

Seminar article

## Focal therapy for prostate cancer: Fact or fiction?

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### Abstract

Prostate cancer is the commonest male cancer diagnosed in men in the UK, and the treatment of organ confined prostate cancer is a subject of much debate. Focal therapy for prostate cancer intends to treat the cancer within the prostate, whilst sparing the majority of the benign prostate tissue. In addition, the intention is to avoid treatment effects in the surrounding structures, the damage of which leads to the side effects commonly associated with radical whole gland therapies. This relies on accurate localization of the prostate cancer by biopsy and imaging followed by treatment using a modality capable of delivery to a focal area within the prostate. Focal therapy lies between the current extremes of radical whole gland treatment and active surveillance. There have been many articles reviewing the concept of focal therapy for organ confined prostate cancer, but with a paucity of data available for analysis. This is being addressed with an increase in the published data on focal therapy, using a number of different modalities. In this review, we address the question of whether the data currently published does in fact support the further development of the focal therapy approach, or whether it is a concept best relegated to the realms of fiction. © 2010 Elsevier Inc. All rights reserved.

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### 1. Introduction

When a man is diagnosed with an organ confined prostate cancer, he is currently faced with a choice between radical therapy and active surveillance (AS). Traditional radical therapies include radical prostatectomy, external beam radiotherapy, and brachytherapy. Radical prostatectomy shows a benefit in disease specific survival and overall survival at 8 years [1]. However, this was in comparison with watchful waiting rather than AS or delayed intervention, which is more commonly practiced now.

Analysis of the CAPSURE 2002 database suggests that 51.6% of men diagnosed with low risk disease were treated with radical prostatectomy between 1999 and 2001 [2]. It has been estimated that the risk of dying of low risk (Gleason 6) screen detected prostate cancer within 15 years, for a man under the age of 70 y, is less than 1%. This model takes into account the lead time associated with screen detected cancers, as well as generational improvements in all cause mortality [3].

It was estimated that there was negligible survival benefit associated with radical treatment in this group of men.

The side effects associated with radical whole gland therapy however, are not negligible. Toxicity associated with surgery includes urinary incontinence and reduction in sexual function, whilst external beam radiotherapy can also cause late effects on the bowel. The impact of these side effects on post-treatment quality of life can be significant [2]. Even with the advent of minimally invasive techniques and robotics, up to 15% of patients have perioperative complications after radical prostatectomy [4]. In addition, continence and potency rates are known to vary widely [4].

The case therefore can be made for the development of an alternative to whole gland radical therapy. AS is one such alternative, where the side effects associated with whole gland treatment are avoided or delayed. It is established that men who are on watchful waiting programs (i.e., intervention with palliative treatment as symptoms require it), experience a deterioration in quality of life as measured by health questionnaires [5,6]. Some studies have shown that men on AS programs suffer negative psychological effects [7–9], although others have not confirmed this [10].

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Concerns of AS include a concern over accurate stratification of risk of progression at diagnosis, which may result in some men with higher risk disease being assigned to a low risk group and offered AS [11]. A Memorial Sloan Kettering series reports men who were deemed suitable for AS on initial biopsy, and chose to have radical prostatectomy. Pathologic whole mount analysis showed 11% to have pathologic T3 disease, and 46% to have Gleason pattern 4, not seen at initial biopsy [12]. Longer term follow-up of men on active surveillance programmes will allow more accurate prediction of local progression and metastatic disease. It has been suggested that whilst progression rates are low in the first 10 years of a watchful waiting cohort, significant disease progression occurs between 15 and 20 years following diagnosis [13]. It remains to be seen whether this will also be true in an AS cohort, who are lower risk group.

With uncertainties in the selection and follow-up of men on AS, many are looking for an approach that could combine the oncologic benefit of treatment of cancer within the prostate, with the benefit to quality of life that comes from preservation of some of the prostate and adjacent structures, such as neurovascular bundles, rectum, urethra, bladder neck, and seminal vesicles. Focal therapy for organ confined prostate cancer is being explored to see if the potential benefits can be realized in clinical application.

