Focal High Intensity Focused Ultrasound in the Treatment of Non-Metastatic Prostate Cancer

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I, Stephanie Guillaumier, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract (290 words)

Introduction

This thesis will explore the adverse events, side-effect profile and efficacy of high intensity focused ultrasound to treat non-metastatic prostate cancer. I will look at the background of prostate cancer and how advances in the diagnostic pathway for prostate cancer, as well as the paradigm shifts in treatment for this disease, have defined the current treatment landscape for localized prostate cancer and how focal therapy fits in.

Objectives

The aim of this thesis is to evaluate the efficacy and medium-term outcomes of focal HIFU from a multicentre registry of over 600 cases treated over the last 10 years in the UK. In so doing, this thesis will explore the use of registries in defining novel treatments as a useful body of evidence that might be used to impact on standard care in the absence of randomized controlled studies which are difficult to conduct within surgical specialties. The future role of focal therapy and high intensity focused ultrasound will be discussed, providing insights into the evolution of this ablative therapy, and how it might take its place within the armamentarium of treatments available for localized prostate cancer.

Results

The multicenter academic focal HIFU registry demonstrates acceptable oncological control in men diagnosed with non-metastatic prostate cancer is achievable with acceptable o

Conclusions

The medium-term data presented in this thesis is the first of its kind and supports the contention that focal therapy has a role in decreasing the genito-urinary side-effects associated with standard whole-gland therapies. Trifecta status of leak-free, pad-free continence, erections sufficient for intercourse, and oncological control is achievable with focal HIFU with acceptable results. Ultimately, long-term data will be necessary, including

research into comparative effectiveness to further establish the future role of focal therapy in treating localized prostate cancer.

Impact Statement

This thesis will make available data supporting the use of focal High Intensity Focused Ultrasound for treatment of non-metastatic prostate cancer. It will provide medium-term evidence of the functional and oncological outcomes from focal HIFU that will help promote this novel technique within the armamentarium of treatment options that are available for non-metastatic prostate cancer. Patients will have an alternative to the two extremes that are active surveillance and radical therapy. However, this data set needs maturation, and long-term outcomes are required, both from this dataset, and from other centres, before this treatment modality can become standard practice for the treatment of non-metastatic prostate cancer. Data in this thesis will also show that dissemination of delivering focal HIFU to units other than tertiary centers is possible, making focal HIFU a more widely available treatment option.

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Chapter 1

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INTRODUCTION

Chapter 1 – Introduction

1.1 The Natural History of Prostate Cancer

Prostate cancer is the most frequent solid tumour among men, the second most common type of cancer in the UK, and accounts for 13% of all new cancer cases in the UK (2014).[1] The introduction of formal and informal screening practices over the last three decades has led to an increase in prostate cancer incidence by about 50%.[2] Currently in the UK, one in eight men will be diagnosed with prostate cancer during their lifetime, and the incidence rates of prostate cancer are projected to rise by 12% between 2014 and 2035.

The natural history of prostate cancer has not yet been fully clarified. However, it is thought to arise from abnormal prostate epithelium resulting from genetic and environmental factors, and progressively develops over many decades into malignancy.[3] The understanding of this disease progression is further complicated by the fact that prostate cancer is known to be heterogeneous and multi-focal. Autopsy studies have revealed that about one-third of men over the age of 50 years display histological evidence of prostate cancer. The majority of these cases exhibit clinically insignificant disease, showcasing the variability and the protracted course of prostate cancer. Some patients live with prostate cancer that remains stable for decades, without treatment. In others, the cancer is aggressive, responds poorly to treatment and can cause death within a few years.[4] Therefore, the likelihood of disease progression is often difficult to predict in the majority of patients. However, high-grade tumours are more aggressive than low-grade, well-differentiated tumours,[5] with the Gleason score being one of the most powerful prognostic predictors of prostate cancer.[6]

1.2 The Diagnostic Pathway of Prostate Cancer

There is no formal screening test used for prostate cancer. A screening test is an investigation or procedure performed on members of a defined asymptomatic population or population subgroup to assess the likelihood of

their members having a particular disease. There are various criteria that screening tests should meet, as set out by Wilson and Junger.[7] Most screening tests do not diagnose the illness. Subjects who test positive generally undergo further evaluation with subsequent diagnostic tests or procedures.[8] The major objective of most screening tests is to reduce morbidity or mortality in the population group being screened for the disease by early detection and where treatment may be more successful. An ideal screening test must be one that is acceptable to patients, preferably non-invasive and not unpleasant to undergo. It should be cost-effective and practical to be used widely as a screening test. Ideally, it would have a positive result if and only if the subject actually has the disease and a negative result if and only if the subject did not have the disease. Most screening tests are unable to reach these criteria and most exhibit false positives and false negatives to varying degrees.[8] Screening tests are normally compared to a 'gold standard', which in itself is the definitive diagnostic.[9] There is, to date, no screening tool for prostate cancer that meets these criteria.

Precise and accurate risk classification of patients with localized prostate cancer is essential for determining the correct management.[10] The current diagnostic pathway results in over-diagnosis and over-treatment.[11] Hence many healthcare systems have rejected the use of formal screening programs.[12,13] Recent randomized controlled studies (RCTs) have not shown improved overall survival from screening. The European Randomized Study of Screening for Prostate cancer (ERSPC) was a multicentre European study allocating men to either screening or standard practice. This study demonstrated a 21% decreased risk of death from prostate cancer for men undergoing screening, at least after 11 years of follow-up.[14] Further, the Prostate Cancer Intervention Versus Observation Trial (PIVOT) whilst showing no overall benefit in treating localised prostate cancer, did show the benefit of surgery compared to watchful waiting in intermediate and high risk disease.[15] This data was previously supported by the Prostate Cancer Group-4 study from Scandinavia, which recruited men diagnosed

clinically, without PSA testing, and therefore represented a much higher risk cancer population. The results showed survival benefits in treating with surgery over watchful waiting, albeit an absolute survival advantage at 10-15 years of 5%.[16] The recent Prostate Testing for Cancer and Treatment study (PROTECT), which was dominated by low risk cancer cases, showed no overall or cancer specific survival advantage of surgery or radiotherapy compared to active monitoring although there was a decrease in metastases from treating such men. In so doing, treatment can positively impact on the natural history of the disease, provided physicians treat men with clinically significant cancer who are likely to survive at least another 10 years were it not for the prostate cancer, by halting disease progression.[17] The critical aspect is for accurate risk stratification of disease at the time of diagnosis. However, the current pathway does not allow for accurate determination of clinically significant prostate cancer from clinically insignificant prostate cancer or indeed, the absence of cancer.[18]

So, according to recent level 1 evidence, men diagnosed with low-risk disease can be managed safely with active surveillance and require no immediate treatment whereas those with intermediate- or high-risk would benefit from radical active treatment.[19,15,16] However, inaccurate risk classification of prostate cancer inevitably leads to overtreatment along with its adverse impact on quality of life in those that have true low-risk disease, and undertreating those with clinically significant disease thus potentially missing the window of cure.[20]

Whilst a surveillance approach offers minimal treatment-related harm, it may confer a psychological burden and a delay in radical treatment.[21] In contrast, radical therapies are well known to come with significant morbidity and a decrease in quality of life.[22] Focal ablative strategies have the potential to offer the middle course between these two extremes: they decrease the risk of disease progression that may occur with active surveillance and provides a lower rate of genito-urinary morbidity than

radical treatment, the evidence of which is further discussed in Section 1.4.2.2.

The current diagnostic strategy involves deploying 10-12 core needles into the prostate with a transrectal approach one by one in a fairly random manner in the hope of hitting significant cancer. It misses important cancer, miss-classifies unimportant as important and vice versa and finds cancer that is indolent and should not be treated but often is due to patient anxiety and physician advice.[23,24] The recent Prostate MR Imaging Study has shown that using mpMRI to triage men will allow 27% of men to avoid unnecessary prostate biopsy and diagnose 5% fewer clinically insignificant disease.

As a result, the inaccuracies from the standard 10-12 core transrectal ultrasound guided (TRUS) biopsies are too great to allow reliable, effective and complete ablation of clinically significant disease with focal therapy. Therefore, changes in the diagnostic pathway are necessary to increase the accuracy of disease localization and characterization within the prostate gland, mainly by the introduction of transperineal prostate biopsies and multiparametric MRI.

1.2.1 Imaging

Magnetic resonance imaging (MRI) in the detection of localized prostate cancer has only recently been incorporated into the clinical diagnostic pathway for prostate cancer in a number of centres in the UK. The ability of MRI to detect, localize and characterize cancer lesions within the prostate was limited until the introduction of multiparametric MRI (mpMRI) which combines a variety of sequences: T1-, T2-weighted images, dynamic contrast (DCE), diffusion weighted imaging (DWI) and/or MR proton spectroscopy imaging (MRSI).[25,26,27,28,29]

Crucial to focal therapy is the detection of clinically significant prostate cancer by mpMRI. Over the past decade, an increasing body of evidence has shown that mpMRI provides the best visualization of the prostate compared

to other imaging modalities, mainly due to the high resolution, high soft-tissue contrast and the ability to image functional parameters simultaneously.[30] These advances in imaging technology have led to a paradigm shift in the diagnosis and treatment of localized prostate cancer. MRI is no longer used solely to stage prostate cancer, but has shifted its role to detection, localisation and characterization of prostate cancer.

Multiparametric MRI allows for accurate detection of larger and high-grade tumours. Therefore, clinically significant tumours are more reliably diagnosed.[28] The functional techniques employed by mpMRI may be used to differentiate between low and intermediate/high-grade prostate cancer.[31,32,33,34] Futterer *et al* carried out a systematic review which revealed a wide variation between studies in the positive predictive value (PPV) of mpMRI (the ability to detect clinically significant disease) of between 34% to 68%.[30] Nonetheless, mpMRI allows for decreased detection of indolent disease and the ability to rule out clinically significant disease[19] - the negative predictive value (NPV) of mpMRI - was found to vary between 63-98% in this systematic review, with most near the upper end of that range. This helps the problem of over-diagnosis and over-treatment in the current diagnostic pathway of prostate cancer. The overall accuracy, sensitivity and specificity ranges between 44-87%, 58-96% and 23-87% respectively, with lower values often being historical series.[30]

In summary, mpMRI improves the process of accurate risk stratification[35] and selection of appropriate candidates for active surveillance,[36] as well as focal therapy. It therefore also improves the decision making process of treatment for localized prostate cancer. To this end, a recent study by Turkbey *et al* has shown that mpMRI is superior to the Epstein, D'Amico and CAPRA scoring systems at assigning patients correctly to active surveillance or active treatment when they compared these classification systems to the gold standard of whole-mount radical prostatectomy. Of 133 patients, 14 were eligible for AS on the basis of the prostatectomy specimens. The sensitivity, PPV and overall accuracy were 93%, 25% and 70%, respectively,

for the D'Amico system, 64%, 45%, and 88% for the Epstein criteria, and 93%, 20%, and 59% for the CAPRA scoring system for predicting AS candidates, while mpMRI had a sensitivity of 93%, PPV 57%, and an overall accuracy of 92%.[37]

