Int. J. Hyperthermia, 2010, 1–8, Early Online

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healthcare

RESEARCH ARTICLE

High intensity focused ultrasound (HIFU) for prostate cancer: Current clinical status, outcomes and future perspectives

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(Received 23 March 2010; Accepted 1 June 2010)

Abstract

Two devices are currently available for the treatment of prostate cancer with HIFU: Sonablate® and Ablatherm®. The outcomes achieved for primary-care patient are very promissing with mid- and long-term progression-free survival rates around 70%, negative postoperative prostate biopsies almost 85%, and an excellent morbidity profile. Moreover, HIFU has a considerable potential for local recurrence after radiation failure. Recently, some early experiences on focal therapy suggest that HIFU could be an excellent option for highly selected patient.

Keywords: *high intensity focused ultrasound, localised prostate cancer, predition and monitoring of tumour response, thermal ablation, ultrasound surgery*

Introduction

The incidence of prostate cancer is increasing worldwide [1, 2]. Of these newly diagnosed prostate cancers, 70% are organ-confined and may be suitable for a local, potentially curative therapy. Many treatment options are available including the two standard treatment options that are surgery or radiation therapy. The morbidity associated with radical treatment is significant. Thus the quest continues for a reliable alternative to open surgery or radiation therapy with the need to find a procedure as minimally invasive as possible. Several new therapeutic options are available now including HIFU, which appears to be an attractive, evolving way to treat prostate cancer either as a primary care or as a salvage option. HIFU is also a very promising technology for focal therapy of prostate cancer.

HIFU history and principles

HIFU produces ultrasound waves that are generated by a spherical transducer. The ultrasound energy is focused on a fixed point. The first description of HIFU was made in 1942 and the ability to destroy tissue established in 1944 [3, 4]. The first experiments on prostate were made on canine and benign human prostate hypertrophy [5–7].

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 tissue, resulting in its destruction through cellular disruption and coagulative necrosis [8]. Two mechanisms of tissue damage are involved: thermal effect and cavitation [9]. The thermal effect relies on

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ISSN 0265–6736 print/ISSN 1464–5157 online
DOI: 10.3109/02656736.2010.498803

the absorption of ultrasound energy by the tissue and its conversion into heat. In the right conditions, the temperature within sonicated tissue will raise to a level sufficient to induce irreversible damages. Cavitation is the result of the interaction of ultrasound and micro-bubbles of water in the sonicated tissue. This interaction may lead to oscillation of these micro-bubbles, violent collapses and dispersion of energy enhancing tissue ablation.

The aim is to treat the entire gland by juxtaposition of elementary lesions. 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.

This technique provides 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 hyper-echoic 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 clearly show the extent of necrosis [10]. MRI has also been used to guide HIFU treatment as well as to monitor temperature changes during HIFU, but this technology is not available yet for transrectal prostate cancer treatment [11].

Currently available HIFU devices

Two devices are currently available for the treatment of prostate cancer: Sonablate® (Focus surgery, Indianapolis, IN) 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. 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).

Ablatherm requires a specific bed with a patient in a lateral position, whereas the Sonablate procedure is conducted in a dorsal position with the patient lying on a regular operating table. Treating in the lateral position allows gas bubbles produced through the heating of the prostate tissue to rise with gravity to a position lateral to the prostate reducing the chance 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), whereas Sonablate uses a single treatment protocol in which the power has to be adapted manually by the operator. Both devices offer 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.

The treatment planning is slightly different between the two devices. With the Ablatherm, the prostate is divided into four to six volume boundaries and treated from the apex to the base slice-by-slice by an entirely computer-driven probe [12]. With the Sonablate, 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 [13].

The risk of urethrorectal fistulas (URFs), which was the only significant complication in the early stages of HIFU development, has been dramatically reduced (incidence between 0 and 0.5% for primary procedures in contemporary series) [14–17].

HIFU indications

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) who are not suitable for a radical prostatectomy whatever the reasons (e.g. age >70 year old, life expectancy ≤10 years, major co-morbidities precluding surgery) or those refusing to undergo surgery [18, 19].

