Technology Insight: high-intensity focused ultrasound for urologic cancers

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SUMMARY

The growing interest in high-intensity focused ultrasound (HIFU) technology is mainly due to its many potential applications as a minimally invasive therapy. It has been introduced to urologic oncology as a treatment for prostate and kidney cancers. While its application in the kidney is still at the clinical feasibility phase, HIFU technology is currently used in daily practice in Europe for the treatment of prostate cancer. Literature describing the results of HIFU for prostate cancer is mainly based on several series of patients from clinical development teams. The latest published results suggest that HIFU treatment is a valuable option for well-differentiated and moderately-differentiated tumors, as well as for local recurrence after external-beam radiation therapy.

KEYWORDS high intensity focused ultrasound (HIFU), kidney cancer, prostate cancer, ultrasound surgery

REVIEW CRITERIA

Papers for this review were identified from Medline and PubMed searches for articles published from January 1997 to February 2005, using the search terms "high-intensity focused ultrasound, prostate cancer", "high-intensity focused ultrasound, kidney cancer", and "high-intensity focused ultrasound, bladder cancer". Older papers were identified from the authors' archive.

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Received 22 November 2004 **Accepted** 22 March 2005
www.nature.com/clinicalpractice
doi:10.1038/ncpuro0150

INTRODUCTION

The ability of high-intensity focused ultrasound (HIFU) technology to destroy tissues at a distance has been known for decades, but the technology did not achieve clinical application in its early stages because of the lack of a suitable imaging system to monitor the procedure. Ultrasound and MRI imaging have made real-time control of the procedure possible, and HIFU is now being developed in many surgical applications as an extracorporeal approach for the destruction of deep tissues, allowing ablation without any skin incision. Validation of HIFU for the treatment of localized prostate cancer is in progress. Although results for 5-year disease-free rates are published,[1,2] long-term outcome data (overall survival rate at 10 years) are not yet available. Clinical research is ongoing for its use in the treatment of other benign and malignant tumors, such as kidney cancer, breast cancer, liver cancer, thyroid nodules and uterine fibroids.

THE HIFU PRINCIPLE

The use of intense focused ultrasound for focal tissue destruction was established in 1942.[3]

Mechanism of action

An ultrasound field applied to tissue results in mechanical stress to cells, thus causing changes in the biologic system. Three effects can be distinguished during the ultrasound emission: mechanical, thermal and CAVITATION. The thermal effect is associated with the absorption of ultrasound energy into the tissue, which is converted into heat.

Temperature elevation in tissues depends on the ABSORPTION COEFFICIENT of the tissue, and the size, shape and thermal response of the heated region. The biologic changes induced by heating are determined by the temperature reached and the duration of exposure (i.e. THERMAL DOSE). For thermal doses above a certain threshold, irreversible tissue damage is induced in the form of coagulation necrosis. For thermal doses below the threshold, the effects depend on the sensitivity of the tissue to heat.[4]

GLOSSARY

CAVITATION
Formation, growth and implosive collapse of bubbles in a liquid irradiated with high-intensity ultrasound resulting in intense local heating

ABSORPTION COEFFICIENT
A measure of the acoustic energy converted into heat in the tissues

THERMAL DOSE
Equivalent time in seconds for an exposure at a reference temperature of 43 °C

SONICATON PARAMETERS
Physical properties whose values determine the behavior of the sound wave applied to tissues

OPERATING FREQUENCY
Number of complete oscillations per second of the sound wave generated by the transducer

PIEZOELECTRIC MATERIALS
Crystals that suffer a mechanical deformation when subjected to an electric potential

POWER DENSITY
Power per unit area normal to the direction of propagation

ACOUSTIC INTENSITY
The mean acoustic power transmitted through a unit area

DURATION OF EXPOSURE
Time during which the sound wave is applied to the tissues at each burst of high-intensity focused ultrasound

ON/OFF RATIO
Quotient of exposure duration and waiting time between bursts of high-intensity focused ultrasound

DUNNING R3327
Experimental model of adenocarcinoma of the prostate in Copenhagen rats

AT2, AT6
Hormone-independent sublines of Dunning R3327

HIFU is being tested for a large number of urologic applications.[4–6] In HIFU, the ultrasound beam that is generated has a very high intensity in the focal area, which rapidly decreases in the surrounding zone of tissue. Focused ultrasound waves are capable of inducing sharp increases in temperature (up to around 70 °C to 100 °C) in a few seconds, destroying a well-determined zone of tissue while the surrounding region remains intact. The volume of tissue destroyed by a single burst of ultrasound is termed the elementary lesion. To create large lesions, several elementary lesions are made side by side, by mechanically moving the transducer, or by electronically positioning the focal point if a phased array is available.

