Report to: College of Physicians and Surgeons of BC

Title: High Intensity Focus Ultrasound for Prostate Cancer.

Report Author:
Martin Gleave, MD.
Professor, Department of Urologic Sciences, UBC
Chair, Genito-urinary (G-U) Tumour Group, BC Cancer Agency

On behalf of the G-U Tumour Group, BC Cancer Agency

BC Cancer Agency Genito-Urinary Tumour Group

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600 West 10th Avenue Tel: 604.877.6000 Vancouver, BC, Canada V5Z 4E6 Fax: 604.877.0505 www.bccancer.bc.ca

Background

This report on the current status of High Intensity Focus Ultrasound (HIFU) as a treatment modality for men with localized prostate cancer is provided at the request of the College of Physicians and Surgeons of British Columbia, and serves as an update on the initial report from the G-U Tumour Group dated February 2005 (appended).

Since 2005, there has been no major advances in HIFU technology, and no randomized or prospective Phase II or Phase III trials have been reported in the literature. The Ablatherm® and Sonablate® devices remain the two principal commercially available technologies in use. The number of machines available worldwide has continued to expand and is now available at over 100 clinical sites around the world.

The devices are approved by Health Canada and the European Union, but are not yet approved by the FDA in the United States. Based on the 2005 report, the College of Physicians and Surgeons has not approved its use in British Columbia. The Ablatherm® and Sonablate® devices are in use in Southern Ontario.

Current Standards of Treatment for Localized Prostate Cancer

Men with localized prostate cancer are divided into low-, intermediate-, and high-risk disease based on baseline T stage, serum PSA, Gleason score, and number of positive cores. In addition, treatment options are prioritized based on age and co-morbidities, both of which predict longevity. Finally treatment options can be guided by the presence of lower urinary tract symptoms that may be either alleviated or aggravated by different treatment options.

For primary treatment, men with localized prostate cancer are most often offered active surveillance, prostatectomy, or radiation therapy. Men with low risk disease are most commonly offered active surveillance, prostatectomy, or brachytherapy. Men with intermediate or high-risk disease are more often treated with prostatectomy or combined hormone therapy plus external beam radiation therapy.

The challenge to any new treatment method is to demonstrate that it can safely eradicate prostate cancer with minimal short- and long-term morbidity to the patient. While HIFU has been used as a primary treatment in low, intermediate, and high risk disease, it is most often offered to men with low to low intermediate risk disease. It is important to note that many of these men are now increasingly offered active surveillance as a primary treatment choice. Currently, there is an NCIC Phase III trial across North America randomizing men with low to low-intermediate risk disease to active surveillance or active treatment (consisting with either prostatectomy or radiation therapy). HIFU is not considered a treatment option in this clinical trial.

For men with recurrent localized prostate cancer after radiation therapy, salvage treatment modalities include salvage prostatectomy, brachytherapy, cryotherapy, and/or androgen deprivation therapy. Several studies report initial experiences with HIFU as a salvage therapy

and are discussed further below. In general, recurrence rates and morbidity (eg incontinence, impotence) are higher in this group of poor prognosis patients.

Methodology

A Medline search was undertaken for publications since 2005 on HIFU and prostate cancer. The review was further restricted to English articles in those that were peer reviewed.

Existing Overviews

The UK's National Centre for Clinical Excellence (NICE) has produced a detailed overview for the recent literature (up to March 2004), and updated recommendations have now been posted online as part of a clinical guideline in prostate cancer in February 2008[1]. The recommendations of this report are now posted online, and state that HIFU is "not recommended for men with localized prostate cancer other than in a context of controlled clinical trials comparing their use with established interventions".

Rebillard and colleagues from the French Association of Urology recently published a systemic literature review, discussed below. [(2)]

Quality of Evidence

As with the initial 2005 review, no randomized studies have been reported to date, and no randomized trials are underway as far as we know. The literature consists of a series of mainly single institution case series reported on 1,000 patients. It is difficult to determine the true total because there are many duplicates reported in different publications. Most papers originate in a few centres and several articles relate to the same study with different numbers of patients and/or different times of follow-up. The completeness of follow-up remains is variable and of poor quality consistent with the retrospective nature of the reported data and confounded by many patients that travel long distances for the treatment and are subsequently difficult to follow. It is well established that single institution case-series are subject to biases in selection and reporting of treatment-induced morbidity.