HIFU outcomes

Among publications on HIFU as a primary therapy for prostate cancer, 15 studies report series of at least 50 patients [13, 16, 17, 20–31], while the others report on fewer patients [12, 32–34].

Follow-up varies significantly between series (range: 6 months to 6.4 years). In most cases, the PSA nadir was reached 3 to 4 months after the HIFU treatment and was ≤0.05 ng/mL in 55% to 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 [16]. A PSA nadir >0.2 ng/mL after HIFU has been associated with a 4 times greater risk of treatment failure (as defined by cancer on biopsy after HIFU) [35]. The five years disease-free survival rate in the longest follow up studies was 66% and the cancer specific survival rate was 98% [24]. Complication rates are low with sloughing occurring in 0.3% to 8.6%. Impotence

occurs in 20% to 77% of patients and bladder outlet obstruction in 12% to 22%.

In our institution we have recently reviewed the outcomes 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 rates at 7 years were 90% and 98%, respectively. The metastasis-free survival rate at 7 years was 96%. The 5 and 7 years biochemical free survival rates were 75%–62%, 59%–50% and 45–39% for low, intermediate and high risk patients, respectively ($p = 0.0001$) (Figure 1) [36].

The disease free survival rate reported after conformal external beam radio therapy (EBRT) at 8 and 10 years was 59% to 68% and 78% to 83.4% with dose escalation and for an ultra-high dose (86.4 Gy) the five year actuarial PSA relapse-free survival was 98%, 85% and 70% for the low, intermediate and high risk groups [37–40]. However, only prospective studies or matched-pair analysis would allow a direct comparison between HIFU and EBRT.

HIFU re-treatment

In case of incomplete treatment or treatment failure, HIFU does not result in a therapeutic impasse. As opposed to 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% [13, 15, 17, 29]. 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, infra-vesical 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 retreat group [15].

Salvage HIFU

The rate of positive biopsy after EBRT for prostate cancer in the literature is between 21% and 32% [41–46]. The 10-year distant metastases-free survival rate in patients with negative/severe treatment effect biopsy outcomes was 90% (CI 86–95) and the corresponding outcome in patients with positive treatment biopsy outcomes was 69% (CI 58–80, $p = 0.0004$). Post-treatment biopsy status was also associated 2with an increased risk of prostate cancer death [45, 46]. There appears to be a role for salvage HIFU therapy with curative intents for some 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 [47]. With a mean follow-up of 18.1 (3 to 122) months, the overall actual five-year specific survival rate was 84%. The actual three-year progression-free (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

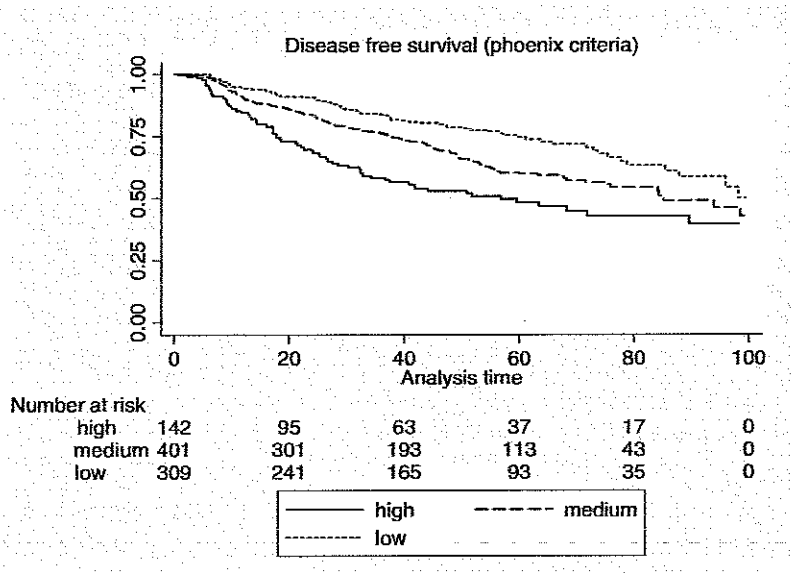

Figure 1. Disease free survival rate according to the risk group.

