Chapter 45
High Intensity Focused Ultrasound (Hifu) in Prostate Cancer

Gilles Pasticier

HIFU is an ablative technique which uses high frequency acoustic waves produced by a transducer and the waves deposit energy as they pass through the tissue in question. First described in the early fifties to destroy brain lesions [1], the ability of focused ultrasound on prostate in dogs and subsequently on human prostate cancer was reported by Gelet et al. in 1993 and 1999 [2, 3]. Gelet et al. published the results of their pilot study in 1996 and results of their first 50 patients in 1999 [3].

To date, around 30,000 patients have been treated worldwide. Two devices – Sonablate® (focus surgery Inc., Indianapolis, USA) and Ablatherm® (EDAP-Technomed, Vaulx-en-Velin, France) are currently available (Figs. 45.1 and 45.2).

Mechanisms of Action

In contrast to its use in ultrasound imaging techniques, the high acoustic energy leads to higher temperatures enough to cause a coagulation necrosis when focused on a precise tissue point [4]. In initial stages there is generation of microbubbles with the absorption of the energy and heat generation. The interaction between microbubbles and ultrasounds produces a cavitation effect resulting in cellular, and subsequent tissue destruction. Both thermal and cavitation effects are responsible of the tissue destruction by coagulative necrosis [5]. The sum of elementary lesions applied tight to each other allows a volume targeting compatible with prostate gland shape destruction.

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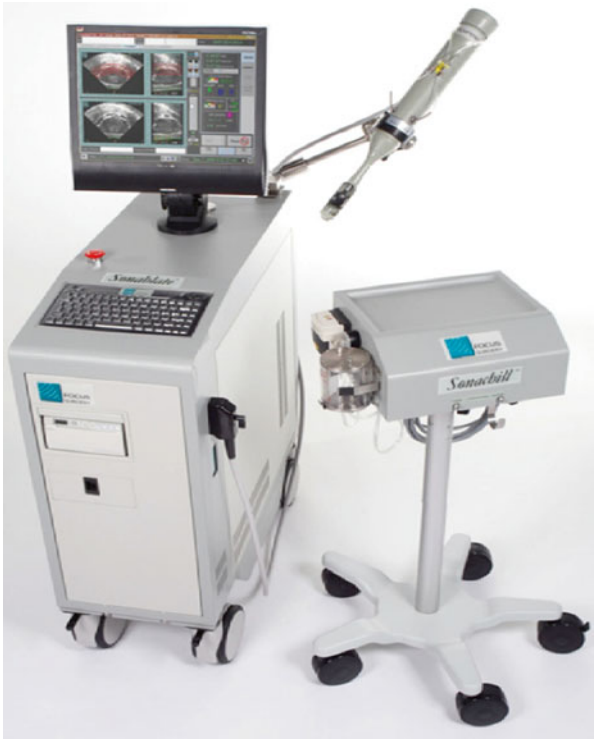

Fig. 45.1 Sonablate® device

Fig. 45.2 Ablatherm® device (Courtesy of EDAP)

Fig. 45.3 Imaging and treatment transducer (Ablatherm® device) (Courtesy of EDAP)

The two available devices – Sonablate® (Focus Surgery Inc, Indianapolis, Ind, USA) and Ablatherm® (EDAP-TMS SA, Lyon, France) deliver focused ultrasound through a transrectal approach. The basic working principles are same apart from some technical differences. A transrectal high-frequency transducer in a balloon filled with water to prevent heating of the rectal wall (thereby minimizing the risk of recto-urethral fistula) is placed in the rectum. There is also a mechanism to monitor rectal temperatures.

Sonablate® offers transducers of different focal lengths (25–45 mm) with a fixed elementary lesion length of 10 mm × 2 mm in width while Ablatherm® includes a unique focal energy transducer (40 mm) and an imaging transducer in the same endorectal probe, thus allowing a real-time control of imaging the treatment (Fig. 45.3); elementary lesion length varies from 19 to 26 mm × 2 mm in width (Figs. 45.4, 45.5, and 45.6). Generally speaking for the two devices, the volume of the prostate at the time of delivery of HIFU has to be less than 35 cc. Therefore, a TURP or even a previous adenomyomectomy in high volume prostates may be beneficial to achieve an adequate volume at the time of HIFU. In fact there is evidence to show that a previous TURP before HIFU, reduces the chances of acute urinary retention and bladder outlet obstruction after HIFU treatment. This can potentially reduce the time of urethral catheterization (4 days vs. 15 days) [6–9].

