Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

**TITLE: High Intensity Focused Ultrasound for Prostate Cancer: A Review of the Guidelines and Clinical Effectiveness**

**DATE:** 25 August 2008

## CONTEXT AND POLICY ISSUES:

It is estimated that one in every seven Canadian men will be diagnosed with prostate cancer during his life time.[1] In 2007, approximately 22,300 men were diagnosed with prostate cancer[2] and in 2008 this number is expected to rise to 24,700.[1] Use of prostate specific antigen (PSA) for screening has contributed to an increasing number of men being diagnosed with small volume, low grade cancer.[3]

Conventional treatments for organ-confined prostate cancer include watchful waiting, radiotherapy, and radical prostatectomy.[4] Transurethral resection of the prostate (TURP) is the gold-standard treatment for benign prostatic hyperplasia (BPH),[5] which is a non-cancerous enlargement of the prostate that commonly occurs in older men.[6] With an increasing number of men being diagnosed with prostate cancer and with an aging population, management of this growing patient population with surgery or radiotherapy might not be feasible. Therefore, there is an interest in a number of emerging minimally invasive therapies as an alterative treatment option.

One such minimally invasive therapy is high intensity focused (or frequency) ultrasound (HIFU).[7] To date, HIFU has been assessed for use as a primary therapy for organ-confined disease and to treat recurrent disease after radiotherapy failure.[8] Treatment with HIFU destroys tissues by inducing damage through thermal and mechanical means.[9] Two HIFU devices have been developed for the treatment of prostate cancer: Ablatherm Integrated Imaging® and Sonablate 500®.[10] Both devices have Class III Medical Device approval by Health Canada.[11] Similarly, both devices have approval in Europe and Japan, but are not yet approved by the Food and Drug Administration in the US.[12] The Ablatherm® system requires the use of a specific bed with the patient in a lateral position whereas the Sonablate 500® system uses a standard operating table

with the patient is in a dorsal position. Patients are given either general or regional anesthesia when treated with either device.[9]

With the increasing use of HIFU to treat prostate cancer, there is a need to review the evidence regarding its use. This report will review evidence for the clinical and cost-effectiveness of HIFU for the treatment of prostate cancer and benign prostatic hypertrophy and guidelines associated with its use for both indications.

**RESEARCH QUESTIONS:**

1. What is the evidence for the clinical effectiveness of high intensity focused ultrasound (HIFU) for the management of patients with prostate cancer?

2. What is the cost-effectiveness of HIFU for management of patients with prostate cancer?

3. What are the guidelines for the use of HIFU in patients with prostate cancer, with recurrent prostate cancer, and patients with benign prostatic hypertrophy?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 3, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2005 and July 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, economic, clinical guideline studies, and clinical trial studies. Internet links are provided, where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials (RCTs), observational studies, and evidence-based guidelines.

**SUMMARY OF FINDINGS:**

The literature search identified two health technology assessments, two systematic reviews, one observational study that was published outside of the search time frame for the systematic reviews, and four guidelines. No RCTs or economic evaluations were identified.

**Health technology assessments**

*Prostate cancer*

The first relevant HTA identified from the literature search was produced by the NHS R&D Health Technology Assessment Programme and reviewed the clinical and cost-effectiveness of new and emerging technologies for early, localized prostate cancer.[4] A total of 15 technologies were included in the review including HIFU. Unfortunately, due to the small body and poor quality of evidence identified for HIFU (no RCTs were identified as a part of their search), a conclusion regarding its effectiveness could not be drawn.

*Benign prostatic hyperplasia*

A second HTA published by the Ontario Health Technology Assessment Commission evaluated an array of energy delivery systems, including HIFU, for the treatment of benign prostatic hyperplasia (BPH).[13] Their inclusion criteria were RCTs comparing HIFU to the gold-standard treatment TURP. No RCTs were identified through their literature search and they were therefore unable to make a recommendation regarding the use of HIFU for the treatment of BPH.

**Systematic reviews and meta-analyses**

A systematic review by Rebillard *et al.* (2008)[14] reviewed the efficacy and safety of HIFU in prostate cancer patients and sought to define indications for HIFU use as a primary therapy. The review selected a total of 30 abstracts and articles published between 2005-2007 evaluating HIFU as a primary therapy for prostate cancer: 25 using the Ablatherm® system and five using Sonablate®. Nearly all of the articles included in this review were case series. No RCTs assessing HIFU have been published and only one non-randomized controlled trial assessing the Sonablate® system was identified. The authors remarked that they had some difficulty determining the absolute number of patients treated with HIFU because some of the articles appear to relate to the same study with different numbers of patients or different durations of follow-up. This is further discussed within the Limitations section.

