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Evidence-based Series 3-16 EDUCATION AND INFORMATION 2012

High-intensity Focused Ultrasound for Prostate Cancer

H. Lukka, T. Waldron, J. Chin, L. A. Mayhew, P. Warde, E. Winquist, G. Rodrigues, B. Shayegan, and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Report Date: July 20, 2009

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Evidence-based Series (EBS) 3-16, consists of three sections:

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-based Series 3-16: Section 1

High-intensity Focused Ultrasound for Prostate Cancer: Guideline Recommendations

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QUESTION

In patients with localized prostate cancer, how does high-intensity focused ultrasound (HIFU) compare with currently accepted curative treatment approaches such as radical prostatectomy, external beam radiotherapy [EBRT], and brachytherapy? Outcomes of interest include overall survival, biochemical failure, metastatic rate, and adverse effects.

RECOMMENDATIONS

- HIFU cannot currently be recommended as an alternative to accepted curative treatment approaches for localized prostate cancer.

QUALIFYING STATEMENTS

- HIFU should be considered an investigational treatment, with its use restricted to clinical trials and to patients for whom other local treatment options are not suitable. Patients should be made aware of currently accepted curative treatment approaches for localized prostate cancer.
- There are no randomized controlled trials (RCTs) that compare the efficacy of accepted curative treatments for localized prostate cancer to indicate the superiority of one approach over another. However, each approach has evolved as a standard treatment option based on mature clinical data from well-designed prospective studies.
- The results from case series of HIFU require confirmation in well-designed prospective studies of sufficient size with appropriate (and validated) endpoints before HIFU can

be considered a standard treatment option. The long natural history of prostate cancer necessitates a long length of patient follow-up to determine efficacy.
- The efficacy and toxicity associated with standard curative treatments administered post-HIFU is unknown.

KEY EVIDENCE

A systematic review of the literature was performed and showed there is currently no randomized evidence comparing the efficacy of HIFU to accepted curative treatments for localized prostate cancer. The clinical evidence on HIFU is comprised of 34 case series (each containing a minimum of 50 patients). Twenty-three series were published as full reports and eleven were published in abstract form.

- Across the 34 studies of HIFU, the number of patients treated ranged from 50 to 1,234 and totalled 7,438 patients. However, owing to multiple counting of patients among series, it is difficult to estimate the true total number of patients treated with HIFU.
- Most patients treated had localized prostate cancer (stage T1-T2) and underwent HIFU because they were unsuitable or unwilling to undergo surgery. Over 90% of patients were treated as primary therapy, and less than 10% of patients were treated as salvage therapy following radiotherapy failure. Gleason scores ranged from 2 to 10 (average was ≤7), mean initial PSA values ranged from 2.1 to 27.7 ng/ml, and mean prostate volumes ranged from 7.8 cc to 36.6 cc. The mean age range of patients was 65 to 74 years.
- HIFU was delivered by the Ablatherm and Sonoblate devices in 27 and seven series, respectively. The majority of studies indicated the use of prototype devices and technical changes over the study course.
- The main outcomes reported in series were negative biopsy rates, PSA levels (nadir, percent of patients with PSA ≤0.5 ng/ml), disease-free survival rates, and adverse effects.
- The definition of "disease-free" and the time point of measurement of this outcome varied significantly among series, making comparisons difficult. The most common definition included a positive biopsy and/or three consecutive PSA rises after the PSA nadir.
- Other outcomes relevant to this review, overall survival (one series) and metastatic rate (no series), were not frequently reported.

HIFU as Primary Treatment (29 studies, n=6912)

- Median patient follow-up ranged from six months to 6.4 years.
- Follow-up biopsies were usually performed three to six months post-HIFU. Negative biopsies ranged from 35% to 95.1% in 21 series.
- Five-year disease-free survival rates ranged from 55% to 95% in five series.
- The percentage of patients reaching a PSA nadir of ≤0.5 ng/ml ranged from 55% to 91% in nine series; and mean PSA nadirs ranged from 0ng/ml to 1.9ng/ml in 17 series.
- The majority of patients were treated with HIFU alone. Retreatment rates ranged from 7.7% to 43% in 11 series. Retreatment was associated with increases in specific morbidities in two series that examined the effect of retreatment.
- Some patients also received neoadjuvant hormonal therapy (NHT) or transurethral resection of the prostate (TURP) prior to HIFU. NHT (range, 4% to 61% of patients in 12 series) was stopped prior to HIFU in all series. In one study that examined outcomes of HIFU combined with TURP, combined treatment was associated with

similar efficacy, reduced catheter time, and a decrease in morbidity and retreatment rates compared to patients treated with HIFU alone.

- The common complications (medians) associated with HIFU included impotence (44% among previously potent patients), urinary tract infections (7.5% of patients), urethral stricture (12.3%), stenosis (7.8%), urinary incontinence (8.1%), urinary retention (5.3%), chronic perineal pain (3.4%), and urethrorectal fistula (1.0%).
- The percentage of patients requiring adjuvant or additional treatment (e.g., radiotherapy or hormonal therapy) after HIFU was reported in five series and ranged from 4% to 61%.
- The series (n=140) with the longest follow-up (i.e., 6.4 years) reported a negative biopsy rate of 86.4% and a five-year disease-free survival rate of 66%. Eight-year actuarial overall and cancer-specific survival rates were 83% and 98%, respectively. After HIFU, the mean PSA nadir was 0.62 ng/ml and a nadir of ≤0.5 ng/ml was reached in 68.4% of patients. The five-year biochemical-free rate was 77%.

HIFU as Salvage Treatment (5 studies, n=512)

- Only five series have examined the efficacy of HIFU as salvage treatment for local recurrence after EBRT. The largest series (n=167) with the longest length of follow-up (18.1 months) reported a negative biopsy rate of 73% and a five-year disease-free survival rate of 17%. A median PSA nadir of 0.19 ng/ml was reached within three months of HIFU. The adverse effects of treatment were urinary incontinence (50% of patients), bladder outlet obstruction (20%) and rectourethral fistula (3.0%).

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Contact Information

For further information about this report, please contact:
Dr. Himu Lukka, Genitourinary Cancer Disease Site Group
Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2
Phone: 905-387-9711 ext. 67699 Fax: 905-575-6326 E-mail: himu.lukka@jcc.hhsc.ca
or
Dr. Eric Winquist, Vice-Chair, Genitourinary Cancer Disease Site Group
London Health Sciences Centre, 790 Commissioners Road East, London, Ontario, N6A 4L6
Phone: 519-685-8600 ext. 53243 Fax: 519-685-8624 E-mail: eric.winquist@lhsc.on.ca

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please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence-based Series 3-16: Section 2

High-intensity Focused Ultrasound for Prostate Cancer: Evidentiary Base

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QUESTION

In patients with localized prostate cancer, how does high-intensity focused ultrasound (HIFU) compare with currently accepted curative treatment approaches such as radical prostatectomy, external beam radiotherapy (EBRT), and brachytherapy? Outcomes of interest include overall survival, biochemical failure, metastatic rate, and adverse effects.

INTRODUCTION

After lung cancer, carcinoma of the prostate is the most common malignancy to afflict the Canadian male population; the estimated number of new cases of prostate cancer in 2008 is 24,700 (1). It is also estimated that in this year 4,300 men will die of prostate cancer making it the third most common cause of cancer deaths in men.

Recent studies suggest that 75% of patients present with localized disease (2). The most important prognostic factors in the management of patients with localized prostate cancer include tumour stage (TNM staging), grade of tumour (Gleason score) and prostate-specific antigen (PSA) level. These factors have correlated with local extent of disease and nodal metastases in surgical series (3), and with biochemical disease-free survival in patients treated with radiotherapy (4). The three prognostic factors have been collated into three risk strata: low-, intermediate- and high-risk, and the criteria for these strata were developed and accepted by the 2000 Canadian Consensus Conference (5).

The management of prostate cancer remains controversial because of its variable natural history, the diversity of available treatments, and the lack of randomized controlled trials (RCT) comparing the different treatment approaches. Low-risk patients are candidates for watchful waiting, surgery (radical prostatectomy), and radical radiotherapy (RT) (either with external beam radiotherapy or brachytherapy). Patients with intermediate-risk disease are usually treated with surgery or RT, and patients with high-risk disease are usually treated

with a combination of RT and adjuvant hormonal treatment. When comparisons are made between the reported results of RT and surgery clinical studies (all retrospective), both treatments appear equally effective in terms of local control and survival (6,7). The decision to employ RT rather than surgery is often made on the basis of patient factors such as patient preference, age, comorbidity, and the availability of surgical expertise.

