EDITORIAL COMMENT

Technical review: High-Intensity Focused Ultrasound for prostate cancer

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The recent report on High-Intensity Focused Ultrasound (HIFU) Therapy for Prostate Cancer produced for the BC Cancer Agency Genio-Urinary Tumour Group by Pickles et al (authors Pickles, Goldenberg, and Steinhoff) and subsequently published in the Canadian Journal of Urology (April 2005) misrepresents HIFU as a therapy which should be offered only within a research setting. The misinterpretation of the literature and the failure of these authors to review updated reports and recent clinical information regarding HIFU in the treatment of prostate cancer have led to conclusions that are incorrect in many factual aspects.

Four points need to be addressed:

General

Pickles et al incorrectly states that HIFU is "generally regarded as experimental by independent authorities" and sites as reference Hummel S et al (article, Reference 2). This is not true and is a misleading use of this reference. In this publication 15 different "emerging" therapies (including brachytherapy) were assessed and HIFU was included. The word "experimental" was not used in the report in regards to these treatments and should not be extended to HIFU unless Pickles et al agree to apply this terminology to brachytherapy as well.

Ablatherm-HIFU is fully approved as a class III device for the treatment of prostate cancer in Canada. It is not investigational and has the same approval status as all other standard medical equipment used in Canada. It is licensed under section 36 of the Regulations which is issued to the manufacturer of a device only "where the Minister of Health is satisfied that the medical device meets safety and effectiveness standards"

Ablalatherm-HIFU is produced by EDAP-TMS, the global leader in the development, production, marketing, and distribution of a portfolio of minimally invasive medical devices. The mere suggestion that EDAP is "dependent on the successful development and commercialization of its HIFU medical devices to achieve and sustain profitability in the future" suggests that the authors had not adequately reviewed the companies corporate information readily available over the Internet. EDAP-TMS, for instance, is a leader in extracorporeal shock wave lithotripsy (ESWL) technology and last year alone over 40 units of their units were sold worldwide.

The NICE report

The Uro-oncology Review by Pickles et al is based on the National Institute of Clinical Excellence (NICE) interim review published in March 2004. NICE is the independent body formed by the British government to determine efficacy and validity of treatments and their appropriateness for use in the National Health Service (NHS) in England. NICE has now issued a revised (March 2005) document (\t "_blank" http://www.nice.org.uk/page.aspx?o=80298) and the reader is encouraged to review this work. Based upon updated information this new report substantially modifies their initial recommendations and this document was not reviewed in the published report of Pickles et al. In short, this revised report concludes (quote)

"Current evidence on the safety and efficacy of high-intensity focused ultrasound (HIFU) as measured by reduction in prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure for the treatment of prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance."

It goes on to state, (quote)

"NICE has considered this procedure because it is relatively new. NICE has decided that the procedure is safe enough and works well enough for use in the NHS".

And finally (quote)

"High-Intensity focused ultrasound (HIFU) may be used to treat carcinoma of the prostate, either as a primary or salvage therapy" (post radiation).

Efficacy

While we agree with Pickles et al that follow-up times are short and information incomplete, the early evidence suggests significant positive results. At present efficacy is based on case series and no randomized reports are available. The main outcomes were negative biopsy rates and PSA nadir levels. Case studies have demonstrated negative biopsy rates between 87% (251/288) with a mean follow up of 13 months, 93% (128/137) in a study with mean follow up of 22.5 months, and 80% (75/94) in a study with 3 year follow up.

The NICE report (March 2005) recommends that, as with all treatment options presently available, long term data are needed to establish whether the

procedure reduces prostate cancer specific mortality. The impact of HIFU therapy should not be disregarded however. Have we all forgotten the paucity of data that was available when brachytherapy was introduced? Do we not remember that radiation oncologists were embracing brachytherapy despite incomplete data, limited short-term patient follow up, and the continued absence of randomized studies?

Safety

From the updated NICE report (quote)
"The Specialist Advisors listed urinary incontinence, rectal fistula, bowel perforation and erectile dysfunction as potential adverse events but noted that HIFU appears to be safer than alternative radical treatments for prostate cancer".
Beginning in 2000 and extending into 2002, significant software upgrades and modification of treatment parameters were incorporated into the HIFU procedure. These changes have led to a marked improvement in treatment success rates and in patient safety. Of greatest significance is the complete elimination of rectal fistulae even in the patient population who had initially received external beam radiation but had shown signs of localized failure. Results from Gelet (submitted for publication) have shown a zero incidence of rectal fistulae in 100 consecutive external radiation failure patients with a 62% negative biopsy rate at 1 year.
This updated material was not reviewed by Pickles et al for their article.
While Pickles et al were unable to find any data on tolerance of repeated treatment, Blana has shown that, as expected, there is a significant increase in impotence with a second treatment, although more importantly there was no significant rise in incontinence rates with retreatment.[1]