Indications for HIFU

It is important to note that most of the available data has been retrospective and long term results and potential use of HIFU as a primary treatment similar to radical prostatectomy or EBRT need to be confirmed by randomised trials. There is also lack of consensus on various PSA thresholds and objective response criteria.

Various guidelines including European Association of Urology (EAU), the American Urologic Association (AUA), the UK National Health Service based National Institute for Health and Clinical Excellence (NICE) Prostate Cancer guidelines and the US Federal Drug Administration do not currently recommend HIFU as a standard treatment for the management of clinically localized prostate cancer [10–12].

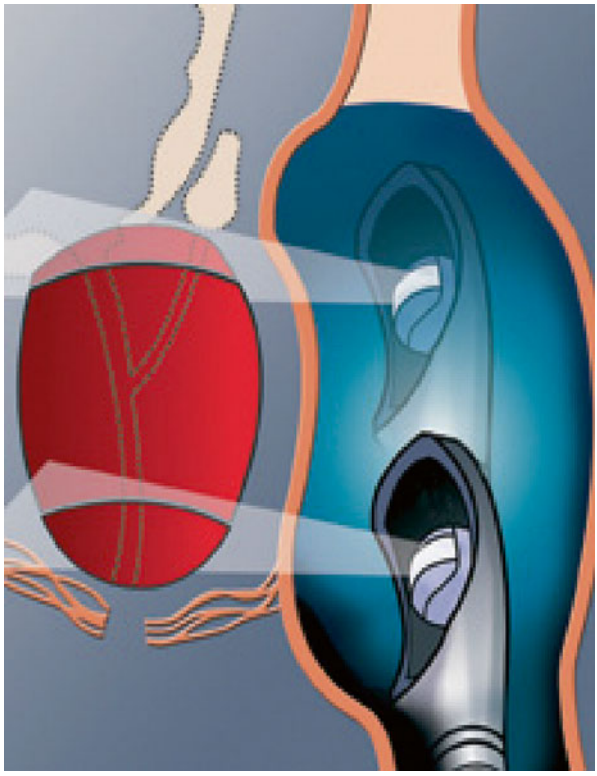

Fig. 45.4 Ultrasound probe used for imaging (Courtesy of EDAP)

However, the management of PCa by HIFU could be considered in three settings:

(a) As a primary treatment for localised prostate cancer (T1c-T2a, N0 M0)
(b) Salvage therapy after failure of EBRT or Brachytherapy
(c) Focal HIFU therapy

Contraindications for HIFU

There are some relative contraindications for HIFU but a rectal thickness >6 mm or rectal stenosis are the true real contra-indications of an HIFU treatment. In patients with of chronic inflammatory bowel disease the choice of treatment of PCa could be challenging and HIFU treatment is a feasible when employed cautiously [13]. As mentioned earlier gland volume is a relative contraindication. Any interference with ultrasound imaging such as prostatic stones can interfere with the procedure. This could be avoided by doing a TURP prior to the procedure.

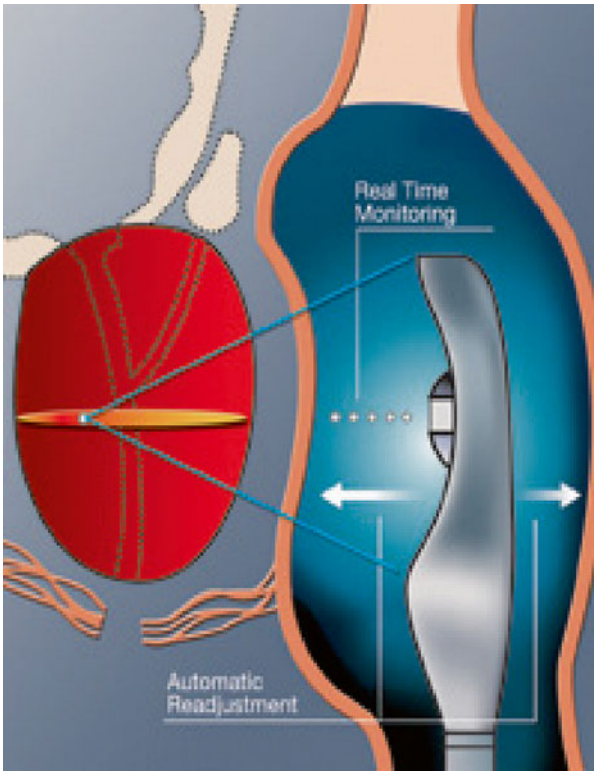

Fig. 45.5 delivering HIFU (Courtesy of EDAP)

