National Institute for Health and Clinical Excellence

839 – Focal therapy using high-intensity focused ultrasound for localised prostate cancer

Consultation Comments table

IPAC date: Thursday 12 January 2012

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1.	Consultee 1 NHS Professional Specialist Adviser	**1**	Existing evidence of efficacy is very limited and immature. I am surprised that NICE is not recommending that focal therapy be done only within the confines of a nationally-approved clinical trial, phase II or III. Surely NHS commissioners cannot be expected to fund this treatment (including the pre-requisite transperineal mapping biopsies under GA) without adequate evidence of efficacy and safety?	Thank you for your comment. Following review at two meetings, the Interventional Procedures Advisory Committee considered current evidence on focal therapy using high-intensity focused ultrasound (HIFU) for localised prostate cancer did not raise major safety concerns, but the evidence on efficacy to be limited in quantity. There was also concerns that prostate cancer is commonly multifocal. The guidance will not be changed. Issues related to the cost and funding of procedures is outside the remit of the IP programme.

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2.	Consultee 2 Manufacturer EDAP-TMS	**1**	BAUS has accepted to review data followed on the @-Registry. @-Registry is an online database (at-registry.com) developped for Ablatherm HIFU users to follow their patients, this anonimized database is managed by an independent company named "Active developpement"	Thank you for your comment. Section 1.5 of the guidance states that NICE supports ongoing data collection in order to provide more evidence on the procedure. The [EUCAP] [LINK] register is being developed to receive data on [HIFU] and when this facility is available clinicians should submit data on all patients undergoing [HIFU] to that
3.	Consultee 4 NHS Professional	**1**	These guidelines are very welcome. They present a balanced view point on focal HIFU. I would like to make a few points: - although prostate cancer is multifocal, there is an increasing recognition that not all lesions are clinically significant. If it were the case, then 1 in 3 men in the general population - who have indolent disease - would require treatment. The key is therefore to define clinically significant from clinically insignificant lesions. There are some good definitions for this now and I would be very happy to provide comprehensive references and synopsis of this data. Focal therapy is therefore primarily about ablating clinically important disease that is measurable - as it is in other solid organ cancers. - I think long term follow-up is important but medium to long term follow-up would be a better remit, perhaps defining 5 year follow-up as optimal with the need for beyond 5-year follow-up in ongoing registry type analyses. Ref: Wolters et al, J Urol, 2011 Ahmed, NEJM, 2009 Ahmed et al, BJUI, 2011 (epub) Ahmed et al, J Urol, 2011 Karavitakis et al, Nature Rev Clin Onc, 2010	Thank you for your comment. The five papers identified by the consultee provide supporting references to this comment. They are, however, not clinical studies on focal HIFU and will not be considered for inclusion into the overview. Section 1.4 of the guidance will be changed.

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4.	Consultee 5 NHS Professional	**1**	Most cancers are multi-focal. The arguments for both radical mastectomy and radical nephrectomy were based on this - in both cases they proved to be largely unfounded. The multi-focality that people refer to comes up because of the random, blind, sampling of the prostate that is currently the standard of care. I write this as a 50 year old and my probability of having prostate cancer today is 40%. If I were to have a biopsy there is a good chance that cancer could be found. Most of this multi-focal disease is low volume, low grade indolent cancer that most men have when they die of other causes. It makes little sense to base a treatment recommendation on something that most experts agree poses little if any threat to the patient. Focal therapy requires a very exacting assessment that takes into account location, volume and risk. Having said all this the question of multifocality needs addressing. Interstingly,the only way to do this is tro treat the index lesion focally and watch the small lesions over time. The question cant be addressed if you remove the prostate - the equivalent of bilateral radical mastectomy.	Thank you for your comment. Section 1.4 states that NICE encourages research into focal therapy using HIFU for localised prostate cancer. The guidance will not be changed.

