catez H, Martin X, Gelet A. Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: oncologic outcomes and morbidity in 1002 patients. Eur Urol. 2014;65(5):907–1464.
66. Thüroff S, Chaussy C. Evolution and outcomes of 3 MHz high intensity focused ultrasound therapy for localized prostate cancer during 15 years. J Urol. 2013;190(2):702–10. 65.
67. Ganzer R, Fritsche HM, Brandtner A, Bründl J, Koch D, Wieland WF, Blana A. Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer. BJU Int. 2013;112(3):322–9.
68. Uchida T, Tomonaga T, Kim H, Nakano M, Shoji S, Nagata Y, Terachi T. Improved outcomes with advancements in high intensity focused ultrasound devices for the treatment of localized prostate cancer. J Urol. 2015;193(1):103–10.
69. Dickinson L, Arya M, Afzal N, Cathcart P, Charman SC, Cornaby A, Hindley RG, Lewi H, McCartan N, Moore CM, Nathan S, Ogden C, Persad R, van der Meulen J, Weir S, Emberton M, Ahmed HU. Medium-term outcomes after whole-gland high-intensity

focused ultrasound for the treatment of nonmetastatic prostate cancer from a multicentre registry cohort. Eur Urol. 2016. pii: S0302–2838(16)00244-X. doi:10.1016/j.eururo.2016.02.054. [Epub ahead of print].
70. Shoji S, Nakano M, Nagata Y, Usui Y, Terachi T, Uchida T. Quality of life following high-intensity focused ultrasound for the treatment of localized prostate cancer: a prospective study. Int J Urol. 2010;17(8):715–9.
71. Li LY, Lin Z, Yang M, Gao X, Xia TL, Ding T. Comparison of penile size and erectile function after high-intensity focused ultrasound and targeted cryoablation for localized prostate cancer: a prospective pilot study. J Sex Med. 2010;7(9):3135–42.
72. Blana A, Rogenhofer S, Ganzer R, Wild PJ, Wieland WF, Walter B. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer. World J Urol. 2006;24(5):585–90; Epub 2006/07/20.
73. Pasticier G, Riviere J, Wallerand H, Robert G, Bernhard JC, Ferriere JM, et al. Salvage radiotherapy (SRT) for local recurrence of prostate adenocarcinoma after primary treatment with high intensity focused ultrasound (HIFU): first series of 100 patients. 2010 ASCO annual meeting. 2010.
74. Munoz F, Guarneri A, Botticella A, Gabriele P, Moretto F, Panaia R, Ruggieri A, D'Urso L, Muto G, Filippi AR, Ragona R, Ricardi U. Salvage external beam radiotherapy for recurrent prostate adenocarcinoma after high-intensity focused ultrasound as primary treatment. Urol Int. 2013;90(3):288–93.
75. Lawrentschuk N, Finelli A, Van der Kwast TH, Ryan P, Bolton DM, Fleshner NE, et al. Salvage radical prostatectomy following primary high intensity focused ultrasound for treatment of prostate cancer. J Urol. 2011;185(3):862–8. Epub 2011/01/18.76 Kane C. Salvage laparoscopic radical prostatectomy following high-intensity focused ultrasound for treatment of prostate cancer.Urol Oncol. 2013 Feb;31(2):273–4.
76. Kane C. Salvage laparoscopic radical prostatectomy following high-intensity focused ultrasound for treatment of prostate cancer. Urol Oncol. 2013;31(2):273–4.
77. Borghede G, Aldenborg F, Wurzinger E, Johansson KA, Hedelin H. Analysis of the local control in lymph-node staged localized prostate cancer treated by external beam radiotherapy, assessed by digital rectal examination, serum prostate-specific antigen and biopsy. Br J Urol. 1997;80(2):247–55.
78. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol. 2001;166(3):876–81. Epub 2001/08/08.
79. Murat FJ, Poissonnier L, Rabilloud M, Belot A, Bouvier R, Rouviere O, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol. 2009;55(3):640–7.
80. Sébastien C, Francois-Joseph M, Pascal P, Laura P, Gilles P, Olivier R, Jean-Yves C, Muriel R, Aurélien B, Florence M-L, Hélène T-C, Xavier M, Albert G. Locally recurrent prostate cancer after initial radiation therapy: early salvage high-intensity focused ultrasound improves oncologic outcomes. Radiother Oncol. 2012. doi:10.1016/j.radonc.2012.09.014.
81. Rouvière O, Sbihi L, Gelet A, Chapelon JY. Salvage high-intensity focused ultrasound ablation for prostate cancer local recurrence after external-beam radiation therapy: prognostic value of prostate MRI. Clin Radiol. 2013;68(7):661–7. doi:10.1016/j.crad.2012.12.010.
82. Berge V, Baco E, Karlsen SJ. A prospective study of salvage high-intensity focused ultrasound for locally radiorecurrent prostate cancer: early results. Scand J Urol Nephrol. 2010;44(4):223–7.