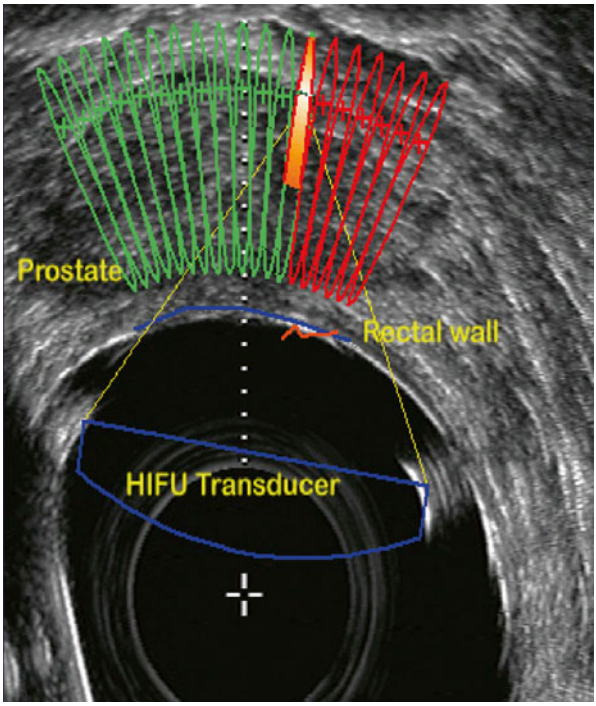

Fig. 45.6 Real time control imaging (Courtesy of EDAP)

Table 45.1 Criteria defined by French Urological Association

Age >70 years and >7 years of life expectancy
Clinical stage T1 or T2
PSA <15 ng/ml
Gleason ≤7
Prostate volume <50 cc

HIFU as a Primary Care Treatment

According to the French Urological Association, HIFU can be an option as a primary care treatment for the specific patients (Table 45.1)

HIFU can be repeated several times – It has been shown that a second HIFU session may improve oncological control [14–16]. However, there is no gain beyond two HIFU sessions and on the contrary there is a possibility of increase in morbidity [17, 18].

Salvage HIFU After EBRT Failure

Considering the high rate of positive biopsies after EBRT of 30–40 % [19] and the significant morbidity involved in salvage prostatectomy [20–23], the role of HIFU as a salvage option has been addressed since 1993 in specialized centres like Lyon University Hospital [24]. The key points in selecting these patients are, to confirm the local recurrence by prostate biopsies, exclude any detectable distant metastasis (with whole body CT scan, bone scintigraphy and eventually with [10] Choline PET/CT). An assessment is then made regarding the benefit of the treatment with a curative intent (considering the predictive factors of success) against the side effects of HIFU in this setting (see results section). In relation to brachytherapy failure, clinical trials are still ongoing with a very few published data at present [25].

Focal HIFU Treatment

The European Randomised Study of Prostate Cancer (ERSPC) has concluded that there is a reduction of mortality of prostate cancer thanks to screening of PCa but the screening has an underlying risk of overdiagnosis and therefore overtreatment [26]. Similarly, Cooperberg et al. have shown that selected men with intermediate risk features active surveillance may be appropriate as in these men the cancer is not likely to progress [27]. Although active surveillance is gaining a growing interest, it is worth noting that between 20 and 30 % of patients are misclassified and nearly 30 % of these patients will ultimately need a radical treatment. The negative impact of active surveillance in terms of progression of the cancer has still to be addressed [28, 29]. Nearly 20 % of PCa are located on one side only according to a series of radical prostatectomies [30]. In such patients, to prevent overtreatment

and undertreatment focal therapy may be the choice. The ideal conditions to for focal treatment are: that the treatment should be feasible (focal destruction proven), there has to be endpoints to address efficacy of treatment, treatment should be cost-effective, feasibility of another type of radical treatment in case of failure. All these criteria must be satisfied before undertaking the clinical trials. Although there are no major safety concerns about the treatment, evidence acquisition regarding mechanism of action and side effects is still lacking.