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5.	Consultee 3 Royal College of Physicians	**1**	HIFU as a primary therapy In general I am happy with the recommendations that limit this to low risk disease however I would point out that HIFU is only available in very few centres. This has implications on how we can conduct proper trials of HIFU and include new centres to get large scale results. I recently tried to look into setting up HIFU in our unit and found that the national tariff for HIFU is very low and does not cover the actual cost of the procedure. Needless to say the trust was not over keen at this stage. One of the HIFU rep also told me that the take up in new centres has been difficult on the NHS. I believe that outside a few centres HIFU is being done mostly in the private sector - UKHIFU own website points this out : The HIFU procedure with the Sonablate is available in almost 20 locations in the UK. In some locations it may be available on the NHS, for those who qualify. Hence how do we best put in place accurate monitoring of a technique that is currently done mainly the private sector (outside a few large volume NHS units)?	Thank you for your comment. The purpose of IP Programme is to assess the safety and efficacy of an interventional procedure. Issues related to the cost and funding of procedures is outside the remit of the IP programme. Section 1.5 of the guidance states that NICE supports ongoing data collection in order to provide more evidence on the procedure
6.	Consultee 3 Royal College of Physicians	**1.4 and 2.5.1**	The guidelines do however recognise that focal therapy could overcome the harms of current treatments in a proportion of men. Therefore, ‘outcomes over medium to long term’ would be a better statement to make in 1.4 and 2.5.1	Thank you for your comment. Sections 1.4 and 2.5.1 of the guidance will be changed.

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7.	Consultee 4 NHS Professional	**2.1**	Please see comment above. The state-of-the-art thinking and discussion now relates ablating the index lesion or clinically significant lesions with low grade low volume lesions which have the same attributes as clinically indolent disease undergoing surveillance. Studies have shown that with such a strategy about 50-75% of men with localised prostate cancer would be suitable for focal therapy. This is important because even with the most intensive sampling strategies such as template prostate mapping, small low grade lesions will be overlooked even if areas are shown to be negative, so effectively almost all focal therapy is a form of index lesion ablation. Most focal therapy series and protocols incorporate this within their remit. Ref: Karavitakis et al, Prostate Cancer Prostate Dis. 2009 Bott et al, BJUI, 2009	Thank you for your comment. Section 2 is intended to be a brief summary of the procedure. The two papers identified by the consultee provide supporting references to this comment. They are, however, not clinical studies on focal HIFU and will not be considered for inclusion into the overview.

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8.	Consultee 5 NHS Professional	**2.1.1**	2.1.1 is incorrect. If symptoms arise from prostate cancer it is nearly always locally advanced. Focal therapy is best seen as a risk reduction strategy. It enables more men to keep their prostate. Currently AS is reserved for men with low grade prostate cancer - mainly Gleason 3 plus 3. Focal therapy allows men with higher risk tumours to be treated and as a result be restored to a low risk status. Prospective cohort studies have demonstrated a return to baseline geneito-urinary function in men who have focal therapy. It is therefore the only intervention currently available that is not associated with signiifcant impariment of continence or sexual function. This is why it is so popular with men who are given it as an option.	Thank you for your comment. Section 2 is intended to be a brief summary of the procedure. It states that although symptoms of localised prostate cancer can include difficulty in passing urine, the condition is often diagnosed at an asymptomatic stage. In section 2.1.2 the guidance states that "All radical treatment options are associated with substantial risks of sexual, urinary or bowel dysfunction". In section" 2.5.2 "the Committee noted the potential for this procedure to avoid many of the complications of more radical treatments for localised prostate cancer in properly selected patients, if further evidence supports its efficacy".
9.	Consultee 1 NHS Professional Specialist Adviser	**2.2**	Very little is known about interpretation of PSA following focal prostate HIFU.	Thank you for your comment.