Improvement in MRI interpretation and detection of disease relies heavily on correlation with a reference test that is accurate, like whole-mount histopathology or transperineal mapping biopsies.[38,39,40,41] There is a growing body of evidence showing that tumour detection increases with tumour size[40,42,43,44] and grade.[43,44] Le *et al* carried out a study on 122 men who underwent mpMRI before radical prostatectomy. This demonstrated that mpMRI performed well for higher grade and larger tumours with a sensitivity of 72% for Gleason $\geq$7 or >1.0cm in maximal diameter. The positive predictive value was 75%. The index lesion was detected in 80%. Size and index tumour status were the strongest predictors of tumour detection. MRI sensitivity increased for higher-grade tumours, however 28% of Gleason $\geq$7 and 28% of tumours >1cm in diameter were missed.[38] In contrast, results from the PROMIS study demonstrate that the sensitivity for mpMRI was 93%, specificity 41% when referenced against transperineal template biopsies, with a positive predicative value (PPV) of 51% and negative predictive value (NPV) of 89%. This was vastly better than TRUS biopsy that was also applied to the same group of men in this study, with a sensitivity of 48% and a NPV of 74%. Therefore, mpMRI can be used as a triage test to identify one quarter of men who can safely avoid unnecessary prostate biopsy without decreasing the detection of clinically significant disease.[45]

Many concerns have arisen with regards to the variation in the interpretation and reporting of mpMRI. A similar situation was seen with reporting of x-ray mammography and breast MRI,[46,47] resolved by establishing a series of recommendations for both modalities. In a similar manner, a European consensus meeting was held with recommendations being recognized for the detection, localization and characterization of prostate lesions, in an attempt to eliminate inconsistencies in reporting

performance characteristics of mpMRI. The panel agreed that the range of scores for detecting the presence or absence of cancer should be 1 through 5. Panel members agreed the following:

- Score 1, indicates clinically significant disease is highly unlikely to be present
- Score 2, clinically significant cancer is unlikely to be present
- Score 3, the presence of clinically significant cancer is equivocal
- Score 4, clinically significant cancer is likely to be present
- Score 5, clinically significant disease is highly likely to be present

These scores should be used for each imaging type (T2-weighted, diffusion-weighted, contrast-enhanced and MR spectroscopy sequences). The maximum diameter of the largest abnormal lesion should be noted. The individual lesions and areas of the prostate should be separately scored for probability of malignancy. The expert panel also recommended that for optimum reporting, the mpMRI should be scored by two radiologists.[25] These recommendations will allow for a more consistent approach to mpMRI reporting.

1.2.2 Prostate Biopsy Strategies

Prior to discussing the various strategies available to biopsy the prostate gland, is it important to first define clinically significant prostate cancer. Determining this definition has, to date, been fraught with difficulty, given that the standard test used is TRUS biopsies, which are now widely regarded to be imprecise. Hence, controversy still surrounds this issue.

Secondly, the implication is that the true prevalence of prostate cancer is still unknown.[18] The rates of disease prevalence have used cystoprostatectomy specimens, calculated at 20% to 30% overall. Of these, around a fifth had Gleason pattern 4 or greater and/or cancer volume of 0.5ml or greater (4% to 6% overall).[48,49] However, we must take into account the narrow age range, since these figures are based on the men

eligible for surgery for bladder cancer who also had their prostates removed. Autopsies have also been used to determine prevalence of significant disease. However, variations in specimen processing as well as age and ethnicity resulted in a wide spectrum of estimates between 6% and 42.6%.[11,50,51] The true prevalence can only be estimated by using a large cohort of men undergoing an accurate test, such as transperineal prostate biopsies. To this end, Valerio *et al* carried out a multicenter study where the prevalence of clinically significant prostate cancer was investigated according to different histological thresholds that are often used to distinguish clinically significant from insignificant prostate cancer. Of 1203 men, 17% had no previous biopsy, 38% had prior negative TRUS biopsy, 24% were on active surveillance and 21% were seeking risk stratification. Overall, 35% had no cancer detected. 29% had clinically significant disease according to University College London (UCL) definition 1 (dominant Gleason 4 or more or maximum cancer core length of $\geq$ 6mm) and 44% according to UCL definition 2 (any Gleason 4 or 5 or a maximum cancer core length or $\geq$ 4mm). This study showed that approximately 1 in 3 to 1 in 2 men undergoing TPM had prostate cancer that met current histological thresholds to define clinically significant disease. It has made clear that template biopsies allows for a better stratification of cancer risk as it samples the whole prostate in a systematic manner. This is further discussed in section 1.2.2.2.

1.2.2.1 Trans-rectal Ultrasound Biopsies

The standard care of the current diagnostic pathway offers transrectal ultrasound (TRUS) prostate biopsies. It remains the most common biopsy strategy employed by urologists. It evolved from digitally-guided TRUS biopsy described by Astraldi in 1937, to the sextant biopsy method described by Hodge *et al* in 1989.[52]

TRUS biopsies are performed by randomly deploying 10-12 needles in order to obtain prostate samples. This procedure is blind to the location of the cancer.[20] It is widely accepted that TRUS biopsies carry significant

imprecision leading to errors of under diagnosis and over diagnosis within the pathway. Standard 12-core TRUS biopsies have several limitations and often miss anterior, midline and apical tumours,[53,48] and are therefore not an adequate mode of disease localization, which is key to focal therapy planning. TRUS biopsies lack sensitivity due to the random and systematic errors involved.[54] If cancer is detected in this mode, the correct risk attribution is possible only in approximately 50%.[55,56] Indeed, at least a third of men are incorrectly classified by Gleason grade at diagnosis and up to 50% are given the incorrect disease burden.[57,58] This biopsy strategy results in incorrect risk stratification of prostate cancer at the diagnostic stage.

The use of effective local anaesthesia with 1% or 2% lidocaine given via the periprostatic block prior to taking TRUS biopsies, has led to the development of extended and saturation biopsies. This involves taking 18 or 20 cores of prostatic tissue in a systematic manner, respectively. This concept emerged in an attempt to increase the accuracy of detection of tumour within the gland. Data produced by several studies looking into this concept show that extended biopsies do not produce a statistically significant benefit.[59] The role of extended and saturation biopsies might have to be reconsidered in light of the emerging advances in mpMRI and targeted, image-guided biopsies.

1.2.2.2 Transperineal Template Mapping Biopsies

Transperineal template mapping biopsies (TPM) have gained significant momentum and are now more widely available, mainly thanks to the recent increase in available evidence on their diagnostic accuracy against a good reference standard such as radical prostatectomy.[18] Transperineal template mapping biopsies involve deploying the biopsy needle using a 5mm transperineal template grid mounted on a stepper using a biplanar ultrasound probe. At least one core is taken at every 5mm of the prostate gland. This method has several advantages over TRUS biopsies. The 5mm brachytherapy grid allows systematic sampling of the prostate and has easy

access to areas commonly missed by TRUS biopsy, namely anterior, midline, anterior horn of peripheral zone and apical tissue. This systematic sampling provides three-dimensional representation of location, volume and extent of the disease. Since TPM biopsy is performed in the lithotomy position, which is often the same position for subsequent focal therapy, the co-ordinates obtained are often used to target treatment.[60]

Most are agreed that transperineal template biopsies allow for more precise disease location.[61,62,63,64,65] Several studies have been published to this effect. Lecornet *et al* performed computer simulation studies comparing standard TRUS with 6 cores, optimized TRUS biopsy with 14 cores and TPM.[65] Standard TRUS missed 47% of lesions 0.5ml or greater and 79% of those measuring 0.2-0.5ml. Another simulation study, by Hu *et al*, reconstructed three-dimensional computer models of whole-mount specimens. A total of 656 foci were reconstructed, of which 149 foci were $\geq$0.2ml and 97 $\geq$0.5ml. This study demonstrated that overall, the accuracy of TPM shown by the area under the receiver operative curve (AUC) was 0.90 as compared with AUC of 0.70-0.80 for TRUS biopsy. At best, TRUS biopsy missed 30-40% of lesions $\geq$0.2ml and $\geq$0.5ml whilst TPM missed 5% of such lesions.[66] Similarly, Crawford *et al*'s study using TPM and a 5mm sampling frame demonstrated 95% sensitivity and 30% specificity in detecting 0.5ml lesions.[67] Ahmed *et al*'s study demonstrated that the total cancer core length from all positive biopsies for a particular lesion that detected more than 95% of lesions 0.5 ml or greater and 0.2ml or greater, was 10mm or greater, and 6mm or greater, respectively.[54] These studies show that TPM is an effective method of stratifying risk appropriately and accurately in men with localized prostate cancer.

Two classifications have been generated specifically for defining clinically significant disease from transperineal biopsies: the Ahmed/UCL and the Marzell-Melamed classifications.[54,68] These classification systems combine the maximum cancer core length (MCCL) and overall Gleason score, and the Barzell-Malamed definition also uses the number of positive biopsies.

Definition 1 of the Ahmed/UCL criteria includes high-risk cancer and assumes clinically significant disease with a volume 0.5ml or greater and/or primary Gleason 4 or greater with a MCCL of 6mm or greater. Definition 2 includes high risk and intermediate risk cancers, and assumes clinically significant disease with a volume of 0.2ml or greater and/or secondary Gleason 4, with a MCCL of 4mm or greater. The volume thresholds of 0.5ml and 0.2ml used in definitions 1 and 2 are derived from the data from Stamey *et al*[69] and Epstein *et al*,[70] respectively. The Barzell-Melamed classification includes high, intermediate and low risk categories with high risk being secondary Gleason 4 or greater, and/or 5 or more positive cores, and/or a MCCL of 6mm or greater. The intermediate category includes primary Gleason 3 or less, and/or 3 or more positive cores, and/or a MCCL of 3mm or greater. Low risk category constitutes primary Gleason 3 and/or 2 or less positive cores with a MCCL of 2.5mm or less.

The disadvantages of template biopsies include the risk of over-diagnosing clinically insignificant disease, notwithstanding the psychological burden this presents to the patient. Furthermore, it is a more laborious process, associated with a 10% risk of urinary retention, increased burden on histopathological processing and cost.

Mapping cancer foci accurately is paramount for focal therapy to be successful in terms of oncological outcomes. Hence, dedicated protocol and biopsy schemes are essential to correctly select patients for focal therapy.[71]

1.2.2.3 MRI-guided Prostate Biopsies

In most solid organ tumours, such as breast, thyroid and liver as well as hollow-organ sites such as bladder and colorectal cancers, the biopsies are targeted to a lesion seen on a mode of imaging. It follows, therefore that prostate cancer, guided by reliable imaging, can rule in and rule out clinically significant cancer with a higher degree of accuracy and certainty. As discussed in the previous section, the recent advances in mpMRI have allowed us to achieve this goal.