Focal therapy requires accurate localization of prostate cancer within the gland. This is usually done with a combination of biopsy and imaging. Different biopsy methods have been assessed for accuracy in comparison to radical prostatectomy whole mount specimens, and it seems likely that some form of three-dimensional mapping, either using a transperineal template, or a flexible transrectal needle (e.g., TargetScan) will be used in the future. It is hoped that this will overcome the random and systematic error associated with a standard transrectal ultrasound guided biopsy.

The best current imaging protocols use multi-parametric MRI, often including dynamic contrast enhancement (DCE), diffusion weighting (DW), with some groups also using MR spectroscopic imaging (MRSI). Some centers use an endorectal coil, whilst others are investigating the potential advantages of a 3 Tesla magnet. It is likely that further refinements in these areas will be important if focal therapy for prostate cancer is to become a therapeutic option in the future. As the issues of localisation of prostate cancer using imaging and biopsy have been discussed extensively elsewhere [14–17], we have not addressed them in full in this article.

## 2. Focal treatment of prostate cancer

If it is established that prostate cancer can be accurately characterized and localized within the gland, the next challenge for focal therapy is to treat that cancer. This can be done using a number of different modalities. Some have suggested that it would make most sense to use a modality

that is already well established in the treatment of cancer. However, focal treatment using a surgical approach is not feasible because of the technical difficulties in accessing the prostate gland. External beam radiotherapy, with modifications such as intensity modulation, could be used to treat one area whilst sparing another, but has not been considered for this. Focal treatment is technically much more straightforward with seed brachytherapy. One study used MRSI to identify prostate cancer within the gland, and gave this volume a radiation boost dose (130%); the remainder of the prostate was, however, also treated, excluding this from analysis as a focal treatment [18].

## 3. What tools are available to treat prostate cancer in a focal manner?

### 3.1. Cryotherapy

Cryotherapy has been used in the treatment of prostate cancer for a number of years, and has been available using a transperineal approach since the early 1990s. Tissue destruction is caused by very cold temperatures that destroy tissue via a number of mechanisms (direct cytolysis via ice crystal formation, intracellular dehydration, pH changes, vascular injury, induction of apoptosis, and activation of immune response). Endothelial damage leads to platelet aggregation and microthrombosis. It is usual to use at least 2 freeze thaw cycles of 3 min freezing at  $-40^{\circ}\text{C}$ , to eradicate tumor.

The cryotherapy probes are inserted with the aid of transrectal ultrasound, often using a transperineal template. The advent of third generation gas based probes, with urethral warming and other technical modifications, which can include hydrodissection of the space between rectum and Denonvilliers fascia, have led to a reduction in the morbidity associated with whole gland cryotherapy [19,20].

Whole gland cryotherapy has follow-up data that extends to 10 years in some [21]. This group report biochemical disease-free status (BDFS) survival according to the Phoenix criteria of 80.56%, 74.16%, and 45.54% for low, intermediate, and high risk groups, respectively. The dependence of BDFS on the original risk stratification is confirmed by other groups, with the greatest rates of BDFS in men with low risk disease [22,23]. El Hayek et al. use a PSA threshold of 1 ng/ml, which other authors would consider high [23]. Using this threshold, 80% of men in the low risk group had BDFS at 48 months, compared with 42.8% in the high risk group. They report a 13% incontinence rate and no cases of rectal injury.

Analysis of a larger population of 1,198 men in low, intermediate, and high risk groups in the COLD registry [24] showed 84.7% 5 year BDFS for low risk men, compared with 73.4% and 75.3% for intermediate and high risk groups, respectively. When the same data are analyzed according to the Phoenix definition of BDFS, the figures are

91.15, 78.5%, and 62.2% for low, intermediate, and high risk groups. Biopsy done without cause was positive in 30 of 207 patients (14.5%), but in those men biopsied for a suspicion of treatment failure, i.e., abnormal or increasing PSA, biopsy was positive in 49 of 129 men (38%). This would give an overall positive biopsy rate of 79/336 (23.5%) in those men who underwent biopsy.

