National Institute for Health and Clinical Excellence

968 – Focal therapy using cryoablation 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 Private Sector Professional	**1**	The provisional recommendations clearly set out the efficacy issue. Urological surgeons should take care to obtain detailed post procedure diary from all patients noting issues such as discomfort, sensations, urinary issues or any other issues they experience.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
2	Consultee 2 Health care Professional	**1**	Section 1 is well written. Entry criteria is crucial. It is probably impossible to obtain long term outcomes in terms of survival. Focus should be on QOL data and surrogate endpoints.	Thank you for your comment.

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3	Consultee 3 NHS Professional	**1**	We believe that the evidence on the efficacy is sufficient enough to warrant the procedure being performed under normal arrangements. Â It is worth noting that the other treatment options for prostate cancer are performed under normal arrangements and we feel cryoablation as a treatment option should be under normal arrangements as the outcomes of the treatments are similar. Â While we do not disagree that prostate cancer may have the potential to be a mulitfocal disease, we do believe that the Urologist treating the patient will have adequately mapped the prostate using mapping biopsy (transrectal, or template guided perineal biopsy) or by the use of advanced imaging techniques.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

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4	Consultee 3 NHS Professional	**1 cont**	Further the Urologist will have the ability to sufficiently monitor the patient with PSA, Imaging, DRE and if necessary further biopsies following cryoablation such that an additional cryoablation treatments may be performed should there be future evidence of prostate cancer disease in other areas of the prostate. Cryotherapy has the advantage of being a very minimally invasive approach that is transforming the care of prostate cancer patients. With respect to biochemical recurrence rates, cryotherapy appears to be as effective for low-risk prostate cancer as other treatment modalities. The EAURF (European Association of Urology Research Foundation), has recognised the EuCAP (European CryoAblation of Prostate) registry, which has a strong emphasis on the collection of data for focal Cryoablation. Â This multi-centric database is hosted by the university of Aarhus (Denmark), under the chairmanship of Prof. Damian Greene (Sunderland Royal Hospital).	Thank you for your comment. Thank you for alerting NICE to the EuCAP Registry. The guidance now recommends submission of data to the register (http://www.cryodatabase.com).

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5	Consultee 4 NHS Professional	**1**	These guidelines are very welcome. They present a balanced view point on focal HIFU. Â 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. Section 1.4 of the guidance has been changed. The papers identified by the consultee are not clinical studies on focal cryoablation and were not considered for inclusion in the overview.
6	Consultee 2 Health care Professional	**2.1**	Excellent description	Thank you for your comment.
7	Consultee 3 NHS Professional	**2.1**	No Comment	Thank you for your comment

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8	Consultee 4 NHS Professional	**2.1**	Focal treatment for localised prostate cancer can take two forms. Treatment may be administered to the dominant lesion, or one lobe can be totally treated. I have performed the latter in two patients with ulcerative colitis who were obviously unsuitable for radiotherapy and did not wish to undergo radical surgery. They both tolerated and recovered from treatment extremely well compared to those whom i have treated by either primary total gland cryotherapy or salvage post dxt.i feel that the guidance should clarify that focal therapy may be either tumour targetted or hemi-gland. The latter is obviously easier to treat in the event of tumour developing in the opposite lobe, as one then treats just the whole of that lobe.	Thank you for your comment. Section 2.1 is intended to be a brief description of the procedure.

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9	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. The Committee considered this comment but decided not to change the guidance. The papers identified by the consultee are not clinical studies on focal cryoablation and were not considered for inclusion in the overview.
10	Consultee 1 Private Sector Professional	**2.2**	Needs to be more specific on how surrounding tissue is preserved.	Thank you for your comment. Section 2.2 of the guidance is intended to be a succinct summary of the procedure.
11	Consultee 2 Health care Professional	**2.2.1**	2.2.1 Suprapubic catheters are not being used for focal therapy. Most urologists will use transurethral catheter only	Thank you for your comment. Section 2.2.1 of the guidance has been changed and reference to ‘supra pubic catheters’ has been removed.