Suspicious areas identified on mpMRI can guide targeted biopsies. Targeting biopsies using TRUS guidance in this manner, can be performed in three ways: cognitive or visual registration, where the operator deploys the biopsy needle in the areas within the gland previously identified on MRI; software registration, where the operator deploys the biopsy needles after registering or fusing the MRI image over the ultrasound images obtained during the procedure using hardware and software data, known as MR-US fusion biopsies[10]; or MRI-guided biopsy performed within an MRI tube, so called 'in bore'.[72]

Most studies to date have compared MR cognitive targeted or visual estimation biopsies with the standard reference of TRUS biopsies.[73,74,75,76] Schoot *et al*'s comprehensive systematic review showed that MRI-targeted biopsies had a higher rate of detection of clinically significant prostate cancer and a lower detection rate of insignificant disease when compared with TRUS biopsies. [77] For example, one of the first studies comparing transperineal cognitive targeted biopsies and TPM with MRI was reported by Kasivisvanathan *et al*, showing that of a total of 182 men, clinically significant cancer was detected by cognitive targeted biopsies and TPM in 57% and 62%, respectively. Clinically insignificant disease was detected in 9.3% and 17%, respectively.[78]

Although the disadvantage of cognitive fusion prostate biopsies is the potential of human error in extrapolating from MRI to TRUS without an actual overlay of images, it does allow for improved accuracy over conventional, blind TRUS biopsies, even though data is still limited.[72,79]

Several MRI-US fusion hardware/software systems are currently available, with new evidence produced from a few studies. Again, MRI-US fusion biopsy studies are compared to the imprecise standard that is TRUS biopsies, either 10-12 core or saturation.[74,80,81,82,83,84,85,85,86] Despite this limitation, these studies show that the number of cores can be substantially

decreased with the targeted approach and still maintain a reasonably high diagnostic performance.[20]

Prostate biopsies targeted to suspicious lesions on mpMRI compare favourably with template mapping biopsies and have the potential to reduce the burden caused by TPM by taking fewer cores, whilst maintaining the detection rate of clinically significant cancer and equally decreasing the detection rate of clinically insignificant cancer.

1.3 The INDEX lesion Hypothesis and Tumour Focality of Prostate Cancer – The Implications for Focal HIFU

Prostate cancer has a long natural history. This means that men who are given the diagnosis may not necessarily be offered treatment if their cancer is graded as low-risk, since it confers no risk to their quality or quantity of life. In other words, most men will not die prematurely from the disease, or indeed have a reduced quality of life, if the cancer is left untreated. The advent of PSA screening has seen an increase in the number of men diagnosed with the disease. With this comes the risk of over-diagnosis and overtreatment, with many men having to suffer the side effects of whole-gland therapy. This is the main reason why the UK still advocates against population based PSA screening.

Prostate cancer is known to be heterogeneous and multifocal. It may contain multiple tumour lesions within the same gland. Traditionally, the heterogeneity of the disease has had to be treated with radical whole-gland treatment, namely prostatectomy and radiotherapy, because of the inability to detect and localize multifocal disease reliably. Research has therefore been focused on improving the delivery of these radical therapies through the use of laparoscopic or robotic surgery and intensity-modulated radiation therapy.[87] The advent of technological advances in the diagnostic modalities of multiparametric MRI and transperineal template biopsies, as

described earlier in this chapter, have led to a successful change in disease identification and accurate disease localization.

The index lesion refers to the largest tumour volume and/or the lesion with the highest Gleason grade. This is presumed to be the determinant of prognosis and progression, in the presence of multifocal disease.[11,42,88] Genetic studies have revealed that the index lesion itself is primarily responsible for disease progression and metastasis.[89,90]

The index lesion is often accompanied by secondary tumours, which usually do not seem to contribute to clinical outcome if they are low grade and small (as they are in the majority of cases). These have been termed as clinically insignificant cancer foci, as they do not seem to affect the 10-20 year mortality rates.[91] The threshold volume for such lesions has been defined as 0.5ml, with a grade less than Gleason 7.[69,70] This is confirmed by a study carried out by Villers *et al* showing that 80% of secondary foci are less than 0.5ml and have the same volume distribution as tumour found incidentally in patients that undergo cystoprostatectomy for bladder cancer.[92] Indeed, Stamey *et al* demonstrated the long doubling time of cancer foci less than 0.5ml, rendering them clinically insignificant.[69]

Secondary small-volume tumours are thought to have no significant influence on the survival of patients if they were left after treating the clinically significant index lesion. This was postulated by a study, carried out by Karavitakis *et al,* which showed that 79% of prostate cancers in men undergoing radical prostatectomy were multifocal and showed that the index lesion harboured pathological parameters of poor prognosis including Gleason score, total tumour volume, extracapsular invasion and seminal vesicle invasion with 86% of the 170 satellite lesions having a total volume of <0.5ml and 99% with a Gleason score of </=6.[93]

In comparison with the above data, there are studies that have found that even tumours of a low volume (<0.2cc) may release tumour cells into the bloodstream and give rise to lymph node metastases.[94,95] Indeed, Ruijter *et*

al showed that a quarter of tumours invading the capsule in multifocal disease were not the index lesion.[96] Thus, tumour volume might not be the sole determinant of tumour aggressiveness, as evidenced by Green *et al*'s study evaluating the DNA ploidy status as an independent prognostic factor for localized prostate cancer. Of 141 cancers in 68 patients, 15% of those 0.01-0.1cc and 31% of those 0.11-1.0cc in volume were non-diploid.[97] In a study by Kikuchi *et al* analyzing 239 patients with a tumour volume of less than 0.5cc, 43 were poorly differentiated tumours, 11 had extracapsular extension, 6 had positive surgical margins and 2 had lymph node metastases, 7 experienced progression within 5 years.[98] The relationship between tumour volume and aggressiveness is not a direct one, and may well be determined by underlying genetic abnormalities and genetic alterations.[99]

The second argument deals with the genetic origin of prostate cancer. There is also still considerable debate as to whether primary prostate cancers give rise to monoclonal or multiclonal metastases. These arguments are pertinent both from a clinical as well as an aetiological perspective.

Multifocal prostate cancer has been reported, both from Europe and the US, in 56-78% of radical prostatectomy series,[92,96,100,101.] However, evidence has shown that 10-44% of radical prostatectomy series have unifocal tumours and 10-40% have unilateral disease. [101,102,103,104,105] Indeed, a recent systematic review has shown that 13%-67% of patients have unifocal or unilateral disease.[103] This data therefore raises the possibility that focal ablation to half the prostate gland that is affected, is a possibility. Ohori *et al*'s study analysed 1000 retropubic prostatectomy specimens from men diagnosed with early stage prostate cancer. 18% of lesions were unilateral. Any extracapsular extension that was present was associated with the largest intra-prostatic cancer lesion. This implies that effectively treating the index lesion would destroy the tumour burden that is likely to result in invasive or metastatic disease.[106]

Contrary to this argument is the data supporting the theory of the monoclonal origin of multifocal prostate cancer. Liu *et al*'s study suggests that metastatic disease is generated from a single pre-cursor cell. The Project to Eliminate Lethal Prostate Cancer (PELICAN) enabled the researchers to analyse 94 malignant tissue samples. These were taken from separate metastatic sites in 30 men who died from metastatic disease. DNA was isolated from each sample and analysed by chromosomal metaphase-based comparative genomic hybridization and/or by genome-wide human single nucleotide polymorphism array 6.0 analysis. This project determined that anatomically separate metastases within the same patient originated from a single precursor cell.[107] This data is further supported by Boyd *et al*'s analysis carried out in a similar manner. 48 separate malignant and high-grade PIN lesions were taken from 18 patients with localized prostate cancer. The high-resolution genome-wide copy-number data indicates that multifocal cases arise from a single precursor cell. Furthermore, this pre-cursor cell also seems to give rise to HGPIN foci as well as multifocal invasive prostate cancer.[108] Therefore, the multifocal origin of metastases seems to not be robust.

There has been much controversy and debate regarding the role of focality of prostate cancer in patient selection and treatment planning for focal therapy. The fundamental principle behind the index lesion hypothesis, as well as the monoclonal origin of prostate cancer is that targeting the index lesion alone should be sufficient to provide oncological control.[109] Focal therapy has usually been applied to the index lesion, being the largest and of the highest grade, leaving the clinically insignificant foci untreated. Indeed, an international multidisciplinary group has suggested that focal therapy may be delivered to the index lesion alone in those patients where the secondary tumours are small volume, as these are unlikely to contribute to the disease outcome.[110]

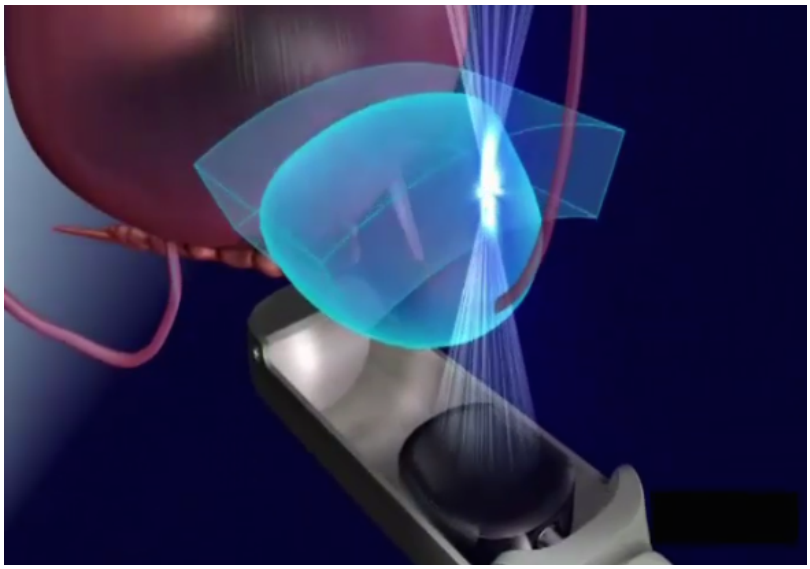
1.4 Focal High Intensity Focused Ultrasound – The Technology

1.4.1 The Physical Principles

Ultrasound refers to mechanical vibrations produced by a crystal or transducer. These vibrations have a frequency above the threshold of human hearing (16kHz) and are produced by applying an alternating voltage across a piezoelectric material, such as lead zirconate titanate. These materials oscillate at the same frequency as the alternating current. The ultrasound waves produced can travel through human tissue. This subsequently leads to alternating cycles of increased and reduced pressure, compression and rarefaction, respectively.

Diagnostic ultrasound is of low frequencies (1-20 MHz) and results in insignificant energy deposit, which is therefore harmless. Therapeutic HIFU uses higher frequencies (0.8-4 MHz) and therefore deposit higher energy within the ultrasound beams. Therapeutic ultrasound can be divided into two groups: 'low' intensity (0.125-3 W/cm^2) or 'high' intensity (>5 W/cm^2). The former can stimulate normal physiological responses to injury. The latter can cause selective tissue destruction if delivered in a focussed manner. The high intensity ultrasound waves are converged by using an acoustic lens, bowl shaped transducer or electronic phased array.

Figure 1: The projection of ultrasound waves created by the transducer, are focused on a target point by the acoustic lens, shaped like a grain of rice.



Zones of high or low pressure are created as ultrasound waves travel through tissue. Tissue damage occurs when, during the high-pressure phase, the energy deposit at the focus is sufficiently high.