HIFU is a technique that uses focused ultrasound to generate areas of intense heat to destroy tissue. The technique has been studied for 50 years, with recent technological developments allowing its use for tumours of the liver, prostate, and other sites. It is increasingly being promoted as a non-invasive therapy for localized prostate cancer, particularly by the companies that manufacture the equipment (i.e., Focus Surgery Inc., who market the Sonablate® device, and EDAP, who make the Ablatherm® device). Both devices are approved for commercial distribution in Canada, the European Union, South Korea, and Russia at the date of publication of this guideline. Neither machine has gained Federal Drug Administration approval in the United States.

The aim of HIFU is to heat and destroy the area of the prostate with cancer by means of a probe that gives out a beam of focused ultrasound. The probe has a cooling balloon around it to protect nearby areas from the high temperature. HIFU is carried out under a spinal or general anesthesia. Transurethral resection of the prostate (TURP) may be performed immediately prior to HIFU in order to prevent problems with urinary retention, reduce the volume of the prostate, and minimise the amount of necrotic debris left after the procedure (8).

Due to increasing patient interest and the current use of HIFU technology in Ontario, the Genitourinary Disease Site Group (GU DSG) felt that an evidence-based guideline was needed to clarify, for both clinicians and their patients, the role of HIFU in the treatment of localized prostate cancer.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (9). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC GU DSG and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on HIFU for prostate cancer. The body of evidence in this review is primarily comprised of data from case series. That evidence forms the basis of the recommendations developed by the GU DSG found in Section 1 of this evidence-based series. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

A literature search was performed to identify published studies on HIFU. MEDLINE (2004 through May 2008 week 4), EMBASE (2004 through 2008 week 22), and the Cochrane Library Databases (2008, Issue 1) were searched for relevant studies using disease-specific and treatment-specific medical subject headings and text words (refer to Appendix 1). The search was later updated to May 2009.

The conference proceedings of the annual meetings of the American Urological Association (AUA) (2008) and the European Association of Urology (EAU) (2008) were also searched for relevant trials.

The reference lists of identified papers as well as relevant review articles were searched for additional studies. The National Guidelines Clearinghouse (http://www.guideline.gov/) and the Guidelines International Network (http://www.g-i-n.net/) websites were searched for existing evidence-based practice guidelines.

Study Selection Criteria

Papers were considered eligible for inclusion in the systematic review if they were:

- RCTs comparing HIFU to currently accepted management approaches (e.g., watchful waiting, surgery, radiotherapy) in patients with prostate cancer.
- Meta-analyses, systematic reviews, or clinical practice guidelines addressing HIFU.

Papers were excluded if they were:

- Non-randomized studies.
- Published in a language other than English, as translation services were not available.

Synthesizing the Evidence

All relevant papers identified by the literature search were assessed against the above selection criteria by two of the authors (TW, HL). Discrepancies regarding eligibility were resolved by consensus.

The evidence on HIFU for prostate cancer is comprised of case series. Therefore, a quantitative synthesis of the data was not possible, and the available data are presented in tabular form. Data extraction was performed by one of the authors (TW), while a second reviewer acted as an independent auditor to verify the accuracy of the data extraction. For presenting data on the complications associated with HIFU, medians and ranges were calculated (for individual study complication data, refer to Table 6 in Appendix 2).

RESULTS

Literature Search Results

No RCTs or meta-analyses were identified by the literature search. Seven systematic reviews were located (10-16). Two clinical practice guidelines were also identified (17,18), which were based on two of the systematic reviews (12,15). Neither the systematic reviews nor the clinical practice guidelines included RCTs. The GU DSG decided to adjust the inclusion criteria to include systematic reviews of studies with nonrandomized study designs.

A number of authors have recently assembled and reviewed the evidence on HIFU; therefore, an existing systematic review published in 2008 was used as the evidence base of this report (10). The original studies summarized in the review were examined to obtain additional data relevant to this review. A literature search was performed (using the same search strategy described above) to identify new studies of HIFU published after the systematic review.

Rebillard et al Systematic Review

The systematic review by Rebillard et al (10) was selected since it was among the most recent (included the medical literature through to July 2007), was the most comprehensive, and used similar systematic review methods to the PEBC. English-language clinical studies that reported on the efficacy and/or safety of HIFU in prostate cancer and included greater than 50 patients were eligible for inclusion. Two independent reviewers screened the literature search results for eligibility and extracted study data. The literature search of MEDLINE, EMBASE, and the conference proceedings of the AUA (2005-2007) and EAU (2005-2007) identified a total of 37 eligible reports on HIFU. Twenty-five reports examined

HIFU as primary treatment, and seven reports examined HIFU as salvage treatment after EBRT.

Update of Rebillard et al

Maintaining the same study selection criteria used by Rebillard et al (10), the updated literature search identified five additional reports that evaluated HIFU as primary treatment.

Another four studies were added later in the guideline process because two abstracts were published as full reports. One was a longer-term follow-up of a previous study, and one was a new study. The data from the updated reports are included in the results.

Overview of the Evidence on HIFU for Prostate Cancer

There is considerable overlap of patients among the case series. Multiple reports appear to relate to the same study or group of patients with different durations of follow-up. Efforts were made to distinguish unique reports based on authors, patient numbers, and other study characteristics; however, this effort cannot completely eliminate the problem of multiple counting of patients. For ease of reporting series results in succeeding text, where multiple references represent a series, only the most recent reference is used.

A total of 34 unique clinical studies of HIFU are included and form the evidence base of this systematic review (19-56). Twenty-three studies were published as full reports (19-22,26-28,31,32,34-36,39,42-46,48-51,58), and 11 were published in abstract form (23-25,29,37,38,40,41,52-54). One study (31) presented longer-term follow-up (8 years) of a previous study (30) with five-year follow-up. Three studies were full reports (34,48,58) of previous abstracts (33,47,55-57). Twenty-nine studies examined the efficacy of HIFU as primary treatment (19-50), and five studies examined the efficacy of HIFU as salvage treatment for local recurrence after EBRT (51-58) (Evidence tables, which summarize characteristics and results of the case series, are in Appendix 2).

HIFU as Primary Treatment for Prostate Cancer

The 29 studies of HIFU as primary treatment were all case series (19-50) (refer to Tables 1 and 2); two series were labelled prospective (21,40), while four were multicentred (21,33,40,42). The number of patients per study ranged from 58 to 1234, giving a total of 6912 treated patients. The total number of patients actually treated with HIFU is unclear, however, owing to multiple counting of patients in series. Most patients treated had localized prostate cancer (stage T1-T2) and received HIFU because they were either unsuitable for or unwilling to undergo radical prostatectomy. Gleason scores ranged from 2 to 10, with the majority of patients having scores of ≤7. Mean initial PSA values ranged from 2.1 to <27.7 ng/ml, and mean prostate volumes ranged from 7.8 to 36.6 cc. The mean age range of patients was 65 to 74 years.

HIFU was administered using the Ablatherm and Sonoblate devices in 22 and seven studies, respectively. A majority of studies cited the use of prototype devices and changes in technical parameters over the study course. Across the 29 studies median follow-up ranged from six months to 6.4 years. The main outcomes reported in series were negative biopsy rates, PSA levels (nadir, % of patients with PSA ≤0.5 ng/ml), and disease-free survival rates. PSA levels at last measurement and the percentage of patients with a stable PSA level were less frequently reported outcomes and therefore are not presented. Two other outcomes of interest to this review, overall survival and metastatic rate, were reported in one series and no series, respectively. Two series reported on cancer-specific survival.

Follow-up biopsies were usually performed three to six months post-HIFU. Negative biopsy rates ranged from 35% to 95.1% in 21 series. Disease-free survival was reported in 14 series; however, the definition of this outcome varied. The most common definition included

a positive biopsy or three consecutive PSA rises after the PSA nadir. Some definitions were strictly biochemical, while others also included initiation of salvage treatment. The time point at which this endpoint was measured also varied. Five-year disease-free survival rates ranged from 55% to 95% in five series. Six series reported the percentage of patients requiring adjuvant or additional treatment after HIFU (range, 2.3% to 21%) (22,23,25,29,31,34). In terms of PSA outcomes, the percentage of patients reaching a PSA nadir of ≤0.5 ng/ml ranged from 55% to 91% in nine series, and mean PSA nadirs ranged from 0 ng/ml to 1.9 ng/ml in 17 series. Many series reported results by prognostic factors (e.g., PSA level, Gleason score, disease risk category); generally among those series, higher negative biopsy rates and disease-free survival rates were observed among patients with low-risk features compared with patients with higher-risk features.

