



# High Intensity Focussed Ultrasound Therapy for Prostatic Tumors: Anaesthesiologists Perspective

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## Abstract

**Background:** High intensity focussed ultrasound (HIFU) is a fairly recent and excellent addition to the armamentarium of minimally invasive surgical therapy. It causes thermal ablation of targeted diseased tissue through intense local heat generation without affecting the intervening healthy tissue. It is a promising advancement in onco-surgery with the potential to revolutionize carcinoma prostate therapy.

**Methods:** A thorough Medline search was done for this review article with the key words: High intensity focussed ultrasound (HIFU), carcinoma prostate, minimally invasive surgery, and anaesthesia. All the relevant articles found in Google, Pub med, e PUB and EBESCO were fully reviewed. The authors' personal clinical experience with HIFU for prostate tumour ablation and its anaesthetic implications are also added in this review.

**Results:** The survival rates after HIFU are comparable to those after surgery, while the results after cryo therapy and brachy therapy are inferior to those of surgery. HIFU can be used as both primary and salvage treatment post- radiotherapy and has a lesser incidence of complications like urinary incontinence and erectile dysfunction. Anaesthesia for prostatic HIFU may pose challenges in patients with concurrent co-morbidities, metastatic tumours and geriatric population. Induction of anaesthesia on trolley, transfer to HIFU table, right lateral positioning on HIFU table and application of rectal probe, transfer to OT table and lithotomy position for TURP, and finally shifting back to transfer trolley post reversal of anaesthesia is time and labour intensive. Spinal metastasis is common with prostatic tumours and general anaesthesia is preferred in such patients.

**Conclusion:** Anaesthesia is largely given to prevent motion which can thwart the millimetre precision of HIFU. Regional anaesthesia with sedation is cost effective, less cumbersome, allows fast-tracking of patients reduces cancer recurrence and has emerged as the anaesthesia of choice. Shifting and positioning of patients under general anaesthesia is more cumbersome with the Albatherm™ device as compared to the Sonablate™ HIFU device. Teamwork and co-ordination between the radiologist, surgeon and the anaesthesiologist is vital for successful HIFU therapy

**Keywords:** High Intensity Focussed Ultrasound (HIFU); Carcinoma Prostate; Minimally Invasive Surgery; Anaesthesia

**Abbreviations:** BPS: Bronchi Pulmonary Sequestration; SCT: Sacrococcygealtrachoma; TTTS: Twin-To-Twin Transfusion Syndrome; TRAP: Twin-Reversed Arterial Perfusion; HIFU: High Intensity Focussed Ultrasound; PET: Positron Emission Tomography; NICE: National Institute for Health and Care Excellence; TURP: Transurethral Resection of Prostate; MAC: Monitored Anaesthesia Care; PNS: Peripheral Nerve Stimulator; BIS: Bi Spectral Index

## Introduction

Ultrasound guided epidural anaesthesia, regional blocks, internal jugular vein cannulations, ultrasound lithotripsy and ultrasound assisted thrombolysis are some of the current medical applications of ultrasound technology [1,2]. Low-intensity ultrasound produces physiological effects such as stimulation of bone-growth, and has the potential to temporarily disrupt the blood-brain barrier for drug delivery. High intensity focussed ultrasound (HIFU) which causes thermal ablation of diseased tissue via intense heat generation locally is the latest promising

advancement in minimally invasive surgery with the potential to revolutionize carcinoma prostate therapy [1,3-5]. It was approved by the FDA in the year 2004. When Magnetic Resonance Imaging (MRI) is used for guidance, the technique is called Magnetic Resonance guided Focused Ultrasound (MRgFUS/ MRgHIFU).