The technology behind HIFU

Several considerations should be made when designing a HIFU system for a specific application. The most delicate technical decisions concern the choice of the transducer, SONICATION PARAMETERS and imaging guidance of the treatment.

The ultrasound therapy transducer is essentially characterized by its OPERATING FREQUENCY, geometry and physical dimensions. Modern PIEZOELECTRIC MATERIALS can operate at sufficient POWER DENSITY and with long-term stability consistent with the requirements of therapy. These materials also allow the design of geometric shapes that can be adapted to different anatomic restrictions.[7] Current urologic HIFU applications use single-focus transducers that are moved mechanically in order to treat a large volume of tissue. Future applications, however, will integrate multiple-element transducers to shift the focal point without moving the device.[8,9]

The 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. In order to find the sonication parameters that best fit a specific therapeutic application, *in vitro* and *in vivo* experiments are conducted or mathematical models are used.[10–12]

MRI is the gold-standard technique used for assessing the efficacy of HIFU treatment. The extent of necrosis can be clearly visualized on gadolinium-enhanced T1-weighted images, as hyposignal zones.[13] MRI has also been used to guide HIFU treatments,[13,14] as it is possible to monitor the temperature changes within tissues with MRI during HIFU.[13] Magnetic resonance elastography (MRE) has also been proposed as a method for assessing the effects of thermal tissue ablation by measuring the mechanical properties of the lesion.[15] HIFU-induced lesions are visible using standard ultrasound as hyperechoic regions,[16] but the extent of lesions is not always accurate. Other ultrasound-based techniques have been proposed to assess the extent of HIFU-induced lesions, such as MRE,[17] the use of contrast-enhanced power Doppler[18] or different techniques for characterizing the acoustic properties of tissues.[19]

HIFU IN ANIMAL CANCER MODELS

The destruction of tumors has been studied in several types of experimental cancers. *In vivo* experiments into the effects of HIFU have been performed on murine glioma,[20] hamster medulloblastoma,[21] and rat Morris hepatoma.[22,23] Studies of prostate cancer models were carried out, using the cell lines DUNNING R3327 implanted in rats, and the AT2 and AT6 cancer sublines, which have a high metastatic potential.[24,25]

Animal models were also used to establish the feasibility of HIFU in ablating kidney tumors, with *in vitro*,[26,27] *ex vivo*[26,28] and *in vivo*[14,27,29] experiments. These animal studies provided evidence that cancerous tissues can be destroyed by HIFU without inducing metastases.[25] Transrectal HIFU delivery has been experimentally validated in dogs for application in the prostate.[30,31]

TREATMENT OF BLADDER CANCER

In the 1990s, a device dedicated to the destruction of superficial bladder tumors with extracorporeal HIFU was developed.[32,33] While both experimental and clinical studies demonstrated the feasibility of this application, the project was prematurely abandoned due to its poor outcomes for treatment and patient management, in comparison to endoscopic surgical approaches.

TREATMENT OF RENAL CANCER

Following studies in animals, HIFU for renal cancer is at an early stage of clinical development. Pilot studies have reported necrosis of the targeted tissue volumes, which progressively reduced in size after treatment. General anesthesia was required for the delivery of an appropriate energy level. Tumors of the upper pole may be difficult targets for HIFU, due to

the absorption of ultrasound energy by the interposed ribs.[34,35] These preliminary experiences demonstrate the feasibility of HIFU as a noninvasive treatment for kidney tumors.

TREATMENT OF PROSTATE CANCER

The most developed clinical applications of HIFU are for diseases of the prostate gland, especially for the treatment of adenocarcinoma of the prostate[7,36] or for benign prostatic hyperplasia.[37] Two devices have been developed for the treatment of prostate cancer. The first results were obtained with the Sonablate® system (Focus Surgery Inc., Indianapolis IN), published in 2002.[6] The results obtained with the Ablatherm® machine (EDAP TMS SA, Vaulx-en-Velin, France) were more extensively reported. The European multicentric study summarized the experience of clinical development of Ablatherm® for prostate cancer.[38] The authors reported their experience separately, for defined subgroups of patients, using their results to establish and fine-tune standardized procedures and patient management protocols (Table 1). In addition to the peer-reviewed literature, oral communications are also of interest when considering a quickly evolving technology such as HIFU. The Cancer Committee of the French Urology Association has produced a review of relevant communications relating to HIFU.[39]

HIFU devices

Ablatherm® equipment and procedure

The Ablatherm® machine has a treatment module that includes the patient's bed, the probe positioning system, the ultrasound power generator, the cooling system for preservation of the rectal wall, and the ultrasound scanner, which is used during the treatment localization phase. There is also a treatment and imaging endorectal probe that incorporates both a by-plane imaging probe working at 7.5 MHz and a treatment transducer focused at 40 mm working at 3 MHz.