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12	Consultee 2 Health care Professional	**2.2.2**	2.2.2 After focal, the patient will be followed with active surveillance of the untreated half of the gland. We are not primarily looking for recurrences but for previously undeteced tumour in the untreated half.	Thank you for your comment. Section 2.2 of the guidance is intended to be a succinct summary of the procedure.
13	Consultee 3 NHS Professional	**2.2**	Generally the standard of care is moving to the insertion of a foley catheter, which will be left in place for 3-7 days, dependent on the patient and the consulting doctor.	Thank you for your comment. Section 2.2 of the guidance is intended as a brief description of the procedure. . The Committee considered this comment but decided not to change the guidance.
14	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. Section 2.2.2 of the guidance has been changed to read follow-up includes 'imaging'. The paper identified is not a clinical study and was not considered for inclusion in the overview.

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15	Consultee 3 NHS Professional	**2.3**	We would like to submit the following scientific evidence for consideration by the committee. 1- An Evaluation of Patient Selection Criteria on Predicting Progression-Free Survival After Primary Focal Unilateral Nerve-Sparing Cryoablation for Prostate Cancer Truesdale MD, Cheetham PJ, Hruby GW, Wenske S, Conforto AK, Cooper AB, Katz AE Cancer J., 2010, 16:544-9. PURPOSE: Focal cryoablation targets unilateral disease, sparing healthy tissue and the ipsilateral neurovascular bundle. Given half the prostate is spared, proper patient selection is imperative to optimize outcomes. We report focal cryotherapy outcome data and evaluate the accuracy of the 2007 Task Force patient selection criteria at predicting disease recurrence.	Thank you for your comment. The paper identified is a review and not a clinical study and was not considered for inclusion in the overview.

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16	Consultee 3 NHS Professional	**2.3 cont**	CONCLUSIONS: Focal cryotherapy is a promising option for carefully selected patients, although optimization of inclusion criteria is required. Current selection criteria are associated with cancer-free survival. Given no accurate definitions for biochemical failure after focal cryotherapy exist combined with our high biochemical failure rate, mandating 12-month follow-up TRUS biopsy may improve accurate detection of cancer progression. Further follow up will determine optimal patient selection criteria and follow-up protocols for patients undergoing primary focal unilateral nerve-sparing prostate cancer treatment.	Thank you for your comment.

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17	Consultee 3 NHS Professional	**2.3 cont**	2- Contemporary results of focal therapy for prostate cancer using cryoablation. Mouraviev V, Johansen TE, Polascik TJ. J Endourol. 2010 May 24:827-34.The concept of focal therapy is rapidly evolving and gaining popularity from both physician and patient perspectives. We review the rationale, candidate selection, and results of the first clinical studies of focal cryoablation for selected patients with low volume and low- to low-moderate–risk features of prostate cancer as an alternative to whole-gland treatment. In spite of improved understanding of the tumor biology of early stage disease, we currently have limited tools to select appropriate patients with low- to low-moderate risk unifocal or unilateral prostate cancer who may be amenable to focal therapy. From a technical point, a number of ablative treatment options for focal therapy are available, with cryoablation having the most clinical experience. Recently, several reports have been published from single and multi-institutional studies that discuss focal therapy as a reasonable balance between cancer control and quality-of-life outcomes.	Thank you for your comment. The paper identified is a review and not a clinical study and was not considered for inclusion in the overview.

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18	Consultee 3 NHS Professional	**2.3 cont**	Retrospective pathologic data from large prostatectomy series, however, do not clearly reveal valid and reproducible criteria to select appropriate candidates for focal cryoablation because of the complexity of tumorigenesis in early stage disease. At this time, a more feasible option remains hemiablation of the prostate with reasonable certainty about the absence of clinically significant cancer lesion(s) on the contralateral side of the prostate based on three-dimensional transperineal prostate biopsy mapping studies. Minimally invasive, parenchyma-preserving cryoablation can be considered as a potential feasible option in the treatment armamentarium of early stage, localized prostate cancer in appropriately selected candidates. There is a need to further test this technique in randomized, multicenter clinical trials.	Thank you for your comment. NICE encourages further research on this procedure.