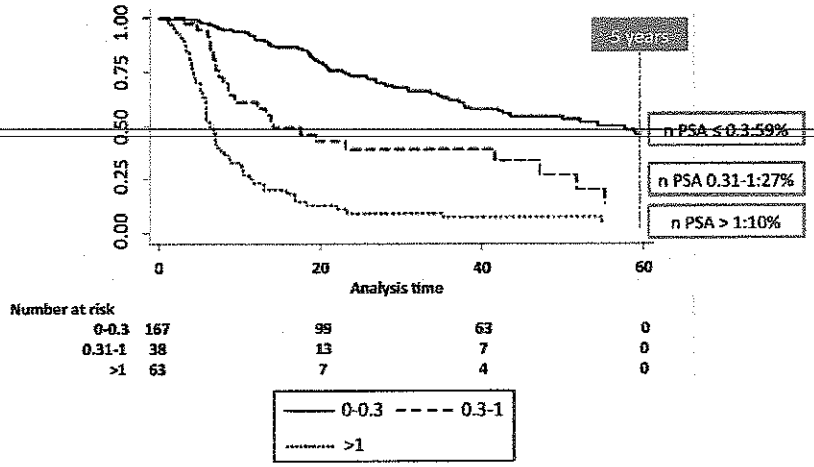

Figure 2. Disease free survival rate after salvage HIFU for EBRT failure.

risk groups. Disease progression was inversely related with the pre-HIFU PSA and the use of (AD) during PCa management (Figure 2). While the technique offers promising results, it has to be balanced with side effects. The morbidity reported was particularly important for incontinence, accounting for 56% of the patients, but only 11% of this group required an artificial urinary sphincter implantation. On the contrary, the risk of URF was only 0.4% with the introduction of a specific treatment algorithm designed for radiation failure: 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.

Nevertheless, the risk–benefit ratio of salvage HIFU compares favourably with those of the other available techniques 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.

Salvage EBRT after HIFU faillure

In a retrospective study, Pasticier et al. include patients treated with salvage radiation treatment after HIFU [48]. 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 ± 1.8ng/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 not different 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.

Future directions

Focal therapy

A short series of prostate hemiablation with HIFU was published in 2009 [49]. Inclusion criteria were men with low to moderate risk (Gleason ≤ 7, PSA ≤ 15 µg/mL), unilateral PCa ($\leq$T2bN0M0) on TRUS biopsy underwent multi-sequence MRI (T2, DCE, diffusion) and 5-mm-spaced transperineal template biopsies to localise disease. All were treated using transrectal HIFU incorporating the entire positive hemiprostate up to urethra. A total of 18 patients were treated. Gleason score was 7 in 78% of the cases and the mean PSA pre-HIFU was 7.3 ng/mL. Incontinence rate was 5.6%. Two patients (11.1%) had positive 6 months protocol biopsy with residual 1 mm Gleason 3+3: one elected for retreatment and the other active surveillance.

The French Urological Association (AFU) has started a study to evaluate hemiablation with HIFU as a primary treatment for patients >50 years, T1C or T2A, PSA <10 ng/mL, Gleason 6, with no more than 2 contiguous biopsies in no more than one lobe after MRI, random and targeted biopsies. To be included the tumour must be >6 mm from the apex and >5 mm from the midline. Only one prostatic lobe is treated (Figure 3).

A similar study is designed for EBRT failure with MRI and biopsy proven unilateral local recurrence.