HIFU generally uses lower frequencies (0.250 to 2 MHz) than medical diagnostic ultrasound (7-14MHz), but at considerably higher energies. HIFU cannot penetrate air or solid bone and hence a Tran rectal ultrasound probe is used to access the prostate

located deep in the bony pelvis [1,3,5]. HIFU has fewer side effects like erectile dysfunction and incontinence as compared to conventional radical prostatectomy or radiotherapy. A thorough MEDLINE search was done for this review article with the key words: High intensity focussed ultrasound (HIFU), carcinoma prostate, minimally invasive surgery, and anaesthesia. All the relevant articles found in Google, Pub med, e-PUB and EBESCO were fully reviewed. An overview on the authors' personal experience on anaesthesia for prostatic HIFU is also reviewed.

### General Indications of HIFU Therapy

Apart from its use in prostate cancer, HIFU has a variety of clinical applications:

- i. Uterine fibroids:** HIFU has become an effective non-invasive treatment option for patients suffering from symptomatic fibroids [6-8]. HIFU provides sustained symptomatic relief for more than two years in most patients but around one fifth of the patients may require additional treatment.
- ii. Face lift (non invasive skin tightening) and fat reduction [9-11]:** Micro focussed ultrasound acts on subcutaneous tissue producing small (<1 mm<sup>3</sup>) thermal coagulation points (5mm deep) without affecting dermal and epidermal skin layers of skin. Collagen fibres in the facial planes (superficial muscular aponeurotic system and of the dermis papillae) as well as the deep reticular dermis are denatured and de novo collagen synthesis is stimulated.
- iii. Phase emulsification of cataracts.**
- iv. Thyroid and parathyroid nodules:** Echopulse™ was the first HIFU device to be used for benign thyroid nodules and hypertrophic parathyroid glands ablation [4].
- v. Breast cancer:** HIFU was approved in 2012 for breast fibro adenoma ablation. After HIFU for breast carcinoma by Wu et al. [12], oedema was noted in the mammary tissue surrounding the treated area which included the tumour with a 1.5-2.0 cm margin of surrounding normal breast tissue which disappeared 7-10 days postoperatively. Half the patients experienced mild local pain, warmth, and sensation of heaviness in the diseased breast but only one sixth patients required 3-5 days oral analgesics. All HIFU treated tumours underwent gross observation after surgical removal of the diseased breast. Neither bleeding of the treated regions nor injury of intervening tissues was identified, indicating the safety of HIFU ablation. Macroscopic and histological examination showed that HIFU treatment induced complete coagulative necrosis of the target tissue.
- vi. Brain tumour, Parkinson's disease, Essential tremors and Neuropathic pain [13-16].**
- vii. Hyper spleenism [17].**
- viii. Non invasive foetal surgery:** HIFU can noninvasively

and effectively occlude blood vessels in uterus avoiding complications like premature delivery which are seen with conventional and endoscopic surgery. Bronchi pulmonary sequestration (BPS), sacrococcygealtrachoma (SCT), twin-to-twin transfusion syndrome (TTTS), twin-reversed arterial perfusion (TRAP) sequence can be treated with HIFU [18].

**ix. Primary and secondary liver cancer:** HIFU is being utilized for both hepato cellular carcinoma and liver metastases from primary carcinomas present elsewhere in the body but is considered curative only for solitary small primary liver carcinomas [19-22].

**x. Renal tumours:** In one trial patients had HIFU followed a week later by surgical removal of the malignant tumour. The pathologists analysed the cancer cells removed to study the effect of HIFU on tumour cells [21]. The other trial was for patients with more advanced cancer that could not be surgically removed.

**xi. Pancreatic cancer:** HIFU provides palliative therapy for symptomatic and pain relief in advanced stages not amicable to surgery [23-24].

**xii. Urinary bladder cancer:** Although being used in some centres, HIFU seems to be of doubtful efficacy since the constant flushing of debris in the bladder and the urine accumulated there theoretically do not allow a build up of adequately high temperatures to affect ablation [23].

**xiii. Pain relief:** Numerous painful conditions like musculoskeletal degeneration, bone metastases and neuropathic pain have benefitted from HIFU [25]. The mechanism by which HIFU produces analgesia is believed to be due to localised de nervation of tissue targets and neurons modulation.