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10.	Consultee 6 Healthcare Other	**2.2**	We propose that IPAC differentiate in its guidance between two HIFU technologies for the treatment of localised prostate therapy: ultrasound-guided MR-guided HIFU. As highlighted in IPG 413 (MR-guided focused ultrasound for uterine fibroids (November 2011)) the advantages of MRI guidance includes the precise visualization of the tissue being ablated using ultrasound, differentiating between normal and abnormal prostate tissue and surrounding structures. Continuous MR guidance allows thermal mapping and monitoring in real time, showing the operator the areas of ablation as they are produced. This assures complete tissue necrosis and increases the safety of the procedure since sensitive structures such as neurovascular bundles or the urethra can be easily visualized and avoided. MR-guided HIFU for treating localised prostate cancer is currently being evaluated in three different studies. When the results of these are available, we anticipate that IPAC will be notified of this procedure and will undertake a review. In order to avoid confusion now or later it will be helpful for clinicians, patients and commissioners to understand clearly the procedure to which the guidance refers.	Thank you for your comment. The IP Programme can only include published data, studies that have not been completed cannot be considered for inclusion into the overview.

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11.	Consultee 4 NHS Professional	**2.2**	Multiparametric MRI is also now a key test used to localise and follow-up patients after focal therapy. Ref de Vischere et al, AJR Am J Roent, 2010	Thank you for your comment. Reference to MR-guidance will be made in section 2.2.1 of the guidance. The paper identified by the consultee describes the role of MRI in follow-up after focal therapy for prostate carcinoma. It is, however, not a clinical study on focal HIFU and will not be considered for inclusion into the overview.
12.	Consultee 5 NHS Professional	**2.2.1**	2.2.1 does need to be emphasised. If the prostate is going to be treated at whole gland level by prostatectomy or by radiotherapy neither location nor burden matters. This is why TRUS biopsy (blind and random) has been sufficient. All that is needed is confrmation of the presence of cancer and treatment is justified. In other words everyone gets the same treatment independent of risk. Focal therapy can only be done if the variables of location, burden and risk are defined with precision. This requires imaging, and image guided biopsies or template biopsies - interventions that are not widely available. Treatment is then individualised. Whilst the early treatments were at the half gland (hemi-ablation) increasingly they are bng directed at the tumour with a margin. Most prostate cancers at dagnosis are between 1-2cc in volume. Most prostates are 40cc in volume. NCRI focal therapy trials looking at sub hemiablation are complete and soon to report.	Thank you for your comment. Section 2 is intended to be a brief summary of the procedure.
13.	Consultee 1 NHS Professional Specialist Adviser	**2.3**	Is there an accepted definition for biochemical disease-free survival following focal HIFU?	Thank you for your comment. Section 2.3.5 is the opinion of the Specialist Advisers.

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14.	Consultee 3 Royal College of Physicians	**2.3**	I am not sure that BAUS Cancer Registry still allows submission of non-major surgery. At UCLH, we keep a non-industry registry of all Focal HIFU carried out by clinicians using the Sonablate500 with PROMS and all other data constantly updated. A number of peer review publications have been released or in press.	Thank you for your comment. NICE supports ongoing outcome data collection in order to provide more evidence on the procedure. The review of published papers identified four papers although these are whole-gland HIFU therapies and not focal HIFU. They are therefore not included in the overview.
15.	Consultee 4 NHS Professional	**2.3**	I agree with these statements	Thank you for your comment.
16.	Consultee 5 NHS Professional	**2.3**	There are a number of NCRI registered studies that are about to report that used the same endpoints as the n20 study referred to here.	Thank you for your comment. NICE is aware of three NCRN registered studies on HIFU.
17.	Consultee 7 NHS Professional	**2.3**	HIFU is generally unproven and has high complication rates and very poor efficacy. It leaves many with strictures, some with fistulae and we have found it not to work in 70% of pts at and almost all when used as a salvage treatment failed. We have abandoned our entire programme due to a very poor efficacy rate which continues to worsen 4 years later. Highly attractive to pts but needs to be further assessed before being sanctioned. The USA have not endorsed this technology for good reason High-intensity focused ultrasound for localized prostate cancer: initial experience with a 2-year follow-up. Challacombe BJ, Murphy DG, Zakri R, Cahill DJ. BJU Int. 2009 Jul104(2):200-4. Epub 2009 Feb 11.	Thank you for your comment. The focus of this guidance is focal HIFU, not HIFU. The paper by Challacombe et al. is on the use of HIFU for localised prostate cancer and did not specify its use as focal therapy. It is therefore outside the scope of the current review.

