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High-Intensity Focused Ultrasound for Prostate Cancer

Report Authors

Dr Tom Pickles	Chair BCCA GU Tumour Group, Radiation Oncologist BCCA.
Dr Larry Goldenberg	Professor of Urology, UBC and Director, The Prostate Centre, VGH.
Dr Gary Steinhoff	Urologist, Victoria BC

BC Cancer Agency Genito-Urinary Tumour Group

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600 West 10th Avenue
Vancouver, BC, Canada V5Z 4E6
www.bccancer.bc.ca

Tel: 604.877.6000
Fax: 604.877.0505

Background

High-Intensity Focused Ultrasound (HIFU) is a technique using focused ultrasound to generate areas of intense heat and thus destroy tissue. It has been studied for 50 years, with recent technological developments allowing its use for tumours of liver, prostate and other sites.[1] It is increasingly being promoted as a non-invasive therapy for localized prostate cancer, and is generally regarded as experimental by independent authorities[2] because no randomized data exists to support its use and duration of follow-up from case series is short. It is being promoted particularly by the companies that make the equipment, eg Focus Surgery Inc who market the Sonablate® device, and EDAP who make the Ablatherm® device.[3] EDAP is dependent on the successful development and commercialization of its HIFU medical devices to achieve and sustain profitability in the future. The Sonablate device is not licensed for use in Canada, but the Ablatherm device is approved for commercial distribution in the European Union, Canada, South Korea and Russia, but neither has gained FDA approval. 18 Ablatherm machines worldwide through 44 clinical sites treated 1477 patients using this technology in 2003.[4]

Methodology

A Medline search was undertaken for relevant articles. Additional information was gleaned from internet searches, and papers cited in the papers reviewed. Our reading was further restricted to English articles and those that were peer reviewed.

Existing Overviews

The UK's National Centre for Clinical Excellence (NICE) has produced a detailed overview of the recent literature (up to March 2004) [5], which is partly based on a review carried out in the UK the previous year [2]. The NICE process for evaluation is currently (February 2005) ongoing and a final report has not yet been issued. Interested readers are encouraged to read their report.

Quality of the Evidence

No randomized studies have been carried out, and there are only case-series reported with a total of approximately 600 patients. It is difficult to determine the true total because many are duplicates reported in different publications. The completeness of follow-up is not documented. This may be an issue where a treatment is only available in a few centres and patients travel long distances. Some papers on HIFU are authored by those who hold patents for the device or participate in company advisory boards.

An additional consideration is that techniques have changed as experience has been gained. In particular there have been hardware and software changes since 2000 which apparently have reduced toxicity. Therefore those patients with the most follow-up were treated with techniques that are no longer in use, and those treated

with newer techniques have shorter follow-up, which may further limit conclusions regarding efficacy and longer-term toxicity. It is noteworthy that most reports quote mean rather than median follow-up, which may be inappropriate where the majority of patients have only recently been treated.

Modern Technique and Patient Selection

Patients treated with HIFU generally have low to intermediate risk prostate cancer. (For definitions see [6]).

The learning curve is well described by Chaussy [7], who suggests that the learning curve using the Ablatherm equipment is as short as 10 patients for a new user with technical skills in ultrasound imaging. Technical enhancements include routine pre-HIFU TURP in those with obstructive symptoms, the use of prophylactic antibiotics, leaving a 5mm margin around the prostate apex untreated (although the heat dissipates further than the ultrasound 'shot'), rectal cooling, and the use of higher frequency transducers (3MHz).

Patients are generally treated under spinal anaesthesia. If a pre-HIFU TURP is performed then it is typically carried out at the same time, and necessitates a short hospital stay.[8] The overall treatment time is 2-3 hours. [1]

Patient selection

In the absence of efficacy data (see below) it is difficult to determine those who may benefit from HIFU. However, extrapolating from radiation and surgical outcomes data we can predict that those patients with a significant risk of extra-capsular extension (ECE) of tumour are likely unsuitable for HIFU. This is because the volume of tissue destruction is designed not to extend beyond the prostate capsule (and in some cases may purposefully or accidentally be less than total prostate ablation, see later).
The probability of ECE may be predicted from the Kattan nomogram [9], which is based on the Partin surgical series [10]. Patients with initial PSA >10ng/ml, who otherwise have good prognosis tumours have a 30% risk of ECE, patients with Gleason 7 cancer, irrespective of PSA have a >30% ECE risk, as do patients with clinical T2a disease, irrespective of PSA or Gleason score. Recent data with percent positive cores (PPC) additionally suggest that those with greater than 50% PPC carry a significantly worse prognosis – even within the low and intermediate risk group. [11]
The remaining patients (those with T1c, initial PSA<10, Gleason score 6 or less, and less than 50% PPC) represent a favorable group of patients who have excellent outcomes irrespective of treatment, and indeed may not require any intervention at all.