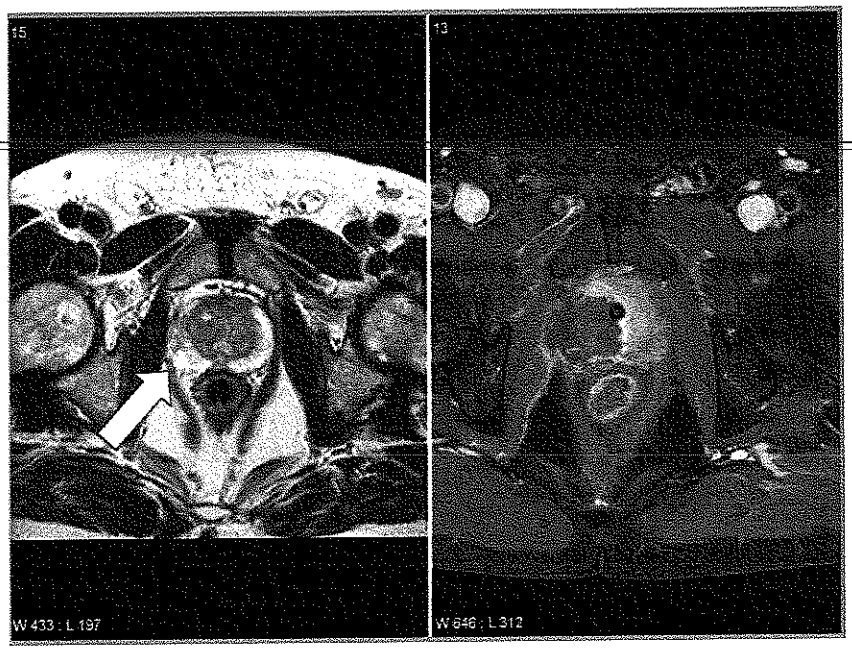

Figure 3. Focal HIFU treatment as primary treatment. The pre-operative MRI on the left shows an enhancing tumour on the left peripheral middle gland proven by targeted biopsies and the post-operative MRI on the right shows the hemi-ablated prostate with no residual enhancement.

These focal approaches need a precise preoperative localization of the cancer with multi sequence MRI associate with targeted and templates biopsies. The recent literature shows some promising results on cancer localization [50–53].

Brachytherapy failure

A study with the Ablatherm® device is in progress in Lyon. Nineteen patients with MRI and biopsy-proven recurrence after brachytherapy have been included so far. Sixteen of them underwent a whole gland ablation and three underwent a focal therapy (Figure 4). The follow up was 15 ± 20 months. Nine patients (47.4%) had undetectable PSA with no hormonal deprivation treatment, eight (42.1%) needed hormonal deprivation treatment for a rising PSA and two (10.5%) are recent cases with very short follow up. The complication rate was high in the first nine cases with three urinary incontinences (grade 3) and one urethro-rectal fistula. For those first patients, we used the treatment acoustic parameters defined for radiation failure. Because of the high rates of complications, 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 urethro-rectal fistula was noticed and no rectal lesion was seen on control MRI, without reduction of the treatment efficacy.

Chemotherapy associated with HIFU

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 [54, 55]. They showed a synergistic inhibitory effect of the HIFU + Docetaxel association. In an ethical comity approved study, 24 high-risk patients (Gleason $\geq 4+3$ 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 with a start at 30 mg/m^2. 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 no 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. Four patients had too short follow-up to give results.

Conclusion

The outcomes achieved for primary-care patients are very encouraging. HIFU does not represent a therapeutic impasse: EBRT is a safe salvage option after HIFU failure. On the other hand, HIFU has a considerable potential for treating local recurrence