Most study patients were treated with HIFU alone, but the number of HIFU sessions delivered indicated there were subsets of patients for whom the HIFU procedure was repeated (for various indications). Eleven studies reported HIFU retreatment rates (19,21, 22,28,31,34,36-38,48,50), which ranged from 7.7% to 43% of patients. Three studies reported results separately for patients undergoing a second HIFU session; in these studies, HIFU retreatment was associated with increases in specific morbidities (i.e., incontinence and impotence). There were also subgroups of patients who received neoadjuvant hormonal therapy (NHT) (12 studies; range, 4% to 61% of patients) or TURP prior to HIFU (four studies; range, 31% to 91% of patients). Hormonal therapy was stopped prior to HIFU in all series. In one study examining outcomes of combined treatment with TURP and HIFU, combined treatment was associated with similar efficacy, reduced catheter time, and significant reductions in morbidity and retreatment rates compared with HIFU alone (22).

In the series with the longest length of follow-up (6.4 years), Blana et al (34) reported a negative biopsy rate of 86.4% among 140 patients. Eight-year actuarial survival data were also presented; overall survival and cancer-specific survival rates were 83% and 98%, respectively. The five-year disease-free survival rate was 66%. Fifteen percent of patients required rescue adjuvant treatment. After HIFU, the mean PSA nadir was 0.62 ng/ml, and a nadir of ≤0.5 ng/ml was reached in 68.4% of patients. The five-year biochemical failure-free rate was 77%.

Complications Associated with HIFU

The most common complications associated with the HIFU procedure included urinary tract infections (UTI), urinary incontinence, urinary retention, and impotence (refer to Tables 3 and 6). Median values for UTIs, stress or urinary incontinence and urinary retention occurred in 7.5%, 8.1%, and 5.3% of patients, respectively. The rate of erectile dysfunction was reported pre- and post-HIFU in ten series; the rate of erectile dysfunction post-HIFU in previously potent patients was 44%. Rectourethral fistulas were observed in 1.0% of patients. Other toxicities that were common included urethral or bladder neck stenosis or stricture, and less common complications included chronic perineal pain, infravesical obstruction, epididymitis, and prostatitis.

HIFU as Salvage Treatment for Local Recurrence after EBRT

Five series examined outcomes of HIFU as salvage therapy for patients with local recurrence after EBRT (refer to Tables 3-5) (51-58). In the largest series (n=167) with the longest length follow-up (18.1 months), Murat et al (55-58) reported a negative biopsy rate of 73% and a five-year disease-free survival rate of 17%. A median PSA nadir of 0.19 ng/ml was reached within three months of HIFU treatment. The adverse effects of treatment were urinary incontinence (50% of patients), bladder outlet obstruction (20%), and rectourethral fistula (3.0%).

Conclusion of Rebillard et al Review

Based on data from 25 case series of HIFU as primary treatment, the review by Rebillard et al concluded that HIFU appears to result in short-term cancer control, as demonstrated by a high percentage of negative biopsies and decreased PSA levels, with a low rate of complications that are comparable to established therapies. However, they indicated longer-term follow-up studies are needed to evaluate cancer-specific and overall survival; preferably through randomized trials comparing HIFU to other treatments and watchful waiting. No conclusions were drawn regarding HIFU as salvage treatment due to the limited amount of evidence.

Other Guidelines

In 2005, the National Institute for Clinical Excellence (NICE) in the United Kingdom systematically reviewed evidence on HIFU from 11 case series (15). Based on that evidence, they issued a guidance (17) supporting the use of HIFU for the treatment of prostate cancer with the proviso that normal arrangements are in place for consent, audit, and clinical governance. More specifically, HIFU is indicated either as primary treatment or salvage therapy after radiotherapy, with the option of performing TURP immediately prior to HIFU. This guidance contradicts the conclusions of their systematic review (15), which states HIFU should be considered an experimental procedure and longer-term data are required before efficacy can be established. In 2008, the NICE published an extensive systematic review and guidance document on the diagnosis and treatment of prostate cancer (12), which also covered evidence on the clinical effectiveness of HIFU. Based on that review of 13 case series, the NICE issued a recommendation against the use of HIFU in men with clinically localized prostate cancer other than in the context of controlled clinical trials comparing its use with established interventions. According to the NICE website (59), the original HIFU recommendation remains current, but should be read in conjunction with the 2008 recommendation.

DISCUSSION

The lack of RCT-level evidence comparing HIFU with currently accepted curative treatments for localized prostate cancer, or even watchful waiting strategies, makes drawing conclusions concerning this treatment difficult. The available evidence on HIFU is comprised of case series data. This evidence is limited in several ways, which precludes the GU DSG from making definitive recommendations on HIFU until higher-level evidence becomes available.

Among series there is a lack of clarity around the total number of patients who have been treated with HIFU. Significant overlap of patients exists among series, with multiple reports of the same study or group of patients reporting results after different lengths of follow-up. This review attempted to identify unique series; however, multiple counting of patients cannot entirely be eliminated, so the true number of patients treated with HIFU is unknown. Further, there is also variability with respect to patient populations. Patients treated with HIFU include those who were unsuitable for surgery, who had local recurrence after EBRT, or who received NHT or TURP prior to HIFU. The largest group of patients treated appear to be those unsuitable for surgery.

One of the major identified problems with the case series is that the median follow-up time is short. The longest series reports data after a median follow up of 6.4 years. However, as techniques, hardware, and software for the HIFU device have changed over time, the patients with the longest length of follow-up were treated with methods and prototype devices no longer in use, and patients treated with newer techniques have the shortest length of follow-up. Due to the long natural history of prostate cancer, longer follow-up is needed

before the efficacy of HIFU can be established. Experience from other modalities (i.e., radiotherapy) generally suggests a minimum of seven to 10 years is required.

The outcomes used to determine the efficacy of HIFU, either as primary or salvage treatment, have mainly been biopsy and PSA-based. The validity of these endpoints after HIFU is unclear, as neither has been validated as a surrogate measure for prostate cancer-specific survival or overall survival. PSA kinetics differ in response to the various treatment modalities; therefore, PSA failure criteria (and biopsy negativity) require validation specific to HIFU. The PSA outcomes reported in series varied significantly, making comparisons difficult. Further, NHT was given prior to HIFU in a number of series. Hormonal therapy is known to confound PSA outcomes, especially when follow-up is short. Retreatment with HIFU was relatively common and varied among series; however, the effect of retreatment on outcomes was not commonly investigated. Therefore it is difficult to know the extent to which this variation affected outcomes and the amount of retreatment (if any) that may be appropriate.

Overall, HIFU appears to affect prostate cancer, as demonstrated by the percentage of negative biopsies and a reduction in serum PSA. As primary treatment, negative biopsy rates measured three to six months post-HIFU range from 35% to 95.1% (among 21 series) and disease-free survival rates at five years range from 55% to 95% (among five series). Overall and cancer-specific survival data are not reported for most series. Common complications associated with HIFU include UTI, urinary incontinence and retention, impotence, and rectourethral fistula. When reviewing the evidence on complications, it should be noted that validated instruments to assess adverse effects were not consistently used or reported in series. The evidence base for HIFU as salvage treatment following radiotherapy failure is limited to just five series; negative biopsy rates among those series ranged from 73% to 80% (four series) and disease-free survival rates ranged from 54% at one-year to 17% at five years. The most frequently reported complications associated with salvage HIFU were urinary incontinence (median 28%) and urethrorectal fistula (median 4%).

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. The GU DSG will monitor the progress of the following trials and review reported results when they become available.

Protocol ID(s)	Title and details of trial
G050103 NCT00295802	Ablatherm integrated imaging high-intensity focused ultrasound for the indication of low risk, localized prostate cancer. Design: phase II/III Treatment groups: high-intensity focused ultrasound vs. cryotherapy Target accrual: not reported Date trial summary last modified: July 28, 2008 Status: active
FOCUS-G000280 IUMC-010235 NCT00030277 NCI-V01-1683	Phase I study of high-intensity focused ultrasound using the Sonoblate system in patients with locally recurrent prostate cancer. Design: phase I Treatment: high-intensity focused ultrasound Target accrual: 20 patients Date trial summary last modified: April 9, 2007 Status: closed

Protocol ID(s)	Title and details of trial
R-05-877 NCT00318240	Prostate Cancer Treatment Following Radiation Failure With High Intensity Focused Ultrasound (HIFU). Design: Feasibility study Treatment: high-intensity focused ultrasound Target accrual: not reported Trial summary last modified: July 16, 2008 Status: Active
UCLCTC-UCLH-HEMI-HIFU EU-20774, UCLH-Hemi-HIFU, ISRCTN25145525, NCT00561262	Phase II Study of Hemiablation Therapy Using High-Intensity Focused Ultrasound in Patients With Localized Adenocarcinoma of the Prostate. Design: Phase II Treatment: Hemiablation therapy using high-Intensity focused ultrasound Target accrual: 60 Trial summary last modified: March 30, 2008 Status: Active
UCLCTC-UCLH-FOCAL-HIFU UCLH-Focal-HIFU, EU-20773, NCT00561314	Phase II Study of High-Intensity Focused Ultrasound Ablation Using the Sonablate System in Patients With Localized Prostate Cancer. Design: Phase II Treatment: High-intensity focused ultrasound Target accrual: 33 Trial summary last modified: March 30, 2008 Status: Active
FSI-002 NCT00485381	Pivotal Study of the Sonablate® 500 HIFU Treatment of Localized Prostate Cancer. Design: Phase II/III Treatment: High-intensity focused ultrasound Target accrual: not reported Trial summary last modified: May 27, 2008 Status: Closed