In terms of potential toxicity and other technical considerations, case series suggest the following selection criteria[1]:

- Prostate volume <30cc [7] - 50cc [12] (if necessary after neoadjuvant androgen ablation downsizing)
- No calcification >5mm (unless removed by TURP first) [7]

[1] This list is not intended to be a complete guide of patient exclusions

— Normal rectal anatomy

Toxicity

The following table summarizes toxicity rates from recent series using modern techniques

Early toxicity		*n*	**Ref**
Duration of suprapubic catheter	12.7 days mean	137	[12]
	32 days mean	218	[13]
	40 days median HIFU-only, 7 days pre-HIFU TURP group	96, 175	[8]
Urinary Tract Infection	48% HIFU-only, 11.4% pre-HIFU TURP	96, 175	[8]
IPSS score pre-post (mean)	6.5 – 8.9 HIFU-only, 6.7 – 3.4 pre-HIFU TURP	96, 175	[8]

Late toxicity	**%**	***n*, mean follow-up**	**Ref**
Recto-urethral fistula	0.7%	137, 22 months	[12]
	3.2%	62, 15 months median	[14]
	1%	102, 19 months	[15]
Chronic pelvic pain	1.5%	137, 22 months	[12]
Post-HIFU TURP rate	11.7%	137, 22 months	[12]
	30%	218, not stated	[13]
	27% HIFU-only, 8% pre-HIFU TURP group	96, 18.7 months 175, 10.9 months	[8]
	32%	62, 15 months median	[14]
Grade 2-3 incontinence	0%	137, 22 months	[12]
	14%	102, 19 months	[15]
	4.8%	62, 15 months median	[14]
Impotence, of those potent prior	57.7%	137, 22 months	[12]
	61%	102, 19 months	[15]
	44.4%	62, 15 months median	[14]

Rectal Fistula

This appears to be the most serious potential complication. Rectal cooling may reduce this risk,[13] as may decreasing the posterior treatment margin (at a risk of leaving a posterior rim of tissue unaffected [16]). Fistulae are much commoner in men who were treated with HIFU following radiation failure.[14,[17] Because of the short distance from prostate capsule to rectal mucosa, complete ablation of tumours that are located in the posterior-peripheral region may be problematic. Unfortunately this is exactly the commonest location for extension of prostate cancer radially beyond the capsule.[18] Patients with abnormal rectal anatomy and thick rectal walls >6mm [19] are excluded from therapy.

Efficacy

A histopathologic study where patients underwent HIFU, followed 1-2 weeks later by radical prostatectomy revealed incomplete HIFU-lesions at the ventral, lateral, and dorsal sides of the prostate lobe treated, and some prostate glands without apparently necrotic features situated within the HIFU lesions, raising the question of whether lethal destruction had occurred.[20] The extent to which technological enhancements to the treatment algorithm may overcome the concerns of the authors [16] is uncertain.

Evaluation of efficacy is particularly difficult given the long natural history of both treated and untreated prostate cancer. End points generally used have been biopsy and/or PSA based. A confounder is the use of neoadjuvant androgen deprivation therapy (ADT), which is used in 40-44% of HIFU patients. [7][12] Even a single injection of an LHRH can lead to delayed testosterone recovery. BC data [21] suggests the median time to recovery of testosterone to a level of 50% of normal takes an additional 10 months after the date the drug is meant to have worn off. This is similar to the mean follow-up in the case series, which averages 14 months. There are no published case reports with longer mean follow-up than 2 years. The quality/completeness of follow-up has not been reported, and as HIFU is only available in a limited number of centres it would be imagined that close follow-up has been problematic given the large distances many patients will have traveled for therapy.