Technique and Patient Selection

Patients treated with HIFU have, for the most part, low to low-intermediate risk prostate cancer. These patients are highly curable with surgery or radiotherapy and are now often followed with active surveillance. The natural history of low-risk disease is long. Progression rates, as measured by PSA doubling time <4 years or higher grade on serial biopsies, are ~20% every 5 years. Hence, impacts of treatment that do not completely ablate the prostate and decrease serum PSA levels to the undetectable range are difficult to assess. HIFU, and especially focal HIFU, falls within this latter category.

While incremental improvements in HIFU technology continue to be reported, no significant advances since 2005 have been reported in the current technique of HIFU. It remains a

minimally invasive treatment with a relatively short learning curve. Patients are treated under spinal anesthesia on an outpatient basis. Hence, operative and perioperative recovery is short but still subject to postoperative complications as discussed below.

Updated Reports on HIFU

Since 2006 there have been 18 published reports on the use of HIFU for primary treatment of localized prostate cancer, 4 on use of HIFU as a salvage therapy in radio-recurrent prostate cancer, and more than 8 editorials and 18 review articles. Data on the Sonablate device are limited to five articles on studies with a limited follow-up (almost 2 years). The Ablatherm device has been investigated more extensively, with 24 publications and a maximum follow-up of 6.4 years. The majority of primary articles report on short term results and are published in low impact, subspecialty journals.

HIFU has been reported as both a primary treatment modality as well as a salvage treatment modality after failed radiotherapy. These two patient populations should be considered distinct and will be discussed separately. Most of the published literature report on the use of HIFU as a primary treatment modality in patients with low- to low-intermediate risk prostate cancer.

Efficacy. Investigators of any new technology often struggle to define appropriate oncologic end points. Efficacy endpoints for HIFU include post treatment negative biopsy rates and PSA failure rates. Use of biopsy data, including an appropriate number of cores, seems reasonable as an initial assessment of efficacy. However, as seen in active surveillance series[3] biopsies in men with patients with low- to low-intermediate risk prostate cancer under sample the gland and often miss persistent cancer.

Differing definitions of PSA response are used in the reports. PSA nadir may be used as a measure of prostate ablation, but it is uncertain to what extent this correlates with subsequent cure. Alternatively a rising PSA profile may indicate recurrent cancer or residual BPH tissue. There is considerable controversy surrounding what constitutes biochemical relapse after radiation therapy, and there is no literature as to the most appropriate measure after HIFU. Many authors, in part, define efficacy based on the Phoenix definition of PSA failure[4]. This may, however, not be appropriate. The Phoenix definition is meant for external-beam radiotherapy, a nonablative treatment for prostate cancer. Authors of the consensus panel outlining the appropriate use of the Phoenix definition specifically state that "these definitions are *not* recommended for use in patients treated with other modalities, such as cryosurgery or radical prostatectomy."[4] In addition, as many as 30% patients failed their initial therapy and required more than one HIFU session, but are not necessarily called a treatment failure. In light of these considerations the oncologic efficacy of HIFU in many series remains questionable.

In a systematic review of HIFU as a primary therapy, Rebillard et al[2] selected 37 articles or abstracts. Most patients were elderly, ~ 70 years of age with low to intermediate risk disease. Study endpoints for treatment success were defined as negative post treatment biopsies (range, 64% - 93%) and/or a PSA nadir value of < 0.5 ng/mL (range, 55%-84%). Five year actuarial disease pre survival rates ranged between 60%-70%. In general, this is similar to large cohorts of low- to intermediate risk patients treated with active surveillance[3]. Treatment outcomes of

very large cohorts of low- to intermediate-risk patients treated with prostatectomy or radiation therapy report PSA free survival rates in excess of 80%. [5,6] The biochemical control rates with brachytherapy for low risk and low tier-intermediate risk prostate patients in BC is 94% at 7 years (with Phoenix definition)[6]. The comparison of outcomes measures across treatment modalities is difficult and complicated by many confounders including patient selection and definition of PSA failure. Use of negative biopsy as an endpoint is compromised by well-known challenges of sampling errors associated with post treatment biopsies. Kaplan-Meier projections of recurrence rates are confounded by differences in definition of PSA failure and risk group stratification, and variable use of combination androgen deprivation therapy, across treatment modalities. For the reasons discussed above we believe that no conclusions can be drawn about the efficacy of treatment, but they do not appear to be superior to available curative intent therapies (surgery and radiation), which both have longer-term follow-up in larger series.

