High-Intensity Focused Ultrasound (HIFU) for Prostate Cancer

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Contents

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15.1 Introduction

The incidence of prostate cancer is increasing worldwide. In Europe, the mortality rate declined from 15 per 100,000 in 1995 to 12.5 per 100,000 in 2006 (Bosetti et al. 2011). 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, potentially curative therapy; secondly, better control of the disease was secured from a

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wider adoption of radical prostatectomies and the use of combines androgen deprivation and radiotherapy for patients with locally advanced disease. But the morbidity associated with the radical treatment of either surgery or radiotherapy is significant, suggesting that radical surgery and/or radiation therapy should only be offered to men who are likely to survive more than 10 years. In the randomized study radical prostatectomy versus watchful waiting of the Scandinavian prostate Cancer Group Study, the incidence of death from prostate at 15 years was 14.6 in the surgery group as opposed to 20.7 in the watchful waiting group (Bill-Axelson et al. 2011). However, among men 65 years or older, there was no significant reduction of deaths or metastatic incidences. Albertsten et al. recently 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 65 years will die as a result of prostate cancer within 10 years of diagnosis (Albertsen et al. 2011). 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 the results of a large series of patients treated with active surveillance (watchful waiting protocol with selective delayed intervention) in 2010 (Klotz et al. 2010a). 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.

15.2 HIFU in Prostate Cancers Models and First Clinical Trials

The first description of HIFU was made in 1942 and the ability to destroy tissue established in 1944 (Lynn et al. 1942; Lynn and Putnam 1944). 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 (Chapelon et al. 1992). In 1993, Gelet et al. established that it was possible to induce irreversible coagulation necrosis lesions in dog's prostates through a transrectal route without damaging the rectal wall (Gelet et al. 1993a). An ethics committee approved the evaluation of the use of HIFU for the treatment of localized prostate cancer in humans. The results of a pilot study were published in 1996 and the preliminary results of the first 50 patients in 1999 (Gelet et al. 1996, 1999).

15.3 Principles

HIFU produces ultrasound waves that are generated by a spherical transducer. The ultrasound energy is focused on a fixed point. The first experiments on the prostate were made on dogs and on men with benign prostate hypertrophy (Gelet et al. 1993a, b; Madersbacher et al. 1993). Ultrasound waves deposit energy as they travel through tissues. For imaging purposes, this deposited energy is insignificant. By increasing the intensity of the waves and focusing them on a single point, HIFU allows the deposit of a large amount of energy into the tissue, resulting in its destruction through cellular disruption and coagulative necrosis (Beerlage et al. 1999). There are two mechanisms involved in the destruction of the tissue: thermal effects and cavitation (Kennedy et al. 2003). The thermal effect relies on the absorption of ultrasound energy by the tissue and its conversion into heat. In the right conditions, the temperature within sonicated tissue will rise to a level sufficient to induce irreversible damage. Cavitation is the result of the interaction between ultrasound and microbubbles in the sonicated tissue. This interaction may lead to oscillation of these microbubbles, violent collapses, and dispersion of energy, enhancing tissue ablation. The aim is to treat the entire gland by a juxtaposition of elementary lesions (Fig. 15.1). The

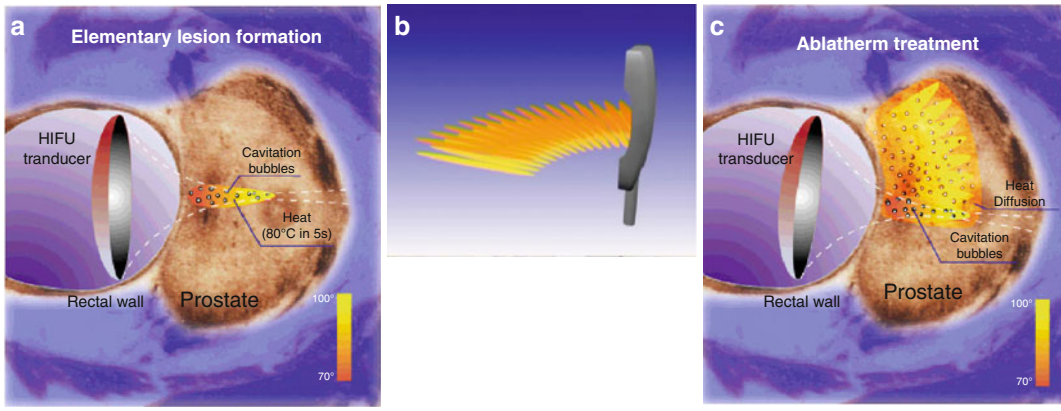


Fig. 15.1 To treat the prostate, the HIFU transducer is previously covered with a balloon filled with coupling liquid. Then, it is inserted into the patient's rectum and positioned close to the rectum wall in such a way that the base of the lesion will stop close to the prostate capsula (**a**). This precise positioning prevents from any rectal wall damage. Prostate treatment is performed by the repetition and juxtaposition of several elementary lesions (**b**). The sum of these elementary lesions creates a continuous volume where tissue is entire destroyed (**c**)

main sonication parameters are acoustic intensity, duration of exposure, on/off ratio, the distance between two elementary lesions, and the displacement path when multiple lesions are made. This technique has the advantage of a transrectal treatment with prostate destruction while sparing the rectum itself. By combining a precise control of the position of the transducer within the rectum and an active cooling of the rectal mucosa, the risk of rectal injury is minimized. HIFU induced-lesions are visible using standard ultrasound as hyperechoic areas, but their extent is not always accurately defined. MRI is the gold-standard technique used for HIFU treatment efficacy assessment. Gadolinium-enhanced T1-weighted images can show very clearly the extent of necrosis (Rouviere et al. 2001). MRI has also been used to guide HIFU treatment as well as to monitor temperature changes during HIFU, but it must be noted that this technology is experimental for transrectal prostate cancer treatment.

15.4 Prostate Modern Imaging: A Critical Key for Improving HIFU Outcomes

Imaging plays a critical role in the management of patients treated with HIFU ablation (Rouviere et al. 2007). Recent progress in modern imaging should improve the outcome of HIFU ablation in the near future. However, additional improvement is still needed at least in three different fields: patient selection and treatment planning, assessment of HIFU ablation in the operating room, and detection of local recurrences.

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

A precise knowledge of the size and location of tumor foci could improve treatment outcome by identifying poor candidates for HIFU ablation (e.g., patients with anterior tumors that might be beyond the focal point of the transducer, or apical tumors close to the urethral sphincter). It could also allow better targeting of the treatment (e.g., the operator could slightly extend the treated volume into the periprostatic tissue around the tumors in order to treat potential microscopic extracapsular extensions).

The need for a precise preoperative mapping of tumor foci is even more important in the perspective of focal HIFU ablation, the success of which will depend not only on the accurate localization of the tumor targets but also on the correct identification of sectors free of cancer.