### Clinical Utility of HIFU for Prostatic tumours

HIFU was authorized in October 2015 by FDA for the ablation of prostate tissue [26]. The standard ultrasound treatment of prostate cancer ablates the entire prostate, including the prostatic urethra. The urethra has regenerative ability because it is derived from bladder squamous-type epithelium rather than prostatic tissue (glandular, fibrotic and muscular). While the urethra is an important anatomical structure, physiology of maturation requires an intact sphincter and bladder neck [27-30]. During HIFU, the sphincter and bladder neck are demarcated and not ablated. According to Gel et al [27] if the Gleason score of the local recurrence is ≤7, HIFU therapy is a very promising curative option for prostatic cancer recurrence after radiotherapy. They undertook 131 HIFU sessions in 118 patients.

The mean post-operative catheterisation time was five days (range 2-46 d). The prostate volume decreased progressively (median 18cc per HIFU to median 13cc 3 months post HIFU) as the necrotic tissue was eliminated in the urine for months thereafter. Follow-up biopsies (at 16.4 months) were negative in 99 patients

(84%). The median nadir PSA (Prostate specific Antigen) was 0.18ng/ml. Sixty-one patients (52%) required no hormonal treatment: they had negative follow-up biopsies and their PSA levels remained stable. Actuarial progression-free survival rate, was 78% for low-risk patients, 49.5% for intermediate-risk patients and 14% for high-risk patients ( $p=0.0002$ ). PSA levels before commencing HIFU therapy had no effect on actuarial progression-free survival rate. Treatment with HIFU allowed local tumour control in 84% of patients treated for prostate cancer recurrence after radiotherapy. Poor results obtained in high-risk patients (stage T3 or PSA  $\geq 20$ ng or Gleason score  $\geq 8$ ) are related to the presence of micro-metastases not detected by the standard examinations.

From 1995 to 2002 HIFU was given using standard treatment parameters. The early complications in the clinical trial conducted by Gel et al [28] were acute retention occurring within three months of treatment due to the migration of necrotic debris into the prostatic urethra, urinary incontinence (43%patients; 23% of them severe, grade 2/3; artificial sphincter was implanted in 11 patients), urethro rectal fistula (occurred between two and six weeks after treatment) and prostatic urethral stenosis. The application of specific parameters in 2002 lead to complete disappearance of urethro rectal fistula, frequency of grade 3 incontinence was reduced from 16 to 5% and the rate of stenosis of the prostatic urethra or bladder neck was reduced from 35 to 6%.

### Advantages of Hi fu Therapy

HIFU noninvasively induces complete coagulative necrosis of the target solid tumour, without requiring surgical exposure or insertion of instruments into the tumour, utilizing real time image guidance [29-33]. It is radiation free, spares the intervening tissue and has provision for different strategies like whole gland, nerve sparing and hemi ablation [34-39]. Minimal invasiveness, minimal hospital stays and minimal side effects are the advantages of HIFU [40-42]. It can be used as both primary and salvage therapy after radiotherapy (Cyber knife, IMRT or Proton Beam Therapy).

### Disadvantages and Side effects

Limitations are that it cannot be utilized for stomach, intestines, lung or any air-filled viscera since bone and air absorb and deflect ultrasound beams. Using focused ultrasound on these lesions becomes dangerous as precision is compromised and healthy tissue may be ablated. Scarring of prostate, expense involved, new treatment for which not much data is available are some disadvantages. Side effects include prostatitis, urinary tract infection, mild rectal pain or discomfort lasting 3-4 days, urinary incontinence including stress incontinence, erectile dysfunction, sterility with almost nil ejaculatory fluid and fistula formation [30,42,43]. Documenting long term side effects requires further research and time.