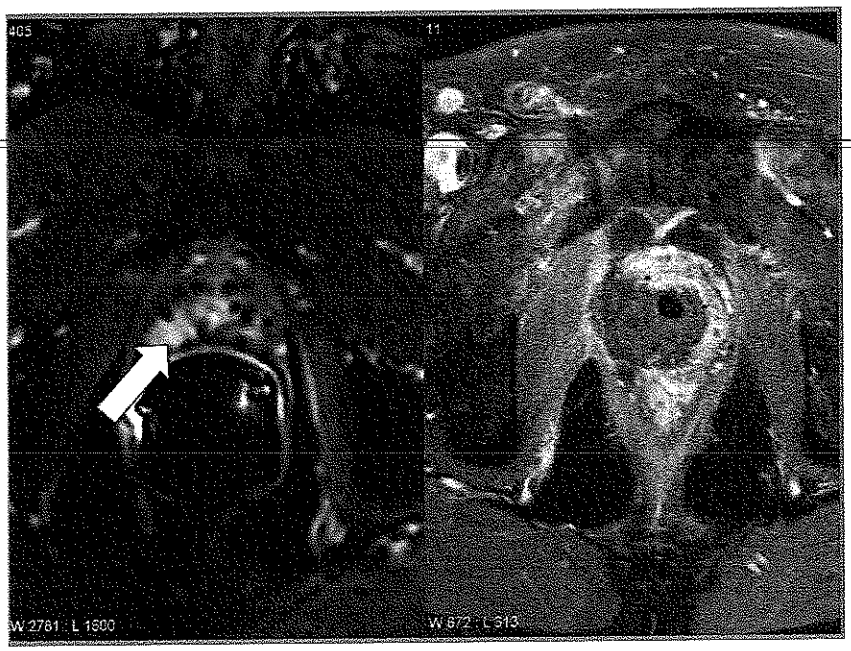

Figure 4. Focal HIFU after brachytherapy failure. The MRI on the left shows an enhancing tumour at the left peripheral zone extending to the right and crossing the midline. On the right, the post-operative MRI shows the destroyed area with no residual enhancement.

after radiation failure. Recently, some early experiences on focal therapy suggest that HIFU provides an excellent opportunity to perform local treatment in low-risk prostate cancer.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Yancik R. Population aging and cancer: A cross-national concern. Cancer J 2005;11:437–441.
2. Ferlay J, Parkin DM. Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46:765–781.
3. Lynn JG, Zwemer RL, Chick AJ, Miller AE. A new method for the generation and use of focused ultrasound in experimental biology. J Gen Physiol 1942;26:179–193.
4. Lynn JG, Putnam TJ. Histology of cerebral lesions produced by focused ultrasound. Am J Pathol 1944;20:637–649.
5. Gelet A, Chapelon JY, Margonari J, Theillere Y, Gorry F, Cathignol D, Blanc E. Prostatic tissue destruction by high-intensity focused ultrasound: Experimentation on canine prostate. J Endourol 1993;7:249–253.
6. Gelet A, Chapelon JY, Margonari J, Theillere Y, Gorry F, Souchon R, Bouvier R. High-intensity focused ultrasound experimentation on human benign prostatic hypertrophy. Eur Urol 1993;23:S44–47.
7. Madersbacher S, Kratzik C, Szabo N, Susani M, Vingers L, Marberger M. Tissue ablation in benign prostatic hyperplasia with high-intensity focused ultrasound. Eur Urol 1993;23:S39–43.
8. Beerlage HP, van Leenders GJ, Oosterhof GO, Witjes JA, Ruijter ET, van de Kaa CA, Debruyne FM, de la Rosette JJ. High-intensity focused ultrasound (HIFU) followed after one to two weeks by radical retropubic prostatectomy: Results of a prospective study. Prostate 1999;39:41–46.
9. Kennedy JE, Ter Haar GR, Cranston D. High intensity focused ultrasound: Surgery of the future? Br J Radiol 2003;76:590–599.
10. Rouvière O, Lyonnet D, Raudrant A, Colin-Pangaud C, Chapelon JY, Bouvier R, Dubernard JM, Gelet A. MRI appearance of prostate following transrectal HIFU ablation of localized cancer. Eur Urol 2001;40:265–274.
11. de Senneville BD, Mougenot C, Moonen CT. Real-time adaptive methods for treatment of mobile organs by MRI-controlled high-intensity focused ultrasound. Magn Reson Med 2007;57:319–330.
12. Ficarra V, Antoniolli SZ, Novara G, Parisi A, Fracalanza S, Martignoni G, Artibani W. Short-term outcome after high-intensity focused ultrasound in the treatment of patients with high-risk prostate cancer. BJU Int 2006;98:1193–1198.
13. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int 2006;97:56–61.
14. Vallancien G, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: Feasibility study. J Urol 2004;171:2265–2267.
15. Blana A, Rogenhofer S, Ganzer R, Wild PJ, Wieland WF, Walter B. Morbidity associated with repeated transrectal high-intensity focused ultrasound treatment of localized prostate cancer. World J Urol 2006;24:585–590.