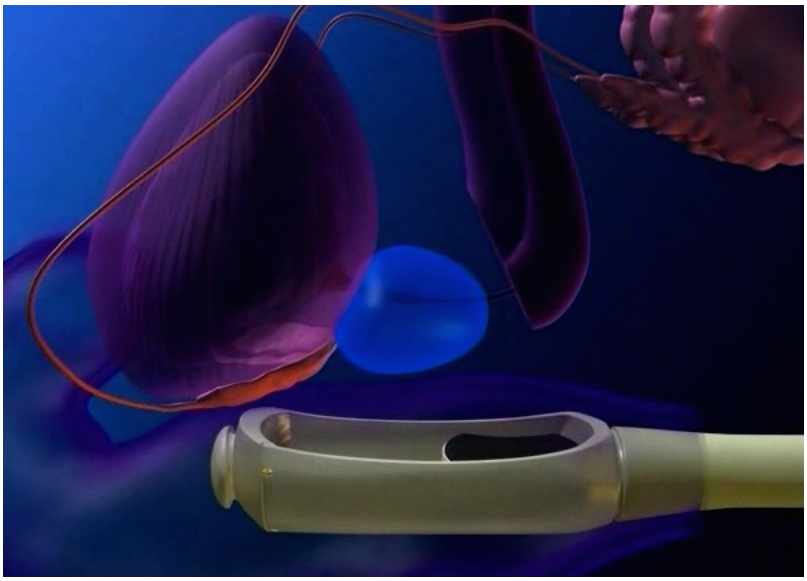
These pressure fluctuations result in shearing motions at a microscopic level, which, in turn, causes frictional energy. Thus, mechanical energy is converted into heat energy. It is this heat energy that subsequently results in protein denaturation, disruption of the lipid cell membrane, coagulative necrosis and irreversible cell death. This is accompanied by an inflammatory response with formation of granulation tissue characterised by immature fibroblasts and new capillary formation at the periphery of the treated necrotic zone. Migration of polymorphonuclear leucocytes occurs two weeks after treatment and is accompanied by fibrosis and scar tissue deposition as evidenced on multi-parametric MRI of the prostate.

The volume of tissue ablation with each HIFU pulse is shaped like a 'grain of rice' that is 1-3 mm transversely and 8-15mm longitudinally (along beam axis). Each pulse is placed adjacent to each other to ablate larger volumes of tissue. Thermal cell kill is achieved at a temperature of 56°C maintained for

1 second. The temperatures achieved during HIFU is greater, up to 80°C so even short pulses will achieve cell kill.[111,112,113]

The depth of penetration of HIFU is 26-28mm. For the larger prostate glands, a prior transurethral resection of the prostate can decrease the gland size to allow effective treatment with HIFU. Some focal HIFU studies include patients that have had a combined procedure of TURP and HIFU. TURP has the benefit of removing calcifications from the transitional zone that would impede the adequate delivery and deposition of thermal energy through HIFU. It has been shown that TURP also reduces sloughing of the urethral mucosa post-HIFU and it may allow complete treatment of the peripheral zone in one HIFU sitting.[114] Indeed, Chaussy and Thuroff compared a series of 175 patients treated with HIFU combined with TURP against outcomes in 96 patients treated with HIFU alone. The follow-up was 18.7 months in the HIFU group and 10.9 months in the combined group. The mean PSA nadir in the HIFU and combined groups were 0.48ng/ml and 0.26ng/ml and the negative biopsies rates were 66.3% and 70.6% in the HIFU and combined groups, respectively. The re-treatment rates were lower in the combined group at 4% when compared with 5% with HIFU alone.[115]

Figure 2: Ultrasound probe showing transducer in relation to the prostate gland and bladder.



1.4.2 HIFU Devices

There are two main transrectal devices available for treatment of prostate cancer: Sonablate 500 (Focus Surgery, Indianopolis, IN) and the Ablatherm Integrated Imaging (EDAP-TMS SA, Vaulz en Velin, France). This chapter will primarily focus on these as the transurethral and MR-guided in-bore HIFU devices have little in the way of clinical data at the time of writing although we will summarise what data there is.

1.4.2.1 Sonablate 500

The Sonablate 500 device has two 4MHz transducers operating at focal distances of 4.5cm, 4cm or 3cm. They are mounted back-to-back. Each transducer has a dual role. The centre is used as an imaging device and takes real-time ultrasound imaging; the periphery is used for treatment. The treatment head within the probe can be flipped according to the desired depth of penetration. The 4cm transducer is routinely used for the anterior and the 3cm one used for the posterior parts of the prostate glands. Pulse duration generally lasts for 3 seconds, followed by a 6 second gap to allow tissue cooling.

Figure 3: The Sonablate console with the Sonablate probe and Sonachill cooling system.

Figure 4: The Sonablate probe fitted onto the stepper.

Figure 5: The Sonablate transducer movements.

The combined imaging and therapeutic roles of the transducer allows for direct visualisation after each pulse of treatment cycle. The Sonablate device does not have a protocol driven treatment. Rather, the power intensity of each pulse is guided by the grey-scale changes within the targeted area that represent steam. These grey-scale 'pop-corning' changes have been termed

'Uchida' changes, named after the Japanese urologists who pioneered work with the Sonablate device.

The Sonablate machine allows for the treatment to be planned and executed in two or three separate blocks. The anterior part of the gland is treated first, followed by the midzone and posterior part. The transrectal probe will require adjustment between each block. The posterior block is always treated using the 3cm focal length with lower energy levels to prevent rectal injury by heat build-up. Rectal cooling is achieved by pumping chilled degassed water at temperatures of 17-20°C. Patients are placed in the dorsal lithotomy position for the Sonablate machine. The next generation now incorporates image-fusion to deliver targeted therapy.[116]

Figure 6: The treatment is planned and executed in three separate blocks to allow complete ablation of the selected area.

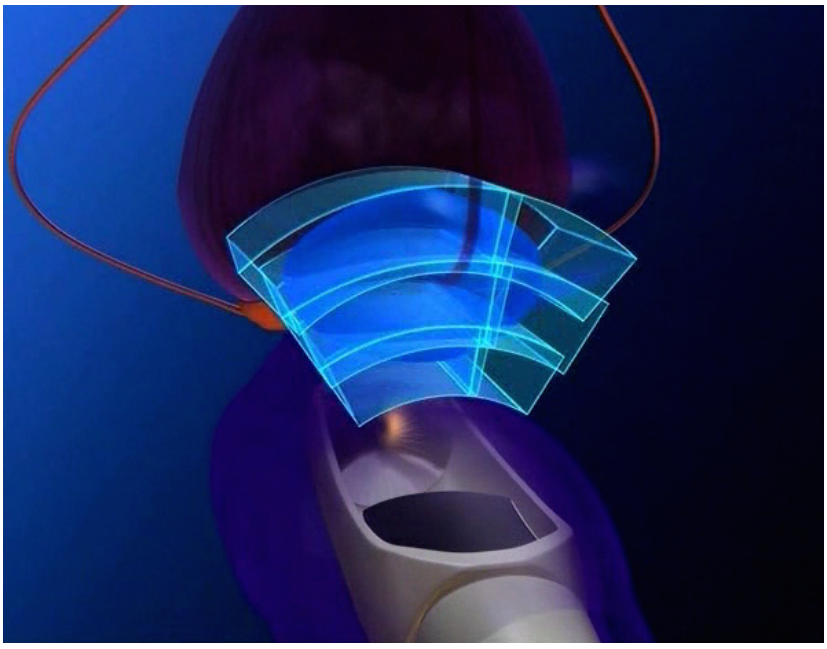


Figure 7: Transducer focused onto the posterior block.

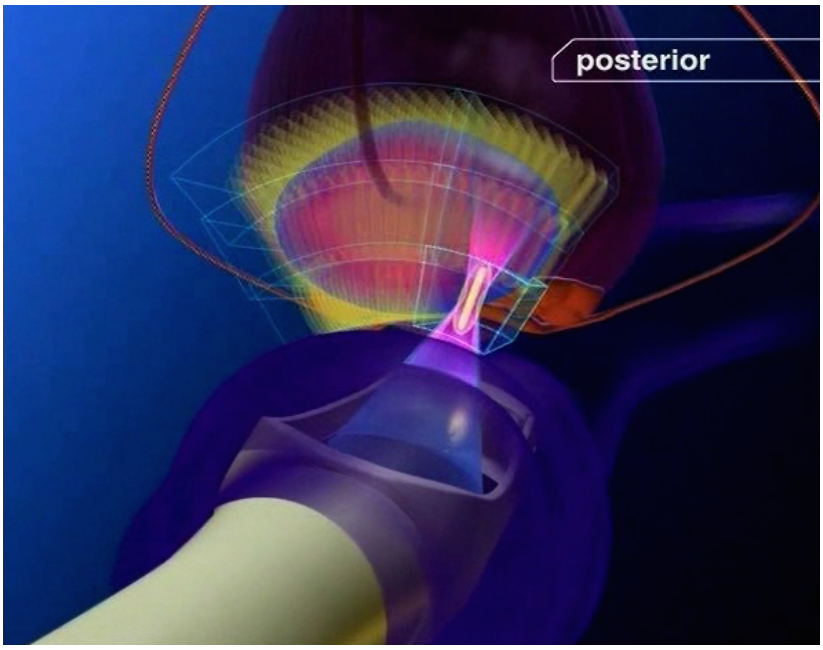


Figure 8: Software of advanced target segmentation and planning.

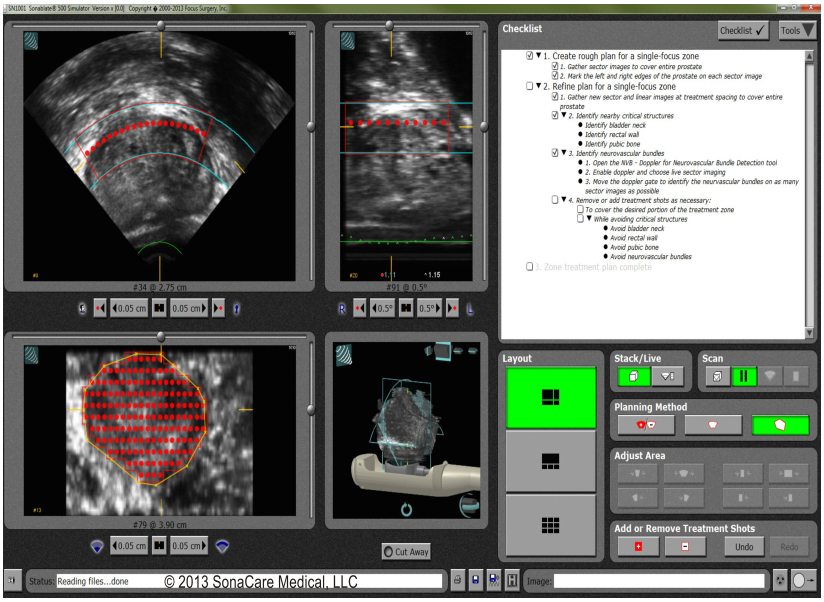
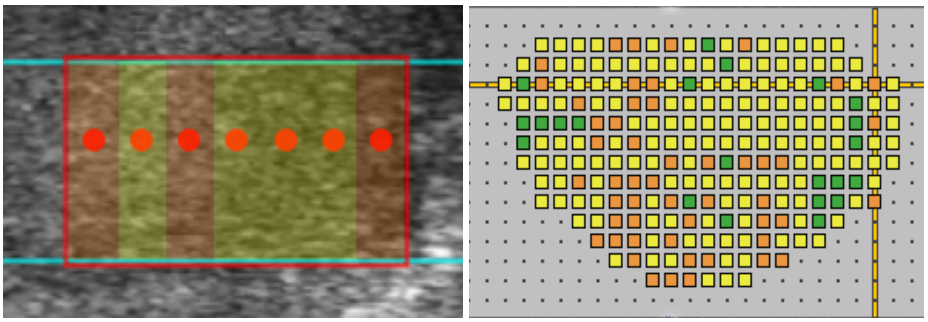


Figure 9: Tissue change monitoring on ultrasound.