CONCLUSIONS

Depending on patient and tumour factors, currently accepted curative treatment approaches for localized prostate cancer consist of surgery, radiotherapy, and brachytherapy. Other approaches include hormonal therapy and active surveillance. Although there are no RCTs comparing these options to indicate the superiority of one approach over another, each has evolved as a standard of care based on extended long-term patient follow-up of greater than seven to 10 years from well-designed prospective clinical studies. After a careful review of the available data on primary HIFU, it is the opinion of the GU DSG that these data do not provide enough evidence to currently recommend its use as an alternative to standard curative treatment approaches. The results from case series require confirmation in well designed, prospective trials of sufficient size with appropriate endpoints and lengths of follow-up. Until data of this level become available, the use of HIFU should be restricted to clinical trials, and to patients for whom other local curative treatment options are not suitable. It is also important to note that the efficacy and toxicity associated with standard curative treatments administered after HIFU is currently unknown.

CONFLICT OF INTEREST

Information on actual or potential conflicts of interest was collected from each author. Seven authors had no conflicts to declare (HL, TW, PW, LM, EW, GR, BS); and one author (JC) declared receiving research support (HIFU equipment) as a principal investigator for a clinical trial. Three authors (HL, PW, GR) consult patients regarding treatment with radiotherapy.

JOURNAL REFERENCE

The following systematic review was published in *Clinical Oncology* (©2010 The Royal College of Radiologists.; http://www.elsevier.com/locate/clon):

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For a complete list of the Genitourinary DSG members, please visit the CCO website at http://www.cancercare.on.ca/

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Contact Information

For further information about this report, please contact:
Dr. Himu Lukka, Genitourinary Cancer Disease Site Group
Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2
Phone: 905-387-9711 ext. 67699 Fax: 905-575-6326 E-mail: himu.lukka@jcc.hhsc.ca
or
Dr. Eric Winquist, Vice-Chair, Genitourinary Cancer Disease Site Group
London Health Sciences Centre, 790 Commissioners Road East, London, Ontario, N6A 4L6
Phone: 519-685-8600 ext. 53243 Fax: 519-685-8624 E-mail: eric.winquist@lhsc.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. National Cancer Institute of Canada. Canadian Cancer Statistics 2008. Toronto (Canada)): National Cancer Institute of Canada; 2008.
2. Cooperberg M, Broering J, Litwin M, Lubeck D, Mehta S, Henning J, et al. The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. J Urol. 2004;171:1393-401.
3. Partin A, Kattan M, Subong E, Walsh P, Wojno K, Oesterling J, et al. Combination of prostate-specific antigen, clinical stage and Gleason score to predict pathological stage of localized prostate cancer. JAMA. 1997;277:118.
4. D'Amico A, Whittington R, Malkowicz S, Fonduruila J, Chen M-H, Kaplan I, et al. Pretreatment nanogram for prostate specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol. 1999;17:168-72.
5. Lukka H, Warde P, Pickles T, Morton G, Brundage M, Souhami L, et al. Controversies in prostate cancer radiotherapy: consensus development. Can J Urol. 2001;8:1314-22.
6. Hanks G, Hanlon A, Schultheiss T, Corn B, Shipley W, Lee W. Early prostate cancer: the national results of radiation treatment from the Patterns of Care and Radiation Therapy Oncology Group Studies, with prospects for improvement with conformal radiation and adjuvant androgen deprivation. J Urol. 1994;152:1775-80.
7. Pilepich M, Bagshaw M, Asbell S, Hanks G, Krall J, Emami B, et al. Definitive radiotherapy in resectable (stage A2 and B) carcinoma of the prostate--results of a nationwide overview. Int J Radiat Oncol Biol Phys. 1987;13:659-63.
8. Vallancien G, Prapotnich D, Cathelineau X, Baumert H, Rozet F. Transrectal focused ultrasound combined with transurethral resection of the prostate for the treatment of localized prostate cancer: feasibility study. J Urol. 2004;171:2265-7.
9. Browman G, Levine M, Mohide E, Hayward R, Ritchard K, Afni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
10. Rebillard X, Soulié M, Chartier-Kastler E, Davin J-L, Mignard J-P, Coulange C. High-intensity focused ultrasound in prostate cancer; a systematic literature review of the French Association of Urology. BJU Int. 2008;101:1205-13.
11. Tsakiris P, Thüroff S, De La Rosette J, Chaussy C. Transrectal high-intensity focused ultrasound devices: a critical appraisal of the available evidence. J Endourol. 2008;22:221-9.
12. National Collaborating Centre for Cancer. CG58 Prostate cancer: evidence review. 2008 [cited 2008 Nov 20]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG58EvidenceReview.pdf.
13. Aus G. Current status of HIFU and cryotherapy in prostate cancer - a review. Eur Urol. 2006;50:927-34.
14. Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localized prostate cancer: a systematic review. Health Technol Assess. 2003;7:1-157.
15. National Institute for Clinical Excellence. Interventional procedures overview of high-intensity focused ultrasound for prostate cancer. 2004 [cited 2008 June 6]. Available from: http://www.nice.org.uk/pdf/ip/IP230overview.pdf.
16. Pickles T, Goldenberg SL, Steinhoff G. Technology review: high-intensity focused ultrasound for prostate cancer. Can J Urol. 2005;12:2593-7.

17. National Institute for Clinical Excellence. High-intensity focused ultrasound for prostate cancer. 2005 [cited 2008 Jun 6]. Available from: http://www.nice.org.uk/pdf/ip/IPG118guidance.pdf.
18. National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. 2008 [cited 2008 Nov 20]. Available from: http://www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline.pdf.
19. Chaussy C, Thüroff S. High-intensive focused ultrasound in localized prostate cancer. J Endourol. 2000;14:293-9.
20. Chaussy C, Thüroff S. Results and side effects of high-intensity focused ultrasound in localized prostate cancer. J Endourol. 2001;15:437-40.
21. Thüroff S, Chaussy C, Vallancien G, Wieland WF, Kiel HJ, Le Duc A, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. J Endourol. 2003;2003:673-7.
22. Chaussy C, Thüroff S. The status of high-intensity focused in the treatment of localized prostate cancer and the impact of a combined resection. Curr Urol Rep. 2003;4:248-52.
23. Thüroff S, Chaussy C. Efficacy of local high intensity focused ultrasound (HIFU) in localized prostate cancer [abstract]. J Urol. 2005;173:279.
24. Thüroff S, Knauer K, Chaussy C. Ten years high-intensity focused ultrasound (HIFU) as local treatment of prostate cancer: profile of side effects [abstract]. Eur Urol. 2006;5:132.
25. Chaussy C, Thüroff S, Knauer K. Ten years application of high-intensity focused ultrasound (HIFU) in prostate cancer (PCA) [abstract]. Eur Urol Suppl. 2006;5:133.
26. Gelet A, Chapelon J, Bouvier R, Rouvière O, Lyonnet D, Dubernard J. Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. J Endourol. 2000;14:519-28.
27. Gelet A, Chapelon J, Bouvier R, Rouvière O, Lyonnet D, Dubernard J. Transrectal high intensity focused ultrasound for the teatment of localized prostate cancer: factors influencing the outcome. Eur Urol. 2001;40:124-9.
28. Poissonnier L, Chapelon J-Y, Rouvière O, Curiel L, Bouvier R, Martin X, et al. Control of prostate cancer by transrectal HIFU in 227 patients. Eur Urol. 2007;51:381-7.
29. Gelet A, Chapelon JY, Murat FJ, Curiel L, Bouvier R, Rouvière O, et al. Prostate cancer control with transrectal HIFU in 124 patients: 7-years' actuarial results [abstract]. Eur Urol Suppl. 2006;5:133.
30. Blana A, Walter B, Rogenhofer S, Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. Urology. 2004;63:297-300.
31. Blana A, Rogenhofer S, Ganzer R, Lunz JC, Schostak M, Wieland WF, Walter B. Eight years; experience with high-intensity focused ultrasonography for treatment of localized prostate cancer. Urology. 2008;72:1329-33.
32. Blana A, Rogenhofer S, Ganzer R, Wild P, Wieland W, Walter B. Morbidity associated with repeated transrectal high-intensity focused ultrasound of localized prostate cancer. World J Urol. 2006;24:535-90.
33. Blana A, Thüroff S, Murat F-J, Walter B, Chaussy C, Gelet A. Long-term results with high intensity focused ultrasound (HIFU) in 140 patients with localized prostate cancer [abstract]. Eur Urol Suppl. 2007;6:199.
34. Blana A, Murat FJ, Walter B, Thuroff S, Wieland WF, Chaussy C, et al. First analysis of the long-term results with transrectal HIFU in patients with localised prostate cancer. Eur Urol. 2008 Jun;53(6):1194-201.
35. Beerlage HP, Thüroff S, Debruyne FMJ, Chaussy C, de la Rosette JJ. Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. Urology. 1999;54:273-7.