Numerous safety features have been incorporated, including a safety ring that stabilizes the rectal wall during transducer movements, a permanent control of the distance between the therapy transducer and the rectal wall, and a patient motion detector that stops the treatment if the patient moves during the firing sequence.

The treatment parameters were selected to optimize the size of the lesion which leaves rectal wall and surrounding tissues intact. The size of the elementary lesion is between 19 and 24 mm in length and 1.7 mm in diameter. Because the shape of the lesion depends on gland perfusion, treatment parameters are different according to the patient's status: 5 s treatment pulse and 5 s shot interval for the first HIFU session in primary-care treatment; 4.5 s treatment pulse and 5 s shot interval for the second session in primary care; and 4 s treatment pulse and 7 s shot interval for local relapse after external-beam radiation therapy.

The treatment is conducted under anesthesia (spinal or general) in the lateral position. The endorectal probe is placed in a latex balloon filled with cooling fluid and introduced into the rectum. Following definition of the target-volume boundaries by the operator, treatment is performed from the apex to the base of the prostate. Usually four to eight successive target volumes are defined in order to treat the entire prostate. At the end of the HIFU session, a Foley-type urinary catheter or a suprapubic tube is positioned.

Sonablate® equipment and procedure

Unlike the Ablatherm® machine, the Sonablate® system has no dedicated bed. Several treatment probes are available, and are selected by the operator according to the size of the elementary lesion required: 10 mm in length and 2 mm in diameter for a single beam performing with 25 mm or 45 mm focal-length probes; 10 mm in length and 3 mm in diameter for a split beam performing with 30, 35 or 40 mm focal-length probes.[6] Treatment parameters might also vary depending on operator choice.

Treatments are performed in a dorsal position under general anesthesia. The probe is chosen depending on prostate size, with larger glands requiring longer focal lengths. The treatment is usually made in three consecutive coronal layers, starting from the anterior part of the prostate and progressively moving to the posterior part, with at least one probe switch during the procedure.

Effects on prostate-specific antigen level

The European multicentric study reported the short-term results at 1 year of follow-up for 402 patients presenting with localized prostate cancer (T1–2 N0–x M0) treated with HIFU from 1995 to 1999.[38] After HIFU treatment, negative control biopsies were reported for 87.2% of the patients, stratified according to the prognosis risk level: 92.1% of patients with negative control biopsies were in the low-risk subgroup, 86.4% were in the

Table 1 Efficacy of HIFU for the treatment of prostate cancer.