### Patient Selection and Imaging

$^{99m}\text{Tc}$ -phosphonates bone scan has limited sensitivity in identifying distant metastasis, whereas lymph node micro

metastasis escapes detection by thoraco-abdominal CT scan and MRI.  $^{18}\text{F}$ -fluorocholine or  $^{11}\text{C}$ -choline positron emission tomography (PET)/CT imaging can detect local recurrences, lymph node and bone metastases at an early stage and is recommended to rule these out before initiating HIFU.

### Current Guidelines

National Institute for Health and Care Excellence (NICE) [44] has issued guidelines to national health services of England, Scotland, Wales and Northern Ireland for the treatment of prostate cancer. NICE guidelines (last updated in 2014) recommend HIFU for prostate cancer as part of a clinical trial, however in some special circumstances HIFU may be given outside of a trial. A trial called INDEX-LITE looked at using HIFU for localized prostate cancer in men [45]. Another trial compared HIFU with surgery for men with prostate cancer.

The procedure is most effective for prostate glands weighing 25gm [28,35,45,46]. Larger glands need to undergo transurethral resection of prostate (TURP) followed by HIFU 2 to 3 months later when the gland would have shrunk to 20 to 25 gram size. As an institutional protocol we perform TURP after each HIFU in the same sitting for enlargement of prostatic urethral channel to get rid of the ablated prostatic tissue. This has the triple advantage of reducing infection rate, diminishing postoperative pain and the psychological benefit of not discovering prostatic tissue debris in the urine (which may even aggravate into acute obstruction of urethra and retention of urine)

Recommendation codes are as follows:

- M71.1 High intensity focused ultrasound of prostate
- Y53.2 Approach to organ under ultrasonic control
- Y53.7 Approach to organ under magnetic resonance imaging control
- ICD-10 code C61.X Malignant neoplasm of prostate.

### Procedural Details

HIFU therapy for carcinoma prostate is generally performed using the ALBATHERMTM device (EDAP-TMS, S.A., Lyons, France). With the patient in right lateral position, an ends rectal probe with an inbuilt ultrasound imaging transducer (7.5MHz) and HIFU therapy transducer (2MHz) is inserted. Imaging, treatment planning and actual treatment are the three steps of HIFU therapy [27,32,39]. The ultrasound beam emitted by the probe is focused to reach a high intensity in the target area. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature. The 45- 85°C temperature attained at the target site by high intensity focussed ultrasound (HIFU) suffices for prostatic tissue ablation. Tissue destruction occurs due to direct heating within the lesion and the mechanical effects of acoustic cavitations [47-49].

Glands up to 40 cc can be treated, the critical dimension being the prostatic height which should be  $<35$ mm as the focal length of

the lens is 4cm [50]. The treatment is planned and administered in four successive blocks by dividing the right and left parts of the prostate gland into a superficial and deep subunit each. The lower boundaries of the 19 to 26 mm long unitary lesions (ellipsoidal target fingers) are marked superior to the hyper echoic rectal surface. The thickness of each elliptical finger is 1.7mm which is precisely the thickness of two adjacent slices (Figure 1). The entire treatment takes about 2-4 hours depending on the prostate size (up to 6 hours with primitive versions). The urethral/ supra pubic catheter inserted postoperatively is withdrawn on the fourth to fourteenth postoperative day.



Figure 1: Planning HIFU therapy using Albatherm™ device.

MRI with gadolinium injection is utilized for monitoring rectal wall integrity followed by proctoscopy if the MRI scan detects abnormalities. Prostate specific antigen measured at 3 months is the most important prognostic marker. Invasive prostatic biopsies need not be done. The transducer operates at 50 watt power (follows the rule of 5): shoots in pulses for 5 seconds and is silent for the next 5 seconds. The soon anatomy of the ablated prostatic tissue is altered only for the next 10 minutes following firing due to bubbling in the tissue. After 10 minute the abated prostatic tissue is son graphically the same as before ablation. A biopsy is not useful for follow up as it cannot distinguish prostatitis from low grade malignancy.