Sample sizes for studies using the Ablatherm® system were typically 100-200 patients. A larger multicentre study looked at 402 patients. Sample sizes for studies using the Sonablate® device were in the range of 63-250 patients. Follow-up times differed dramatically between the included studies. The longest follow-up was for the Ablatherm® device (6.4 years). The patient profile of the included studies were men with an average age of 70 years, stage T1 or T2 N0M0 disease (tumour is confined to the prostate and has not spread to any lymph nodes or distant sites), a Gleason score of less than seven (intermediate grade; the Gleason score ranges from two to 10 with 10 having the worst prognosis), mean PSA level between 7 and 28 ng/mL, and a prostate volume of less than 40 mL. A proportion of studies used HIFU in conjunction with TURP and others reported the use of neo-adjuvant androgen deprivation therapy.

The majority of studies used a combination of PSA levels and negative biopsy rates in their measurement of efficacy, although there were a number of differences between studies in terms of when these measurements were taken. The negative biopsy rate ranged from 51%-96% with the Ablatherm® device and 64%-87% with the Sonablate® technology. Importantly, most of the studies evaluated biopsies three months following HIFU treatment which might be too premature to speculate what the negative biopsy rate would be in the longer term. PSA nadir (lowest PSA level achieved following treatment) was reached on average, within three to four months. Disease free survival (DFS) rates were calculated differently across studies; however, this systematic review determined the five-year actuarial DFS rate to be 60%-70%. One study in particular had a longer mean follow-up time than most, 6.4 years.[15] In this study, the DFS rate was 59% at 6 years. This same study also reported an eight year overall survival rate of 83% and a cancer-specific survival rate of 98%. Studies involving the Sonablate® device did not measure actuarial DFS and instead measured biochemical DFS which was defined as three consecutive rises in PSA level after a PSA nadir had been reached. The five-year biochemical DFS rate for Sonablate® was 78%.[14]

More complete data regarding complications associated with HIFU therapy was available for the Ablatherm® device. The most common complications included stress urinary incontinence (6%-28% patients), urinary tract infection (0%-58%), urethral/bladder neck stenosis or strictures (1%-31%), and erectile dysfunction (31%-77%).[14]

The authors described the ideal indications for primary HIFU therapy as patients at least 70 years of age, with clinical stage T1-T2 N0M0, a Gleason score of less than seven, PSA level of less than 15 ng/mL, and a prostate volume less than 40 mL. In particular, those patients that are either not candidates for surgery or radiotherapy or have refused those particular treatments are candidates for HIFU.

A second systematic review authored by Wilt *et al.* (2008)[16] compared the effectiveness of treatments for prostate cancer and HIFU was included in their comparison . Based on eight uncontrolled studies in which the rates of biochemical disease free progression was between 68% and 87%, the authors concluded that level of evidence for effectiveness was low (defined in their study as: inconsistent results, studies of low quality, or from populations with little relevance to current patients or practice). Based on the available evidence, the authors did not make conclusions regarding the use of HIFU for the treatment of prostate cancer.

**Randomized controlled trials**
No RCTs were identified.

**Observational studies**

Our defined literature search identified one observational study that was not reviewed as a part of a systematic review described above. This study was published outside of the time frame evaluated within the systematic review and addresses the use of HIFU in the treatment of recurrent prostate cancer.

Zacharakis *et al.* (2008)[17] investigated the use of HIFU as salvage therapy in men with recurrent disease following failure with external beam radiotherapy. This study reviewed 31 cases of men with organ-confined recurrent prostate cancer treated with Sonablate 500®. The mean age of patients was 65 years with a mean PSA level of 7.73 ng/mL. Mean follow-up time was 7.4 months. Half of the patients had a PSA level of less than 0.2 ng/mL at the last follow-up. Also at follow-up, three patients had metastatic disease, two had evidence of local recurrence, and four others had biochemical failure. Seventy-one percent of patients had no evidence of disease following salvage HIFU therapy. The authors suggested that salvage HIFU can be performed in a day-case setting and is safe and well tolerated. The authors recognized that longer follow-up duration will be necessary to determine whether salvage HIFU therapy is as effective as other salvage treatment such as surgery, brachytherapy, or cryotherapy.