	Poissonnier *et al.*[2] (2003)	Chaussy *et al.*[42] (2003)	Thüroff *et al.*[44] (2000)	Vallancien *et al.*[36] (2004)	Gelet *et al.*[45] (2004)	Blana *et al.*[1] (2004)
Study period	1993–2002	1996–1999	1995–1999	1999–2001	1997–2002	1997–2002
Number of patients	120	271 96[a], 175 [b]	402	30 TURP 22, BNI 8	71[c]	146
Disease stage	T1b–c 50.8% T2 49.2%	T1–2 N0–x M0	T1–2 N0 M0	T1–T2 N0 M0	T1 21.1%[d] T2 39.5%[d] T3 21.1%[d] Unknown 18.3 %[d]	T1–T2 N0 M0
Age (years)	71.2 ± 5.34	65.8 ± 7.6[a], 68.4 ± 6.8[b]	69.3 ± 7.1	Median age 72 (range 61–79)	67 ± 5.86	66.9 ± 6.7
Prostate volume (ml)	33.6 ± 16.5	21.7 ± 6.8[a], 20.5 ± 9.8[b]	28 ± 13.8	Median 30 (range 11–45)	21.4 ± 11.1	23 ± 7.7
Baseline PSA (ng/ml)	≤10	≤15 8.6 ± 3.2[a], 8.0 ± 3.4[b]	10.9 ± 8.7	≤10 Median 7 (range 1–10)	At diagnosis 20.4 (range 3.5–60) Nadir after radiotherapy 1.46 (range 0.0–4.3) Before HIFU 7.73 ± 8.10	<15 Mean 7.6 ± 3.4
% patients with Gleason score	Score 2–6 64. 6 Score 7–10 35.4	Score 2–6 69.8[a], 74.3[b] Score 7 26.0[a], 21.7[b] Score 8–10 4.2[a], 4.0[b]	Score 2–4 13.2 Score 5–7 77.5 Score 8–10 9.3	Median score 6 (range 4–7)	Score 2–6 33.8[e] Score 7 18.3[e] Score 8–10 47.9[e]	Score ≤7 at baseline Mean score 5 ± 1.2
Prognostic factors	Not available	LR 38.5%[a], 40.6%[b] IR 57.3%[a], 54.3%[b] HR 4.2%[a], 5.1%[b]	LR 28.4% IR 48.0% HR 23.6%	Not available	Time to recurrence 38.5 months (range 6–120) 30% hormones stopped before HIFU	Not available
Mean follow-up (months)	27 (range 3–96)	18.7 ± 12.1[a], 10.9 ± 6.2[b]	407.3 days	20 (range 3–38)	14.8 (range 6–86)	22.5 (range 4–62)
Evaluation criteria	Biopsies every 3 months. PSA every 3 months, failure if 3 consecutive increases	Biopsies Nadir PSA and PSA stability IPSS and QOL Morbidity	Sextant biopsies PSA	Biopsies at 1 year PSA IPSS and QOL Sexual function	Sextant biopsies at 3 months PSA every 3 months if rising PSA	Sextant biopsies at 3, 12 and 24 months PSA every 3 months IPSS and QOL
Negative biopsy rate (%)	86	87.7 [a], 81.6 [b]	Overall 87.2 LR 92.1 IR 86.4 HR 82.1	80	80	93.4
Nadir PSA (ng/ml)	Mean 0.49 ± 0.91	Median 0.0[a], 0.0[b]	Mean 1.8 (range 0–27) Median 0.6	Median 0.9	Mean 1.97 ± 4.58 Median 0.20	Median 0.07 Median PSA at 22 months 0.15
Urinary catheter time (days)	Mean transurethral 11 [a] , 6[b]	Mean suprapubic 40[a], 7[b]	Not available	Median transurethral 2	Mean transurethral 5 (range 2–46)	Mean suprapubic 12.7 (range 1–59) 12% TURP post-HIFU

[a] Group 1 patients were treated with HIFU monotherapy, [b] group 2 patients were treated with a TURP and HIFU combined, [c] all had local recurrence after radiotherapy, [d] before radiotherapy, [e] before HIFU.
BNI, bladder neck incision; HIFU, high-intensity focused ultrasound; HR, high risk; IR, intermediate risk; IPSS, International prostate symptom score; LR, low risk; PSA, prostate-specific antigen; QOL, quality of life; TURP, transurethral resection of the prostate; TxNxMx, tumor–node–metastases cancer staging.

GLOSSARY

NADIR PSA
Lowest level of prostate-specific antigen achieved after treatment

intermediate-risk subgroup, and 82.1% were in the high-risk subgroup. Biopsy results appeared to be influenced by the number of positive biopsy samples at the pretreatment disease work-up, and by the sonication parameters, which were refined during the course of the study. The NADIR PSA was generally observed 3–4 months after HIFU treatment, whereas the mean post-treatment PSA was somewhat elevated due to the inclusion of patients that did not respond to treatment (mean

PSA level 1.8 ng/ml, range 0–27 ng/ml, median nadir PSA 0.6 ng/ml). The post-treatment PSA was significantly influenced by prostate volume, completeness of HIFU treatment and the sonication parameters. Due to the short mean follow-up period (407 days), the stability of post-treatment PSA levels was not assessed.

