

**High Intensity Focused Ultrasound (HIFU) in Localized Prostate Cancer Treatment: Review Study**Khalid S. Alzimami<sup>1</sup>, Mustafa Z. Mahmoud<sup>2,3</sup>, Mohammed A. Alkhorayef<sup>1</sup>, Abdelmoneim Sulieman<sup>2</sup><sup>1</sup>. Radiological Sciences Department, College of Applied Medical Sciences, King Saud University, Riyadh- Saudi Arabia<sup>2</sup>. Radiology and Medical Imaging Department, College of Applied Medical Sciences, Salman bin Abdulaziz University, Al-Kharj- Saudi Arabia<sup>3</sup>. Basic Sciences Department, College of Medical Radiological Sciences, Sudan University of Science and Technology, Khartoum- Sudan  
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**Abstract:** High intensity focused ultrasound (HIFU) is a highly precise medical procedure that applies high intensity focused ultrasound energy to locally heat and destroys diseased or damaged tissue through ablation. This study intended to review HIFU to explain from a fundamental how HIFU works, to evaluate the evidence on the role of HIFU for the treatment of prostate cancer (PC) as well as to review the technologies used to perform HIFU and the published clinical literature regarding the procedure as a primary treatment for PC. Studies addressing HIFU in localized PC were identified from a search of the internet scientific databases. The literature outcomes analysis was limited to journal articles written in English and published between 2000 and 2013. HIFU possesses characteristics that make it an attractive curative therapy option. HIFU is a non-invasive approach that uses precisely delivered ultrasound energy to achieve tumor cell necrosis without radiation or surgical excision. In current urological oncology, HIFU is used clinically in the treatment of PC. Clinical research on HIFU therapy for localized PC began in the 1990s, and the majority of PC patients treated predominantly with the Ablatherm device. HIFU is a highly effective standard treatment with a large indication range over all tumor stages of PC. In localized PC treatment, HIFU is associated with high efficacy, low operative morbidity and no systemic side effects.

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**1. Introduction**

Prostate cancer (PC) is one of the most frequently diagnosed cancers in the male population in the world (ACS, 2009). According to the American Cancer Society (ACS), PC represents 25% of newly diagnosed cancers every year (ACS, 2009). In Europe, the mortality rate for PC was 21.1% in 2008 (ECO, 2013).

High intensity focused ultrasound (HIFU) is a non-invasive therapy that has been used for localized PC or salvage therapy in the 1990's. It is a technique that uses focused ultrasound waves to thermally ablate a portion of tissue situated at the focal point. High power ultrasound can be focused on a targeted point to cause a rise in temperature between 70-80 °C. This can result in thermal tissue coagulation necrosis, cavitation and heat shock. Each sonication heats only a small focal target, so multiple sonications, raster scanner, volumetric focus steering or some other beam translating method must be utilized to ablate an entire target area (Jolesz, 2009). Transrectal HIFU ablation is a minimally invasive treatment for PC that has been evaluated since the early 1990s (Gelet et al., 1993a; Gelet et al., 1993b

and Chapelon et al., 1992). It can be proposed either for patients with clinically localized PC who is not candidates for surgery or as a salvage treatment of local recurrences of PC after external beam radiation therapy (EBRT) (Poissonnier et al., 2007; Chaussy et al., 2005; Murat et al. 2009 and Gelet et al., 2004).

Five year disease free survival rates after HIFU ablation of clinically localized PC fall within the 66–78% range, which challenges the results of radiation therapy (Poissonnier et al., 2007; Blana et al., 2004 and Uchida et al., 2006). Although knowledge that tissue destruction could be achieved with HIFU has been around since the 1930s, efforts to clinically implement this technology were delayed due to the absence of imaging technology to monitor the procedure (Chaussy, 2011). Some medical associations recommend HIFU for treatment of PC but its accuracy is still not clear (Heidenreich et al., 2013). In the past ten years, many men have had their PC treated with HIFU. Most patients have been treated in Europe and Japan. For example, the National Institute for Clinical Excellence (NICE) is a government body in the United Kingdom which evaluates new treatments. It has reviewed the clinical

data associated with HIFU and concluded that the evidence is sufficient and recommended its use to the UK's National Health System (NICE, 2013).