Unfortunately, for many years, prostate imaging has yielded suboptimal results in prostate cancer detection and localization, and the results

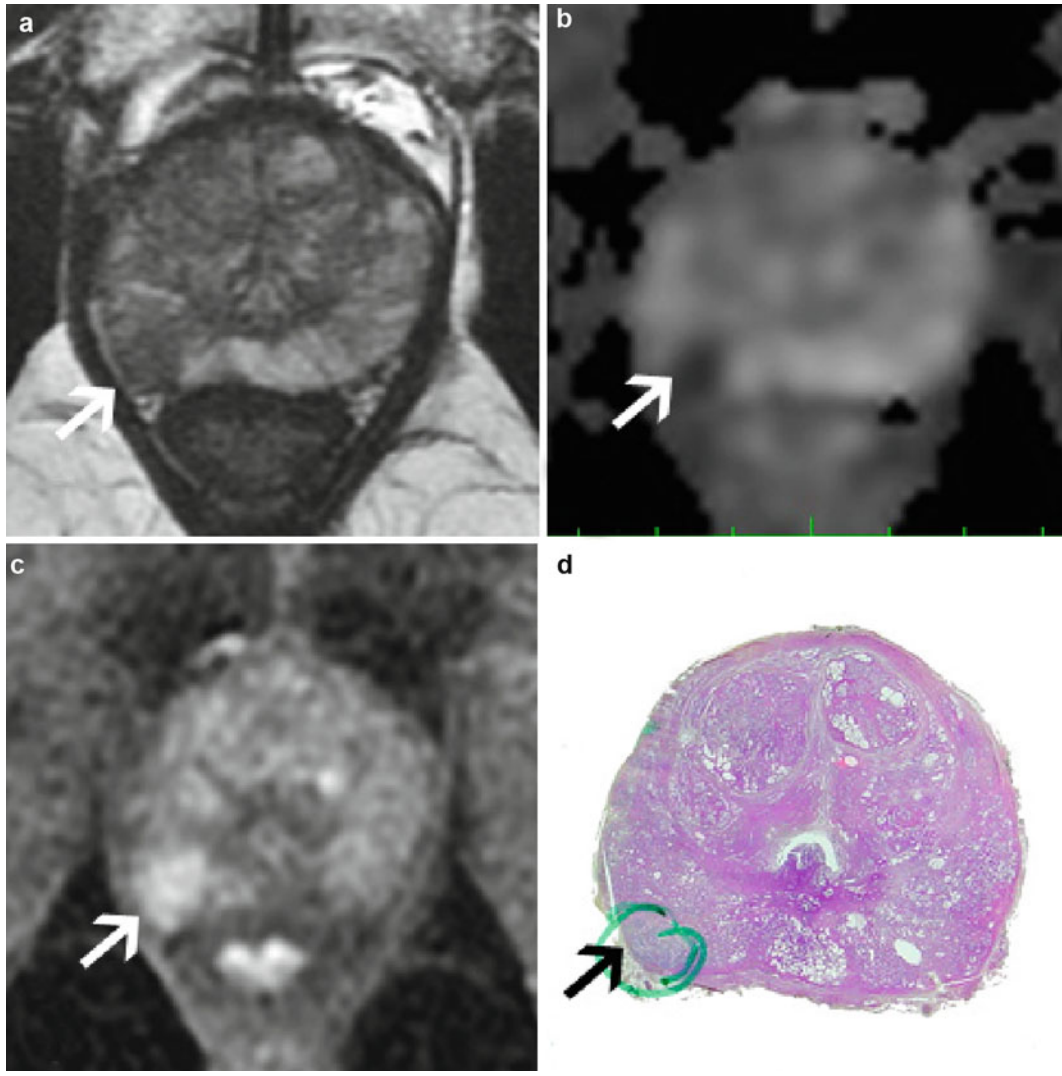


Fig. 15.2 Multiparametric axial MR images (**a** – T2-weighted image; **b –** apparent diffusion coefficient (*ADC*) map computed from diffusion-weighted images (*b* values: 0 and 2,000 s/mm²); **c –** dynamic contrast-enhanced image) and **d –** axial section of the prostatectomy specimen obtained in a 66-year-old patient with a Gleason 8 prostate cancer of the right midgland and base at biopsy. MR 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*). **d –** The analysis of the prostatectomy specimen was confirmative and showed in that area a Gleason 8 cancer. The rest of the gland did not contain cancer

in the US-based techniques have been particularly disappointing (Rouviere et al. 2007).

Nonetheless, excellent results have been recently published with MRI, especially since dynamic contrast-enhanced (DCE) and diffusion-weighted sequences have been used in addition to the classical T2-weighted imaging. There is now a large and concordant body of literature showing that this so-called prostate multiparametric MRI allows a good detection of high-grade prostate cancers (Gleason score ≥ 7), with an excellent negative predictive value, in candidates to radical prostatectomy (Girouin et al. 2007; Villers et al. 2006; Turkbey et al. 2010) but also in the more challenging population of patient candidates for biopsies (Cheikh et al. 2009) (Fig. 15.2). The

detection of anterior tumors, which are usually missed by random biopsies, is also excellent (Lemaitre et al. 2009).

In 2008, we started a database in order to collect information on the precise correlation between MR and pathological specimen findings in patients who received a radical prostatectomy at our institution (CLARA-P database). To date, 127 patients imaged either at 1.5 T ($n=65$) or 3 T ($n=62$) have been included. The MR images were reviewed by 2 independent readers and compared to histological findings. Both readers detected all Gleason ≥8 tumors. The detection rates for Gleason ≤ 6 tumors with a volume of 0.05–0.5, 0.5–2, and >2 cc were 27–37%, 42–51%, and 67–83%, respectively. For Gleason 7 tumors, the detection rates were respectively 61–64%, 80–83%, and 96%. There was no difference between 1.5 T and 3 T results (Bratan et al. 2011).

These results suggest that MRI is an excellent screening tool, with a good negative predictive value, for Gleason ≥ 7 tumors.

MRI does, however, still have some weaknesses that need to be corrected.

First, its sensitivity for Gleason ≤ 6 cancers remains suboptimal, and even when the tumor volume is >0.5 cc. Second, its specificity needs to be improved: approximately 40% of suspicious areas noted in the CLARA-P database were benign. However, the two readers were able to stratify the risk of malignancy by attributing a suspicion score to each suspicious MR abnormalities. Thus, at 1.5 T, 12–37% of score 1 (likely benign), 30–52% of score 2 (indeterminate), 78–82% of score 3 (likely malignant), and 97–100% of score 4 (definitely malignant) abnormal MR areas were cancers. These figures were 5–22%, 22–45%, 45–62%, and 93–96% at 3 T (Bratan et al. 2011). Third, the reproducibility of multiparametric MRI needs to be improved. The good results obtained in specialized university centers are not always reproduced in daily practice. Intensive research is ongoing in order to validate simple suspicion scores aimed at helping nonspecialized radiologists identify abnormal areas seen at MRI. But promising results have also been obtained with computer-aided diagnosis software (Niaf et al. 2011; Puech et al. 2009).

After radiation therapy, MRI, and especially DCE MRI, has also shown promising results in detecting and localizing local recurrences (Rouviere et al. 2004; Haider et al. 2008). It seems that postradiation local recurrences are even easier to localize than untreated prostate cancer because of the favorable contrast between poorly enhancing postradiation fibrosis and recurrent cancer (Fig. 15.3). Besides, MRI 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 (unpublished results).