Effects on prostate tissue

The potential for HIFU in the treatment of prostate cancer was established histologically in a clinical trial using HIFU delivered 1–2 weeks before radical prostatectomy. As the whole prostate gland was removed for histologic examination, the effect of HIFU on prostate tissue could be studied under clinical conditions. HIFU was delivered to regions of the prostate where biopsies had revealed cancer. On histologic examination of the specimens a sharp demarcation was seen between the HIFU-treated and untreated areas, with complete necrosis (no vital tissue) in the treated regions reported for all patients.[40] Fat-saturated gadolinium-enhanced MRI can demonstrate accurately the extent of the tissue damage induced by HIFU. The treatment area appears as a non-enhancing hypointense zone surrounded by a peripheral rim of enhancement 3 to 8 mm thick. These abnormalities correspond to a nucleus of coagulation necrosis surrounded by a peripheral zone of inflammation. Treatment-induced MRI abnormalities usually disappear in 3–5 months, in a centripetal way, and MRI is not suitable for long-term monitoring.[41]

Influence on patient survival

Longer patient follow-up and survival curves were presented in a series of 120 patients with localized prostate cancer and baseline PSA levels of <10 ng/ml. These patients were unsuitable candidates for radical prostatectomy, and had life expectancies of at least 10 years.[2] Actuarial 5-year disease-free rate was 76.9% for the overall patient population, this was significantly increased to 85.4% for well-differentiated tumors (GLEASON SCORE 2–6) compared to 61.3% for poorly-differentiated tumors (Gleason score 7–10). There was no significant difference in the actuarial disease-free rates according to prostate volume or to the number of positive samples at baseline biopsy. Nadir PSA was reported as a major prognostic factor, with an actuarial 5-year disease-free rate of 86% for patients with a nadir PSA <0.5 ng/ml.

Blana *et al.* reported results from a study of 146 patients with localized prostate cancer.[1] Patients had a baseline PSA ≤15 ng/ml, and a Gleason score ≤7. The mean follow-up period was 22.5 months, ranging from 4 months to 62 months. After HIFU treatment, 93.4% of the patients had negative control biopsies. The median nadir PSA was 0.07 ng/ml, and PSA level was maintained at 0.15 ng/ml after a mean follow-up of 22 months. Although a satisfactory cure rate is observed in low-risk and intermediate-risk patients treated with HIFU as a single therapy, a combined treatment should be considered for high-risk patients. No severe urinary STRESS INCONTINENCE grade II-III was observed, while 12% of the patients underwent transurethral prostate resection (TURP) during follow-up because of urinary obstruction. Sexual function was preserved in 47.3% of the patients, and no significant changes in international prostate symptom scores were reported. These 5-year disease-free results were similar to those reported in large series of standard treatments for localized prostate cancer (Table 2).

Adverse effects

The most commonly reported adverse event was prolonged urinary retention. In order to reduce the urinary catheter time and to improve morbidity associated with HIFU in the immediate follow-up period, a treatment combining TURP with HIFU was studied. In total, 30 patients with localized prostate cancer received combined TURP and HIFU treatment in one treatment session, performed under the same anesthesia.[36] Of these patients, 25 received a single HIFU session, and five patients received two HIFU sessions (within the same treatment session). The mean duration of the combined procedure was 2 h 48 min. Transurethral catheter time was 2 days, and mean hospital stay was 3 days. After 6 months, 80% of the patients presented negative control biopsies, and median post-HIFU PSA was 0.9 ng/ml. The mean post-treatment international prostate symptom score was 6.7, compared to a mean pretreatment score of 7.5. Potency was preserved for 73% of the men that were potent before the procedure.

The benefit of combining TURP with HIFU has been confirmed in a series of 271 patients presenting with localized prostate cancer and a baseline PSA <15 ng/ml.[42] For the 271 men in the study, 96 received only HIFU, and 175 patients received a combined TURP and HIFU treatment. The mean resected prostate weight was 15.7 g (range 2–110 g, median 12.5 g).

GLOSSARY

GLEASON SCORE
Sum of grades assigned to the two largest cancerous areas of tissue samples; grades range from 1 (least aggressive) to 5 (most aggressive)

STRESS INCONTINENCE
Impaired urethral sphincter function leads to involuntary leakage of urine during physical exertion with increased intra-abdominal pressure

Table 2 Efficacy of standard treatments of localized prostate cancer.

	Kupelian *et al.*[46] (2002)	Kuban *et al.*[47] (2003)	Potters *et al.*[48] (2004)	Dearnaley *et al.*[49] (2005)
Number of patients	1,682	4,839	1,819	126[a]
EBRT results using ASTRO criteria	8 years data FBR: 70% (628 patients)	5 years data FBR: 59% 61% with >70 Gy	7 years data FBR: 77% (340 patients)	5 years data FBR: 59% with 64 Gy 71% with 74 Gy
Radical prostatectomy results	8 years data Criteria: PSA<0.2 FBR: 72% (1,054 patients)	—	7 years data Criteria: PSA<0.2 FBR: 79% (746 patients)	—
Brachytherapy results	—	—	7 years data Criteria: ASTRO FBR: 74% (733 patients)	—

[a]All these patients had previous androgen suppression.
ASTRO, American Society for Therapeutic Radiology and Oncology; EBRT, external-beam radiation therapy; FBR, free of biochemical relapse; PSA, prostate-specific antigen.