Basic research in the urological application of HIFU began in the 1980s, primarily in France and the USA, when computer technology became sufficient to facilitate the control and management of this fascinating energy source. The first clinical prototypes for use in urology emerged during this period. Early clinical trials of HIFU therapy for PC during the mid-late 1990s found a relationship between the coagulated prostate volume with HIFU and obstruction, and analysis of prospective studies also found a high rate of urinary tract infections in this necrotic tissue. As the result of the association between HIFU and obstruction, and consistent with the whole gland concept of therapy, HIFU has been routinely combined with an adjuvant transurethral resection of the prostate (TURP) since 2000 to debulk the tumor mass and radically resect the middle lobes, calcifications, abscesses, and bladder neck (Chaussy and Thuroff, 2003; Chaussy and Thuroff, 2001 and Chaussy and Thuroff, 2009).

Recently, the combination of magnetic resonance guided focused ultrasound surgery (MRgFUS) has been introduced due to a better ability to plan and monitor treatments in real time (Dick and Gedroyc, 2010). This technique is approved by the Food and Drugs Administration (FDA) for PC and fibroid ablation and shows great potential in bone metastasis pain palliation. Promising results for treatment of liver, breast and brain tumor and prostate, were also obtained (Dick and Gedroyc, 2010).

Due to increase patient interest and the current use of HIFU technology worldwide, this article reviews HIFU to explain from a fundamental how HIFU works and to evaluate the evidence on the role of HIFU for the treatment of PC as well as to review the technologies used to perform HIFU and the published clinical literature regarding the procedure as a primary treatment for PC.

## 2. Material and Methods

An inclusive literature review was carried out in order to review the scientific foundation of HIFU and it was discussed in terms of how it has resulted in the development of two distinct devices. The merits and limitations of each are addressed. The PubMed, SAGE, MEDLINE and ScienceDirect database was searched in January 2014 for publications containing any combination of HIFU and PC in the title of the report. Abstracts resulting from this search were reviewed for relevance to the clinical outcomes from the procedure.

Full manuscripts were retrieved and reviewed if they contained information regarding evaluation the evidence on the role of HIFU for the treatment of PC as well as the technologies used to perform HIFU and the published clinical literature regarding the procedure as a primary treatment for PC. Only those papers published between 2000 and 2013 were included in the outcomes analysis.

There were no restrictions on the country of origin where the publications were produced, which help to provide a range of opinions and experiences. Articles identified from the refined search results were further reviewed on an individual basis for content.

## 3. Results and Discussion

### *HIFU fundamentals*

The premise behind HIFU is the destruction of tissue by depositing large amounts of energy into it. This is accomplished by doing by increasing the intensity of the waves and focusing the waves on a single point. If done in the right conditions it will raise the temperature of tissue to a level sufficient to induce irreversible damage in a discrete volume of tissue (Linke et al., 1973).

The deposit of energy during HIFU can result in two mechanisms of tissue damage (Hill et al., 1995). Elevation of tissue temperature leads to melting of lipid membranes and protein denaturation. This is the desired effect of HIFU. If large deposits of energy occur mechanical damage may result in gas bubble formation and/or cavitation (Barnett et al., 1994). Gas can form inside tissue during HIFU as a result of several mechanisms (Curiel et al., 2004).

The first mechanism is simple boiling that will occur if the temperature of the tissue is increased beyond the boiling point of the liquids it contains. This will create air pockets that have the potential of reflecting the ultrasound signal and modify, in an uncontrollable way, the HIFU lesion (Curiel et al., 2004). The second mechanism is cavitation and can be either inertial cavitation or stable cavitation. During inertial cavitation gas micro bubbles form within tissue due to the negative pressure caused by HIFU. Upon subsequent collapse due to the higher pressure of the surrounding medium the temperature and pressure inside the micro bubble will increase rapidly. This can lead to the dissipation of the gas into the surrounding medium in the form of a shock wave (Curiel et al., 2004).

Inertial cavitation is relatively unpredictable in terms of formation and dissipation of energy and is avoided during HIFU. Stable cavitation is the oscillation of existing micro bubbles in the tissue and it is not associated with a violent collapse and dispersion of energy. Micro bubble oscillations can

result in sheering forces and viscous damping heating. Although stable cavitation is currently avoided during the procedure there is some experimental evidence that stable cavitation may be able to enhance tissue ablation during HIFU and is being further investigated (Curiel et al., 2004).

A reproducible but small volume of ablation is created for each pulse of energy during HIFU. The geometry of each ablation volume is an ellipsoid, and the size of the ellipsoid is a function of crystal geometry. Treatment of cancer of the prostate is accomplished by systematically pulsing energy throughout the target volume at different locations until the entire volume has been ablated (Foster et al., 1993).