Comments

HIFU is not experimental therapy. Its acceptance by the updated NICE report confirms its status as a proven treatment modality for prostate cancer. At present over 65 clinical sites worldwide are actively treating patients (not 18 as reported in the article) with clinical experience exceeding 6,000. In 2004 alone over 1,700 patients were treated in Europe. Significant modifications in treatment parameters have virtually eliminated complications such as rectal fistulae that were a concern with previous generations of instruments.
The indications for High Intensity Focused Ultrasound in the treatment of prostate cancer includes new patients with organ confined disease (clinical stage T1 and T2) who are not surgical candidates or who refused standard treatment due to potential complications (the reader is directed to the recent report by Grady, W.M., Russell, K., in Gastroenterology, April, 2005,[2] which confirms a 70% rise in the risk of rectal cancer in those patient who receive full course external beam radiation for localized prostate cancer. Only that portion of the rectum irradiated during the prostate treatment demonstrated an increased risk of cancer). The second group of patients considered candidates for HIFU is those who have failed external radiation and present with organ confined recurrent prostate cancer. Up until now the only options for this difficult to treat group has been hormonal therapy. HIFU gives new hope to these patients.
Beginning in early 2005 The Royal Marsden Hospital in London, England, a world leader in external beam radiation treatment for prostate cancer will begin offering HIFU therapy for localized disease both as primary therapy and in post radiation failures patients. Similarly Dr. Vallancien from Institut Montsouris, Paris, a world leader in laparoscopic radical prostatectomy surgery has begun to offer HIFU in patients not considered candidates for radical surgery and those not accepting of the potential risks.
The opening of an Ablatherm-HIFU centre in Canada is a North American first and allows Canadians the opportunity to be treated with this new modality closer to home. From a physician point of view, the new centre will allow us to expand the present database and explore fully the treatment of prostate cancer using High Intensity Focused Ultrasound (Ablatherm-HIFU).

Sincerely,

Dr. C. Andreou
Dr. A. Blana
Dr. W. Orovan
Dr. M. Hassouna
Dr. J. Warner
Dr. E. Woods

1. Wieland WF, Walter B, Rogenshofer S, Blana A. Proceedings of SPIE, Vol. #5686. Submitted for publication, *Journal of Endourology* (2005)
2. Grady WM, Russell K. Ionizing radiation and rectal cancer: victims of our own success. *Gastroenterology* 2005;April, V.128, 4th ed:1114-1117.

Reply by authors: Physicians who are confused by the conflicting claims made in the editorial and our evidence-based review should take the opportunity to review the relevant literature themselves before making a decision about the current status of HIFU. By design, our review was restricted to peer-reviewed publications and excluded abstracts and promotional material put out by the company. This is presumably why patient numbers differ. We stand by all the statements made in our review. More recent abstracts (e.g. AUA 2005) continue to suffer from short follow up with means of only 2-3 years. The views of the authors of this editorial should be considered in the light of their involvement in the provision of HIFU as a for-profit venture in Ontario.

In reviewing the literature on management of localized prostate cancer (including brachytherapy, radical prostatectomy etc.,) one must bear in mind recent changes in the understanding of its natural history, including issues of over diagnosis and over treatment. Variability in PSA levels may reflect BPH more than small volume cancer. Very early results may therefore reflect biological variations in PSA post-benign ablation and may bear no relation to longer term cancer outcomes. Toxicity outcomes from HIFU are not trivial, and must also be factored in.

Patients may not able to detangle technical sense from nonsense. Cancer patients in particular are vulnerable to the 'hard sell". The Maple Leaf HIFU web site (http://www.hifu.ca/) is an example of this. This web site contains the following misleading messages. a) Patient exclusions are not described, indeed it is suggested that "every patient advised to have a radical prostatectomy or radiation therapy is a candidate". b) If HIFU does not work it is confidently stated that "In those developing a recurrence, they remain candidates for surgery, radiation or hormone therapy," yet this is uncertain, given how little published data there is on the efficacy and safety of salvage therapy post-HIFU. c) Brachytherapy is described as being associated with "not uncommon" tumour recurrence, whereas in fact brachytherapy has excellent long-term control rates (eg 90% after 12 years as reported by Potters, J Urol. 2005 May;173(5):1562-6). d) We are helpfully reminded that radical prostatectomy "can be curative" but, "it usually results in impotence and can result in moderate to severe urinary incontinence." e) Side effects are mentioned in each brief paragraph describing surgery, external radiation and brachytherapy, but are not included in the same brief paragraph on HIFU, although they are elsewhere.

While this particular issue is about a new therapy for prostate cancer, and not benign disease or a diagnostic test, there are questions that should be asked of any new therapy. How should it be evaluated? Who should promote it? Are standards for medical devices as stringent as for prescription drugs, and if not, why not?

We support the formal evaluation of HIFU as a promising new modality – perhaps the Maple Leaf HIFU Company will consider funding and performing the first randomized trials of this emerging therapy? It is doubtful that phase 2 data from another non-academic centre will provide the level of evidence we require to change practice.

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