1.4.2.2 Ablatherm

The Ablatherm device uses two transducers: one for imaging (7.5 MHz) and one for treatment (3 MHz) and allows ablation within 25 mm of the prostate. Each pulse is of 4-5 seconds, followed by an interval of 4-7 seconds. This device has recently been updated to the Focal One device to incorporate image-fusion but uses a similar approach to what is described here.

This device uses pre-defined treatment algorithms with pre-set energy levels: as a primary procedure, as a re-treatment and for radiation failure. The operator cannot individually control the energy level for each pulse. The treatment is planned slice by slice from apex to bladder neck after the ultrasound scan of the prostate is obtained and reconstructed in 3D. Treatment is delivered to each lobe, anterior to posterior. The transrectal probe is incorporated into a table, which also holds the pump and cooling mechanism. The patient is placed on this table in the right lateral position. In addition, the Ablatherm device has a safety ring that stabilizes the rectal wall intra-operatively as well as a patient motion detector.[113,117] The new Focal-One device, which incorporates image-fusion, has very similar features to the previous Ablatherm generation and works very much in the same way to deliver the HIFU pulses although it is reported to be more precise.

The Sonablate system was chosen over Ablatherm to be used in our centres as it is a more precise way of delivering the ablation. Firstly, as Sonablate's

treatment probe has two transducers, it allows not only treatment, but also imaging of the prostate after every pulse of energy delivered. This allows precise monitoring of tissue changes, which in turn, allows the operator to make changes in energy delivery to ensure precise and complete ablation of required tissue. Ablatherm is unable to do this as treatment delivery is defined prior to the start of the procedure and cannot be changed during treatment. Secondly, positioning the patient in the lithotomy position is significantly easier than the right lateral position, which is used with the Ablatherm system.

The total theatre time with the Sonacare system varies between 60 to 120 minutes with an ablation time between 50-80 minutes depending on the volume of tissue that requires ablation.

There is a difference in terms of cost between the two systems, with the Ablatherm device costing at Euro 950,000 and Sonablate at Euro 400,000. The Ablatherm consumables total at Euro 1000as opposed to Sonablate's consumables, which total at Euro 500. Renting the Ablatherm device costs Euro 12,000 per day whilst it only costs Euro 4000 per day to rent the Sonablate.

Table 1: Comparison of Sonablate 500 and Ablatherm devices.

	Ablatherm Integrated imaging	**Sonablate 500**
Company	EDAP TMS SA, France	Sonacare Inc, USA
Since	2005	2001
Table	Integrated	Standard
Patient Position	Right lateral	Lithotomy or Supine
Frequency	7.5 MHz for treatment planning; 3MHz for treatment	4MHz for treatment and planning
Focal Point	4.5cm	3-5cm
Transducer	Single treatment probe with two transducers	Single treatment probe with two transducers of different focal lengths.
Power	Pre-defined for each treatment	Manual adjustment by operator
Ablation Temperature	>85 °C	80-98°c
Imaging	Real time	Real time
Active Cooling system	Yes	Yes
Rectal wall cooling	Yes	Yes

HIFU was first established for use in Benign Prostatic Enlargement (BPE). It was then translated for use in localised prostate cancer and one of the first focal HIFU series to be reported was Madersbacher *et al*'s study on 29 patients who underwent focal HIFU prior to RP. These men were diagnosed with unilateral localised disease. They showed that focal HIFU was possible without compromising the integrity of intervening structures such as rectum and urethral sphincter.[118] The ability of HIFU to achieve well-defined areas of coagulative necrosis was later confirmed with another study demonstrating the potential for HIFU to treat localised prostate cancer in a focal manner.[119]

One of the next series to appear is by Muto *et al* where whole-gland and focal HIFU was performed and compared. Indeed, no significant differences were noted in the 2-year biochemical DFS rates for the patients at low and intermediate risk between whole-gland and focal therapy. Interestingly, there were also no differences noted in the QOL parameters.[120] Indeed, Murat *et al* looked at the outcome on erectile dysfunction after 56 patients underwent hemiablation HIFU. For the 52 patients with a pre-HIFU IIEF-5 of more than 17, 28 patients had a post-HIFU IIEF-5 score of more than 17. After the second HIFU session, 20% of the 15 patients with an IIEF-5 of more than 17 remained with the same outcome.[121]

Ahmed *et al*'s group have published three series on focal HIFU for localised prostate cancer. The first comes from 2011 as a phase I/II trial, where 20 men were treated with hemiablation HIFU. 95% retained their potency while 95% were pad-free. 89% of men achieved the trifecta status of cancer control, erections sufficient for intercourse and pad-free, leak-free continence at 12 months. These results demonstrated the feasibility of hemiablation as one form of focal therapy. However, with the increased precision in the diagnostic pathway of prostate cancer, more precise characterisation has made treating the cancer more focally possible. [122]

In fact, the same group published similar findings on 42 men who received focal HIFU with 92% having no clinically significant cancer on follow-up biopsies in 30/39 men that were biopsied. 4 men had re-treatment with no evidence of disease on MRI at 12 months. They report 89% of men having sufficient erections for penetration and all men with no baseline incontinence achieved pad-free continence at 12 months. [123]

The third trial also reported similar findings. A total of 56 patients were treated with focal HIFU, of which 85.7% had no measurable prostate cancer post-HIFU. 40 patients were leak-free, pad-free and had erections sufficient for penetration. Of 41 patients with good baseline function, 22 (53.7%

achieved the trifecta status of pad-free, leak-free continence, good erectile function and absence of clinically significant disease.[124]

The most recent hemiablation HIFU data published comes from van Velthoven's group, where 50 patients were treated and with a median follow-up of 35 months. Median time to PSA nadir was 3 months, with biochemical recurrence occurring in 28% and 36% according to Phoenix and Stuttgart definitions. Post-operative biopsies were carried out in only 8 patients, of which, 3 were positive in the contralateral untreated gland, 1 in the ipsilateral lobe and 2 patients had bilateral positive biopsies. Complete continence was documented as 94% and erections sufficient for intercourse as 80%.[125]

Targeting treatment to a discrete area of prostate tissue preserves surrounding structure, and in doing so helps maintain patients' functions and quality of life. Focal HIFU has recently emerged as one of the minimally invasive techniques that may provide acceptable morbidity rates while conferring acceptable short-term oncological outcomes. Medium term and long term data on cancer control is required.

Table 2: Primary Focal HIFU

Study	Device	D'Amico Risk Groups	Mean follow-Up	Post-HIFU Histology (%)	BDFS	PSA Kinetics	Secondary Treatment Actual (%)	Metastases-specific survival (%)	Cancer-specific survival (%)
Madersbacher et al (1995)	Sonablate N=29	NR	NR	NR	NR	NR	NR	NR	NR
Beerlage et al (1999)	Ablatherm N=14	NR	NR	28% negative	NR	19%(PSA<0.5) 50%(PSA0.5-4) 30%(PSA>4)	NR	NR	NR
Muto et al (2008)	Sonablate N=29	Low 86.2%; Inter 13.8%	32 Median	76.5% negative	Low 83.3% Inter 53.6%		NR	NR	NR
Murat et al (2009)	NR N=56	NR	42 Median	NR	76% (3 yrs) 60% (5 yrs)	PSA nadir 0.8 (after 1st HIFU) PSA nadir 0.47 (after 2nd HIFU)	NR	NR	NR
El Fougon et al (2011)	Ablatherm N=12	NR	120 Median	NR	NR	NR	NR	100%	100% (10 yrs)
Ahmed et al (2011)	Sonablate N=20	Low 25%; Inter 75%		89% negative					
Ahmed et al (2012)	Sonablate N=42	Low 27%; Inter 63%; High 10%							
Ahmed et al (2015)	Sonablate N=56	Low 12.5%; Inter 83.9%; High 3.6%	NR	85.7% negative	NR	NR	NR	NR	NR
Van Velthoven et al (2014)	Ablatherm N=31	Low 54.8% Inter 38.7% High 2%	36.3	NR	66% (5 yrs) 59% (7 yrs)	68.4% (PSA≤0.5)	NR	NR	NR
Van Velthoven et al (2016)	Ablatherm N=50	Low 48% Inter 52%	35	25% negative	Low 75% (5-yrs) Inter 36% (5-yrs)		NR	93%	100%

Chapter 2

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The Rationale for Focal Therapy and Focal HIFU: Pros and Cons

Chapter 2 – The Rationale for Focal Therapy and Focal HIFU: Pros and Cons

2.1 The Rationale for Focal Therapy

Focal therapy has emerged as an alternative option to standard treatments. Focal therapy has been defined as 'individualized treatment that selectively ablates known disease and preserves existing function, with the overall objective of minimizing morbidity without compromising life expectancy'.[126] The main aim of focal therapy is tissue preservation with selective ablation, allowing preservation of existing functions and minimising the impact on the quality of life. It offers a more individualized treatment for localised prostate cancer. Although there are a number of different ablative energies in existence, HIFU is at the forefront.

The controversies surrounding focal therapy are on-going, with a new body of evidence emerging to support encouraging short-term oncological and functional outcomes. This thesis will provide much-needed, new evidence in terms of the medium-term oncological and functional outcomes of focal HIFU used in the treatment of clinically significant localised prostate cancer.

2.2 The Pros and Cons

2.2.1 Active Surveillance is less morbid than Focal Therapy

A recent study has shown that whole-gland therapy in the form of radical prostatectomy confers no significant survival benefit over active surveillance.[15,127] Hence active surveillance can be offered to those diagnosed with low-risk or clinically insignificant disease. Those that, over time, have biochemical progression or their disease upgraded and re-classified to higher risk pathology, can be offered treatment at the time. This approach will also reduce the risk of overtreatment of low-risk prostate cancer that is associated with the current diagnostic pathway.[128]

An active surveillance phase II study has reported an overall survival of 85% and a disease-specific survival of 99% with a median follow-up of 8 years.

The number needed to treat to avoid one PCa death in a favourable-risk screen-detected population is between 80 to 100.[129] The European Randomised Study of Screening for Prostate Cancer (ERSPC) confirmed that the prostate-cancer specific survival was 100% at a 10-year follow-up. Deaths from other causes occurred in almost a quarter of the patients.[130]

Here we argue that the aim of focal HIFU should not be used as an alternative to active surveillance treating clinically insignificant and/or low-risk disease but should be offered as treatment with curative intent to those with clinically significant disease that is suitable for focal therapy approaches, and thus be an active part of the armamentarium we possess in treating localized prostate cancer. Patient selection for focal therapy is therefore paramount to ensure this type of treatment is successful.