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18.	Consultee 2 Manufacturer EDAP-TMS	**2.4**	In the case series of 12 patients (El Fegoun et al. 2011) it is reported that "No urinary incontinence was observed" (page 216). In the case series of 20 patients (Ahmed et al. 2011) it is reported that "95% were pad free" continent. Maybe it could be interesting to detail these continence status reported in those Focal studies.	Thank you for your comment. Both studies are in Table 2 of the overview and the outcomes are in the guidance.
19.	Consultee 4 NHS Professional	**2.4**	I agree with these statements.	Thank you for your comment.
20.	Consultee 5 NHS Professional	**2.4.3**	2.4.3 Bladder neck stensis is very rare - almost unheard of in focal therapy. The specialist advisors may be getting confused with whole gland HIFU. Acute retention is also very rare. The results from the n20 study show as have others that focal therapy is often associated with a retun to baseline genitor-urinary function. Again it is important to discriminate between whole gland therapy and focal therpy - the two are very different.	Thank you for your comment. Bladder neck stenosis was listed by one Specialist Adviser as an adverse event that has been reported in the literature. It was therefore included in Section 2.4.3 of the guidance.

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21.	Consultee 4 NHS Professional	**2.5**	I disagree that the natural history of prostate cancer is uncertain. Large epidemiological studies and RCTs of screening have incresingly shown what the natural history of untreated prostate cancer - even high risk - can be. It therefore seems that longterm data is not absolutely necessary - and 5-year medium outcomes if demonstrating acceptable cancer control with significantly lower toxicity should make this treatment an option for men with low to intermediate risk prostate cancer. This would allow men to have equitable access to a low toxicity therapy in a timely fashion.	Thank you for your comment. The committee considered this comment on the natural history of prostate cancer but decided not to make any changes to section 2.5.1 of the guidance.
22.	Consultee 5 NHS Professional	**2.5.1**	2.5.1 The uncertainty does not relate to the natural history of prostate cancer. The uncertainty in most cases rests with the imprecision conferred by a test (TRUS biopsy) that has inherent systematic and random error, is unstabe if re-applied (negative to positive, positive to negative - unique for a cancer test)and has up to 40% discordnace when compared to a good reference standard.	Thank you for your comment. The committee considered this comment but decided not to make any changes to section 2.5.1 of the guidance.
23.	Consultee 3 Royal College of Physicians	**2.5.1**	In the focal cryo guideline, there was mention that the natural history of prostate cancer is uncertain. I do not think this is the case anymore. There are plenty of epidemiological studies and RCTs demonstrating with excellent data that the natural history is quite well understood and that our current diagnostic and therapeutic strategy leads to over-diagnosis and over-treatment.	Thank you for your comment. The committee considered this comment on the natural history of prostate cancer but decided not to make any changes to section 2.5.1 of the guidance.

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24.	Consultee 1 NHS Professional Specialist Adviser	**2.5.2**	2.5.2 This is also the aim of Active Surveillance (in properly selected patients), a much less costly management strategy.	Thank you for your comment. The purpose of IP Programme is to assess the safety and efficacy of interventional procedures. Cost is outside the remit of the IP Programme.
25.	Consultee 3 Royal College of Physicians	**General**	I would only ask that research is prioritised in this area. The approach is intuitively appealing and so has been coming into practice without a strong evidence-based. Research should be encouraged and supported.	Thank you for your comment. Section 1.4 of the guidance states that NICE supports further research into the procedure for localised prostate cancer.
26.	Consultee 3 Royal College of Physicians	**General**	A few specific comments to make: I personally do not think focal therapy is about any one particular ablative technology. It is the concept which is important. This is important to clarify as low dose rate brachytherapists, those using HDR brachy or Cyberknife as well as other technologies (RFA, electroporation, PDT, photothermal laser) are all following the focal therapy route. It seems to me that NICE should be able to anticipate this increase in this area via a generic focal therapy guideline.	Thank you for your comment. This guidance focuses on focal therapy for localised prostate cancer using HIFU only.
27.	Consultee 3 Royal College of Physicians	**General**	There is an increasing recognition and acceptance that despite multifocality of disease, only clinically significant lesions lead to disease progression. There are no good definitions of what clinically significant disease constitutes.	Thank you for your comment.