36. Lee H, Hong J, Choi H. High-intensity focused ultrasound therapy for clinically localized prostate cancer. Prostate Cancer and Prostatic Diseases. 2006;9:439-43.
37. Mallick S, Dufour A, Fouques Y, Bensadoun H. High intensity focused ultrasound for the treatment of localized prostate cancer: are its efficacy and morbidity dogmatic [abstract]? J Urol. 2006 [cited 2008 Jun 10]. Available from: http://www.abstracts2view.com/aua_archive/view.php?nu=200691912.
38. Zizzi V, Piccinni R, Cafarelli A, Sblendorio D, Berardi B, Tempesta A. High-intensity focused ultrasound (HIFU) in prostate cancer [abstract]. Eur Urol Suppl. 2006;5:133.
39. Ganzer R, Rogenhofer S, Walter B, Lunz J-C, Schostak M, Wieland WF, et al. PSA nadir is a significant predictor of treatment failure after high-intensity focussed ultrasound (HIFU) treatment of localized prostate cancer. Eur Urol. 2008;53:547-53.
40. Conort PC, Rischmann PR, Bensadoun H, Pfister CP, Chevalier DC, Saussine CS, et al. Treatment of localised prostate cancer by high intensity focused ultrasound (HIFU); results of the first French prospective study on patients not previously treated; minimum of five years follow-up [abstract]. Eur Urol Suppl. 2008;7:119.
41. Murat F-J, Poissonnier L, Pricaz E, Rouvière O, Chapelon JY, Colombel M, et al. Residual prostate cancer after a first HIFU session: oncological benefits of a second session [abstract]. Eur Urol Suppl. 2008 [cited 2008 Jun 10]. Available from: http://www.uroweb.org/publications/eau-abstracts-online//?AID=18967.
42. Uchida T, Baba S, Irie A, Soh A, Masumori N, Tsukamoto T, et al. Transrectal high-intensity focused ultrasound in the treatment of localized prostate cancer: a multicenter study. Hinyokika Kiyo. 2005;51:651-8.
43. Uchida T, Ohkusa H, Nagata Y, Hyodo T, Satoh T, Irie A. Treatment of localized prostate cancer using high-intensity focused ultrasound. BJU Int. 2006;97:56-61.
44. Uchida T, Ohkusa H, Yamashita H, Shoji S, Nagata Y, Hyodo T, et al. Five years experience of transrectal high-intensity focused ultrasound using the Sonoblate device in the treatment of localized prostate cancer. Int J Urol. 2006;13:228-33.
45. Uchida T, Illing RO, Cathcart PJ, Emberton M. The effect of neoadjuvant androgen suppression on prostate cancer-related outcomes after high-intensity focused ultrasound therapy. BJU Int. 2006;98:770-2.
46. Uchida T, Illing RO, Cathcart PJ, Emberton M. To what extent does the prostate-specific antigen nadir predict subsequent treatment failure after transrectal high-intensity focused ultrasound therapy for presumed localized adenocarcinoma of the prostate? BJU Int. 2006;98:537-9.
47. Mearini L, D'urso L, Collura D, Zucchi A, Formiconi A, Muto M, et al. Transrectal high-intensity focused ultrasound (HIFU) using the sonoblate®500 for the treatment of prostate cancer; the Perugia-Torino experience [abstract]. Eur Urol Suppl. 2008;7:120.
48. Mearini L, D'Urso L, Collura D, Zucchi A, Costantinni E, Formiconi A, et al. Visually directed transrectal high intensity focused ultrasound for the treatment of prostate cancer: a preliminary report on the Italian experience. J Urol. 2009;181:105-11.
49. Muto S, Yoshii T, Saito K, Kamiyama Y, Ide H, Horie S. Focal therapy with high-intensity-focused ultrasound in the treatment of localized prostate cancer. Jpn J Clin Oncol. 2008;38:192-9.
50. Misraï V, Rouprêt M, Chartier-Kastler E, Comperat E, Renard-Penna R, Haertig A, et al. Oncologic control provided by HIFU therapy as single treatment in men with clinically localized prostate cancer. World J Urol. 2008;26:481-5.
51. Gelet A, Chapelon JY, Poissonnier L, Bouvier R, Rouvière O, Curiel L, et al. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasoundography. Urology. 2004;63:625-9.

52. Poissonnier L, Gelet A, Chapelon J-Y, Bouvier R, Colombel M, Curiel L, et al. Local recurrence of prostate cancer after external beam radiation: early experience of salvage therapy using high intensity focused ultrasound [abstract]. Eur Urol Suppl. 2005;7:79.
53. Mallick S, Dufour A, Fouques Y, Bensadoun H. Salvage therapy using high-intensity focused ultrasound for local recurrence of prostate cancer after radiation therapy [abstract]. Eur Urol Suppl. 2006;5:132.
54. Murat F-J, Chapelon JY, Poissonnier L, Bouvier R, Curiel L, Martin X, et al. Salvage HIFU for radiorecurrent prostate cancer: factors influencing the outcome [abstract]. Eur Urol Suppl. 2006;5:133.
55. Murat F-J, Poissonnier L, Rouvière O, Chapelon J-Y, Bouvier R, Martin X, et al. Salvage high intensity focused ultrasound (HIFU) treatment for recurrent prostate cancer after radiation therapy: high efficacy in patients with good initial prognosis [abstract]. J Urol. 2007 [cited 2008 Jun 10]. Available from: http://www.abstracts2view.com/aua_archive/view.php?nu=200794031.
56. Murat F-J, Poissonnier L, Pricaz E, Rouviere O, Mege F, Chapelon JY, et al. Prognostic factors for salvage HIFU success after external beam radiation failure (EBRT) failure [abstract]. Eur Urol Suppl. 2008;7:119.
57. Murat FJ, Poissonnier L, Rouvière O, Chapelon JY, Bouvier R, Martin X, et al. High efficacy of salvage HIFU treatment for radiorecurrent prostate cancer in patient with good initial prognosis [abstract]. J Urol. 2007;6:200.
58. Murat FJ, Poissonnier L, Rabilloud M, Belot A, Bouvier R, Rouviere O, 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. 2009;55:640-9.
59. National Institute for Clinical Excellence. High-intensity focused ultrasound for prostate cancer. 2005 [cited 2008 Jun 10]. Available from: http://www.nice.org.uk/Guidance/IPG118.
60. Thüroff S, Chaussy C. High-intensity focused ultrasound: complications and adverse events. Mol Urol. 2000;4:183-7.
61. Chaussy C, Thüroff S. High-intensity focused ultrasound in prostate cancer: results after 3 years. Mol Urol. 2000;4:179-82.
62. Thüroff S, Knauer K, Chaussy C. 10 years high intensity focused ultrasound (HIFU) as local treatment of prostate cancer: profile of side effects [abstract]. J Urol. 2006 [cited 2008 Jun 10]. Available from: http://www.abstracts2view.com/aua_archive/view.php?nu=200794031.
63. Thüroff S, Kiel HJ, Knauer K, Buehrend H, Chaussy C. High-intensity focused ultrasound (HIFU) in prostate cancer - side effects after 1000 treatments in 8 years [abstract]. Eur Urol Suppl. 2005;4:82.
64. Chaussy C, Thüroff S. Side effects of transrectal high intensity focused ultrasound (HIFU) in the local treatment of prostate cancer in 8 years [abstract]. J Urol. 2005 [cited 2008 Jun 10]. Available from: http://www.abstracts2view.com/aua_archive/view.php?nu=20054055.
65. Poissonnier L, Gelet A, Chapelon JY, Curiel L, Bouvier R, Rouvière O, et al. Prostate cancer control with transrectal HIFU in 230 patients: five-year results [abstract]. Eur Urol Suppl. 2005;4:44.

Appendix 1: Literature search strategies.