Complications. Complication rates from HIFU therapy have not changed significantly since the initial GU Tumour Group report in 2005. Risks of Grade 1 stress incontinence range from 6% - 16%, while risks of Grade 2 to 3 stress incontinence range between 0% and 10%. In an attempt to reduce the risk of stress incontinence many authors now recommend sparing of the prostate apex from HIFU ablation. Risk of erectile dysfunction ranges greatly between 31% and 77%. The risk of requiring a TURP following HIFU ranges between 2% and 33% with an accepted risk in the 10%-15%. Other less frequent complications include risks of urethra stricture or pelvic and perineal pain, all ranging between 1% and 13%. Rare but serious complications such as rectal urethra fistula are reported in 1%-2% or patients. While the risk of incontinence may be slightly lower with HIFU, the adverse event profile is otherwise qualitatively and quantitatively similar to risks reported with anatomical prostatectomy and brachytherapy. Erectile dysfunction was reported in 20–77% of previously potent patients, and while no worse than that reported after prostatectomy or radiotherapy, highlights that HIFU is not “non-invasive”.

One report by Misrai et al [7] reported on 119 patients treated with the Ablatherm® device. In their group of patients with a mean age of 68 and the mean follow-up of close to four years, 43.7% experienced a biochemical recurrence which is higher than one would expect in a similar group of patients treated with surgery or brachytherapy. They conclude that patients with high-risk features are poor candidates for HIFU and emphasize very careful selection to include low risk patients only.

Several reports have been published in the last two years on HIFU as a salvage treatment option for patients with locally radiorecurrent prostate cancer. [8,9] These publications report a higher 40%-50% risk of urinary incontinence but a otherwise acceptable morbidity and a reasonable tumour control in this higher risk group of patients with more limited salvage treatment options.

Based on their systematic review of HIFU as a primary therapy, Rebillard et al concluded that suitable patients for HIFU include: older patients (≥70 years) with clinical stage T1-T2 N0M0 prostate cancer, a Gleason score of <7, a PSA level of <15 ng/mL and a prostate volume of <40 mL, in particular if they refuse or are unsuitable for radical therapy. Most Canadian oncologists feel this group of low-risk, elderly patients do not require treatment and currently recommend for active surveillance. Patients with larger prostate glands have higher PSA nadir levels presumably

because it is not possible to ablate all prostate cancer/tissue in those with larger glands. Larger prostate glands (>30cc) are described as a contraindication to treatment by Chaussy.[10]

Issues and Recommendations

While dramatic improvements have occurred for all treatment modalities for localized prostate cancer over the past two decades, no single treatment is universally accepted as the preferred therapeutic option. As such, a variety of alternative treatment strategies are being evaluated to determine their role in patient management. Many of these new options are considered "less invasive" such that treatment is more convenient or has a quicker recovery than traditional therapies such as prostatectomy, external-beam radiation therapy, or brachytherapy. Treatment considerations for prostate cancer, however, require a balance of oncologic outcomes (curing the cancer) while at the same time minimizing the impact of treatment on both short-term and long-term quality of life. Improvement in one area often comes at the expense of other areas. For example, recent reports on safety data are based on newer techniques including apex sparing and nerve sparing, both of which may reduce side effects but compromise efficacy. Therefore, any new technology or procedure must be evaluated in terms of multiple treatment outcomes to determine its role in the management of men with prostate cancer.

HIFU is often presented in the literature as well as to patients as a non-invasive procedure with minimum or no side effects that is cancer and organ ablative. Certainly the treatment can be delivered safely with rapid return to normal physical activities. However, is HIFU a valid alternative to brachytherapy or prostatectomy in terms of short and long-term morbidity? Brachytherapy is a daycare procedure, and robotic prostatectomy is evolving towards a daycare or overnight operation. Risk of urinary incontinence, urinary tract infection, urinary obstruction, and pelvic pain following HIFU is qualitatively and quantitatively similar to brachytherapy and prostatectomy delivered by expert and experienced clinicians. Over 50% of patients potent prior to HIFU experienced significant erectile dysfunction following treatment[11]. These outcomes certainly temper the enthusiasm for HIFU as a minimally invasive treatment alternative. Most reports on HIFU suffer from short-term follow-up, variable pitfalls of use of surrogate markers of progression, and a re-treatment rate.