GLOSSARY

RESECTION CHIPS
Small prostate tissue pieces resulting from transurethral resection of the prostate

SECONDARY INFRAVESICAL OBSTRUCTION
Strictures of the bladder neck or of the urethra after a prostate treatment procedure

Table 3 Efficacy of local salvage therapies following failure of external-beam radiation therapy for prostate cancer.

	Salvage prostatectomy	Cryotherapy	Brachytherapy	HIFU
	[a]Amling *et al.*	[a]Chin *et al.*	[a]Grado *et al.*	Gelet *et al.*[46]
Number of patients	108	118	37	71
Free of biochemical relapse (%)	43	40	34	38
Incontinence (%)	51	20	6	22
Rectal injury (%)	6	3.3	6	6
Bladder neck contracture (%)	21	8.5	14	17

[a]The figures for these three studies are taken from Touma *et al.*[50]

Cancer was present in the RESECTION CHIPS for 51.6% of the patients. Mean follow-up was 18.7 ± 12.1 months in the HIFU-only group, and 10.9 ± 6.2 months in the combined treatment group. Histologic results were similar in the two groups, with a post-treatment negative biopsy rate of 87.7% versus 81.6% respectively (not significant). Median nadir PSA was 0.0 ng/ml in both groups. Median suprapubic catheter time was 40 days in the HIFU-only group versus 7 days in the combined treatment group. This study demonstrates the advantages of the combined procedure over using HIFU alone.

Patients treated with HIFU as a primary local therapy combined with TURP generally have low morbidity; grade I (4–6%) or grade II (0–2%) urinary stress incontinence, and SECONDARY INFRAVESICAL OBSTRUCTION (5–10%) are the most commonly reported adverse events. Severe incontinence and urethra–rectal fistula are now a rare occurrence, particularly when safety margins and contraindications are respected, such as a rectal-wall thickness of over 6 mm or abnormal rectal anatomy. Potency preservation is directly related to the positioning of elementary lesions on the lateral sides of the prostate, a conservative approach being balanced with a higher retreatment rate.[43,44]

HIFU as a salvage therapy

HIFU has also been administered as a salvage therapy after external-beam radiotherapy. Results from 71 patients presenting with local recurrence were reported. All the men were diagnosed due to biochemical relapse and recurrence was confirmed by biopsy.[45] Hormonal therapy, either as an adjuvant treatment to radiotherapy or at biochemical relapse, was given to a third of the patients; this was stopped before treatment with HIFU. Following HIFU treatment, 80% of the

patients had negative control biopsies, and the median nadir PSA was 0.2 ng/ml. Despite these apparently satisfactory local results, 40 patients (56.3%) needed an adjuvant therapy during follow-up (mean follow-up 14.87 months, range 6–86 months). The reason for adjuvant therapy was an isolated increase of PSA (36.6%), or residual local tumor (19.7%). In this patient group, four men died from metastatic disease. The high rate of patients with rising PSA levels despite local disease control led to the conclusion that patients with local recurrence after radiation therapy might benefit from HIFU, providing that a precise disease-progression work-up, beyond any standard protocol, can confirm that the cancer has not extended outside of the prostate.

A higher incidence of adverse events is reported in patients treated with HIFU as salvage therapy after external-beam radiotherapy, compared to primary-care patients. Nevertheless, the risk–benefit ratio is better for HIFU than for the other salvage options: less morbidity, with reported efficacy results similar to those reported for the other local therapies, including 5-year disease-free survival (Table 3). Salvage HIFU treatments are now performed with dedicated sonication parameters in order to reduce treatment-related morbidity.

CONCLUSION

HIFU technology is currently used in routine clinical practice for prostate diseases only, although other promising targets are already identified. Device developments and improvements in imaging techniques could place it on the front line of noninvasive therapies.

The main advantages of the HIFU therapy should be observed in all applications; the treatment may be repeated if needed, and may be performed as a second-line treatment when surgery is no longer possible.

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Acknowledgments
The authors wish to acknowledge Jean-Yves Chapelon PhD and Laura Curiel PhD from the INSERM U556 for their assistance in the description of technological aspects of HIFU.

Competing interests
The authors declared competing interests; go to the article online for details.

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