83. Zacharakis E, Ahmed HU, Ishaq A, Scott R, Illing R, Freeman A, et al. The feasibility and safety of high-intensity focused ultrasound as salvage therapy for recurrent prostate cancer following external beam radiotherapy. BJU Int. 2008;102(7):786–92.
84. Uchida T, Shoji S, Nakano M, Hongo S, Nitta M, Usui Y, et al. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. BJU Int. 2010;107(3):378–82.
85. Sylvester JE, Grimm PD, Wong J, Galbreath RW, Merrick G, Blasko JC. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: seattle experience. Int J Radiat Oncol Biol Phys. 2010;81:376–81.
86. Heidenreich A, Richter S, Thuer D, Pfister D. Prognostic parameters, complications, and oncologic and functional outcome of salvage radical prostatectomy for locally recurrent prostate cancer after 21st-century radiotherapy. Eur Urol. 2010;57(3):437–43.
87. Yutkin V, Ahmed HU, Donaldson I, McCartan N, Siddiqui K, Emberton M, Chin JL. Salvage high-intensity focused ultrasound for patients with recurrent prostate cancer after brachytherapy. Urology. 2014;84(5):1157–62.
88. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010;28(1):126–31.
89. Conti SL, Dall'era M, Fradet V, Cowan JE, Simko J, Carroll PR. Pathological outcomes of candidates for active surveillance of prostate cancer. J Urol. 2009;181(4):1628–33; discussion 33–4.
90. Mouraviev V, Mayes JM, Sun L, Madden JF, Moul JW, Polascik TJ. Prostate cancer laterality as a

rationale of focal ablative therapy for the treatment of clinically localized prostate cancer. Cancer. 2007;110(4):906–10.
91. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status to predict biochemical failure after radical prostatectomy. J Urol. 2001;165(1):119–25.
92. Stamey TA, McNeal JE, Yemoto CM, Sigal BM, Johnstone IM. Biological determinants of cancer progression in men with prostate cancer. JAMA. 1999;281(15):1395–400.
93. Mullins JK, Bonekamp D, Landis P, Begum H, Partin AW, Epstein JI, Carter HB, Macura KJ. Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance. BJU Int. 2013;111(7):1037–45.
94. Wise AM, Stamey TA, McNeal JE, Clayton JL. Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology. 2002;60(2):264–9.
95. Noguchi M, Stamey TA, McNeal JE, Nolley R. Prognostic factors for multifocal prostate cancer in radical prostatectomy specimens: lack of significance of secondary cancers. J Urol. 2003;170(2 Pt 1):459–63.
96. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. 2008;38(3):192–9. Epub 2008/02/19.
97. Ahmed HU, Freeman A, Kirkham A, Sahu M, Scott R, Allen C, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011;185(4):1246–54.
98. Ahmed HU, Dickinson L, Charman S, Weir S, McCartan N, Hindley RG, Freeman A, Kirkham AP, Sahu M, Scott R, Allen C, Van der Meulen J, Emberton M. Focal ablation targeted to the index lesion in multifocal localised prostate cancer: a prospective development study. Eur Urol. 2015;68(6):927–36.
99. Feijoo ER, Sivaraman A, Barret E, Sanchez-Salas R, Galiano M, Rozet F, Prapotnich D, Cathala N, Mombet A. Cathelineau X focal high-intensity focused ultrasound targeted hemiablation for unilateral prostate cancer: a prospective evaluation of oncologic and functional outcomes. Eur Urol. 2016;69(2):214–20.
100. Van Velthoven R, Aoun F, Marcelis Q, Albisinni S, Zanaty M, Lemort M, Peltier A, Limani K. A prospective clinical trial of HIFU hemiablation for clinically localized prostate cancer. Prostate Cancer Prostatic Dis. 2016;19(1):79–83.
101. Albert G, Sebastien C, Olivier R, Flavie B, Jean-Yves C. Focal treatment of prostate cancer using focal one device: pilot study results. J Ther Ultrasound. 2015;3(Suppl 1):O54 (30 June 2015).
102. Ahmed HU, Cathcart P, McCartan N, Kirkham A, Allen C, Freeman A, Emberton M. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer. 2012;118(17):4148–55.
103. Baco E, Gelet A, Crouzet S, Rud E, Rouvière O, Tonoli-Catez H, Berge V, Chapelon JY, Eggesbø HB. Hemi salvage high-intensity focused ultrasound (HIFU) in unilateral radiorecurrent prostate cancer: a prospective two-centre study. BJU Int. 2014;114(4):532–40.
104. Paparel P, Curiel L, Chesnais S, Ecochard R, Chapelon JY, Gelet A. Synergistic inhibitory effect of high-intensity focused ultrasound combined with chemotherapy on Dunning adenocarcinoma. BJU Int. 2005;95(6):881–5.
105. Paparel P, Chapelon JY, Bissery A, Chesnais S, Curiel L, Gelet A. Influence of the docetaxel administration period (neoadjuvant or concomitant) in relation to HIFU treatment on the growth of Dunning tumors: results of a preliminary study. Prostate Cancer Prostatic Dis. 2008;11(2):181–6.