16. Lee HM, Hong JH, Choi HY. High-intensity focused ultrasound therapy for clinically localized prostate cancer. Prostate Cancer Prostatic Dis 2006;9:439–443.
17. Poissonnier L, Chapelon JY, Rouvière O, Curiel L, Bouvier R, Martin X, Dubernard JM, Gelet A. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol 2007;51:381–387.
18. Rebillard X, Davin JL, Soulie M. [Treatment by HIFU of prostate cancer: survey of literature and treatment indications]. Prog Urol 2003;13:1428–1456.
19. Associazione Urologi Italiani (AURO) The Association of Italian Urologist (TAoUI). Guidelines, Prostate Cancer. 2009;2:76–77.
20. Uchida T, Nakano M, Shoji S, Omaat N, Harano H, Nagata Y, Usui Y, Terachi T. Ten year biochemical disease free survival after high intensity focused ultrasound (HIFU) for localised prostate cancer: Comparison with three different generation devices. J Urol 2009;181:228.
21. Ahmed HU, Zacharakis E, Dudderidge T, Armitage JN, Scott R, Calleary J, Illing R, Kirkham A, Freeman A, Ogden C, Allen C, Emberton M. High-intensity-focused ultrasound in the treatment of primary prostate cancer: The first UK series. Br J Cancer 2009;101:19–26.
22. Blana A, Brown SCW, Chaussy C, Conti GN, Eastham JA, Ganzer R, Murat FJ, Rebillard X, Rewcastle JC, Robertson CN, et al. Primary prostate HIFU without pretreatment hormone therapy: Biochemical survival of 468 patients tracked with the -registry. J Urol 2009;181:227.
23. Mearini L, D'Urso L, Collura D, Zucchi A, Costantini E, Formiconi A, Bini V, Muto G, Porena M. Visually directed transrectal high intensity focused ultrasound for the treatment of prostate cancer: a preliminary report on the Italian experience. J Urol 2009;181:105–112.
24. Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, Gelet A. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. Eur Urol 2008;53:1194–1201.
25. Misrai V, Rouprêt M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, Bitker MO, Richard F, Conort P. Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. World J Urol 2008 Oct;26:481–485.
26. Blana A, Rogenhofer S, Ganzer R, Lunz JC, Schostak M, Wieland WF, Walter B. Eight years' experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology 2008;72:1329–1334.
27. Ganzer R, Rogenhofer S, Walter B, Lunz JC, Schostak M, Wieland WF, Blana A. PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localised prostate cancer. Eur Urol 2008;53:57–53.
28. Uchida T, Ohkusa H, Yamashita H, Shoji S, Nagata Y, Hyodo T, Satoh T. Five years experience of transrectal high-intensity focused ultrasound using the Sonablate device in the treatment of localized prostate cancer. Int J Urol 2006;13:228–233.
29. Thuroff S, Chaussy C, Vallancien G, Wieland W, Kiel HJ, Le Duc A, Desgrandchamps F, De La Rosette JJ, Gelet A. High-intensity focused ultrasound and localized prostate cancer: Efficacy results from the European multicentric study. J Endourol 2003;17:673–677.
30. Chaussy C, Thuroff S. Results and side effects of high-intensity focused ultrasound in localized prostate cancer. J Endourol 2001;15:437–440; discussion 447–448.
31. Gelet A, Chapelon JY, Bouvier R, Rouvière O, Lasne Y, Lyonnet D, Dubernard JM. Transrectal high-intensity focused ultrasound: Minimally invasive therapy of localized prostate cancer. J Endourol 2000;14:519–528.
32. Challacombe BJ, Murphy DG, Zakri R, Cahill DJ. High-intensity focused ultrasound for localized prostate cancer: Initial experience with a 2-year follow-up. BJU Int 2009;104:200–204.
33. Maestroni U, Ziveri M, Azzolini N, Dinale F, Ziglioli F, Campaniello G, Frattini A, Ferretti S. High Intensity Focused Ultrasound (HIFU): A useful alternative choice in prostate cancer treatment. Preliminary results. Acta Biomed 2008;79:211–216.
34. Koch MO, Gardner T, Cheng L, Fedewa RJ, Seip R, Sanghvi NT. Phase I/II trial of high intensity focused ultrasound for the treatment of previously untreated localized prostate cancer. J Urol 2007;178:2366–2371.
35. Uchida T, Illing RO, Cathcart PJ, Emberton M. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? BJU Int 2006;98:537–539.
36. Crouzet S, Murat FJ, Rouviere O, Poissonnier L, Martin X, Colombel M, Chapelon JY, Gelet A. Outcomes of HIFU for prostate cancer in 880 consecutive patients. J Urol 2010;183:759.
37. Pollack A, Hanlon A, Horwitz EM, Feigenberg S, Uzzo RG, Price RA. Radiation therapy dose escalation for prostate cancer: A rationale for IMRT. World J Urol 2003;21:200–208.
38. Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, Coen JJ, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol 2010;28:1106–1111.
39. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67–74.
40. Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y, et al. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: Toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 2008;71:330–337.
41. Borghede G, Aldenborg F, Wurzinger E, Johansson KA, Hedelin H. Analysis of the local control in lymph-node staged localized prostate cancer treated by external beam radiotherapy, assessed by digital rectal examination, serum prostate-specific antigen and biopsy. Br J Urol 1997;80:247–255.
42. Crook J, Malone S, Perry G, Bahadur Y, Robertson S, Abdolell M. Postradiotherapy prostate biopsies: What do they really mean? Results for 498 patients. Int J Radiat Oncol Biol Phys 2000;48:355–367.
43. Pollack A, Zagars GK, Antolak JA, Kuban DA, Rosen II. Prostate biopsy status and PSA nadir level as early surrogates for treatment failure: Analysis of a prostate cancer randomized radiation dose escalation trial. Int J Radiat Oncol Biol Phys 2002;54:677–685.
44. Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol 2001;166:876–881.
45. Zelefsky MJ, Reuter VE, Fuks Z, Scardino P, Shippy A. Influence of local tumor control on distant metastases and cancer related mortality after external beam radiotherapy for prostate cancer. J Urol 2008;179:1368–1373.
46. Zapatero A, Minguez R, Nieto S, Martin de Vidales C, Garcia-Vicente F. Post-treatment prostate biopsies in the era of three-dimensional conformal radiotherapy: What can they teach us? Eur Urol 2009;55:902–909.