Medline	Embase
1. prostatic neoplasms/ 2. high intensity focused ultrasound.mp. 3. exp ultrasound, high-intensity focused, transrectal/ 4. HIFU.mp. 5. prostate.mp. 6. 1 or 5 7. 2 or 3 or 4 8. 6 and 7	1. exp high intensity focused ultrasound/ 2. high intensity focused ultrasound.mp. 3. HIFU.mp. 4. prostate cancer/ 5. prostate.mp. 6. or/1-3 7. or/4-5 8. 6 and 7

Appendix 2: Evidence tables.

Table 1: Case series of HIFU as primary treatment for prostate cancer: study and patient characteristics.

Series First author, year, (reference)	No. of patients (No. of HIFU sessions)	Mean follow-up, mos	Patient Characteristics (mean)				
			Age, yrs	Stage, %	PSA, ng/ml	Prostate volume, cc	Gleason score distribution, %
Ablatherm Device							
Chaussy 2000 (19) Thüroff 2000 (60)	65	10	NR	NR	NR	NR	4-7, 92.3 8-10, 7.7
Chaussy 2001 (20) Chaussy 2000 (61)	184 (232)	6.4	72	NR	12	26 (median)	2-4, 9.5 5-7, 80 8-10, 10.5
Thüroff 2003 (21)	402 (602)	13.6	69.3	NR	10.9	28	6
Chaussy 2003 (22)	96 HIFU 175 TURP+HIFU (303)	18.7 10.9	65.8 68.4	NR	8.6 8	21.7 20.5	2-6, 69.8 7, 26 8-10, 4.2 2-6, 74.3 7, 21.7 8-10, 4
Thüroff 2005 (23)	412 low-risk 557 high-risk (>1000)	28.5 33.3	68 70	NR	NR	35 25	1-3, 100 1-3, 29
Thüroff 2006 (24) Thüroff 2006 (62) Thüroff 2005 (63) Chaussy 2005 (64)	1078 1st HIFU 156 2nd HIFU (>1300)	NR	NR	NR	NR	NR	NR
Chaussy 2006 (25)	309 low-risk 364 high-risk	15.8 11	73 74	NR	20 14	7.8 18	4-5, 0 4-5, 60
Gelet 2000 (26)	82 (154)	17.6	71	T1, 46.3 T2, 48.8	8.11	34.9	2-4, 9.8 5-6, 48.8 7, 25.6 8-10, 15.9
Gelet 2001 (27)	102 (182)	19	70.8	T1, 46.1 T2, 46.1	8.38	33.3	2-6, 53.9 7-10, 46.1
Poissonnier 2007 (28) Poissonnier 2005 (65)	227	27.5	68.8	T1, 54 T2, 46	6.99	23.9	2-6, 67 7, 33
Gelet 2006 (29)	190	40.4	NR	NR	NR	NR	NR
Blana 2004 (30) Blana 2008 (31)	163 (195)	57.6	66	T1a, 6.7 T1b, 6.1 T1c, 11 T2a, 55.8 T2b, 20.2	7.9	23	2-6, 138 7, 25
Blana 2006 (32)	174 1st HIFU	13	68.2	NR	11.3	23.5	5.3

Series First author, year, (reference)	No. of patients (No. of HIFU sessions)	Mean follow-up, mos	Patient Characteristics (mean)				
			Age, yrs	Stage, %	PSA, ng/ml	Prostate volume, cc	Gleason score distribution, %
	49 2nd HIFU	13					
Blana 2007 (33) Blana 2008 (34)	140	76.8	69.1	NR	7	25.9	2-6, 84 7, 16
Beerlage 1999 (35)	111 (143)	12	NR	NR	NR	NR	NR
Lee 2006 (36)	58	14	70	T1, 55.2 T2, 44.8	10.9	36.6	2-6, 51.7 7, 29.3 8-10, 19
Mallick 2006 (37)	247	22.3	68.6	NR	9.52	25.1	2-4, 11.7 5-7, 85.8 8-10, 2.5
Zizzi 2006 (38)	108 (123)	22.5	74.2	NR	27.7	NR	6.1
Ganzer 2008 (39)	103	58.8	65.7	T1, 26.3 T2, 73.8	7.6	24	5 (median)
Conort 2008 (40)	117 (179)	62	69	NR	8.4	31	6
Murat 2008 (41)	227 2nd HIFU	25	69.9	NR	2.1	9.5	NR
Misrai 2008 (50)	119	46.8	68	T1a, 3 T1b, 2 T1c, 82 T2a, 13	8.2	25	4-6, 68 7-8, 32
Sonoblate Device							
Uchida 2005 (42)	72 (89)	14	72	T1, 56 T2, 44	8.10	22.1	2-4, 13 5-7, 76 8-10, 8
Uchida 2006 (43)	63 (76)	23.3	70.5	T1, 62 T2, 38	11.2	28.5	2-4, 21 5-7, 73 8-10, 6
Uchida 2006 (44)	181 (209)	18	70	T1, 51 T2, 49	9.76	21.6	2-4, 13 5-7, 74 8-10, 6
Uchida 2006 (45)	250	NR	68.5	T1, 53 T2, 47	8.9	23.4	6
Uchida 2006 (46)	115	NR	69.5	T1, 54 T2, 46	10.8	26.2	6
Mearini 2008 (47) Mearini 2009 (48)	163	23.8 (median)	72 (median)	T1, 44 T2, 42 T3, 14	7.3 (median)	32.4 (median)	2-4, 14.2 5-7, 76.6 8-10, 9.2
Muto 2008 (49)	70	34	72	T1, 81.4 T2, 18.5	4.6	33	≤5, 7.1 6-7, 75.8 8-10, 11.4

Abbreviations: cc, cubic centimetres; HIFU, high-intensity focused ultrasound; ml, millilitres; mos, months; N, number of patients; NR, not reported; PSA, prostate-specific antigen; TURP, transurethral resection of the prostate; yrs, years.

Table 2: Case series of HIFU as primary treatment for prostate cancer: selected outcomes.

Series First author, year, (reference)	N	Outcomes			
		Negative biopsy rate, %	% of patients achieving PSA < or ≤0.5ng/ml	Mean PSA nadir, ng/ml	Disease-free survival, % (time-point)
Ablatherm					
Chaussy 2000 (19) Thüroff 2000 (60)	65	83	91	NR	NR
Chaussy 2001 (20) Chaussy 2000 (61)	184[a]	80	61	1.3	NR
Thüroff 2003 (21)	402	87.2[b]	NR	1.8[b]	NR
Chaussy 2003 (22)	96 HIFU 175 TURP+HIFU	87.7 81.6	NR	0.48 0.26	NR
Thüroff 2005 (23)	412 low-risk 557 high-risk	93.7 82	NR	0 0.1	NR
Thüroff 2006 (24) Thüroff 2006 (62) Thüroff 2005 (63) Chaussy 2005 (64)	1078 1st HIFU 156 2nd HIFU	NR	NR	NR	NR
Chaussy 2006 (25)	309 low-risk 364 high-risk	75 51	NR	0 0	NR
Gelet 2000 (26)	82[c]	78	83	1.02	62 (5-yr)
Gelet 2001 (27)[d]	102[d]	75	NR	NR	66
Poissonnier 2007 (28) Poissonnier 2005 (65)	227[e]	86	84	0.33	66 (5-yr)
Gelet 2006 (29)	190	NR	NR	0.48 (median)	61 (7-yr)
Blana 2004 (30) Blana 2008 (31)	163[f]	92.7	83[f]	0.07[f] (median)	75, 66[f] (5-yr)
Blana 2006 (32)	174 1st HIFU 49 2nd HIFU[g]	NR	NR	NR	NR
Blana 2007 (33) Blana 2008 (34)	140[h]	86.4	68.4	0.62	66 (5-yr)
Beerlage 1999 (35)	111	68	55	NR	NR
Lee 2006 (36)	58[i]	NR	78	0.2	81, 5[i]
Mallick 2006 (37)	247	NR	63.6	NR	71.3
Zizzi 2006 (38)	108[j]	95.6, 67.3[j]	76.6, 41.6	NR	NR
Ganzer 2008 (39)	103	95.1	NR	0.1	95, 55, 0 (5-yr)[k]
Conort 2008 (40)	97	NR	NR	1.9	NR
Murat 2008 (41)	227 2nd HIFU	77[l]	NR	0.66	53 (4-yr)

Series First author, year, (reference)	N	Outcomes			
		Negative biopsy rate, %	% of patients achieving PSA < or ≤0.5ng/ml	Mean PSA nadir, ng/ml	Disease-free survival, % (time-point)
Misrai 2008 (50)	119	35	NR	1.2 (median)	NR
Sonoblate					
Uchida 2005 (42)	72	68	NR	NR	78, 76 (1-yr, 2-yr)
Uchida 2006 (43)	63	87	NR	1.38	75 (3-yr)
Uchida 2006 (44)	181[m]	NR	NR	NR	78 (5-yr)
Uchida 2006 (45)	96 HIFU 150 NHT+HIFU	68	NR	NR	NR
Uchida 2006 (46)	115	64	NR	NR	NR
Mearini 2008 (47) Mearini 2009 (48)	163	66.1	NR	0.15 (median)	78.1
Muto 2008 (49)	70[n]	88.1	NR	NR	85.9. 50.9, 0[l] (2-yr)

Abbreviations: HIFU, high-intensity focused ultrasound; ml, millilitres; mos, months; N, number of patients; ng, nanogram; NHT, neoadjuvant hormonal therapy; NR, not reported; PSA, prostate-specific antigen; TURP, transurethral resection of the prostate; yrs, years.