#### ***HIFU experimental identification and essential clinical parameters***

Computer simulation, in vitro and in vivo studies were conducted to identify and refine the ultrasound parameters required for the clinical treatment of prostatic disease. The destruction of PC with HIFU in these studies provided the evidence that prostate cancerous tissues can be destroyed by HIFU without inducing metastases, and that prostatic tissue can effectively be targeted through Transrectal delivery of HIFU (Gelet et al., 1993; Oosterhof et al., 1997 and Foster et al., 1993).

Essential clinical parameters for the medical use of HIFU include the ultrasound frequency (MHz), the acoustic intensity (Watts), the duration of application (shot time), the intervals of the pulses (delay time), the lateral distance between elementary lesions, the longitudinal displacement of the energy source when applying multiple lesions and the penetration depth (focal point) dependent on the applicator design (Chaussy, 2011).

These multiple technical parameters are essential in the assembly of a HIFU system with a dedicated application for specific tissue. Complex technical decisions are involved in HIFU operation, and include the selection and design of the piezoelectric energy applicator, the parameters of ultrasound treatment (MHz, Watts), the application algorithm (impulse delay relation), the imaging system, the intraoperative target and safety features, target localization during treatment with transrectal ultrasound (TRUS) and controls (Chaussy, 2011).

Current standard urological applications use HIFU transducers with a fixed but adjustable focal point to be moved mechanically to treat a larger tissue volume (Curiel et al., 2002 and Tan et al., 2000).

#### ***Commercially available HIFU devices and treatment technologies***

As of 2011, two transrectal HIFU devices were commercially available for the treatment of PC, the Ablatherm [Edap Technomed, Lyon, France] and the Sonablate500 [Indianapolis, IN, USA]. Although neither device has received FDA approval for marketing in the US, regulatory clearance is likely for the Ablatherm device when the results of a prospective trial become available (Chaussy, 2011).

Nevertheless the foundation science and technology of both systems is identical but there are several technological differences between the two devices. These differences, for the most part, arise from different schools of thought with regards to how best design the optimal HIFU treatment system. Specifically, the differences arise in how the manufacturers went about choosing operating frequencies and intensities. This is an optimization based on the effects that modifying these parameters have on image quality and ablation ability (Chaussy, 2011).

The Ablatherm machine consists of 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 used during the treatment localization phase. There is also a treatment and imaging endorectal probe that incorporates both a biplanar imaging probe working at 7.5 MHz and a treatment transducer focused at a maximum of 45 mm working at 3 MHz (Lukka et al., 2011).

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 treatment if the patient moves during the firing sequence (Chaussy and Thuroff, 2010). HIFU is delivered as a single session therapy under spinal anesthesia for duration of 2 to 3 hours. The treatment is conducted with the patient in the lateral position (Chaussy and Thuroff, 2010).

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; and 10 mm in length and 3 mm in diameter for a split beam performing with 30 mm, 35 mm or 40 mm focal length probes (US HIFU, 2013).

Treatment parameters may also vary depending on operator choice. Treatment is

performed with the patients 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 (US HIFU, 2013).

#### ***Measurement of HIFU effects on PC tissues***

Most patients treated with HIFU presented with localized cancer (Lukka et al., 2011). Usually HIFU is used as a standalone procedure with a 5 year disease free survival rate (biochemical) of 77% for Ablatherm and 45%-84% for Sonablate (Warmuth et al., 2010). Best results after HIFU in terms of negative biopsies and low (prostatic specific antigen) PSA levels were achieved in patients with low grade PC (Warmuth et al., 2010). Based on The French Association of Urology (AFU) review, HIFU is the best short term cancer control in terms of percentage of negative biopsies and decrease of PSA serum levels (Blana et al., 2008).

However, cautious optimism is recommended, as long-term results have not yet been provided. HIFU was delivered to regions of the prostate where biopsies had revealed cancer, and histologic examination found a sharp demarcation between HIFU treated and untreated areas, with complete necrosis in all specimens (Beerlage et al., 1999). Treated areas appear as a non enhancing hypointense zone surrounded by a peripheral rim of enhancement 3 mm to 8 mm thick. These abnormalities correspond to a nucleus of coagulation necrosis surrounded by a peripheral zone of inflammation. Treatment induced abnormalities visible with MRI usually disappear in 3 months to 5 months in a centripetal manner, and HIFU-induced tissue contraction results after about 6 months in small prostates of approximately 5cc (Rouviere et al., 2001).

#### ***Indications for HIFU Therapy of PC***

The most widespread use of HIFU, and initially the only indication for its use, has been in patients with localized PC who are not candidates for surgery because of age, general health status, a prohibiting comorbidity or a preference not to undergo a radical prostatectomy (Chaussy, 2011). However, with the accumulation of clinical experience and expansion of research protocols these indications have broadened (Gelet et al., 2004) and (Chaussy and Thueroff, 2006).