Onik was the first to report the use of cryotherapy as a tool for focal ablation of prostate cancer when he proposed 'the male lumpectomy' [25]. Since then, the clinical database of men receiving focal cryoablation has been developed, albeit with variation in the definition and extent of focal ablation (Table 1). Onik reports results of 48 men with at least 2 year follow-up [26], with 94% of men having stable PSA according to ASTRO criteria, and biopsies negative for cancer in all 24 men who underwent routine biopsy. In addition, all men were continent, and 36 out of 40 men maintained potency to their satisfaction. Another report by Onik details the results of focal cryoablation in 55 men [27]. It is not clear whether men have been included in each of the reported groups, or whether they are distinct cohorts.

An update on this data presented at the Society of Interventional Radiology (SIR) 34th Annual Scientific Meeting showed results for 120 men, with stable PSA in 112 men (93%) and potency rates of 85% [28].

Lambert and colleagues report 3 year outcomes for a cohort of 25 men who underwent focal cryoablation for primary unifocal prostate cancer [29]. Treatment typically comprised a hemiablation, using 4 probes in 1 lobe. Men with a PSA of >1.0 ng/ml or a nadir + 2 ng/ml underwent biopsy. In 7 of the 25 men who underwent biopsy, 2 men had prostate cancer in the untreated side, and one had cancer in the area of previous cryosurgery. Repeat cryosurgery rendered each of these 3 men biochemically free of disease, although further biopsy status is not reported. Interestingly, the definition of biochemical failure was determined as a PSA nadir to 50% of the pretreatment level according to this definition, 84% of men did not experience biochemical failure. The authors justify this use of an alternative PSA endpoint because of the intentional preservation of 1 complete lobe of the prostate.

In terms of morbidity, 17 men remained potent, with no patients reporting worsening lower urinary tract symptoms, incontinence, rectal pain, sloughing, or fistula formation. These data are encouraging, however, it does not seem that data was collected using recognized health outcomes measures.

Bahn et al. also report data from a cohort of 31 men with unilateral disease on biopsy, who underwent primary focal cryoablation [30]. In this group, focal treatment is defined as less than complete ablation, with particular attention to the

Table 1  
Summary of published work using cryotherapy as a focal prostate cancer treatment

	Onik 2008 [26]	Onik 2007 [27]	Lambert 2007 [29]	Bahn 2006 [30]	Ellis 2007 [32]	Dhar 2009 [34]
Number of patients	48	55	25	31	60	795
Mean preoperative PSA	7.8		6	4.95	7.2	<4 (17%) 4–10 (69%) 10–20 (10%) >20 (3%) ? (1%)
Gleason score			6 (52%) 7 (48%)	5 (9.8%) 6 (64.5%) 7 (25.8%)	6	<6 (33%)  6 (41%) 7 (19%) 8 (4%) 9 (2%)
T stage			T1c		T1c	<T2b=90% ≥T2B=10%
Risk stratification						
Low	48%	47.3%	100%		66.7%	47%
Medium	37.5%	36.4%	0%		23.3%	43%
High	14.5%	16.3%	0%		10%	11%
Focal treatment	Focal/NS	Focal/NS	Hemablation	Less than complete ablation	Focal/NS	?
Mean follow-up (months)			28	70	15.2	12
Failure criteria	ASTRO	ASTRO	Greater than 50% PSA nadir	ASTRO	ASTRO	ASTRO+PHOENIX
% failure	6%	5%	12%	7.2%	19.6%	
Biopsy rate	24/48=50%	26/55=47%	7/25=28%	25/28=89%	35/60=58%	198/795=25%
Positive biopsy rate	0/24	0/26	3/7	24/25	14/35	36/198
Positive biopsy rate in whole cohort	0/48	0/55	3/25	24/28	14/60	36/795=4.5%
Potency rate	90%	85%	71%	88.9%	70.6%	65%
Continence rate	100%	100%	100%	100%	96.4%	97.2%