15.4.2 Postoperative Evaluation of the Ablated Area

Ideally, imaging should show the amount of prostate volume destroyed at the end of the HIFU ablation session so that in the event of unsatisfactory results, another HIFU ablation can be performed immediately. Unfortunately, transrectal ultrasound, used to guide HIFU treatment, cannot show the ablated area with the necessary accuracy (Rouviere et al. 2007).

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 (Rouviere et al. 2001; Kirkham et al. 2008).

We have recently shown that contrast-enhanced ultrasound (CEUS), using Sonovue™ as a 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 safely considered to have been entirely destroyed. On the other hand, prostate sectors showing any degree of enhancement can be considered to contain living (benign or malignant) tissue (Rouvière et al. 2011) (Fig. 15.4). These results should

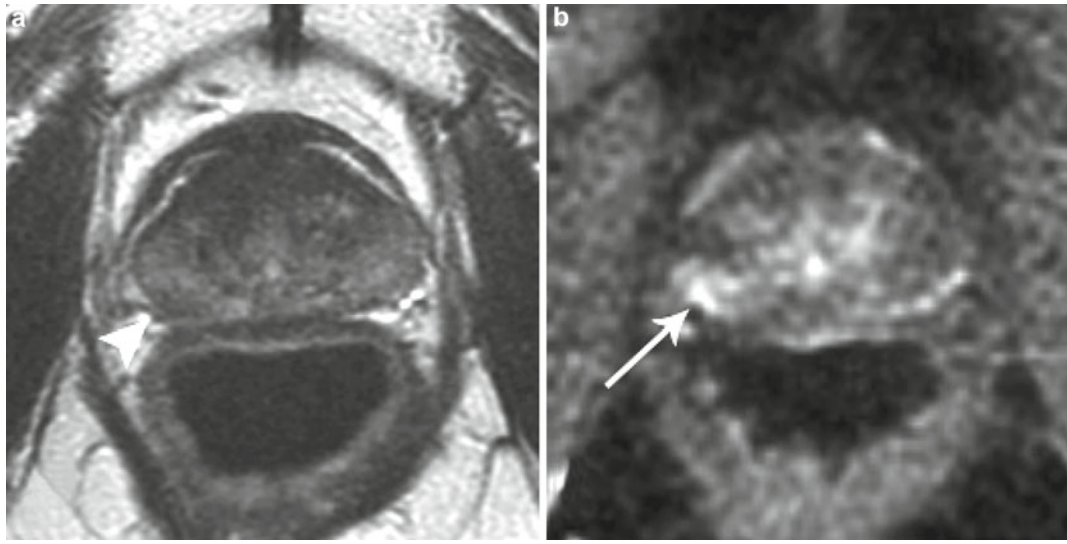


Fig. 15.3 Multiparametric MR images (**a –** T2-weighted image; **b –** dynamic contrast-enhanced image) obtained in a 69-year-old patient with history of radiation therapy for prostate cancer 10 years before. The nadir of the PSA level after radiation therapy was 0.8 ng/ml. The PSA level had slowly 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

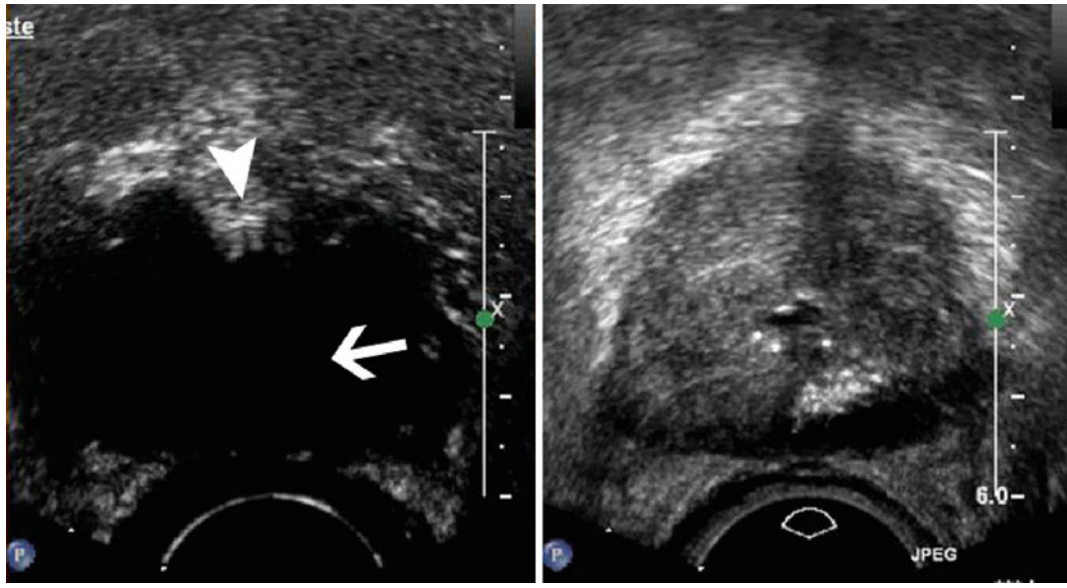


Fig. 15.4 Contrast-enhanced ultrasound (CEUS) axial image (*left part* of the figure), with corresponding low mechanical index gray-scale image (dual mode; *right part* of the figure), obtained after HIFU ablation of a local recurrence of prostate cancer after radiation therapy in a 68-year-old patient. 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

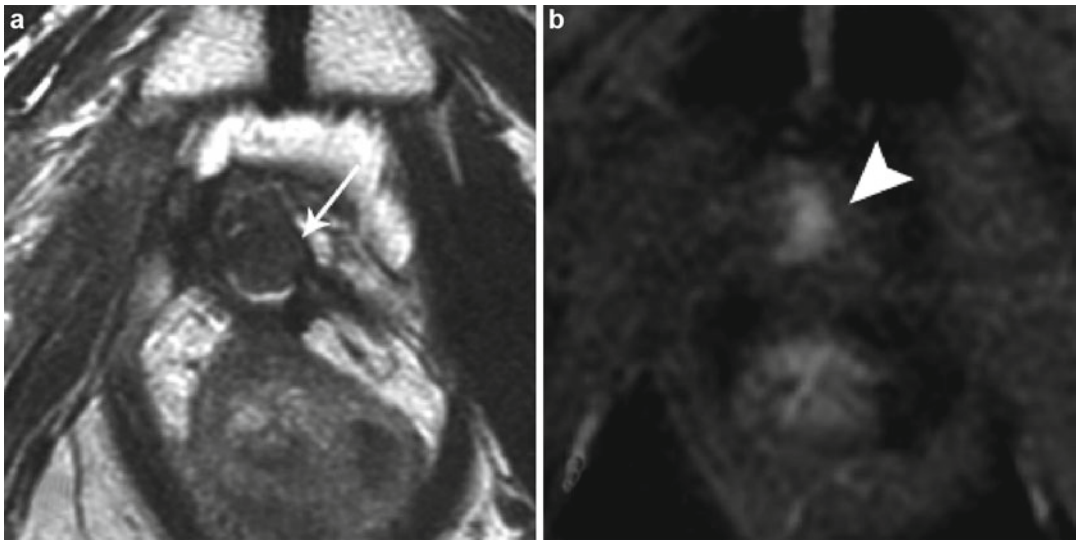


Fig. 15.5 Multiparametric MR images (**a –** T2-weighted image; **b –** dynamic contrast-enhanced image) obtained in a 76-year-old patient with history of HIFU ablation for prostate cancer 5 years before. The nadir of the PSA level after HIFU ablation was 0.03 ng/ml. The PSA level had slowly increased 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

allow immediate re-treatment of the parts of the gland showing residual enhancement and that are within the range of the transducer.