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19	Consultee 3 NHS Professional	**2.3 cont**	3- Focal cryotherapy for prostate cancer. Tsivian M, Polascik TJ. Curr Urol Rep. 2010 May11(3):147-51. Focal therapy for prostate cancer has emerged an interesting concept as a less morbid option for the treatment of localized low-risk disease. Despite the growing interest in focal therapy, this approach has not yet gained sufficient popularity nor provided enough data to be discussed outside the experimental application. Herein we summarize the available data on focal cryotherapy and focus on the targets to be achieved in order to increase the applicability of focal cryotherapy to clinical practice. A cautious approach to candidate selection and generation of solid scientific data that would result in wide consensus on patient selection strategies and follow-up schemes would provide the tools necessary to take the path of focal therapy.	Thank you for your comment. The paper identified is a review and not a clinical study and was not considered for inclusion in the overview.
20	Consultee 3 NHS Professional	**2.3 cont**	Currently available focal cryotherapy data demonstrate excellent short-term results and a favourable quality-of-life profile. Although the future role of focal treatment is debated, a growing amount of science is generated in support of this minimally invasive approach.	Thank you for your comment.

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21	Consultee 3 NHS Professional	**2.3 cont**	4- Nerve-sparing focal cryoablation of prostate cancer Polascik TJ, Mayes JM, Mouraviev V. Curr Opin Urol., 2009 19:182-7. PURPOSE OF REVIEW: We evaluate the rationale, candidate selection, and results of the first clinical studies of focal cryoablation for select patients with low volume and low-to-low - moderate risk features of prostate cancer as a possible alternative to whole gland treatment. SUMMARY: The concept of focal therapy is evolving with the understanding of the biologic variability (clinically aggressive, significant, or insignificant) of prostate cancers that may require different treatment approaches. Minimally-invasive, parenchyma-preserving cryoablation can be considered as a potential feasible option in the treatment armamentarium of early stage, localized prostate cancer in appropriately selected candidates.	Thank you for your comment. The paper identified is a review and not a clinical study and was not considered for inclusion in the overview.

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22	Consultee 3 NHS Professional	**2.3 cont**	5- The "male lumpectomy": focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Onik G, Vaughan D, Lotenfoe R, Dineen M, Brady J. Urol Oncol. 2008, 26:500-5. BACKGROUND: The use of breast sparing surgery, i.e., "lumpectomy", revolutionized management of breast cancer. Lumpectomy confirmed that quality of life issues can successfully be addressed without compromising treatment efficacy. Complications of prostate cancer treatment, including impotence and incontinence, affect the male self image no less than the loss of a breast does a woman. Traditional thinking held that prostate cancer was multifocal and therefore not amenable to a focal treatment approach. Recent pathology literature indicates, however, that up to 25% of prostate cancers are solitary and unilateral. This raises the question of whether these patients can be identified and treated with a limited "lumpectomy" or focal cancer treatment.	Thank you for your comment. This study is included in the main extraction table.

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23	Consultee 3 NHS Professional	**2.3 cont**	CONCLUSION: These preliminary results indicate a "male lumpectomy" in which the prostate tumor region itself is destroyed, appears to preserve potency in a majority of patients and limits other complications (particularly incontinence), without compromising cancer control. If confirmed by further studies and long-term follow-up, this treatment approach could have a profound effect on prostate cancer management.	Thank you for your comment.

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24	Consultee 3 NHS Professional	**2.3 cont**	6- Rationale for a "male lumpectomy," a prostate cancer targeted approach using cryoablation: results in 21 patients with at least 2 years of follow-up. Onik G. Cardiovasc Intervent Radiol. 2008, 31(1):98-106. BACKGROUND: Prostate cancer in men raises many of the same issues that breast cancer does in women. Complications of prostate cancer treatment, including impotence and incontinence, affect the self-image and psyche of a man no less than does the loss of a breast in a woman. We present a pilot study in which 21 patients were treated with a focal cryoablation procedure. CONCLUSION: These preliminary results indicate a "male lumpectomy," in which the prostate tumor region itself is destroyed, appears to preserve potency in a majority of patients and limits other complications, without compromising cancer control. If these results are confirmed by further studies and long-term follow-up, this treatment approach could have a profound effect on prostate cancer management.	Thank you for your comment. This paper has been added to Appendix A of the overview.