[a] 48% of patients received NHT.
[b] Negative biopsy outcome based on 288 patients; mean PSA nadir based on 212 patients.
[c] 5% of patients received HIFU as salvage after EBRT; 9% of patients received NHT.
[d] Follow-up to Gelet et al 2000; 8% of patients received HIFU as salvage after EBRT; 4% of patients received NHT.
[e] 33% of patients received NHT.
[f] 37% of patients received NHT; data provided by abstract (ref 30); disease-free survival using two different definitions.
[g] 46% of patients received NHT; 31% of patients had TURP before HIFU.
[h] 16% of patients received NHT.
[i] 29% of patients received NHT; 91% received TURP before HIFU; failure-free rate for T1 and T2 patients, respectively.
[j] 34.3% of patients received NHT; negative biopsy rate for low-intermediate-risk and high-risk patients, respectively.
[k] For patients with PSA <0.2, 0.2-1, and >1, respectively.
[l] Among 182 patients who agreed to biopsy.
[m] 52% of patients received NHT.
[n] 34% of patients received NHT; for low, intermediate, and high-risk patients, respectively.

Table 3: Common complications associated with HIFU for prostate cancer.

Complication	Median (range) %	N*	No. of Studies† (References)
HIFU as Primary Treatment			
Urinary retention	5.3 (<1 to 8.8)	1185	8 (21,26-28,36,43,44,49)
UTI	7.5 (1.8 to 47.9)	3071	11 (21,22,24,26-28,31,32,34,38,49)
Urethrorectal fistula	1.0 (0 to 2.7)	2692	10 (21,24.26,27,30,32,35,38,43,44)
Urethral stricture	12.3 (1.8 to 24)	712	8 (28,36,38,42-44,48,49))
Stenosis (urethra, bladder, neck)	7.8 (<1 to 17)	1171	6 (21,26-28,35,37)
Urinary incontinence (any degree)	8.1 (<1 to 34)	3803	17 (21,22,24,26-28,31,32,34-38,42-44,49)
Infravesical obstruction	17 (13.6 to 24.5)	575	3 (31,32,34)
Chronic perineal pain	3.4 (0.9 to 13.4)	1233	7 (26-28, 31,32,34,37)
Impotence‡	44 (20 to 77)	611	11 (23,25-28,31,34,42-44)
Epididymitis	6.1 (3.2 to 8.3)	316	3 (42-44)
Prostatitis	6.2 (5.6 to 6.8)	180	2 (38,42)
HIFU as Salvage Treatment after EBRT			
Urinary retention	16	50	1 (53)
UTI	1.4	71	1 (51)
Urethrorectal fistula	3.0 (0 to 5.6)	512	5 (51-54,58)
Urethral stricture	10	118	1 (54)
Stenosis (urethra, bladder, neck)	17 (17 to 17)	177	2 (51,52)
Urinary incontinence (any degree)	28 (10 to 49.7)	512	5 (51-54,58)
Chronic perineal pain	18	50	1 (53)
Impotence‡	47	50	1 (53)

Abbreviations: EBRT, external beam radiation; UTI, urinary tract infection.
*Total number of patients contributing to the median.
†Total number of studies contributing to the median.
‡Reflects studies that measured impotence among previously potent patients.

Table 4: Case series of HIFU as salvage treatment after EBRT: study and patient characteristics.

Series First author, year, (reference)	N	Mean follow-up, mos	Patient Characteristics (mean) after EBRT				
			Age, yrs	Stage, %	PSA, ng/ml	Prostate volume, cc	Gleason score distribution, %
Ablatherm Device							
Gelet 2004 (51)	71	14.8	67	NR	7.73	21.4	2-6, 34 7, 18 8-10, 48
Poissonnier 2005 (52)	106	15.7	68	NR	7.85	19.9	2-6, 39 7, 21 8-10, 41
Mallick 2006 (53)	50	16	70	<T2a, 88 T2a-c, 12	5.3	NR	7
Murat 2006 (54)	118	16.4	68.9	NR	7.8	NR	≤6, 32 7, 24 ≥8, 44
Murat 2008 (55-57) Murat 2009 (58)	167	18.1	68.4	NR	6.89	18	Undefined, 14 ≤6, 23 7, 23 ≥8, 40

Abbreviations: cc, cubic centimetres; HIFU, high-intensity focused ultrasound; ml, millilitres; mos, months; N, number of patients; NR, not reported; PSA, prostate-specific antigen; yrs, years.

Table 5: Case series of HIFU as salvage treatment after EBRT: selected outcomes.

Series First author, year, (reference)	N	Outcomes			
		Negative biopsy rate, %	% of patients achieving PSA < or ≤0.5ng/ml	Mean PSA nadir, ng/ml	Disease-free survival, % (time-point)
Ablatherm					
Gelet 2004 (51)	71	80	NR	1.97	38 (30 mos)
Poissonnier 2005 (52)	106	84	57	NR	40.5 (40 mos)
Mallick 2006 (53)	50	NR	66	NR	54 (1-yr)
Murat 2006 (54)	181	84	62	NR	78, 49.5, 14[a]
Murat 2008 (55-57) Murat 2009 (58)	167	73	NR	2.38	17 (5-yr)[b]

Abbreviations: HIFU – high-intensity focused ultrasound; ml – millilitres; mos – months; N – number of patients; ng – nanogram; NR –not reported; PSA – prostate-specific antigen; yr – year.
[a] For low-, intermediate-, and high-risk patients, respectively.

Table 6: Complications of HIFU as primary treatment for prostate cancer: individual study data.

Device	Ablatherm																				Sonoblate				
Reference	(21)	(22)		(23)		(24)		(25)		(26)	(27)	(28)	(31)	(32)		(34)	(35)	(36)	(37)	(38)	(40)	(41)	(42)	(48)	(49)
N	402	96	175	412	557	1078	156	309	364	82	102	227	137	223	49	140	111	58	247	108	72	63	181	160	70
Group		HIFU	HIFU + TURP	Low risk	High risk	1st HIFU	2nd HIFU	Low risk	High risk					1st HIFU	2nd HIFU										
Complication	%																								
Urinary retention	8.6									6.1	4.9	8.8						3.4				1.6	<1		5.7
UTI	13.8	47.9	11.4			9.5	15.2			6.1	7.8	1.8	6.7	4.0	4.1	7.1				38.3					6.7
Urethro-rectal fistula	1.2					<1	<1			1.2	<1		<1	0	2.0		2.7			<1		1.6	1.1		
Urethral stricture												1.8						6.9		9.5	18	24	22	15	8.3
Stenosis (urethra, bladder, neck)	3.6									17.1	16.7	11.9					<1		3.3						
Urinary incontinence (any degree)	14.7	15.4	6.9			1.7	2.2			15.9	22.5	13.2	8.0	7.6	16.3	34.3	8.1	15.5	9.3	4.1	1.4	1.6	<1		5.8
Infravesical obstruction													24.5	19.7	14.3	13.6									
Chronic perineal pain										1.2	2	3.1	3.7	<1	4.1	5.7			13.4						
Impotence				46	51	55	75	34	58	77	61	39	44.7	49.8	81.6	43.2			27.8	67.8	39	23.5	20		
Epididymitis																					8	3.2	6.1		
Prostatitis																				6.8	6				

Abbreviations: HIFU – high-intensity focused ultrasound; N – number of patients; TURP – transurethral resection of the prostate.

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Evidence-Based Series #3-16: Section 3

High-intensity Focused Ultrasound for Prostate Cancer: EBS Development Methods and External Review Process

H. Lukka, T. Waldron, J. Chin, L. A. Mayhew, P. Warde, E. Winquist, G. Rodrigues, B. Shayegan, and Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Genitourinary Cancer Disease Site Group

Report Date: July 20, 2009

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the GU DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on HIFU for prostate cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. No major issues were raised by the Report Approval Panel. Editorial suggestions were incorporated.