concept of nerve sparing cryoablation reported by Onik [25,31]. At a mean follow-up of 70 months BDFS according to the ASTRO definition is 92.8% with a 96% negative biopsy rate (24/25 men). One man had a positive apical biopsy on the untreated side, and underwent whole gland cryoablation, with biochemical and clinical disease-free status at the time of the report. Potency was assessed by patient completed questionnaires (modified version of the Brief Male Sexual Function index), and showed maintenance of potency in 13/27 men (48.1%), with a further 11 men potent with oral pharmaceutical assistance giving an overall rate of 88.9% (24/27 men). No complications were reported, although it is noted that incontinence is reported as any leakage of urine 3 months after treatment, rather than at any time point post-treatment.

The group from Texas report their results of focal cryoablation followed by penile rehabilitation using a vacuum device, in 60 men [32]. As with their report of primary whole gland cryotherapy [33], men were encouraged to use the vacuum device on a regular basis following cryosurgery. In the focal treatment group, all men lost potency immediately after the procedure. However, at 6 months, 22 of 36 men had regained potency (with or without pharmaceutical assistance), and at 12 months, 24 of 34 men (70.6%) had potency according to the same definition. This compared very favorably with a return to potency rate of 29.1% in men who underwent whole gland cryoablation by the same team. It should be noted, however, that in the whole gland treatment group with longer follow-up, potency did return at later time points with 51.3% potency at 4 years.

An analysis of the COLD registry looking at focal treatment only showed 795 men with a median of 1 year follow-up [34]. They report that 65% (87/134) of men were sexually active at 1 year post-procedure, with a 2.8% incontinence rate. Three rectal fistulae (0.4%) were reported between 3 and 12 months postoperatively. Men underwent prostate biopsy if postprocedure PSA was suspicious or rising. Thirty-six men had biopsies positive for cancer, which represented 25% of the men who were biopsied, or 4.5% of the whole cohort.

In summary, it seems that a ‘less than whole gland’ approach either with subtotal cryoablation with unilateral nerve sparing or hemiablation can, in selected men, offer good cancer control with significant improvements in morbidity compared with whole gland treatments (see Table 1).

### 3.2. High intensity focused ultrasound (HIFU)

A high energy density generated into a tight focus by ultrasound causes tissue destruction. Therapeutic HIFU uses a frequency of between 0.8 and 3.5 MHz, causing heating and “inertial cavitation.” Tissue damage can occur when the temperature is raised to 56°C for at least 1 second. Coagulative necrosis results with a subsequent inflammatory response. In prostate HIFU, temperatures are typically above

80°C. Two transrectal devices for prostate cancer treatment currently exist: the Sonablate 500 (Focus Surgery, Indianapolis, IN) and the Ablatherm device (Edap-Technomed, Lyon, France).

As with cryosurgery, it is important that this ablative technology demonstrates good short- to medium-term efficacy for whole gland treatments prior to its use as a focal modality. A recent report of whole gland HIFU therapy using the Sonablate 500 device has shown potency rates of 70%, with mild stress urinary incontinence, without pad use, in 12/172 (7%), with a 1/172 (0.6%) using pads [35]. No fistulae were seen, and there was no rectal toxicity; 78.3% achieved a post treatment nadir of 0.5 mcg/ml or less, with 57.8% achieving a nadir of 0.2 mcg/ml or less. No evidence of disease (NED) was reported as either a nadir less than 0.5 mcg/ml, or a negative biopsy in the presence of a higher nadir. NED was seen in 159 out of 172 patients after one HIFU treatment.