85% of patients had negative prostatic biopsies and 83% had PSA nadirs at 7 years post HIFU denoting disease free status in a study on 803 patients. If required, HIFU treatment can be repeated and it does not preclude the use of other modes of therapy like surgery, radiation or hormonal treatment, to treat local recurrence.

**Safety Precautions**

Rectal cooling, patient movement detection by a reflector, and real time rectal wall monitoring are the main safety features. A coolant which is distilled water coloured with methylene blue is circulated at the site to prevent thermal injury to the surrounding normal tissue. In the sagittal view, the anatomical apex of prostate is first identified and the lower limit is set as 3.5 mm cranial to it. Upper limit is identified by the balloon of the urinary catheter lying close to the bladder neck. Rectal wall is seen as a hyper echoic white reflecting surface inferior to the prostate in the coronal section.

**Anaesthetic Implications**

When this procedure is performed in a radiological suite, which is usually away from the main operation theatre complex, all standard ASA principles of MAC (Monitored Anaesthesia Care) must be strictly followed. All precautions for anaesthesia in remote location apply. Purpose of anaesthesia is to prevent motion artifacts as the pain is usually mild and from 3-5 on the VAS score. Lying still for several hours (1 to 4 hours depending on size of prostate) may be difficult without sedation. A protocol or dexmedetomidine infusion is helpful. Respiratory excursions may need to be halted especially while ablating intra abdominal tumours. The slightest movement such as that during coughing or sighing can move the gland, compromise precision and damage surrounding tissue including nerves [49]. In this eventuality, the HIFU planning needs to be repeated to ensure removal of entire diseased tissue and prevent nerve injury. Extracorporeal HIFU is performed under MAC with or without sedation and analgesia after adequate skin preparation. HIFU for prostatic lesions necessitates general anaesthesia or neuraxial blocks with sedation [49-51] (and a rectal enema the night before surgery).

**Positioning for HIFU therapy of carcinoma prostate**



Figure 2: Positioning of the patient in the right lateral position on the Albatherm™ HIFU table.

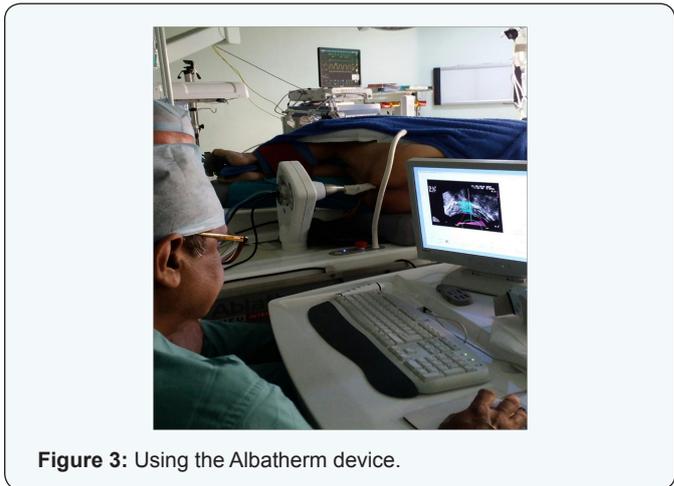


Figure 3: Using the Albatherm device.

Patient is positioned supine with an attachment fixed to the caudal end of the OT table for Son ablate HIFU device while the patient needs to be positioned in the right lateral position on a custom made HIFU table when using the Albatherm device (Figure 2 & 3).

## General Anaesthetic Considerations for Prostatic HIFU

It is generally indicated in elderly patients with spinal metastasis or patients with contraindications to regional anaesthesia (spinal deformity, local anaesthetic allergy, patients on anticoagulant therapy) [51]. Induction of anaesthesia is to be done on a separate table or on the trolley used to transport the patient to the operating room and the anaesthetized patient then carefully lifted and positioned onto the HIFU table. The breathing circuit including side stream capon graphic sampling line, intravenous fluid line and the monitoring cables (ECG lines, pulse oximeter probe, temperature probe, peripheral nerve stimulator (PNS) cable and bispectral index (BIS) cord) have to be carefully detached and reconnected after positioning the patient.