15.4.3 Detection of Post-HIFU Local Recurrences

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

Because local recurrences (or residual cancers) after HIFU ablation can be treated by a second session of HIFU ablation or by radiation therapy (Pasticier et al. 2008); it is imperative that they be detected early. The precise location of these recurrences can also help in selecting the salvage treatment (e.g., anterior recurrences may be better treated by radiation therapy).

Even if color Doppler can sensitize TRUS (Rouviere et al. 2006), US-based techniques are not accurate enough to detect early local recurrences and guide the 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 (Ben Cheikh et al. 2008; Rouviere et al. 2010) (Fig. 15.5). However, DCE MRI does lack 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 washout 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.

15.4.4 Toward an Increased Integration of Imaging and Therapy

Imaging has become so essential for patient selection, treatment planning and guidance,

Fig. 15.6 Ablatherm® device

assessment of tissue destruction, and detection of local recurrences that it is likely that imaging and therapy will become increasingly integrated in the future.

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 (Salomir et al. 2006). Contrast-enhanced MRI could immediately assess the volume of tissue ablated, and re-treatment would be quite easy in cases of incomplete tissue destruction. This MR-guided integrated approach is probably the ideal solution, but it will be expensive and will require dedicated scanners.

Another approach, much less expensive, will be to keep 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 early to know which approach will prevail in the future.

15.5 HIFU Devices and Techniques

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

The Ablatherm has both the imaging (7.5 MHz) and therapeutic (3 MHz) transducers included in a unique endorectal probe focused at 40 mm. Ablatherm requires a specific bed with a patient on a lateral position (Fig. 15.6). 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 HIFU-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 (Chavrier et al. 2000). 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 last Ablatherm device (integrated imaging) offers a real-time ultrasonic monitoring of the treatment. In the Ablatherm system, 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 (Fig. 15.1). The prostate is usually divided into 4–6 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 shot. 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 urethra-rectal fistula was reported between 0% and 0.6% for primary procedures.

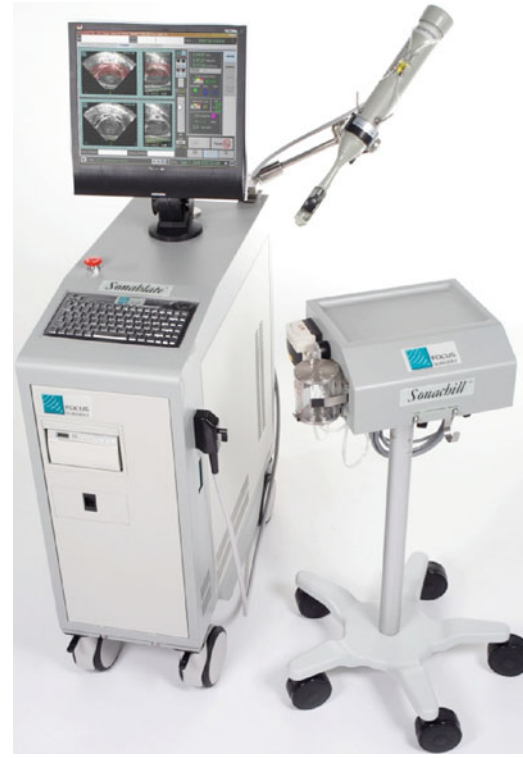


Fig. 15.7 Sonablate® device

The Sonablate uses a single transducer (4 MHz) for both imaging and treatment. Several probes are available with many focal lengths (from 25 to 45 mm) (Fig. 15.7). 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 (Uchida et al. 2006a). The probe chosen depends on the prostate size, with larger glands requiring longer focal length probes.

The size of the prostate is one drawback of HIFU technology: Due to the limitation of the focal lengths of therapy transducers, it is not yet possible to treat a prostate gland greater than 35 cc.

In order to reduce the size of the prostate, and in particular the distance between the rectal wall and the prostate's anterior part, a TURP could be carried out 2 months before the HIFU session. Moreover, the TURP dramatically reduces the catheter duration after the HIFU session (Vallancien et al. 2004; Chaussy and Thuroff 2003; Thuroff and Chaussy 2000) and reduces the risk of bladder outlet obstruction, which is one of the main side effects observed after HIFU. Most of the team performed a TURP at the time of the HIFU treatment in order to reduce the duration of catheterization. The TURP can be performed before the HIFU treatment (Vallancien et al. 2004; Chaussy and Thuroff 2003; Thuroff and Chaussy 2000; Netsch et al. 2010) or after (Sumitomo et al. 2010).

15.6 HIFU Outcomes

In most cases, the PSA nadir was reached 3–4 months after the HIFU treatment and was ≤0.05 ng/ml in 55–91% of the cases. The most commonly reported adverse event was prolonged urinary retention, but this has been dramatically reduced by performing a TURP at the time of the HIFU treatment. The urinary catheter is generally removed at post-op day 2 or 3. Incontinence after HIFU as a primary therapy is low: grade I 4–6% and grade II 0–2%. The rate of incontinence increases in cases of HIFU re-treatment or salvage HIFU. Other infrequently reported side effects are urinary tract infection, urethral stricture, and chronic pain. Urethral rectal fistula has been reported in the early experience but is now a very rare occurrence, particularly when safety margins and contraindications are respected.

The HIFU contraindications included a rectal wall thickness >6 mm, a rectal stenosis, chronic inflammatory disease of the intestines, and intense prostate calcifications not removed by the TURP.

15.7 HIFU as Primary Care Treatment

The recommendations and updated guidelines on the use of HIFU for prostate cancer as a primary treatment concern patients with localized prostate cancer (clinical T1–T2 stage Nx/0 M0 prostate cancer) 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 etc., or the simple refusal on the part of the patient to undergo one (Rebillard et al. 2003; AURO 2009). Among publications on HIFU as a primary therapy for prostate cancer, 16 studies report a series of at least 50 patients (Uchida et al. 2006a, b, 2009; Crouzet et al. 2010a; Lee et al. 2006; Poissonnier et al. 2007; Ahmed et al. 2009; Blana et al. 2008a, b, 2009; Mearini et al. 2009; Misrai et al. 2008; Ganzer et al. 2008; Thuroff et al. 2003; Chaussy and Thuroff 2001; Gelet et al. 2000), while the others report on fewer patients (Ficarra et al. 2006; Challacombe et al. 2009; Maestroni et al. 2008; Koch et al. 2007). Follow-up varies significantly between series (range: 6 months to 6.4 years). In most cases, the PSA nadir was reached 3–4 months after the HIFU treatment and was = 0.05 ng/ml in 55–91% of the cases. 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 (Lee et al. 2006; Ganzer et al. 2008). 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) (Uchida et al. 2006c).