A report from another center, using the Ablatherm device, in which 31 men were given primary HIFU treatment over a 3 year period was recently reported [36]. Using the same criteria of PSA success as Ahmed’s group (that defined by the Food and Drug Administration of a nadir of 0.5 ng/ml or less), 75% of men failed. In addition, 2 urethral strictures were seen in the primary group (7%). The paper also reports 2 prostatic fistulae, but this was in the group of 12 men who underwent salvage treatment after failed external beam radiotherapy, rather than primary HIFU. The authors concluded that their HIFU program had been suspended pending further evidence of safety and efficacy, although this has strategy has been questioned as the series represented the early learning curve.

Longer term results, with prototype or first generation Ablatherm devices in men with low to intermediate risk disease are reported by Blana and colleagues [37]. A group of 140 men were treated between October 1997 and August 2001. Mean follow-up was 6.4 years, with negative biopsies in 86.4% of men and PSA nadir of 0.5 ng/ml or less in 68.4%. Actuarial BDFS rates using the Phoenix criteria were 77% and 69% at 5 and 7 years, respectively.

HIFU is well suited to focal treatment in the prostate, and has been developed for this by a number of groups.

Muto et al. report HIFU results from a cohort of 70 men who had focal ablation using the Sonablate 500 device. In 29 men with unilateral cancer defined by multiregional biopsies, the entire peripheral zone and half of the transitional zone were ablated; in the remaining 41 men, whole gland ablation was performed [38]. Scheduled biopsies were done at 6 and 12 months. Twenty-five out of 28 men who had focal therapy had negative biopsies at 6 months; with 13 out of 17 having negative biopsies at 12 months. Time of indwelling catheter was significantly reduced in the focal therapy group compared with the whole gland group. Stricture and symptomatic urinary tract infection were also higher in the whole gland therapy group (8.6% vs. 4% for stricture and 11.4% vs. 4% for infection). There was a

difference in the BDFS according to ASTRO criteria in men with high risk disease when compared with men with low risk disease. Interestingly, there was no statistical difference between the whole gland and focal therapy groups (around 50% at 12 months). This lack of difference may be due to the fact that some men had hormone treatment prior to treatment, and others chose to continue on hormone treatment after a positive post treatment biopsy. Longer term follow-up of this would, of course, be valuable.

Barret et al. report a series of 12 men who have undergone hemiablation with Ablatherm HIFU, with 2 men having died from other causes. No evidence of disease is reported as 58% at 10 years. This report was presented as a poster, and, to our knowledge, a paper has not been published from this cohort. The exact nature of the focal therapy is not fully explained. Four of the 12 men had intermittent hormone therapy for a rising PSA [39].

Ahmed and Emberton have presented interim results from 2 prospective ethics committee approved HIFU focal therapy studies, using the Sonablate 500 device, measuring early toxicity outcomes with validated questionnaires. Interim results presented at the EAU 2009 annual conference as well as at the Focal Therapy conference in Amsterdam demonstrated absence of cancer in the treated areas in 33/37 (86%) of men (negative prostatic biopsies at 6 months) with return of erectile function sufficient for penetration and a pad-free urinary continence rate of 95% [40,41,42].

In summary, whilst variable results have been presented by different groups with whole gland HIFU, it is well suited to the delivery of focal treatment for prostate cancer. Ongoing studies with different definitions of focal treatment are due to be reported fully in the near future, which will clarify the place of HIFU in this field.

### 3.3. Photodynamic therapy

Photodynamic therapy (PDT) uses a photosensitizing drug, which is activated by low power laser light of a wavelength specific to the photosensitizing drug. The activated drug reacts with tissue oxygen to form reactive oxygen species, which are responsible for localized necrosis around the light delivery fibre.