47. Murat FJ, Poissonnier L, Rabilloud M, Belot A, Bouvier R, Rouviere O, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radio-recurrent prostate cancer. Eur Urol 2009;55:640–647.
48. Pasticier G, Riviere J, Wallerand H, Robert G, Bernhard JC, Ferriere JM, et al. Salvage radiotherapy (SRT) for local recurrence of prostate adenocarcinoma after primary treatment with high intensity focused ultrasound (HIFU): First series of 100 patients. Paper presented at the 2010 ASCO Annual Meeting, June 4–8, Chicago, IL, USA.
49. Ahmed HU, Sahu M, Govindaraju SK, Arumainayagam N, Scott R, Illing RO, et al. High intensity focused ultrasound (HIFU) hemiablation trial in localised unilateral prostate cancer: Interim results. Eur Urol Supp 2009;8:334.
50. Villers A, Lemaitre L, Haffner J, Puech P. Current status of MRI for the diagnosis, staging and prognosis of prostate cancer: Implications for focal therapy and active surveillance. Curr Opin Urol 2009;19:274–282.
51. Puech P, Potiron E, Lemaitre L, Leroy X, Haber GP, Crouzet S, et al. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: Correlation with radical prostatectomy specimens. Urology 2009;74:1094–1099.
52. Puech P, Betrouni N, Makni N, Dewalle AS, Villers A, Lemaitre L. Computer-assisted diagnosis of prostate cancer using DCE-MRI data: Design, implementation and preliminary results. Int J Comput Assist Radiol Surg 2009;4:1–10.
53. Lecornet E, Ahmed HU, Moore CM, Emberton M. Conceptual basis for focal therapy in prostate cancer. J Endourol 2010;24:811–818.
54. Paparel P, Curiel L, Chesnais S, Ecochard R, Chapelon JY, Gelet A. Synergistic inhibitory effect of high-intensity focused ultrasound combined with chemotherapy on Dunning adenocarcinoma. BJU Int 2005;95:881–885.
55. Paparel P, Chapelon JY, Bissery A, Chesnais S, Curiel L, Gelet A. Influence of the docetaxel administration period (neoadjuvant or concomitant) in relation to HIFU treatment on the growth of Dunning tumors: Results of a preliminary study. Prostate Cancer Prostatic Dis 2008;11:181–186.