HIFU Outcomes

HIFU as a Primary Care Treatment

Oncological outcomes: Table 45.2 show results of HIFU as a primary treatment for the major series. As mentioned earlier, one of the limitations to address HIFU results properly is the relative heterogeneity of endpoints. Many series have used Phoenix definition to assess the biochemical failure. One of the main criticisms of usage of Phoenix definition is that it has been exclusively for radiation and not for other physical agents [34].

Usually PSA nadir is achieved around 3 months after HIFU. As the nadir value has a strong predictive value with a threshold of 0.2 and 0.5 ng/ml [35, 36], it is used as a criteria to evaluate the results. This can also be supplemented with systematic biopsies if it is deemed that nadir PSA values are insufficient. Early post HIFU evaluation with positive biopsies gives at least three options with a curative intent: treatment with a second HIFU session, salvage radiotherapy (as it has shown excellent oncological control after HIFU) and finally even radical prostatectomy after HIFU is a feasible option [18, 37–39]. All these endpoints taken together, the efficacy of HIFU can be evaluated through its biochemical results, or through an "adjuvant treatment free survival rate" since the decision of an additional treatment clearly represents a failure of HIFU treatment. Irrespective of the type of device used, HIFU achieves a biochemical control of prostate cancer in 58–83 % patients depending on the risk group and the adopted definition. Disease free survival rates range from 47 to 72 % according to high, intermediate, low-risk group disease at a median follow-up of 42 months [14, 31–33].

Functional Outcomes

Due to the effects of tissue destruction and high temperature effects in the prostate, patients can encounter voiding problems after HIFU, either due to outlet obstruction or urinary incontinence. Obstruction can be due to a urethral stenosis and/or a bladder outlet obstruction: these symptoms may be observed 3–12 months after the

Table 45.2 Results of primary HIFU treatment

Author	Institution (device S/A)	Year	No of patients	Median/mean follow-up (months)	Negative biopsy rate	Definition of success	5 year BFSR	5 year DFSR
Uchida et al. [31]	Tokyo (S)	2009	517	24 (median)	–	Phoenix	72 %	–
Ahmed et al. [32]	London (S)	2009	172	12 (mean)	–	PSA nadir ≤0.5	78 %	
						Psa nadir ≤0.2	58 %	
						NED[a]	92 %	
Blana et al. [33]	Regensburg/ Lyon (A)	2008	140	76 (mean)	86 %	Phoenix	77 %	66 %[b]
Thuroff et al. [15]	European multicentric (A)	2003	402	13 (mean)	87 %	–	–	–
Crouzet et al. [14]	French multicentric	2010	803	42 (mean)	85 %	Phoenix	83 % LR	72 % LR[c]
							72 % IR	56 % IR
							68 % HR	47 % HR

S/A device: Sonablate® or Ablatherm®, *BFSR* biochemical free survival rate, *DFSR* disease free survival rate, *NED* non evidence of disease, *LR/IR/HR* low-/intermediate- /high-risk disease

[a]PSAn ≤0.5 or negative biopsy

[b]PSA nadir <2 and negative biopsies

[c]PSA < nadir +2 and negative biopsies with no adjuvant treatment

procedure and are reported be seen in 3–15 % of cases. These symptoms require endoscopic intervention in 3–10 % of cases [8, 40]. The rate of urinary leakage is reported to be between 0.5 and 22.5 % [17, 41–43]. In most cases it resolves within 1 year. Generally speaking, in most series significant grade 3 urinary incontinence mentioned is ≤5 %. Potency after HIFU has been prospectively addressed in a quality of life survey on 326 patients, showing that 52–78 % of patients remained potent after HIFU with gradual improvement in a 24 months-period [44].

Salvage HIFU After EBRT Failure

Oncological Outcomes

Table 45.3 summarizes the results of oncological outcomes in patients who were treated with HIFU after failure of radiotherapy treatment. With the Sonablate® device, Uchida et al. described a 52 % biochemical control rate while Zacharakis et al. reported no evidence of disease in 71 % of their patients in their series; also half of their patients achieved a PSA level of <0.2 ng/ml [25, 45].