For prostate cancer treatment, the photosensitizer can be given intravenously or orally. Light delivery fibers are placed in the prostate within hollow plastic needles, using a brachytherapy style perineal template and transrectal ultrasound. The photosensitizing drug can either be activated whilst in the vasculature [e.g., palladium bacteriopheophorbide photosensitisers, Padoporfin and Padeliporfin, Steba Biotech, The Hague, Netherlands] or whilst in the tissue [e.g., mesotetrahydroxylphenyl chlorine (mTHPC, Foscan, Lab Biolitec Pharma Ltd., Dublin, Ireland), or amino levulinic acid (ALA)].

PDT is being evaluated as a treatment for organ confined prostate cancer, as a whole gland or a focal therapy treatment. The first clinical report of PDT was in 1990 by

Windahl and colleagues [43]. Two men received PDT with a hematoporphyrin photosensitizer, after a 2-stage TURP. One man died of previously undiagnosed lung cancer 6 months later, and post mortem examination showed no evidence of disease. The second person had a post-treatment biopsy at 3 months, which was negative for cancer.

The next clinical study was a report of PDT using mTHPC in post-radiotherapy recurrence [44]. This feasibility study used a variety of imaging and needle techniques, and monitored post-treatment effects with MRI and PSA, as well as biopsy.

The same group reported a small series of 6 men with previously untreated prostate cancer who underwent focal treatment with mTHPC PDT during the same period [45]. Each treatment was designed to treat biopsy positive areas, along with the peripheral zone of the same lobe. Four men underwent repeat treatment after positive biopsy after 3 months. The photosensitizer used is activated 3 to 5 days after administration, and can be activated in the skin by strong outdoor or indoor light for some weeks afterwards. This necessitates skin and eye protection measures to reduce light exposure in the weeks following drug administration. The procedure was well tolerated on the whole, with 1 procedure of 10 resulting in an episode of urinary sepsis, which required intravenous antibiotics, and no episodes of incontinence or rectal toxicity. The PSA fell by up to 67%, and post-treatment imaging showed evidence of necrosis, although this was patchy in some treatments. Biopsies of treated areas revealed necrosis and fibrosis. Light delivery was done using a combination of cylindrical diffusers and bare ended fibers, with needle placement done in an interventional MR scanner for some patients, and with TRUS guidance for others. With improvements in pre- and post-treatment characterization with both biopsy and MRI, along with developments in needle placement techniques, light delivery apparatus, and photosensitizers, these results do not reflect the current work ongoing in the field.

Vascular targeted photodynamic therapy (VTP) uses a photosensitizer activated a few minutes after administration, whilst still in the vasculature of the prostate. A class of drugs known as palladium bacteriopheophorbide have been developed for use in prostate cancer. The initial version of the drug (Padoporfin, WST-09, Tookad) was used as a salvage treatment for local recurrence after radical radiotherapy in a study in Canada [46–48]. This showed that VTP effect could be evaluated on 1 week post-VTP MRI, and that areas of nonenhancement on MRI at 1 week correlated with negative 6 month biopsies. This group determined that complete response required a light dose of 23J/cm to 90% of the prostate volume, and that, 8/13 men who had received this light dose had negative biopsies at 6 months.

The same photosensitizer was also used in a group of men in the primary treatment setting. Many of the men in the initial study were in a dose escalation phase, and full

results are awaited, although some data has been represented at conferences.

A newer version of the photosensitizer has been developed (Padeliporfin, WST-11, Tookad Soluble), and this is currently in multicenter trials in men with low risk prostate cancer, in Europe and the USA.

#### 4. Conclusion

Technological developments have enabled the concept of focal therapy for prostate cancer to be explored in clinical studies. Whilst early work with a number of different modalities shows promise in terms of oncologic efficacy and reduction in morbidity, it is essential for further development in this field that future studies ensure careful pre- and post-treatment characterization of the prostate in terms of biopsy and imaging, as well as PSA kinetics, and that post-treatment toxicity and efficacy are meticulously reported.

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