External Review by Ontario Clinicians

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the GU DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GU DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review February 25, 2009)
Question
In patients with localized prostate cancer, how does high-intensity focused ultrasound (HIFU) compare with currently accepted curative treatment approaches such as radical prostatectomy, external beam radiotherapy [EBRT], and brachytherapy?

Outcomes of interest include overall survival, biochemical failure, metastatic rate, and adverse effects.

Draft Recommendations

- HIFU cannot currently be recommended as an alternative to accepted curative treatment approaches for localized prostate cancer.

Qualifying Statements

- HIFU should be considered an investigational treatment, with its use restricted to clinical trials and to patients for whom other local treatment options are not suitable. Patients should be made aware of currently accepted curative treatment approaches for localized prostate cancer.
- There are no randomized controlled trials (RCTs) that compare the efficacy of accepted curative treatments for localized prostate cancer to indicate the superiority of one approach over another. However, each approach has evolved as a standard treatment option based on mature clinical data from well-designed prospective studies.
- The results from case series of HIFU require confirmation in well-designed prospective trials of sufficient size with appropriate (and validated) endpoints before HIFU can be considered a standard treatment option. The long natural history of prostate cancer necessitates a long length of patient follow-up to determine efficacy.
- The efficacy and toxicity associated with standard curative treatments administered post-HIFU is unknown.

Key Evidence

A systematic review of the literature was performed and showed there is currently no randomized evidence comparing the efficacy of HIFU to accepted curative treatments for localized prostate cancer. The clinical evidence on HIFU is comprised of 34 case series (each containing a minimum of 50 patients). Twenty-three series were published as full reports and 11 were published in abstract form.

- Across the 34 studies of HIFU, the number of patients treated ranged from 50 to 1234 and totalled 7438 patients. However, owing to multiple counting of patients among series, it is difficult to estimate the true total number of patients treated with HIFU.
- Most patients treated had localized prostate cancer (stage T1-T2) and underwent HIFU because they were unsuitable or unwilling to undergo surgery. Over 90% of patients were treated as primary therapy; and less than 10% of patients were treated as salvage therapy following radiotherapy failure. Gleason scores ranged from 2 to 10 (average was ≤7), mean initial PSA values ranged from 2.1 to <27.7 ng/ml, and mean prostate volumes ranged from 7.8 cc to 36.6 cc. The mean age range of patients was 65 to 74 years.
- HIFU was delivered by the Ablatherm and Sonoblate devices in 27 and seven series, respectively. The majority of studies indicated the use of prototype devices and technical changes over the study course.
- The main outcomes reported in series were negative biopsy rates, PSA levels (nadir, percent of patients with PSA ≤0.5 ng/ml), disease-free survival rates, and adverse effects.
- The definition of "disease-free" and the time point of measurement of this outcome varied significantly among series, making comparisons difficult. The most common definition included a positive biopsy and/or three consecutive PSA rises after the PSA nadir.

- Other outcomes relevant to this review, overall survival (one series) and metastatic rate (no series), were not frequently reported.

HIFU as Primary Treatment (29 studies, n=6912)

- Median patient follow-up ranged from six months to 6.4 years.
- Follow-up biopsies were usually performed three to six months post-HIFU. Negative biopsies ranged from 35% to 95.1% in 21 series.
- Five-year disease-free survival rates ranged from 55% to 95% in five series.
- The percentage of patients reaching a PSA nadir of ≤0.5 ng/ml ranged from 55% to 91% in nine series; and mean PSA nadirs ranged from 0 ng/ml to 1.9 ng/ml in 17 series.
- The majority of patients were treated with HIFU alone. Retreatment rates ranged from 7.7% to 43% in 11 series. Retreatment was associated with increases in specific morbidities in two series that examined the effect of retreatment.
- Some patients also received neoadjuvant hormonal therapy (NHT) or transurethral resection of the prostate (TURP) prior to HIFU. NHT (range, 4% to 61% of patients in 12 series) was stopped prior to HIFU in all series. In one study that examined outcomes of HIFU combined with TURP, combined treatment was associated with similar efficacy, reduced catheter time, and a decrease in morbidity and retreatment rates compared to patients treated with HIFU alone.
- The common complications associated with HIFU included impotence (44% among previously potent patients), urinary tract infections (7.5% of patients), urethral stricture (12.3%), stenosis (7.8%), urinary incontinence (8.1%), urinary retention (5.3%), chronic perineal pain (3.4%), and urethrorectal fistula (1.0%).
- The percentage of patients requiring adjuvant or additional treatment (e.g., radiotherapy or hormonal therapy) after HIFU was reported in five series and ranged from 4% to 61%.
- The series (n=140) with the longest follow-up (i.e., 6.4 years) reported a negative biopsy rate of 86.4% and a five-year disease-free survival rate of 66%. Eight-year actuarial overall and cancer-specific survival rates were 83% and 98%, respectively. After HIFU, the mean PSA nadir was 0.62 ng/ml and a nadir of ≤0.5 ng/ml was reached in 68.4% of patients. The five-year biochemical-free rate was 77%.

HIFU as Salvage Treatment (5 studies, n=512)

Only five series have examined the efficacy of HIFU as salvage treatment for local recurrence after EBRT. The largest series (n=167) with the longest length of follow-up (18.1 months) reported a negative biopsy rate of 73% and a five-year disease-free survival rate of 17%. A median PSA nadir of 0.19ng/ml was reached within three months of HIFU. The adverse effects of treatment were urinary incontinence (50% of patients), bladder outlet obstruction (20%) and rectourethral fistula (3.0%).

Methods

Targeted Peer Review: During the guideline development process, six targeted peer reviewers from Ontario, Quebec, and British Columbia considered to be clinical and/or methodological experts on the topic were identified by the GU DSG. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as

reviewers. Three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 25, 2009. The GU DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. Medical and radiation oncologists and surgeons working in the field of genitourinary cancer in Ontario were identified from the PEBC database and were contacted by email to inform them of the guideline and to solicit their feedback. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on March 15, 2009. The consultation period ended on April 15, 2009. The lead author reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 7.

Table 7. Responses to nine items on the targeted peer reviewer questionnaire.

Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods. *(Consider: The appropriate stakeholders were involved in the development of the guideline. The evidentiary base was developed systematically. Recommendations were consistent with the literature. Consideration of alternatives, health benefits, harms, risks, and costs were made.)*				2	1
2. Rate the guideline presentation. *(Consider: The guideline is well organized. The recommendations were easy to find.)*				1	2
3. Rate the guideline recommendations. *(Consider: The recommendations are clinically sound. The recommendations are appropriate for the intended patients.)*				2	1
4. Rate the completeness of reporting. *(Consider: The guideline development process was transparent and reproducible. How complete was the information to inform decision making?)*				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. What are the barriers or enablers to the implementation of this guideline report? Responses are compiled in the comments section below.					
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
7. Rate the overall quality of the guideline report.				2	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)

8. I would make use of this guideline in my professional decisions.				1	2
9. I would recommend this guideline for use in practice.				1	2

Summary of Written Comments

The targeted reviewers had few suggestions for improving the guideline. One reviewer felt that the description of toxicity in the text should be expanded and have a separate heading. In response to this comment, the section on complications associated with HIFU was placed under a separate subheading. One reviewer noted that the development of such new technologies as HIFU is immature, and thus their effect on efficacy cannot as yet be evaluated.

Professional Consultation: Two responses were received. Key results of the feedback survey are summarized in Table 8.

Table 8. Responses to three items on the professional consultation survey.

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.					2
3. I would recommend this guideline for use in practice.					2

Summary of Written Comments

The main points contained in the written comments were that caution is warranted with respect to the use of HIFU. More trials and longer follow-up data are needed.

Final DSG Deliberations

Following completion of internal and external review, the document was circulated to all members of the GU DSG for final approval. Some members disagreed with the proposed recommendations, indicating that the recommendations should more strongly support the use of HIFU for prostate cancer. However, the writing committee felt that the available evidence is still too preliminary (low level of rigor and short follow-up period) to recommend the use of HIFU outside of prospective studies.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GU DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For further information about this report, please contact:
Dr. Himu Lukka, Genitourinary Cancer Disease Site Group
Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2
Phone: 905-387-9711 ext. 67699 Fax: 905-575-6326 E-mail: himu.lukka@jcc.hhsc.ca
or
Dr. Eric Winquist, Vice-Chair, Genitourinary Cancer Disease Site Group
London Health Sciences Centre, 790 Commissioners Road East, London, Ontario, N6A 4L6
Phone: 519-685-8600 ext. 53243 Fax: 519-685-8624 E-mail: eric.winquist@lhsc.on.ca

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.