2.2.2 Limitations to Disease Localization

One of the arguments against focal therapy is the limitation with prostate mapping as well as the identification and treatment of all intra-prostatic lesions. Precise disease localization is not possible with TRUS biopsy, which incorrectly grades unilateral disease in up to 50%.[54] With the advent of the technological advances in mpMRI, as discussed in Chapter 1 Section 1.2.1, substantiated by the recently published data from the PROMIS trial, we know that mpMRI allows visualization of discrete lesion within the prostate having an excellent negative predictive value and better sensitivity than TRUS biopsy at detecting clinically significant disease at 89% and 93% respectively.[45]

2.2.3 Residual Disease

The potential for residual disease after focal therapy is another argument against focal HIFU becoming a standard treatment modality. This is also true for radical treatments. When the concept of nerve-sparing prostatectomy was first introduced, there was much skepticism surrounding a procedure that was declared to be 'cancer-sparing surgery'.[131] Walsh *et al* demonstrated the oncological safety of nerve-sparing prostatectomy

heralding a dramatic shift in the treatment of prostate cancer.[132] A similar outcry arose with the introduction to nephron-sparing surgery, until the RCT from Van Poppel *et al* involving a total of 541 patients showed that there was no significant difference in overall survival between partial or radical nephrectomy for renal cell carcinoma.[133] Partial nephrectomy is now considered to be a standard treatment for patients with clinically localized renal cell carcinoma, irrespective of surgical approach.[134]

2.2.4 Prostate cancer is a Multifocal Disease

Treatment of breast cancer, which like prostate cancer is also a multifocal solid tumour, has also focused on treating the tumour rather than the whole breast, hence the development of wide local excision as opposed to radical mastectomy. There was much opposition to this approach in its initial stages, especially given that breast carcinoma, like prostate cancer is known to be multifocal. However, even in the presence of multifocality, 90% of local recurrences of breast cancer occur in the index quadrant.[135,136] Although multifocal, prostate cancer is monoclonal in origin. It is the index lesion that drives forward the progression to local invasion and metastases in most cases. Lesions left behind after targeted treatment, predominantly leave behind a less aggressive tumour that does not go on to metastasize within a significant period of time.[137] This is described earlier in Chapter 1 Section 1.3.

2.2.5 Limitations of HIFU

One limitation of HIFU is the transmittance of the ultrasound waves over longer focal distances. Tumours located in the anterior portion of the gland are not ideal to be treated by HIFU, particularly with a large prostate gland and a high antero-posterior distance. The ultrasound waves have to travel a longer distance to reach the focal point necessary for delivery of energy. In addition, the oedema and swelling created by energy deposition pushes the anterior gland further away from the posteriorly placed ultrasound probe. The target area is therefore pushed further away from the probe.[138,139,140] It has been proposed that focal cryotherapy is the ablative modality of choice

for anterior lesions, as the transperineal approach of the probes allows easy access to this part of the gland.

HIFU is a repeatable procedure in cases of primary failure. Whole-gland or systemic treatments remain potential options in case of failure, although radical prostatectomy may be more difficult due to tissue fibrosis. There is scope for further research in this area.

2.2.6 No Consensus on Follow-up of Patients after focal HIFU

It is true that no consensus has yet been reached regarding follow-up after focal HIFU and indeed focal therapy. Prostate biopsies have been seen as the validated tool to assess tumour recurrence. Biochemical failure has been difficult to define, hence discussions have centered around time to, and rates of, re-treatment. The consensus panel from 2015 have agreed a re-treatment rate of <20% may be acceptable.[141]

2.2.7 The Issue of Overtreatment

Many have voiced their concerns that focal HIFU treats men with low-risk disease, thus submitting patients to overtreatment. In a systematic review carried out by Valerio *et al*, 2350 cases of localised prostate cancer were treated with focal therapy across 30 studies.[142] Around half of these men were diagnosed with intermediate- or high-risk disease. Indeed, the UK INDEX trial, and focal HIFU registry cases, investigating the efficacy of focal HIFU, have moved away from treating low volume low-risk disease.[143] Overtreatment also occurs with other treatment modalities including radical prostatectomy[144] and radiotherapy.[145]

2.3 Conclusion

Focal therapy for localized prostate cancer may represent a paradigm shift in managing this disease with the body of evidence so far supporting the further evaluation of this approach.

Chapter 3

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The Role of the Registry in Surgical Practice

Chapter 3 – The Role of the Registry in Surgical Practice

3.1 Introduction

The ongoing controversies surrounding the efficacy of focal therapy will remain unless the level of evidence supporting it is raised. High quality evidence is required. However, novel surgical techniques face various difficulties in the assessment of their efficacy.

3.2 Randomized Controlled Trials in Surgery

Randomized controlled trials (RCTs) are considered the gold standard for generating valid scientific evidence on benefits and harms of treatments in surgery.[146,147] The power behind RCTs lies in its rigorous design, which eliminates random or systematic bias therefore reducing the risk of incorrect conclusions being made on the treatment efficacy in question. It has therefore been widely accepted for evaluating efficacy for medical treatments. Evaluating healthcare intervention is paramount however, and many now consider RCTs to be the only valid method of comparing treatment effectiveness.[148] On the other hand, observational studies are reported to introduce bias and as such are viewed to lend less validity in estimating treatment efficacy. Recent experimental studies have emerged showing that treatment effect estimates in randomized and non-randomized studies do not necessarily show advantages of one over another. Therefore, the superiority of RCTs should not be assumed.[149,150]

The quality and quantity of RCTs in the surgical field is however, acknowledged to be limited. The field of surgery presents particular hurdles in performing RCTs. In fact, treatments in general surgery are half as likely to be based on evidence gained from RCTs than those in internal medicine.[151,152]

In the field of prostate cancer, this would mean setting up an RCT comparing focal therapy to radiation or to radical prostatectomy in patients with significant prostate cancer.

Once a surgical procedure is accepted as standard management, it becomes extremely difficult testing it against a placebo, due to lack of physician and patient equipoise. In addition, and perhaps of more concern, are the ethical issues that inevitably arise if an intervention was denied to men that did not enter into the study. This will subsequently lead to a difficulty in recruitment of patients into trials. Patient equipoise is well known to prevent recruitment in trials comparing surgical and non-surgical treatments. Indeed, it represents 82% of problems preventing type 3 trials.[153]

Technical problems such as the learning curve associated with new surgical procedures should also be taken into consideration. Performance quality requires frequent repetition over time.[148] Adverse events are more frequent during the learning curve period. Bias is unsurprisingly introduced when randomizing between familiar and unfamiliar procedures. Hence, surgical learning curves often cause difficulties in both the timing and performance of RCTs for new techniques.[148] Blinding is another point that makes recruitment into surgical RCTs especially problematic. Indeed, inadequate blinding of surgeons and/or patients is often seen in surgical trials.[153]

Attempts have been made to address the lack of RCTs in focal therapy with the Partial Prostate Ablation versus Radical Prostatectomy Trial (PART), which compares partial ablation with focal HIFU and radical prostatectomy in intermediate risk men. Due to recruitment failure, the study has been changed to PDT (Photodynamic Therapy) versus radical prostatectomy, clearly demonstrating the difficulties just discussed in relation to RCTs.

3.3 The Registry - An Alternative Option to Randomized Controlled Trials

An alternative solution to the problems faced by surgical RCTs, is the use of registries, which are gaining in popularity within the surgical research field. A registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified

outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)."[154]

A clinical registry is a collection of standardized information about a group of patients who share a condition or experience, although there is no consistent definition of this term used within the field of health research at present.[155,156] There are several research registries currently in existence. For example, in the US, The Breast Cancer Surveillance Consortium, started in 2013 and The Registry Study for Radiation Therapy Outcomes, started in 2016. (https://patientregistry.ahrq.gov) In the UK, examples of successful registries include The National Joint Registry set up in 2002 by the National Health Service and Welsh Government.[157]

There are several uses for patient registries that can operate at a single center or across several, in a collaborative effort. Traditionally, registries were created for research purposes; to generate and collect observational data used to answer a specific research question. Registries can be used to describe the natural history of a disease or condition, monitor best outcome practices in treatment, to develop therapeutics, determine cost-effectiveness of treatments, services or products, or develop research hypotheses, among others. Some may also include collection of blood or tissue samples.[155] They can also be used to recruit patients for clinical trials.

Registries also vary in complexity from recording product use to collecting prospective data on types and outcomes of treatments, risk factors and clinical events. Follow-up can be prospective or retrospective, or even a combination of both. There can be a wide spectrum in mode and duration of follow-up, ranging from a few days, to decades.[158]

As such, observational data from registries is a valuable source of information bridging important gaps in available evidence.[159,160] For example, observational data were used to compare coronary artery bypass

graft surgery with percutaneous coronary intervention.[161] The trial included mainly patients with single- or two-vessel coronary disease and did not reflect the use of other therapies available such as off-pump surgery, minimally invasive surgery and drug-eluting stents. Although it appeared that myocardial infarction and mortality were comparable for primary coronary intervention (PCI) and coronary artery bypass grafting (CABG) among patients with similar levels of coronary disease, registry data showed a strong gradient of benefit of CABG by severity of disease.[161]

The Food and Drug Administration (FDA) have used observational data from registries in several situations. For example, safety data from the acyclovir pregnancy registry were used to change the FDA pregnancy labeling category from category C (risk cannot be ruled out) to category B (no evidence of risk in humans).[162] The National Institute of Clinical Excellent (NICE) also uses registries for decision support; the British Society for Rheumatology Biologics Register has provided information for evaluation of anti–tumor necrosis factor α drugs.[163]

Technological advances have catapulted medical device development. Medical device registries play a pivotal role in validating efficacy of novel interventional technologies and medical devices. Unlike clinical trials, device registries allow assessment of medical device performance in a real-world setting. Registries permit the collection of data over a large number of patients receiving treatment in diverse clinical settings and include clinical outcomes over time allowing appropriate assessment of a medical device. Adverse events from treatment or the device can be identified. Treatment outcomes may be affected by patient and device factors, both of which may be captured though the registry. Device malfunctions, which may vary from manufacturing problems to errors of design and environmental factors, may also be identified through a registry. Linking device exposure and long-term outcomes, registries enable follow-up that can span decades.[154] As such, registries can provide realistic estimates of how well new interventional techniques may work in everyday practice. However, careful analyses and

interpretation is required. Often, the available evidence is poor, with trials including small patient cohorts and insufficient follow-up. Recent policy initiatives at NICE are supporting the use of registries in assessing the safety of new intervention in clinical practice.[164,165] An additional role of registries is the use of data as comparative information for audit and clinical governance purposes.[166]

Many authors have criticized the use of registries for various reasons. Concerns have arisen surrounding the validity of registry data in assessing comparative effectiveness. Many have expressed concern that selection bias can be introduced which, in turn, will affect outcomes, particularly because the treatment choice in everyday life is influenced by patient characteristics as well as clinical factors, including specialty, training and national guidelines.[158] In the case of our focal HIFU registry, centre bias may have been introduced, as the majority of patients were treated at one institution, University College London Hospital, NHS Trust.

Some authors have noted the lack of standardization of data collection. In addition, if more than one registry exists for a single condition, competition for patients may limit a given data set. This holds particularly true for rare diseases, affecting a small cohort of patients. This will make meta-analysis across registries problematic.[155] Entering data into a registry, in a continuous manner, with updates at regular time intervals, may improve the quality of the data collected, as does regular monitoring and auditing of data entry. Corrective steps should be implemented as necessary to improve data quality. Our HIFU registry had quality assurance implemented by employing data managers who performed three monthly audits on the quality of data entered. An update on all registry patients was carried out every six months over a two-year period.

Despite these concerns, patient registries have been a valuable source of data and research that meets the needs of patients, families and physicians alike.