**Economic evaluations**
No economic evaluations were identified.

**Guidelines**

In 2005, a group was established by the National Institute for Clinical Excellence (NICE) in the UK to oversea the production of guidelines. This group is made up of health professionals, representatives of patient and caregiver groups, and technical experts. Evidence used in development of the guidelines included published literature and unpublished information from

relevant stakeholder groups. The quality of the identified literature was assessed and the evidence graded. Clinical guidelines were published by NICE in 2008[18] and did not recommend HIFU as a therapy for patient population with localized disease other than in a clinical trial setting; however, HIFU therapy in the context of a clinical trial following radiotherapy or brachytherapy failure was recommended.

In 2007, the American Urological Association (AUA) developed guidelines pertaining to the management of clinically localized prostate cancer.[19] These guidelines were developed by a multi-disciplinary expert panel. Guideline development involved an extensive review of the literature and a peer-review process. The AUA were unable to reach a conclusion regarding the outcome of HIFU therapy given the minimal data currently available.

The European Association of Urology, with input from a group of experts, published guidelines on prostate cancer in (2007).[20] They categorized HIFU as experimental or investigational and recommended a longer follow-up duration in order to assess its role in the management of prostate cancer. They also suggested that the procedure is time consuming with 10 grams of prostate tissue being treated in one hour.

### Limitations

There are a limited number of systematic reviews evaluating HIFU in the context of prostate cancer or BPH. Despite the relatively large number of observational studies evaluating the use of HIFU as either a primary or salvage therapy in the treatment of localized prostate cancer, there have not been any RCTs published using this technology which adds to the poor overall quality of evidence surrounding the use of HIFU. The number of patients varied greatly between studies and most were conducted in a single centre.

Most authors of systematic reviews or narrative reviews regarding HIFU commented on the difficulty they had determining the absolute number of patients that had been treated with HIFU. The majority of reports have been published by a select group of investigators and some of the articles appear to relate to the same study however, different sample size and durations of follow-up are reported. Although Blana *et al.* (2007)[15] reported on the long-term efficacy of HIFU therapy in prostate cancer patients with a mean follow-up duration of 6.4 years, the majority of other studies had a much shorter follow-up time. The end point used in most studies was biochemical DFS based on PSA levels; however, the definition of PSA end point was highly variable. Treatment protocols varied widely within and between studies. For example, some studies reported the use of TURP or androgen deprivation therapy prior to patients being treated with HIFU. In addition, a proportion of early patients were treated with older prototypes of the HIFU devices, thereby making a conclusion regarding safety a challenge.

## CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Despite the fact that patients have been receiving HIFU therapy since the 1990's, no RCTs involving HIFU have been published. The majority of studies were small and had a short follow-up duration. Only one of the systematic reviews identified focused specifically on HIFU and only observational studies were included in this review. The differences in end point definition, follow-up durations, and treatment protocols made it difficult to compare results between studies.

Interestingly, although in 2005 NICE issued guidance to the National Health Services in the UK stating that there was sufficient evidence on the safety and efficacy of HIFU to support its use for the treatment of prostate cancer,[21] the 2008 NICE clinical guidelines for the treatment of

prostate cancer did not recommend HIFU therapy for localized disease outside the context of a clinical trial.[18]

No economic evaluations were identified, thereby not allowing for any cost-effectiveness comparisons of HIFU with other conventional therapies such as radical prostatectomy or radiotherapy.

In general, it is difficult to draw definitive conclusions regarding the use of HIFU therapy in the treatment of BPH or prostate cancer. Based on the available literature, the gold-standard therapy for BPH would still be TURP[22] although a number of other minimally invasive therapies are being investigated.[5] With respect to prostate cancer, the literature search suggested that the target population for HIFU for prostate cancer patients would be older patients with low-risk disease, who are either not a suitable candidate for surgery or radiotherapy, or have refused those particular interventions.[14] Alternatively, salvage HIFU therapy may be considered in patients who have recurrent disease following surgery or radiotherapy.[6,17] The lack of high quality evidence for the use of HIFU perhaps should be considered when deciding which treatment is most appropriate for prostate cancer patients.

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