Biopsy: Sampling the peripheral parts of the prostate, especially adjacent to the rectum and apex (where HIFU-ablation may have been purposefully avoided) is required and thus biopsies of the other parts of the prostate are less likely to detect residual cancer. The negative biopsy rate after partial and complete prostate treatment are equivalent (92 v 87%, p=0.32 [19]), suggesting that sampling may be an underlying problem. The use of neoadjuvant ADT may make interpretation difficult. Negative biopsy rates range from ~60-80% [5], but at a short mean follow-up of 14 months.

PSA: 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. 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.
Where follow-up is short, true relapse rates are underestimated because some patients have not yet had sufficient time for the required 3 rises to occur for the widely-used ASTRO definition. [22] PSA nadir <0.5ng/ml rates vary from 55 to 83% [5] and PSA control rates (ASTRO definition) vary from 66% to 82% (after 3 years follow-up.[8] Patients with larger prostate glands have higher PSA nadir's (2ng/ml >40cc, compared with 0.4ng/ml <40cc),[19] 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. [7]

For the reasons discussed above we believe that no conclusions can be drawn about the efficacy of treatment, a view shared by the Health Technology Assessment review.[2]

Re-treatment and tolerance of other therapy

More than one HIFU session was used in the early development of HIFU, particularly where only partial prostate treatment was used. Modern techniques, which employ whole-gland ablation and pre-HIFU TURP, have reduced the need for multiple treatments from 11.4% to 4%. [8]

We were unable to find any detailed data on tolerance of repeated treatment, nor tolerance of subsequent conventional therapy after HIFU failure. A prior TURP (and thus presumably HIFU ablation) sharply increases the risk of incontinence and other GU toxicity after radiation therapy.[23] Brachytherapy would be contraindicated after HIFU. Blana [12] comments that the risk of complications increases with multiple treatments, but does not provide data in support of the statement.

In the absence of data showing that salvage therapy after HIFU is both safe and effective we do not feel it is appropriate to promote HIFU as a measure that can be repeated and /or followed by conventional therapy.

Treatment of patients with recurrent disease after radiation therapy

Over a 7 year time period, Gelet and colleagues [17] treated 71 patients who had failed external radiation therapy and who were thought to have sole localized recurrence on the basis of positive prostate biopsies. The mean follow-up is short at 15 months, so efficacy results are premature. Actuarial projections of disease–free survival at 2 years were ~42%. The negative biopsy rate was 73%, presumably indicating high rates of failure outside the prostate. As referenced in the paper, the equivalent disease-free control rates with surgery are 43% and 31% with cryotherapy. However these rates were achieved after very much longer follow-up of 10 and 5 years respectively. The importance of patient selection in this group of patients makes comparison between series unwise. A recent review of the role of cryotherapy is referenced for the interested reader.[24]

Recommendations on the use of HIFU for prostate cancer

1. A new therapy such as HIFU must be developed in a controlled academic manner within the context of a clinical trial, which **should be approved by an Ethical Review Board (ERB)**, who should also monitor patient selection, 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 therapies gleaned from its radiation database and linkages with MSP data as required.

2. ERB-approved consent forms must include the **preliminary nature of toxicity and efficacy outcomes**, the presence of a learning curve, and detailed information regarding conventional alternative strategies (radical prostatectomy, brachytherapy, external radiation, androgen ablation or watchful waiting. This will require appropriate consultation with a Radiation Oncologist, and independent data and safety monitoring.

3. **Patients who may be suitable** for such an experimental protocol include those who are not appropriate for proven curative therapy of prostate cancer (radical prostatectomy, brachytherapy and external beam radiation therapy) and those with a pure localized recurrence after radiation therapy. This latter group is particularly at risk of significant long-term complications and the potential benefit of such treatment must be balanced against toxicity, other available options, and the natural history of recurrent prostate cancer.

Conclusions

Efficacy data does not allow meaningful assessment as to the benefit – risk ratio of HIFU treatment. HIFU cannot currently be recommended as standard therapy but could be further explored in ERB-monitored phase 1-2 studies. This will require full informed consent as to the nature of the evidence, toxicity and alternative options.

BCCA- GUTG Approved 2 Feb 2005

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