Funding may also present a hurdle in initiating and maintaining a registry. In the UK, research funding bodies such as NICE or the UK Treasury's review of research and development can allow the funding required to support registries for surgical procedures.[167]

Whilst RCTs remain the corner stone of clinical evidence, there is much to be said about the role registries can play in guiding physicians in their selection of treatment options.

3.4 Assessment of Medical Device Approval

Both medical devices and pharmaceutical agents are approved through a regulatory pathway that follows a phased approach. It begins with studies of safety and tolerability in healthy human volunteers (phase I) and terminating in post-market evaluation (phase IV). Phase I assesses for safety, Phases I-IIa assess toxicity, Phases I-IIb looks at ideal dosage and efficacy is looked at in phases II-III. Phase IV studies are traditionally post-marketing studies which verifies the efficacy of the agent 'in the real world'.[168]

In the 1990s, Europe introduced the Conformité Européenne (CE) mark.[169] Once a medical device achieves the CE mark in one European country, it can be registered and used in clinical practice in any other country within the European Union, as well as some non-European countries that recognize the CE mark. In Europe there are four categories into which medical devices are classified: Class I, IIa, IIb and III, according to the type of contact with the patients, the clinical purpose and risks of adverse events inherent in their use.[168,169,170] Class I medical devices are considered very low risk devices and can be placed on the market after a self-approval of CE conformity issued by the manufacturer of the device. The other categories are more high risk and have to undergo regulatory approval via submission to a notified body entitled to regulate device approval in Europe. [169,170,168]

All medical devices placed on the UK market have to comply with device-specific legislation. In the UK, the regulatory system is governed by the Medical Devices Regulations 2002. The designated Competent Authority for medical devices in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA) (Devices Division).[171]

3.5 The Role of the Registry in the Assessment of Novel Health Technology in Focal HIFU

The feasibility and outcome efficacy of focal HIFU for localized prostate cancer should be discussed within the context of how new health technologies are evaluated in order to provide meaningful results. Assessment of health technology refers to the evaluation of procedures undertaken by health providers. Effectiveness, cost or impact is appraised.[172] The Balliol collaboration has set out the steps in which novel surgical procedures should be judged. There are four stages – Idea, Development, Evaluation and Assessment and Long-term results, represented by the acronym 'IDEAL'.[173] These four stages represents the first stage of two, with Stage II being divided into two substages. IIa is the Development phase and IIb is the Evaluation phase. All four stages have a specific aim, primary outcome, outcome measure and methodology.[174]

As per NICE guidelines clinicians offering focal HIFU as treatment for localized prostate cancer have to "*inform the clinical governance leads in their trusts, ensure that patients and their carers understand the uncertainty about the procedure's efficacy and the risks (specifically the risk of sexual dysfunction) and provide them with clear written information*." Within UK sites participating in the Focal HIFU academic registry, all Trusts and hospitals were informed and approval for this procedure was gained. A patient information sheet (PIS) was created and given to all patients prior to their consent for the procedure.

NICE also stipulated that "*patient selection and treatment should be carried out by a multidisciplinary urological cancer team*". Indeed this was presented to every patient enrolled into our focal HIFU registry.

"*Encouragement into further research into focal therapy using HIFU for localised prostate cancer*" is also mentioned in the NICE guidelines. The evidence presented in this thesis builds upon this statement and fills the gap currently present in the procedure's efficacy in the medium-term, as well as providing valuable evidence regarding the genito-urinary side-effects associated with focal HIFU.

NICE recommends that all patients undergoing focal HIFU should be entered into a registry. In accordance with these guidelines, the UK independent, academic, prospective registry was set up in 2004 incorporating both whole-gland and focal HIFU to the prostate, the results of which are presented in this thesis.[175]

The role of our own academic HIFU registry has played a crucial role in securing FDA approval for the Sonablate® 450 device in the US. The FDA regulates medical products, devices and drugs. A *de novo* request for classification of the Sonablate® 450 into class II was submitted under section 513(f)(2) of the FD&C Act in March 2015. Also provided was a profile of safety and effectiveness of the device, data provided by our HIFU registry. The approval gained in October 2015, is the first approval of its kind for tissue ablation of the prostate. The FDA has given it's approval for the device as: "*A high intensity ultrasound system for prostate tissue ablation is a prescription device that transmits high intensity therapeutic ultrasound (HITU) energy into the prostate to thermally ablate a defined, targeted volume of tissue, performed under imaging guidance*."

FDA identifies the Sonablate® 450 device as a prescription device under 21 CFR Part 801.109 that is indicated for transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue. The FDA concluded that

Sonablate® 450, and substantially equivalent devices of this generic type should be classified into class II, under the generic name, high intensity ultrasound system for prostate tissue ablation.[176]

Health Canada approved EDAP's Focal One HIFU device in January 2015, which allows it to be marketed for the treatment of prostate cancer in Canada. The Ablatherm HIFU device also gained clearance from the FDA to market Ablatherm® Integrated Imaging HIFU in the US in November 2015.[177]

3.6 Conclusion

Enhancing evidence-based data through registries provides timely, reliable and effective data that represents the real world practice. There are strengths and limitations to all types of evidence. Perhaps efforts should be focused on what provides quality research and data rather than the trial design itself.

Chapter 4

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Materials and Methods

Chapter 4 - Methods and Materials

4.1 The Focal HIFU Registry

The University College London Hospital (UCLH) Joint Research Office granted institutional review board exemption. Our programme of health technology assessment followed the Medical Research Council (UK) guidelines for evaluating complex interventions.[178] These guidelines were recently incorporated and applied to surgical innovation within the IDEAL framework.[179]

Focal transrectal HIFU was a surgical innovation that commenced in 2006 in the UK and was approved for clinical use by the UK's NICE under special arrangements. That is, all cases had to be prospectively and consecutively entered into an academic registry, discussed in a multidisciplinary meeting and given written information on the advantages and disadvantages of the procedure.

Between 1st January 2006 and 31st December 2015, 625 consecutive patients underwent primary focal HIFU for non-metastatic prostate cancer using the Sonablate®500 device (Sonacare Inc., USA) within 9 centres. Focal HIFU treatment was offered to patients diagnosed with non-metastatic prostate cancer with Gleason 6 through 9, stage T1c-T3bN0M0 and PSA of </=20ng/ml. Gleason 6 required a minimum of 3mm of disease.[180] Patients were classified into low, intermediate and high risk groups according to the D'Amico risk classification system. The D'Amico system was used in this study as the NCCN criteria over-estimates the proportion of men with high risk disease, and indeed, was a criticism on one of the previous trials from UCL, which is included within this patient cohort. The D'Amico classification is a pre-treatment stratification of prostate cancer based on clinical factors. The low risk category includes those men with a PSA <10ng/ml, Gleason 6 or below and stage T1c to T2a prostate cancer. Intermediate risk includes those with a PSA of 10-20ng/ml, Gleason 7 disease, with a stage of T2b. The high risk category includes men with a PSA more than 20, Gleason 8 or

higher disease and a stage of T2c or higher. [181] Table 3 shows a comparison of the various criteria of each risk stratification system.

Table 3. Criteria comparison of risk stratification systems.

Risk classification	D'Amico	NCCN	NICE
Very low	N/A	- PSA density <0.15 ng/mL/g **and** - T1c **and** - Gleason score ≤6/grade group 1 **and** - PSA <10 ng/mL **and** - Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/cores	N/A
Low	- PSA < 10 ng/ml **and** - Gleason Score < 6 **and** - Clinical stage T1c or T2a	- PSA <10 ng/mL **and** - T1-T2a **and** - Gleason score ≤6/grade group 1	- PSA <10ng/ml **and** - Gleason score ≤6 **and** - Stage T1-T2a
Intermediate	- PSA of 10-20 ng/ml **or** - Gleason Score of 7 **or** - Clinical stage T2b	N/A	- PSA 10-20ng/ml **or** - Gleason score 7 **or** - Stage T2b
Favourable – Intermediate	N/A	- T2b-T2c **or** - Gleason score 3+4=7/grade group 2 **or** - PSA 10–20 ng/mL **and** - Percentage of positive biopsy cores <50%	N/A
Unfavourable – intermediate	N/A	- PSA 10–20 ng/mL **or** - T2b-T2c **or** - Gleason score 3+4=7/grade group 2 **or** - Gleason score 4+3=7/grade group 3	N/A
High	- PSA > 20 ng/ml **or** - Gleason Score > 8 **or** - Clinical stage T2c or T3	- PSA >20 ng/mL **or** - T3a **or** - Gleason score 8/grade group 4 **or** - Gleason score 4+5=9/grade group 5	- PSA >20ng/ml **or** - Gleason score 8-10 **or** - Stage >/=T2c
Very high	N/A	- T3b-T4 **or** - Primary Gleason pattern 5 **or** - >4 cores with Gleason score 8–10/grade group 4 or 5	N/A

Localisation of disease was performed using multi-parametric MRI followed by transperineal mapping biopsies and/or MR-targeted biopsies. Men unable to have a high quality mpMRI could still be treated if they had template mapping biopsies. Intermediate and high-risk cases also underwent a radioisotope bone-scan and/or cross-sectional CT to rule-out distant metastases.

All surgeons underwent a rigorous period of training involving online learning, observation of five cases on two separate occasions in an expert centre, on-site proctoring by an expert urologist for five or more cases and then followed by the presence of an expert clinical applications specialist for all subsequent treatments.