In contrast to radiation therapy, HIFU can also be used in intermediate and high risk patients. Most studies have used HIFU with inclusion of these

patient groups with reasonable outcomes, but as with the other curative therapies, high risk patients have a lower success rate than low risk patients. Remaining contraindications common to both HIFU devices include a missing or small rectum, and a damaged rectal wall from previous prostatic or rectal therapies (Chaussy, 2011; Ficarra et al., 2006 and ASTRO, 1997).

#### ***Efficacy of HIFU for PC therapy***

There is no universal consensus on the definition of biochemical failure in patients treated with HIFU (Chaussy, 2011). The lowest negative biopsy rate was reported by Gelet et al. (2001) when included patients treated with prototype devices. Another series of negative biopsy rate less than 80% who included patients with high risk PC (Poissonnier et al., 2003 and Blana et al., 2003).

In more recent series, negative biopsy rates have ranged from 93%-96% (Rouviere et al., 2001 and Blana et al., 2003). Stricter criteria for treatment failure were applied by Gelet et al. (2000) with failure defined as any positive biopsy or three successive elevations in PSA with a velocity  $\geq 0.75$  ng/ml/year.

Retreatment rates have also been reported in the literature but their interpretation is confounded by the former practice of using two treatment sessions with only one prostatic lobe treated in each session. This approach was common in the studies of Gelet et al. (2001) and Poissonnier et al. (2007) and the only series that did not use this approach were two studies involving high risk patients and reported by Ficarra et al. (2006).

#### ***Future perspectives of HIFU for cancer treatment***

HIFU is a non-invasive method of destroying a target tissue without skin incision whilst sparing adjacent tissues and organs, using real time imaging guidance and control. The HIFU treatments involve relatively a little pain and can be carried out with conscious sedation and on an outpatient basis. Such technology provides a personalized treatment, adjusted to the individual patient anatomy, pathology and treatment response.

The combination of Magnetic Resonance Imaging (MRI) and Focused Ultrasound (FUS), known as "MRgFUS", provides the ability to plan and monitor treatments in near real time, with MRgFUS further increasing the safety profile of FUS due to real time temperature mapping (Jolesz et al., 2002).

Combined strategies have been recently addresses, in order to match advantages of both imaging modalities (Auboiroux et al., 2012). Moreover, MRgFUS allows achieving a higher

degree of accuracy in ablation of affected tissue (Damianou, 2004; Tempany et al., 2003 and Siddiqui et al., 2010). In particular, MRI has the unique ability to monitor temperature and cavitation level in real-time (McDannold et al., 2006 and Ghobrial et al., 2005).

Another exciting opportunity for HIFU application in cancer therapy is its combination with pharmacological agents, particularly with modulators of apoptosis such as bortezomib. Bortezomib is boronic acid inhibitor for selective suppression of chymotryptic threonine protease activity. The administration alone or in combination with chemotherapy or radiation, bortezomib demonstrated anti-tumor activity (sensitizing the cancer cells to apoptosis) (Ghobrial et al., 2005). Poff et al. (2008) showed that pulsed HIFU could be exploited for tumor growth inhibition and induction of apoptosis in combination with anti-cancer drugs (bortezomib).

Opposite to thermal induction, the mechanical impact from HIFU might be considered as an alternative for eliciting of apoptosis. In recent study researchers exploited MR-guided HIFU for induction apoptosis, where moderate acoustic power was applied (5 Watt acoustic power, 5 Hz frequency; 0.1 duty cycle) (Cvetkovic et al., 2012).

The data of microscopic examination revealed an absence of thermal damage and destruction of the tissues, while apoptotic index achieved a peak (after 24 hours) comparing to control population. Finally, HIFU induced apoptosis or HIFU enhanced apoptosis induction will open more avenues for a novel non-invasive therapeutic approach of cancer treatment (Cvetkovic et al., 2012).

#### 4. Conclusion

HIFU is a highly effective standard treatment with a large indication range over all tumor stages of PC. In localized PC treatment, HIFU is associated with high efficacy, low operative morbidity and no systemic side effects. As a palliative therapy, an effective local tumor reduction decreases local morbidity and even kills cells insensitive to hormone therapy or radiation therapy.

Unlike certain other localized therapies, HIFU is effective in salvage therapy and can result in acceptable side effects. The use of HIFU does not preclude other therapeutic options, such as hormonal therapy and unlike such therapies; HIFU does not provoke a negative cell selection.

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