The 7 years disease-free survival rate in the longest follow-up multicenter studies was 75%, 63%, and 62% for low-, intermediate-, and high-risk patients, respectively, and the 8 years cancer-specific survival rate was 99% (Crouzet et al. 2010a). Complication rates are low, with sloughing occurring in 0.3–8.6%. Impotence occurs in 20–77% of patients and bladder outlet obstruction in 12–22%. Incontinence rates reported in a recent study were grade I (4–17.5%) and grade II and III (0–5%) (Chaussy et al. 2005; Crouzet et al. 2011). In our institution, we have recently reviewed the results of 880 patients. Mean age was 70 years. Stratification according to D'Amico's risk group was low, intermediate, and high in 36%, 48%, and 16%, respectively. Median follow-up was 41 months. Median PSA nadir was 0.1 ng/ml. The overall and cancer-specific survival

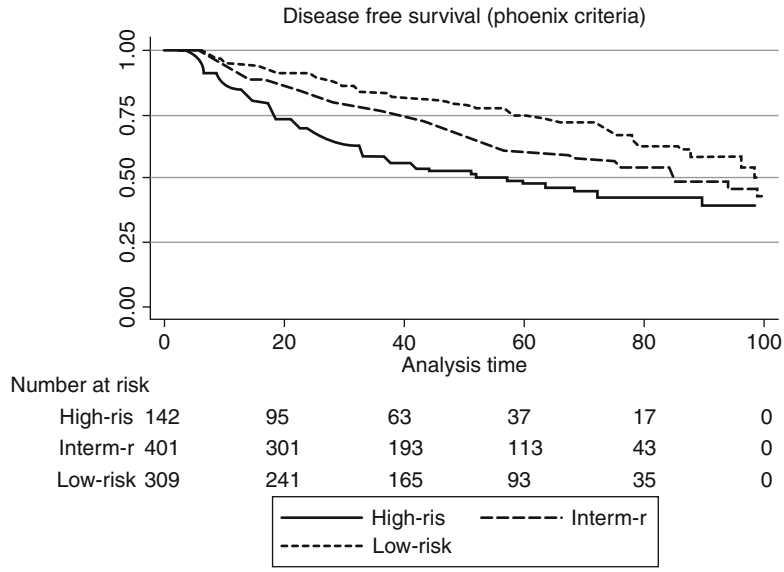


Fig. 15.8 Biochemical survival rates for low-, intermediate-, and high-risk patient after HIFU

rate at 7 years was 90% and 98%, respectively. The metastasis-free survival rate at 7 years was 96%. The 5- and 7-year disease-free survival rates were 75–62%, 59–50%, and 45–39% for low-, intermediate-, and high-risk patients, respectively ($P=0.0001$) (Fig. 15.8) (Crouzet et al. 2010b).

In a study from a prospective database, Shoji et al. included 326 patients who filled self-administered questionnaires on urinary function, QOL, and sexual assessment (Shoji et al. 2010). The FACT G, FACT-prostate, and IIEF 5 were used. 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. The total FACT-G score significantly improved at 24 months ($P=0.027$) after HIFU. At 6, 12, and 24 months after HIFU, 52%, 63%, and 78%, respectively, of the patients who had not received neoadjuvant hormonal therapy were potent.

In a prospective study, Li et al. compared the IIEF score, penile color Doppler ultrasound, and penile length and circumference on patients treated for prostate cancer with HIFU or cryoablation (Li et al. 2010). A total of 55 patients in the HIFU group and 47 in the cryoablation group were included. At 36 months, cryoablation patients experienced a lower erectile function recovery rate compared to HIFU patients (cryoablation = 46.8%; HIFU = 65.5%; $P=0.021$). No significant decreases in penile length and circumference were found in the two groups (all P values ≥ 0.05).

Finally, HIFU treatment seems to be standardized with similar outcomes between centers (Rebillard et al. 2003).

15.8 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. The re-treatment rate is estimated in the literature to be between 1.2% and 1.47% (Uchida et al. 2006a; Crouzet et al. 2010a; Thuroff et al. 2003; Blana et al. 2006). 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 re-treatment (Blana et al. 2006).

15.9 Salvage EBRT After HIFU Failure

EBRT is feasible after HIFU. In a retrospective study, Pasticier et al. included patients treated with salvage radiation after HIFU (Pasticier et al. 2010). A total of 100 patients were included, with a median follow-up of 33 months. Mean doses of radiation were 71.9 ± 2.38 Gys; 83 patients underwent only radiation treatment, and 17 patients underwent radio-hormonal treatment. The mean delay between HIFU and EBRT was 14.9 ± 11.8 months. Mean PSA before salvage EBRT was 2.1 ± 1.8 ng/ml, and the nadir PSA after EBRT was 0.28 ± 0.76 ng/ml, with 17.4 ± 10.8 months to reach nadir. The incontinence rate was the same both before and 1 year after salvage EBRT. 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 EBRT and the time to reach nadir after EBRT. Recently, similar results were published by Ripert et al. which reported the disease-free survival rate after salvage radiotherapy after HIFU was 83.3% at 36.5 months (Phoenix criteria) and there was no major EBRT-related toxicity at 12 or 24 months (Ripert et al. 2011).

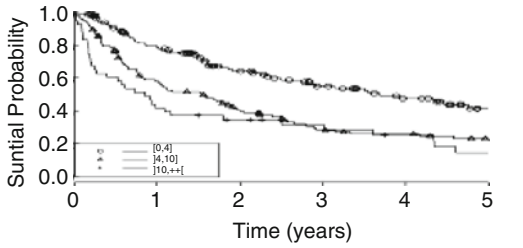
15.10 Salvage Surgery After HIFU Failure

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 (Lawrentschuk et al. 2011). 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. Salvage surgery after HIFU is difficult to perform due to fibrotic reaction. In selected patients with a long life expectancy, experienced surgeons alone should perform the salvage surgery after HIFU.