Similar results were observed with the Ablatherm® device by Berge et al.; in a series of 46 patients, the median nadir PSA was 0.3 and the failure rate was 39.1 % in a median follow-up of 9 months [46]. In their series of 167 patients treated with 194 HIFU sessions, Murat et al. have reported mid-term results of salvage HIFU with a median follow up of 18 months. In this series the median nadir PSA was 0.19 ng/ml and the local control rate achieved was 73 % confirmed with negative biopsies. They further observed that the actuarial 3-year progression-free was significantly lower in the following circumstances: (a) worsening of the pre-EBRT stage with 53, 42 and 25 % for low-, intermediate- and high-risk groups patients respectively; (b) increase in the pre-HIFU PSA value and (c) the use of Androgen Deprivation associated with radiation therapy [18]. The threshold of 4 ng/ml for the pre-HIFU PSA value was further clearly identified as a reliable landmark to help decision making [47] (Fig. 45.7). The message is that to achieve satisfactory oncological outcomes, salvage HIFU has to be considered when PSA values are <4 ng/ml, so early referral of failed EBRT patients is of importance. Indeed another recognised factor in salvage HIFU therapy is to try to identify patients who have pure local recurrence and to exclude those who have metastasis.

Functional Outcomes

Some of the side effects of HIFU cannot be totally ignored and therefore it is important to balance potential side effects of HIFU salvage therapy in patients who had EBRT, against the oncological benefits. Urinary incontinence rates range between 7 and 52 % [18, 25, 45, 46]. Murat et al. [18] reported that urinary incontinence

Table 45.3 Results of salvage HIFU

Author	Institution (device S/A)	Year	No of patients	Median/mean follow-up (months)	Neg. biopsy rate	Median nadir PSA	5 year BFS	5 year DFSR
Uchida et al. [25]	Tokyo (S)	2011	22	24 (median)	91 %[a]		LR 100 %	–
							IR 86 %	
							HR 14 %	
Zacharakis et al. [45]	London (S)	2008	31	7 (mean)		–	71 % NED	
Murat et al. [18]	Lyon (A)	2009	167	18 (mean)	73 %[b]	0.19		LR 53 %
								IR 42 %
								LR 25 %
Berge et al. [46]	Oslo (A)	2010	46	9 (median)	–	0.3	–	

S/A device, *S* Sonablate®, *A* ablatherm®, *BFSR* biochemical free survival rate, *DFSR* disease free survival rate, *LR* low risk, *IR* intermediate risk, *HR* high risk, *NED* non evidence of disease

[a]Biopsies performed on 12 patients

[b]All patients underwent control biopsies

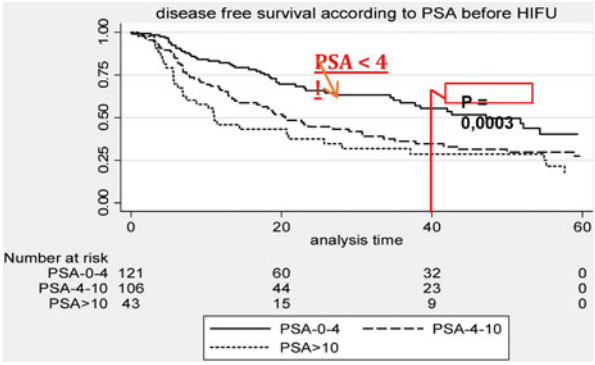

Fig. 45.7 Salvage HIFU & Disease free survival rat e according to pre-HIFU PSA (Based on data from Ref. [47])

accounted for nearly 50 % and artificial sphincter implantation was required in 11 % of their cases. Urethral stenosis or bladder neck strictures are observed between 16 and 36 % of cases, requiring sometimes an endoscopic intervention. Urethro-rectal fistula is a serious complication after salvage HIFU and was first described in 6 % of cases in the initial experience before 2000 [24]. After definition of specific post-radiation parameters, it dramatically decreased and no fistula has been observed in 111 consecutive patients with the use of these new parameters [18]. The risk of urethrorectal fistula is currently considered to be less than 1 % with the modern HIFU devices. Fistulae associated with the anterior part of the prostate, clinically manifest as osteitis pubis. Berge et al [46] described osteitis pubis in 2 of their cohort of 46 patients. Early diagnosis of anterior fistula is important as it can be effectively resolved with prolonged antimicrobial therapy; if the diagnosis or treatment is delayed, urinary diversion may be required to solve the problem. If these potential complications of salvage HIFU are carefully considered before the treatment decision is made and measures are taken to prevent them, they do not compare unfavourably with the other methods such as salvage prostatectomy or cryotherapy [20–23, 48]. It is therefore imperative that appropriate selection is made for HIFU treatment so that better results are obtained in patients who have recurrence after radiation therapy.