Since the left upper limb lies superior to the right one it is more convenient to have an intravenous access and PNS electrodes placed here. Apart from routine ASA monitors, invasive monitoring may also be required in indicated, high risk cases (patients with comorbidities and post chemotherapy patients). Maintenance is with balanced anaesthesia technique using inhalational anaesthetic like sevoflurane in medical air, a neuromuscular blocking agent like atracurium and an opioid like fentanyl. If TURP is also planned after HIFU, then the patient is to be shifted back to the OT Table (with attachments for performing TURP) before reversal of anaesthesia. The concerns of long duration anaesthesia also need to be addressed in this situation. Induction of anaesthesia on trolley, transfer to HIFU table, right lateral positioning on HIFU table and application of rectal probe, transfer to OT table and lithotomic position for TURP, and finally shifting back to transfer trolley post reversal of anaesthesia consumes about an hour extra over and above the actual time required for HIFU planning and execution and TURP. Shifting and positioning requires trained OT staff and is more labour intensive especially with the Albatherm HIFU device. Leaving necrotic prostatic tissue behind may result in bacteraemia and urinary tract infections and hence the requirement of TURP posts HIFU and a good antibiotic cover.

## Regional Anaesthesia for Prostatic HIFU

If performed under subarachnoid block (preferred over general anaesthesia) [51], there are two options. Firstly, the patient can be made to lie down in the right lateral position on the HIFU table itself and subarachnoid block performed. The drawback is a unilateral block in this case. The block is denser on the right side than on the left. Here it is beneficial if the surgeon operates on the left lobe first followed by the right lobe as the effect of subarachnoid block would wane in this order. Secondly, the spinal can be given in a sitting position on the HIFU table itself. Here the drawback would be a saddle block or a lower level of anaesthesia. These problems can be circumvented by giving epidural block with epidural catheter insertion which provides ample time for TURP to be performed in addition. Regional block is preferred also when HIFU is being performed as a day care surgery.

During ablation of renal, hepatic or other intra abdominal tumours nasopharyngeal temperature probe insertion can monitor and prevent hyperthermia which may occur especially if the target area is located in vicinity of blood vessels. A temperature above 38.5°C can result in cardiac arrhythmias. HIFU for prostatic tumours has coolants circulating in the rectal probe which prevent hyperthermia. Regional anaesthesia is the preferable modality for HIFU as it is less cumbersome, cost effective, better suited for day care patients and known to reduce cancer recurrence [52] as compared to general anaesthesia especially opioids [53,54] which may promote cancer recurrence.

## Future Perspectives

Sonablate 450, Sonablate 500 (Focus surgery, Indianapolis, IN, USA), developed by Sonacare Medical has obtained FDA approval in 2015 but for Albatherm, FDA approval for carcinoma prostate treatment is still elusive. Focal one TM is robot assisted HIFU, which provides pre treatment MRI import and fusion, intra treatment precise contouring of target zone and post treatment validation imaging with contrast enhanced ultrasound. Health Canada approved EDAP's Focal One HIFU device in 2014, which allows it to be marketed for the treatment of prostate cancer in Canada.

## Conclusion

Technological progress has catalysed a shift from open surgery towards minimally invasive techniques. HIFU satisfies the ultimate objective of totally non-surgical tumour ablation. HIFU produces focal areas of destruction deep in fresh living tissue with minimal effects at the surface and no effects on the intervening tissue. Anaesthesia is largely given to prevent motion which can thwart the millimetre precision of HIFU. Regional anaesthesia with sedation is cost effective, allows fast-tracking of patients and reduces cancer recurrence and has emerged as the anaesthesia of choice.

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