15.11 Salvage HIFU After EBRT or Brachytherapy

15.11.1 EBRT Failure

The rate of positive biopsy after external beam radiotherapy (EBRT) for prostate cancer in the literature is between 25% and 32% (Borghede et al. 1997; Zelefsky et al. 2001). 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 (AD). Local control was achieved with negative biopsies in 73% of the cases, with a median PSA nadir of 0.19 ng/ml (Murat et al. 2009). With a mean follow-up of 18.1 (3–122) months, the overall actual 5-year specific survival rate was 84%. The actual 3-year progression-free survival rate (PSA greater than nadir + 2 ng/ml, positive biopsy, or salvage treatment requirement) was 53%, 43%, and 25%, respectively, for low- and intermediate-risk patients according to D'Amico's risk groups. Disease progression was inversely related to the pre-HIFU PSA and the use of (AD) during PCa management. In a recent study, we examined the outcomes of salvage HIFU in 290 consecutive patients (nonpublished, submitted data). The mean PSA nadir post-HIFU was 1.54 ± 3.38 ng/ml (median 0.14). The estimated cancer-specific and metastasis-free survival rates at 5 and 7 years were 80% (95% CI 72.7–88.5%) and 79.6% (95% CI 73.5–86.2%), respectively. In the multivariate analysis, three factors were significantly linked to disease progression. The increase of the progression-free survival rate (PFSR) with the pre-HIFU PSA level was statistically significant ($P = 0.0002$) (Fig. 15.9). A previous AD treatment increased the PFSR by a factor of 1.3 ($P = 0.01$), and a Gleason score over or equal to 8 increased it by a factor of 1.2 ($P = 0.01$) compared to a Gleason score less than or equal to 6. While the technique offers promising results, it has to be



At risk						
[0,4]	129	90	61	42	29	15
]4,10]	119	63	39	24	20	14
]10,++[	40	18	13	10	7	4
Events						
]0,4]	-	25	40	48	53	56
]4,10]	-	48	67	77	79	81
]10,++[	-	25	20	29	31	34

Fig. 15.9 Progression-free survival rate according to the pre-HIFU PSA value

weighed against the side effects. Since 2002, the Ablatherm® device included specific acoustic parameters for salvage HIFU. The acoustic dose was adapted to the low blood flow inside the gland fibrosis induced by radiation. For incontinence, 54% of the patients had no incontinence after salvage HIFU, and 25% had a grade I incontinence (no pads + grade I = 79%). The risk of URF was only 0.4% with the introduction of a specific treatment algorithm designed for radiation failure. The impotence rate increased from 36.9% before salvage HIFU to 58.7% after treatment (Berge et al. 2010). With the Sonablate, the biochemical survival rate was 71% at 9 months (Zacharakis et al. 2008) and 52% at 5 years (Uchida et al. 2010).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.

15.11.2 Brachytherapy Failure

Sylvester et al. reported 15-year biochemical relapse-free survival rate and cause-specific survival following I (125) prostate brachytherapy in 215 patients: 15 years BRFS for the entire cohort was 80.4%, and the cancer-specific survival rate was 84% (Sylvester et al. 2011). There was no significant difference between the low- and intermediate-risk group. Salvage surgery is a challenging procedure after Brachytherapy (Heidenreich et al. 2010). A study with the Ablatherm® device is being conducted presently in Lyon which includes 26 patients (mean age 67 years) with MRI and biopsy-proven recurrence after brachytherapy (nonpublished data). Nineteen of them underwent a whole gland ablation, and 7 underwent a focal therapy (hemiablation). The mean follow-up was 19 months. The mean PSA before HIFU was 5.02 ± 4.8 ng/ml (median PSA 0.35ngml). Nine patients have undetectable PSA with no hormonal deprivation treatment; 8 needed hormonal deprivation treatment for a rising PSA, and 9 are recent cases with a very short follow-up. The complication rate was high in the first nine cases with three urinary incontinences (grade 3) and one urethrorectal fistula. For those first patients, we used the treatment acoustic parameters defined for radiation failure. Because of the high rates of rectal injury and sever incontinence, new specifically designed treatment parameters for brachytherapy failure were developed, with a decrease in the acoustic dose according to the intense prostate fibrosis. Since the introduction of those new parameters, no urethrorectal fistula occurred, and no rectal lesion was seen on control MRI and without any reduction of the treatment's efficacy.

15.12 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.

15.12.1 Focal Therapy as Primary Care Treatment

The ERSPC trial indicates that we need to treat 48 men for prostate cancer in order to save one

life. 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 (Klotz et al. 2010b). Of 117 patients treated radically, the PSA failure rate was 50%, which was 13% of the total cohort. As is the case with breast cancer and kidney cancer, improvements in screening meant that many men with early-stage prostate cancer are amenable to organ-sparing procedures. Focal therapy is emerging as an alternative to active surveillance in the management of low risk, low grade, and 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 (Conti et al. 2009). Mouraviev et al. identified unilateral cancers in 19.5% of 1,186 radical prostatectomy specimens (Mouraviev et al. 2007). This study suggests that almost 20% of the patients who are candidates for radical surgery could be amenable to hemiablation using thermal therapy targeting one lobe of prostate. A careful selection of patients is needed. The literature showed a direct correlation between the Gleason score and the outcomes after radical surgery (Blute et al. 2001). 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 (Stamey et al. 1999). Focal therapy (hemiablation) must be used only in carefully selected patients (Gleason 6, small unilateral cancer foci) included in prospective trials. The main problem is to identify appropriate patients using MRI and biopsies (transrectal or transperineal). Accurate characterization of the spatial distribution of cancer foci within the gland will be the key to the success of focal therapy. The concept of an index tumor does, however, potentially allow for the use of focal therapy on patients with bilateral tumors. Some evidence exists which shows that the largest tumor (the index lesion) is the main driver of progression, outcome, and prognosis; small secondary cancers might be clinically irrelevant (Wise et al. 2002; Noguchi et al. 2003). Focal therapy can be performed using several techniques: cryotherapy, HIFU, brachytherapy, and interstitial laser therapy with or without photodynamic therapy (PDT). 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).

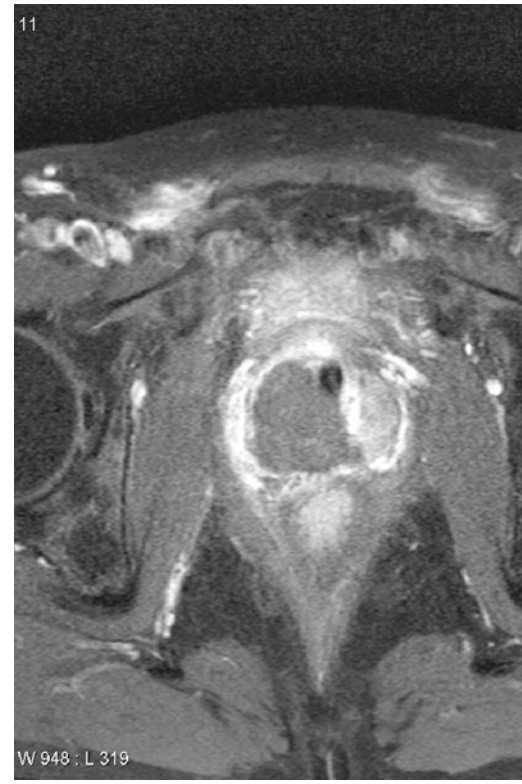
In 2008, Muto et al. reported the outcomes of 29 patients treated with Sonablate™ device (Muto et al. 2008). In selected patients whose cancer was confined to only one lobe by multiregional biopsies, the total peripheral zone and a half portion of the transitional zone were ablated. The prostate volume decreased from 35.8 c to 30.3 cc, and 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 3 patients (10.7%). Seventeen patients underwent control biopsies 12 months after the procedure: A residual cancer foci was found in four patients (23.5%); only one patient had a urethral stricture. No significant differences were noted in the 2-year disease-free survival rates for low- and intermediate-risk patient treated with between whole (90.9% and 49.9%, respectively) and focal therapy (83.3% and 53.6%, respectively). The period of the indwelling urethral catheter after HIFU session was 15 ± 4 days. The frequency of urethral stricture and symptomatic tract infection was 4% in both cases. No significant change was found on IPSS score and maximal flow rate before and 12 months after the procedure. No information was provided about the potency.