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25	Consultee 3 NHS Professional	**2.3 cont**	7- Focal cryosurgery: encouraging health outcomes for unifocal prostate cancer. Lambert EH, Bolte K, Masson P, Katz AE. Urology. 2007, 69(6):1117-20. OBJECTIVES: Owing to the ability to better detect small-volume tumors, we have seen an increasing population of men with low-risk unifocal prostate cancer. We report our safety and efficacy experience of focal cryoablation of the prostate to maintain potency and preserve genitourinary function in men with localized, unifocal disease. CONCLUSIONS: Focal cryoablation of the prostate has exhibited minimal morbidity and promising efficacy in our 3-year observation. Longer follow-up is necessary to determine its role in the treatment of patients with low-risk unifocal prostate cancer.	Thank you for your comment. This study is included in the main extraction table (table 2) of the overview.
26	Consultee 4 NHS Professional	**2.3**	The definition of biochemical disease free survival in this setting is contentious, as the untreated lobe will still produce PSA and setting a cut of of Â 1.0ng/ml or less is very arbitrary. Even use of the Phoenix classification is open to criticism, as benign tissue in the untreated lobe is likely to grow with time causing PSA to rise	Thank you for your comment. The Committee considered this comment in detail and adjusted the text on follow-up to; “After treatment patients are usually followed up regularly with prostate-specific antigen (PSA) measurements, imaging, and repeated biopsies to detect recurrence”.

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27	Consultee 2 Health care Professional	**2.3**	PSA is not a good marker for treatment effect after hemiablation. PSA rise will most likely stem from the untreated side. However, stable PSA is a surrogate endpoint telling that everything is OK. The only way to confirm treatment effect is repeat biopsies with the same number and technique as for entry biopsies. Number of follow-up biopsies from the treated side should be related to prostate volume. The treated half usually shrinks to 25 % of original volume.	Thank you for your comment. The Committee considered this comment and Section 2.2.2 of the guidance has been changed to read follow-up includes 'imaging and repeated biopsies'.
28	Consultee 4 NHS Professional	**2.3**	Agree	Thank you for your comment.
29	Consultee 2 Health care Professional	**2.4**	The COLD registry from US contains data from 1100 focal procedures. I believe these have been published by now. You may ask prof Jones, Cleveland	Thank you for your comment. This paper from this work has been added to the main extraction table (table 2) of the overview.
30	Consultee 3 NHS Professional	**2.4**	No Comment	Thank you for your comment.
31	Consultee 4 NHS Professional	**2.4**	Agree	Thank you for your comment.

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32	Consultee 4 NHS Professional	**2.5**	The Committee should point out that one study in BJUI concluded that primary cryotherapy was the cheapest of treatment options in localised prostate cancer, although I accept that this related to total gland cryotherapy. Nevertheless,the study indicates Â there is a potential for cost saving. Finally, the suppliers of the freezing needles at present only market kits for total gland cryotherapy and half, therefore, have to be discarded at the end of the procedure. Perhaps NICE should recommend, or take up the issue with the suppliers,that they begin to market more limited & cheaper kits suitable for treating one lobe only.	Thank you for your comment. Cost-effectiveness is not part of the remit of the Interventional Procedures Programme.
33	Consultee 2 Health care Professional	**2.5**	Excellent section. A main concern is to reduce the number of radical(over)treatment procedures, and the number of patients receiving hormone treatment after failing radiotherapy without salvage cryoablation being considered	Thank you for your comment.
34	Consultee 3 NHS Professional	**2.5**	No Comment	
35	Consultee 4 NHS Professional	**2.5**	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. Section 2.2 of the guidance has been changed and includes 'imaging' as a method of follow-up. The paper identified is not a clinical study on focal cryoablation and was not considered for inclusion in the overview.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."