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28.	Consultee 3 Royal College of Physicians	**General**	HIFU as salvage therapy - I think this needs to be a separate section for the guidelines as results are very different from primary HIFU Here there is outcome data form the UK that needs to be considered in the guidelines. The paper from UCL recently echoes that from other centres (Ahmed et al 2011) : At mean follow up of 20 months, If PSA non-responders were included, 1- and 2-year progression-free survival rates of 59% and 43%. If PSA non-responders were excluded, 1- and 2-year progression-free survival rates were 62% and 48%. About 38% of men needing pads or leaking, 20% needing TURP or BNI and 4.7% fistula rate. The paper concludes that this is a high risk procedure. I think this paper needs to be considered in the guidelines and salvage HIFU considered carefully – it has best results in men who were initially low risk disease Other references they could look at: Uchida T, Shoji S, Nakano M, Hongo S, Nitta M, Usui Y, Nagata Y. High-intensity focused ultrasound as salvage therapy for patients with recurrent prostate cancer after external beam radiation, brachytherapy or proton therapy. BJU Int. 2011 Feb107(3):378-82. Murat FJ, Poissonnier L, Rabilloud M, Belot A, Bouvier R, Rouviere O, Chapelon JY, Gelet A.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 Mar55(3):640-7.	Thank you for your comment. The current guidance focuses on focal HIFU only. The paper by Ahmed et al 2011 discusses whole-gland salvage HIFU, not focal therapy, for localised prostate cancer recurrence after external beam radiation therapy. Thus, it was not considered for inclusion in the overview. The papers by Uchida et al 2011 and Murat et al 2009 did not specify the use of HIFU for focal therapy and were not considered for inclusion in the overview.

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29.	Consultee 3 Royal College of Physicians	**General**	A statement should be made regarding the need to evaluate focal salvage therapy following localised recurrence after external beam radiotherapy using these two modalities (and any other ablative technology for that matter). There is one publication on this using focal salvage cryo and another on focal salvage HIFU.	Thank you for your comment. The paper on focal salvage HIFU the consultee has identified did not specify the use of HIFU as focal therapy. Thus, it will not be considered for inclusion in the overview.
30.	Consultee 3 Royal College of Physicians	**General**	In responding to NICE oncological consultations the NCRI/RCP/RCR/ACP/JCCO generally do so as a joint activity. For this consultation we have received three expert views which are all valid but address different areas of the consultation. We would therefore wish to submit these as individual responses rather than an NCRI/RCP/RCR/ACP/JCCO submission.	Thank you for your comment.
31.	Consultee 4 NHS Professional	**General**	Investigator in diagnosis and minimally invasive therapies in prostate cancer including focal therapy in the UK using a number of ablative modalities including HIFU with industry and academic funding (MRC, Wellcome, NIHR-HTA, US NIH, prostate cancer charities)	Thank you for your comment. This is an introduction of the expert who has provided his views on the consultation document.
32.	Consultee 7 NHS Professional	**General**	HIFU is generally unproven and has high complication rates. It leave many with strictures, some with fistulae and we have found it not to work in 70% of pts at Guys High-intensity focused ultrasound for localized prostate cancer: initial experience with a 2-year follow-up. Challacombe BJ, Murphy DG, Zakri R, Cahill DJ. BJU Int. 2009 Jul104(2):200-4. Epub 2009 Feb 11.	Thank you for your comment. Please see response to comment 17.

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