More recently, a short series of prostate hemiablation with HIFU was published (Ahmed et al. 2011). Inclusion criteria were men with

low-moderate risk (Gleason = 7, PSA = 15 μg/ml), unilateral PCa (=T2bN0M0) on TRUS biopsy, and underwent multisequence MRI (T2, DCE, diffusion) and 5 mm-spaced transperineal template biopsies to localize disease. All were treated using transrectal HIFU incorporating the entire positive hemiprostate up to urethra. A total of 20 patients (mean age 60.4 years) were treated. Of the men, 25% had low-risk and 75% intermediate-risk cancer. The mean PSA pre-HIFU was 7.3 ng/ml. Ninety-five percent were pad free. An erection sufficient for penetrative sex occurred in 95% of the patients. 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 re-treatment and the other active surveillance. Eighty-nine percent achieved the trifecta status.

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, and with no more than 2 contiguous biopsies in no more than one lobe after MRI and 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 (Picture 15.1). The study is in progress.

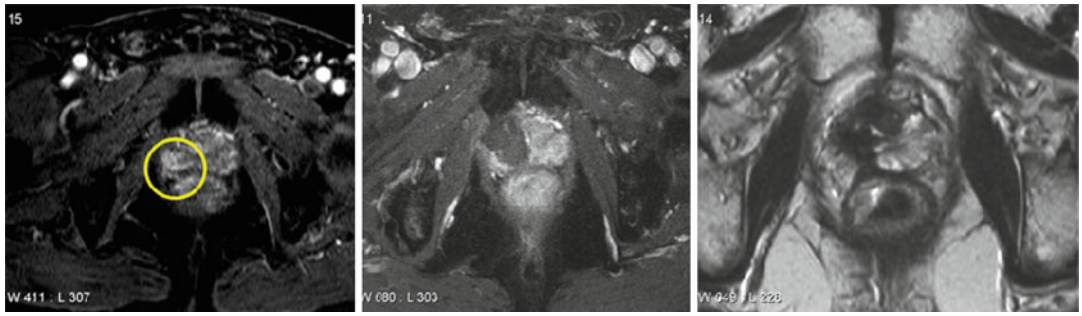
Exciting developments are pending that will make HIFU an even more effective treatment option for focal therapy: Dynamic focusing using annular or phase array transducers will create HIFU lesions able to precisely follow the shape of the targeted cancer foci. The key point will be to achieve an accurate mapping of the cancer foci.



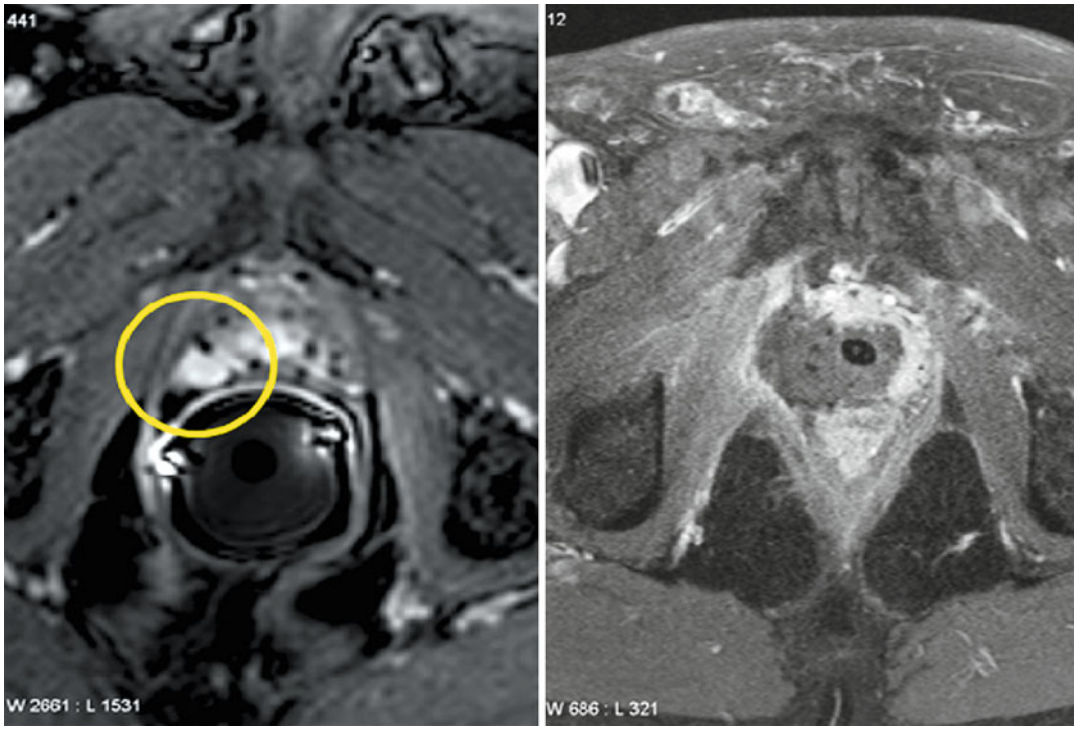
Picture 15.1 Hemiablation as primary treatment

15.12.2 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. A study designed for EBRT failure with MRI and biopsy-verified unilateral local recurrence is currently being conducted in Lyon (AFU 2011). Only one prostatic lobe is treated. Systematic control MRI is performed one week and one year after the HIFU session (Picture 15.2). All patients underwent control biopsies at least 12 months after the procedure. Twenty-one patients were included (mean age 65 years). The mean PSA value falls from 3.06 to 0.34 ng/ml after FSH. Control biopsies were negatives in the treated lobe in 9 of 10 patients who underwent biopsies. Severe incontinence only occurred in one patient. FSH seems to offer similar results with the other focal thermal therapy options. Eisenberg et al. reported the results of partial salvage cryoablation (Eisenberg and Shinohara 2008). Nineteen patients were included. The BFSR (ASTRO) at 3 years was



Picture 15.2 Focal salvage HIFU after EBRT



Picture 15.3 Focal salvage HIFU after brachytherapy

50%. Complications included incontinence (1), urethral stricture (1), and urethral ulcer (1). In patients with unilateral relapse after EBRT, focal therapy with HIFU or cryotherapy can achieve a local control of the disease with minimal morbidity. This focal salvage treatment can also be used for brachytherapy failure (Picture 15.3, Uchida et al. 2010). The results are promising, but longer follow-up is required.

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

15.13.1 Androgen Deprivation

Promising preliminary results on HIFU and hormonal deprivation in patients with locally advanced disease and/or high-risk PCa have been

published (Ficarra et al. 2006). At 12 months after the procedure, 28 patients (93%) were continent. Seven of the thirty men (23%) had a positive prostate biopsy. At the 1-year follow-up, only 3 of the 30 patients with high-risk prostate cancer had a PSA level of >0.3 ng/ml.