Focal HIFU Treatment

Muto et al. reported their first series of focal HIFU therapy in 2008 in patients who had unilateral disease [49]. In this retrospective study, patients presenting with unilateral low-risk or intermediate-risk disease were treated with a partial HIFU (total peripheral zone and half portion of transitional zone) and were compared to those treated with whole gland HIFU-ablation on the same period. The disease free survival rates at 2 years were similar in both the groups – 90.9 and 49.9 % versus 83.3 and 53.6 % in whole treatment and partial treatment groups respectively.

Emberton et al. conducted a small sized prospective phase I/II trial in the UK using the sonablate® device after receiving the approval of the UK National Cancer Research Network. The 20 enrolled patients had unilateral disease, Gleason ≤7 (4+3), PSA ≤15 ng/ml, and ≤cT2bN0m0 tumors. Their recruitment included an assessment by multiparametric MRI and template transperineal mapping biopsies. The outcomes of this small but very tightly followed cohort showed a preservation of erections sufficient for intercourse in 95 %, a total continence in 90 % and a negative biopsy rate of 89 % at 12 months. The trifecta (good erections, continence and no evidence of disease) was achieved in 89 % of patients [50]. This study appears to offer some promise for further evaluation of focal HIFU therapy/hemiablation albeit with some limitations that have to be acknowledged (small number of patients, lack of follow up, selection bias in patients cohort, residual foci of acini found in the treated area). One of the critical points to support this approach relies on the ability of predicting precisely where the cancer is present inside the gland and where it is not present. More advances in imaging diagnostic techniques will help to evolve focal therapy. Longer follow-up is also required to address the oncological outcomes. A French prospective national study using the Ablatherm® device is currently being conducted. Interim results have already been presented on 11 patients receiving a first treatment for localised prostate cancer: 78 % had negative control biopsies, no significant difference was noted before and after treatment on functional evaluation with international prostate symptom scoring (IPSS), international index of erectile function (IIEF), international continence society (ICS) and quality of life QLC-30 scores. The second part of the presentation reported on 21 patients with post-radiotherapy relapse receiving a salvage focal treatment. In this setting, the median PSA dropped from 3.06 to 0.34 ng/ml, with 85 % of patients remaining continent and all patients (with or without pharmacological aid) remained potent [51].

Future of HIFU

In the next two decades more attention would be given to focal therapy of prostate cancer because of the ongoing advances in the imagery of prostate. Radical therapy of prostate cancer has major side effects and HIFU in this regard is a well fitted technology for both focal and total therapy but needs randomised controlled trials and long term follow up of patients. This will give more information on oncological outcomes particularly when HIFU is the primary treatment. For the salvage HIFU option, a better knowledge of predictive factors of failure would help in a better patient selection. In addition, an adequate and specific definition of HIFU failure is also needed.

Combination of HIFU with others treatment modalities is possible: high risk cancers have been treated with a combination of HIFU and androgen deprivation therapy [52], A synergistic effect has been shown when using docetaxel in a neoadjuvant form just before HIFU in agressive tumors such as Dunning model [53].

A major challenge to achieve a complete and precise necrosis of the prostate targeted area and thus improve the oncological results while preserving the function

is to have a real-time temperature control during treatment as well as the ability to modify within a real time feedback model the thermal energy applied. The MRI when coupled with transurethral ultrasound transducers fulfils these features: prototypes have been described and successfully used on animals models [54, 55]. Following preclinical studies, a phase I clinical study has started in Toronto applying a transurethral ultrasound thermotherapy to 8 patients just before prostatectomy: the main objective of this study was to calculate the average radial distance between the targeted volume and the isothermal curve at 55 °C: the procedure was found to be feasible through a 15 min application of focused ultrasound. The average calculated distance was about 1 mm [56, 57].

Conclusions

High-intensity focused ultrasound treatment needs a thorough evaluation as to its efficacy in cancer outcomes and long-term quality of life. HIFU should be evaluated in a multicenter trial setting with uniform criteria right across all centre that use it. Otherwise it is not likely to be widely accepted as a primary treatment. From previous uncontrolled studies we know that HIFU has a role in the management of localized prostate cancer, as a salvage treatment in post-radiation therapy failure, or as a focal treatment. Another advantage is that HIFU can be repeated, Patients who were treated with HIFU as a primary treatment could undergo salvage radiation therapy or salvage radical prostatectomy after failure. This new and evolving technique is likely to find a place in the future armamentarium of treatment of prostate cancer.

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