At the present time, results presented for first-generation HIFU systems do not clearly support HIFU as a valid alternative to radiotherapy or prostatectomy. However, this does not suggest that HIFU should be abandoned. Improvements in technology and imaging will likely improve treatment outcomes. However, only through appropriately planned and conducted trials will we develop an understanding of how to include any new treatment as an option for prostate cancer.

As with most new and developing technologies, there are varying incentives for recommending their use. In Canada, because of lack of data and consensus on it long term efficacy and utility, HIFU is not covered by any provincial health care plan. Hence, the cost of HIFU is paid privately, and at ~$25,000, is currently over 3 times the current cost of prostatectomy and twice that of brachytherapy. Additional costs are incurred if TURP is required before HIFU, or if additional HIFU treatments are required.

In conclusion, efficacy data does not allow meaningful assessment as to the benefit – risk ratio of HIFU as a primary treatment for localized prostate cancer, and hence cannot currently be recommended as standard therapy given current alternatives. HIFU must be developed in a controlled manner within the context of a clinical trial, which **should be approved by an Ethical Review Board (ERB)**, who should also monitor patient selection, informed consent, accrual, complication rates and other outcomes information. The BCCA GU Tumour Group should also receive patient treatment data so that it may be added to data on other comparative modalities including active surveillance, prostatectomy, and radiotherapy.

In cases of radiorecurrent localized prostate cancer, where treatment options are more limited and associated with significant morbidity, HIFU could be considered a salvage treatment option associated with discussion of alternatives including salvage prostatectomy, cryotherapy, brachytherapy, or androgen deprivation therapy. Although again this should be in the context of an ethics approved protocol with the intention of collecting data prospectively for the purpose of publication in a peer reviewed journal.

References

1. High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. Rebillard X, Soulié M, Chartier-Kastler E, Davin JL, Mignard JP, Moreau JL, Coulange C; Association Francaise d'Urologie. BJU Int. 2008 May;101(10):1205-13

2. National_Institute_for_Clinical_Excellence, *High-intensity focused ultrasound for prostate cancer.* http://www.nice.org.uk/page.aspx?o=80298, 2004.

3. Active surveillance for early-stage prostate cancer: review of the current literature. Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, Warlick CA, Holmberg L, Bailey DE Jr, Wallace ME, Kantoff PW, Carroll PR. Cancer. 2008 Apr 15;112(8):1650-9

4. Roach M 3rd, G. Hanks and H. Thames Jr. *et al.*, Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference, *Int J Radiat Oncol Biol Phys* **65** (2006), pp. 965–974.

5. Comprehensive prospective comparative analysis of outcomes between open and laparoscopic radical prostatectomy conducted in 2003 to 2005.
Touijer K, Eastham JA, Secin FP, Romero Otero J, Serio A, Stasi J, Sanchez-Salas R, Vickers A, Reuter VE, Scardino PT, Guillonneau B.
J Urol. 2008 May;179(5):1811-7;

6. **Morris J, Keyes M, Palma D** *et al.* Evaluation Of Dosimetric Parameters And Disease Response After ^{125}iodine Transperineal Brachytherapy For Low- And Intermediate risk Prostate Cancer. Int. J. Radiation Oncology Biol. Phys 2008; **in press**

7. Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. Misraï V, Rouprêt M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, Bitker MO, Richard F, Conort P. World J Urol. 2008 Oct;26(5):481-5.

8. Murat F-J, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol. In press

9. Salvage HIFU for recurrent prostate cancer after radiotherapy. Chalasani V, Martinez CH, Lim D, Chin J. Prostate Cancer Prostatic Dis. 2008

10. Chaussy, C. and S. Thuroff, *High-intensity focused ultrasound in prostate cancer: results after 3 years.* Molecular Urology, 2000. **4**(3): p. 179-82.

11. Blana, F.J. Murat and B. Walter *et al.*, First analysis of the long-term results with transrectal HIFU in patients with localized prostate cancer, *Eur Urol* **53** (2008), pp. 1194–1203.