15.13.2 Chemotherapy

Experimental studies have demonstrated the potential of chemotherapy associated with HIFU. Paparel et al. evaluated in a rat model the therapeutic effect of HIFU combined with docetaxel on AT2 Dunning adenocarcinoma (Paparel et al. 2005, 2008). They showed a synergistic inhibitory effect of the HIFU + docetaxel association.

In an ethical-committee approved study, 24 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/m^2 with one febrile neutropenia and one transient alopecia grade 1, and seven patients received 40 ml/m^2 with adverse effects. The follow up was 15.8 ±9.9 months. A complete response with undetectable PSA was observed in 13 patients (54%). An AD was used in seven cases for rising PSA. The results for four patients are too early to be conclusive.

15.14 MRI-Guided HIFU

15.14.1 Principle

Magnetic resonance imaging (MRI) is an imaging technique based on the magnetic moment (spin) of hydrogen particles present in the water (H_2O) of a living body. It provides an excellent soft tissue contrast and is often considered to be the "gold standard" for tumor detection (Leach 2009). It is, therefore, an excellent choice for soft tissue target definition. MRI also has two other benefits: temperature monitoring and tissue coagulation detection. These resulted in the combination of ultrasound transducers with MRI (Hynynen et al. 1993, 1996) that have been proposed for interventional therapies such as HIFU. The sensitivity of MRI signals, the resonance frequency of protons at a temperature in the human body, is of particular interest in achieving the guidance of these therapies. The possibility of measuring the temperature rise is to ensure the adequate deposited thermal dose and thus prevent damage to adjacent tissues and treatment effectiveness in the target area. MRI-compatible methods to deliver these exposures have undergone such rapid development over the past 10 years such that clinical treatments are now routinely performed.

Most methods used for temperature mapping by MRI (Quesson et al. 2000; McDannold 2005; Rieke and Butts Pauly 2008) use temperature-dependent proton resonance frequency shift (Ishihara et al. 1995) as a measure of temperature elevation that has been shown to be linear even above the thermal coagulation threshold (Peters et al. 1998). A phase image is obtained just prior to the ultrasound exposure, and then a series of images is acquired during and after HIFU sonication. By subtracting the phase of each voxel from the baseline, a phase difference image is obtained that is proportional to the temperature elevations. This method provides thermometry with high spatial and temporal resolution but does not work in fat where the proton screening coefficient is not temperature dependent (Peters et al. 1998; Kuroda et al. 1998). The temperature history obtained from the serial images is used to calculate thermal dose in order to determine tissue damage (McDannold et al. 2000).

15.14.2 Works in Progress

Several devices have been developed on this principle combining HIFU and MRI, and a significant number of applications have been explored, especially for the treatment of uterine fibroids (Okada et al. 2009) or tumors of the brain (Larrat et al. 2010), the esophagus (Melodelima et al. 2004), the liver, the kidney (Quesson et al. 2011),

and the prostate (Fig. 15.10). Manufacturers have, in turn, developed probes therapy compatible with their own MRI devices such as the Sonalleve (Philips) or compatible with commercially available MRI devices such the ExAblate (InSightec).

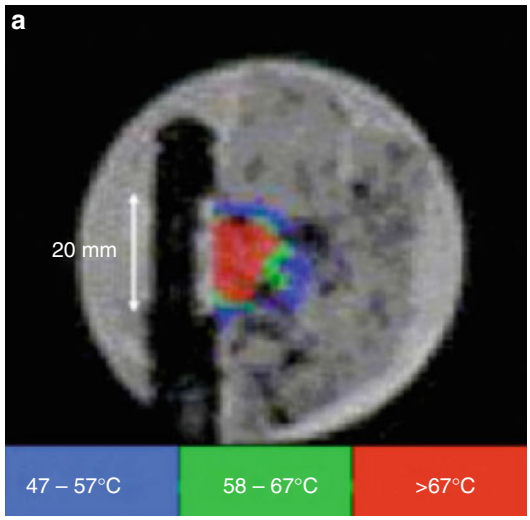


Fig. 15.10 Examples of HIFU guided by MRI: (*a*) temperature measurement to control the treatment of esophagus tumors (Beerlage et al. 1999)

All of the current clinical results of HIFU are based on an open-loop concept where thermometry is obtained during prior sonications. With MRI, an alternative method is to use thermometry to control the power during the sonication (Salomir et al. 2000) so that the desired exposure is induced without wasting energy, as it is the case with the open-loop concept (Fig. 15.11). Feedback control may allow reduced treatment times for thermal coagulation of prostate with intraurethral applicators that slowly rotate to sweep the whole gland (Chopra et al. 2005). These closed-loop feedback systems reduce the complexity of operating the systems and can make the energy delivery optimal and thus minimize the treatment times.

15.15 Conclusion

The outcomes achieved for primary care patients seem close to those obtained by radiation therapy. 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,

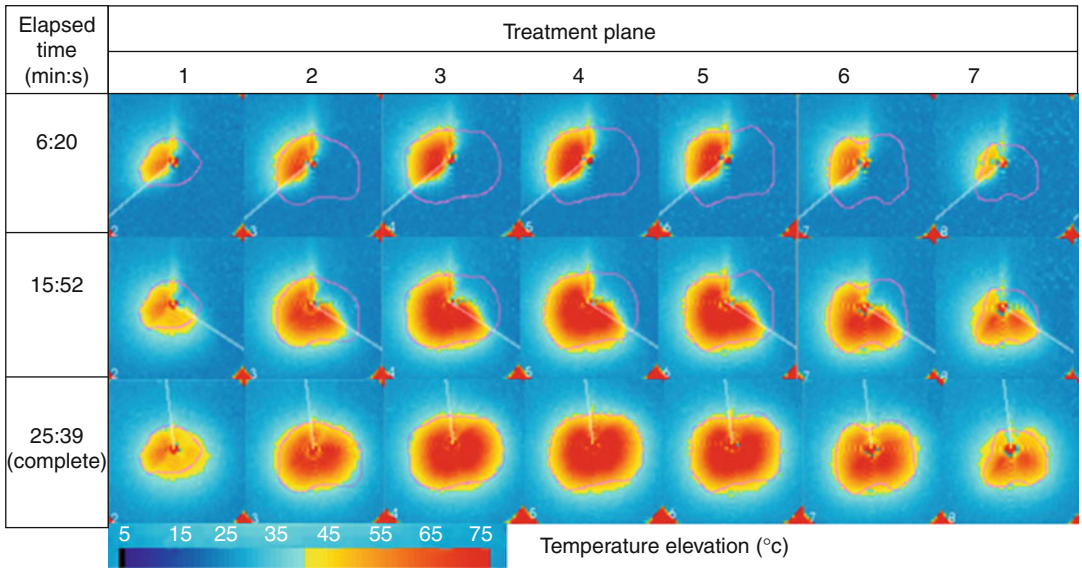


Fig. 15.11 Toward 3D conformal prostate treatments (3 T). Simultaneous treatment with seven planar transducers (5 mm long) using active MR temperature feedback from nine planes (After Chopra et al. 2005). Prostate shape is taken from a clinical patient

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 achieve a local control of the disease in low-risk prostate cancer and in early identified local relapse after EBRT.

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