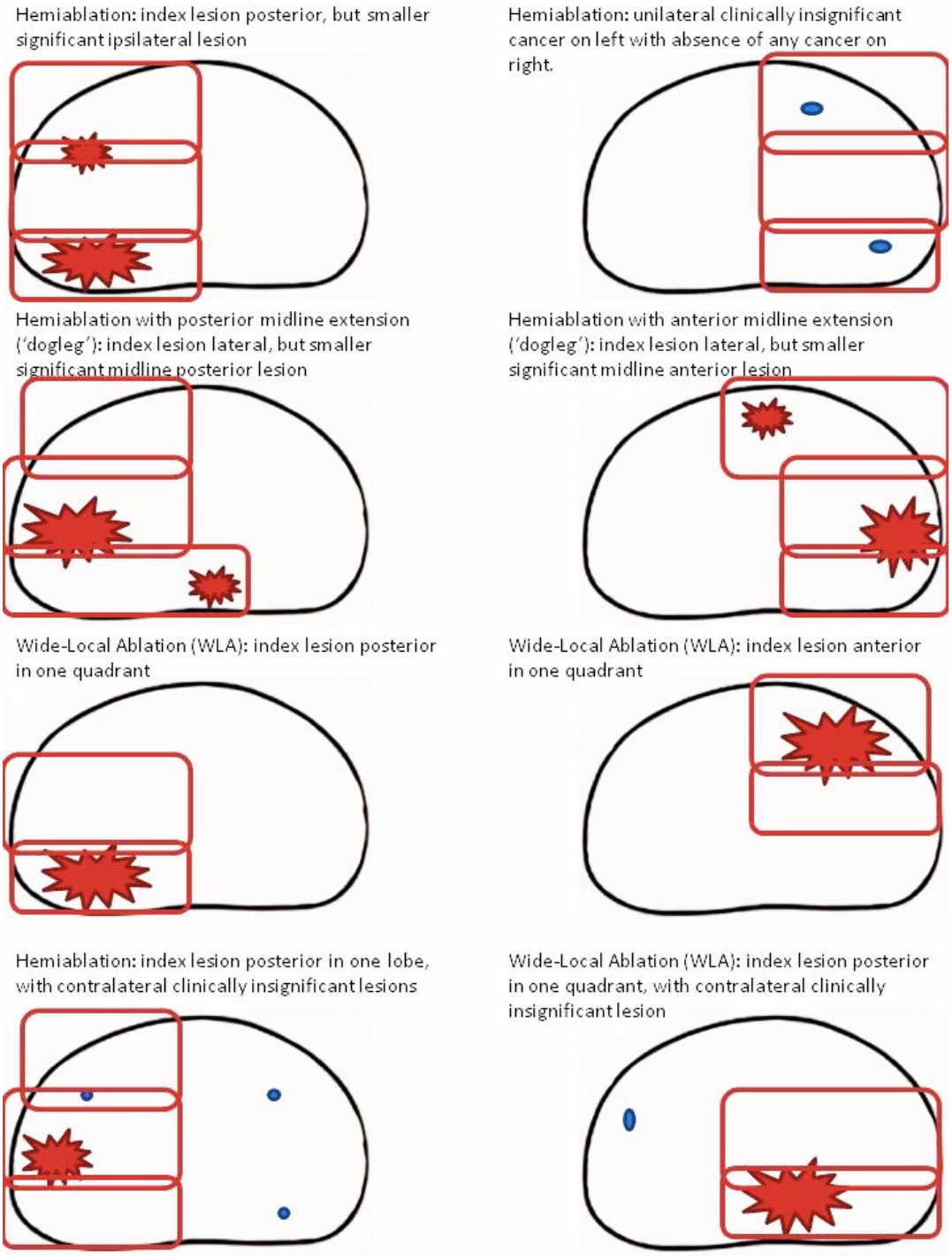
All patients gave pre-operative consent after appropriate counseling and detailed discussions on the benefits as well as complication rates and side-effect profile of hemiablation HIFU including: bleeding, infection, lower urinary tract symptoms, urethral stricture, bladder neck stenosis, urinary retention, urinary incontinence, erectile dysfunction and anaesthetic risks. In particular, discussions also clarified the possible need of re-treatment or transition to other treatments, including radical whole-gland therapy, and the need for long-term follow-up with regards to possible ipsilateral recurrence or progression, as well as *de novo* disease on the contralateral side.

The treatment was delivered using the Sonablate®500 device (Sonacare Inc., USA) within nine centres. The procedure carried out in the lithotomy position under general anaesthesia to prevent patient movement. Most patients were discharged on the same day of treatment and the maximum length of stay was less than 48 hours. A 16Ch urethral catheter was usually inserted pre-operatively, and clamped, to aid treatment planning. The ultrasound probe is placed in the rectum. The boundaries of the prostate were identified and prostate volume calculated. The volume to be treated

was planned using live longitudinal and sagittal ultrasound images, and depended on the location and size of the lesion.

Treatments were delivered in a quadrant or hemigland fashion using 2-4 treatment blocks, depending on the gland volume as well as tumour volume and location. Hemigland ablation was defined as destruction of one lobe of the prostate, whereas quadrant ablation was defined as destruction of half one lobe. Index lesion ablation alone was conducted in patients with multifocal disease provided untreated areas harbored no more than 3mm of Gleason 6 on systematic or template biopsies (Figure 10).

Figure 10: Types of focal therapy using HIFU carried out in men with non-metastatic prostate cancer.



The aim of treatment was destruction of the lesion with a safety margin of at least 5mm. Since focal HIFU is a targeted therapy with the aim of preservation of function, safety margins were defined to ensure protection

of the contralateral neurovascular bundle, external sphincter and bladder neck. Each ultrasound pulse lasted 4 seconds, with a 6 second interlude to allow cooling of tissue. The urethral catheter was removed during midline blocks treating around the urethra. This was re-inserted upon completion of treatment. Intra-operative intravenous antibiotics were administered and patients were routinely prescribed a 5-day course of oral antibiotics post-operatively. The urethral catheter was removed 5 to 7 days after the HIFU procedure. Most patients were discharged on the day of treatment.

Up to two re-treatments with focal HIFU were offered as part of the intervention. All men were advised to undergo 3 to 6 monthly serum PSA testing. A mpMRI was routinely performed regardless of PSA kinetics at 1 year and every 1-2 years thereafter. Two rises in PSA after the nadir level was achieved, without predefining the level of rise, was investigated with a prostate biopsy, or mpMRI followed by biopsy if the mpMRI was suspicious. We have previously reported on the high negative predictive value of mpMRI in the post-focal HIFU setting for clinically significant prostate cancer.[182] Clinically significant tumours are defined as an index volume of greater than 0.5cm^3 and a Gleason score of 7 or higher.[183,184] Clinically significant cancer on biopsy of untreated areas was defined as 'out-of-field' progression.

Redo-HIFU was offered when either, a) clinically significant cancer on biopsy occurred in-field or out-of-field and where the mpMRI staging indicated that the disease was still localised or, b) when the mpMRI demonstrated a clear in-field recurrence (mpMRI Likert score 5) associated with a rising PSA. Other considerations for redo-HIFU were the absence of intra-prostatic calcification or difficult disease location such as apical disease overlapping the external urinary sphincter. Patients were also routinely offered the option of radical prostatectomy or radical radiotherapy.

Follow-up consisted of three-monthly serial serum PSA measurements. An individual PSA nadir was calculated for each patient, due to the presence of untreated prostate. MRI and transrectal, MR-targeted or template transperineal biopsies were carried out in cases of PSA progression at 12 months. Positive biopsy of the ablated area, 'in-field' recurrence, requiring further intervention, was considered as treatment failure. Positive biopsies of the contralateral untreated area were defined as 'out-of-field' recurrence and were not considered to be treatment failure but as metachronous disease development.

Physicians assessed post-operative adverse events during follow-up clinic visits every 3-6 months in the first year, and every 6-12 months in year 2 and beyond. Functional outcomes were assessed by patient reported outcome measures using validated questionnaires, collected at 1-2 and 2-3 years following focal HIFU treatment. Validated questionnaires used included the International Prostate Symptom Score (IPSS), International Index of Erectile Function 5 item (IIEF-5),[185] and EPIC Urinary Continence domain.[186] All data was audited and quality controlled by two data managers.

The International Society of Urological Pathology (ISUP) has issued guidelines for the grading of prostate cancer based on a consensus conference held in 2014. These recommendations were a further development of the 2005 ISUP modified Gleason grading. The 2014 provided clarification on the morphological criteria and definitions of the various grading patterns of acinar and intraductal carcinoma. The ISUP recommend that the Gleason scores $\leq$6, 3+4=7, 4+3=7, 8, 9 and 10 be reported as five groups, ISUP Grades 1 to 5 respectively.[187,188] During the data collection period, the new grading system was still being implemented, and therefore for the purpose of standardization the team continued with the old grading system.

As part of the University College London Clinical Trials Group, my personal

involvement included accessing case notes at all participating sites, collating and entering the data into the Focal HIFU registry database. This was done for the 625 patients enrolled into the registry. Throughout the two years, I updated the registry four times, at 6 monthly intervals.

I ran weekly focal HIFU clinics to assess and counsel pre-operative patients, obtain, ensured patients filled out pre-operative quality of life questionnaires, as well as actively recruited patients for the INDEX trial. This enabled me to enter necessary data into the focal HIFU registry simultaneously. I also followed-up post-operative patients, taking blood samples for PSA testing when this was not carried out in primary care, and organized follow-up investigations, namely imaging and post-operative biopsies, as necessary.

I also participated in weekly Prostate clinics, where I saw patients with both benign and malignant prostate pathology, organized the necessary per-operative investigations and handed out quality of life questionnaires. I actively recruited patients into the various clinical trials run by the UCL group including INDEX, PROMIS, SMART Target, PRORAFT and NanoKNIFE. In these clinics, I also counseled patients for focal HIFU and focal cryotherapy procedures and booked patients onto theatre lists appropriately.

I attended and presented patients at the focal therapy MRI meetings on a weekly basis. The purpose of these meetings was to assess patient suitability for focal therapy and determine the most appropriate ablative treatment modality for each patient. It also allowed me to identify patient's eligibility for the INDEX trial and for focal HIFU. In addition, I also attended weekly Urology MDT meetings.

During my assigned theatre lists, which occurred twice a week, I gained expertise in delivering focal HIFU and focal cryotherapy. I also ran weekly lists of template as well as cognitive and fusion targeted transperineal

prostate biopsies. My log book comprises a total of 48 focal HIFU cases, reaching and 217 transperineal prostate biopsies, achieving level 4 competency for both. Through these theatre lists, I actively participated in the INDEX, PROMIS and SMART Target trials.

Working on the statistical analysis for the three cohort groups, I met with Susan Charman once a month. As further statistical analysis was required, I had set up weekly Skype meetings with Max Peters. In addition, I had regular meetings with the UCL Clinical Trials Group to help set up the electronic version of the registry.

4.2 Primary outcomes of the focal HIFU cohort

There are currently no accepted intermediate endpoints for cancer-control following focal HIFU. As a result, we decided to use failure-free survival (FFS) defined as avoidance of local salvage therapy (surgery or radiotherapy), systemic therapy, metastases or prostate cancer-specific death. This excluded any definitions incorporating biochemical PSA kinetics, as there are none that are valid in this setting.

4.3 Secondary outcomes of the focal HIFU cohort

Our main secondary outcomes included rates of metastases-free survival, prostate cancer-specific and overall mortality. The focal HIFU study group also report biopsy outcomes when carried out as well as adverse events and side effects. Urinary continence status was defined as being completely pad-free (0 pad usage) as well socially continent (0-1 pads per day). The latter definition is commonly used in many series reporting radical prostatectomy outcomes (in which 1 pad or less is counted as continent).[189] We also report on complete pad-free, leak-free urinary continence in which any level of leakage, even of a few drops was regarded as incontinent. Erectile function was defined as the ability to complete penetrative sexual activity with or without oral phosphodiesterase-inhibitor medication. We also evaluated whether certain baseline factor might predict for FFS.

4.4 Statistics

As a cohort registry study there was no prior sample size calculations. Our decision to analyse and publish these data were based on the registry being open for 10 years and this cohort having achieved approximately 5-year median follow-up. Baseline characteristics are presented as mean (standard deviation [SD]), median (interquartile range [IQR]) or as proportions, as appropriate. Kaplan-Meier estimates of time-to-event outcomes are described with 95% confidence intervals (95%CI) in those men with at least 6 months follow-up. Adverse events are reported as proportions only, and for these the entire cohort was included in order to reduce selection bias. Urinary continence was evaluated using EPIC Urinary Continence domain questionnaire with a pad-free definition and a socially continent definition (0-1 pads).

Table 4. Cox regression model for progression free survival based on univariable analysis on Age, Prostate volume, Pre-HIFU PSA, Gleason score and T stage. (n=538)

Cox regression model for progression free survival					
Univariable analysis	**HR (95%-CI)**	**p-value**	**Multivariable analysis**	**HR (95%-CI)**	**p-value**
Age (per year increase)	1.01 (0.98-1.05)	0.5	**Age (per year increase)**	NS	NS
Prostate Volume (per cc increase)	1.01 (0.99-1.02)	0.4	**Prostate Volume (per cc increase)**	NS	NS
Pre-HIFU PSA (per point increase)	1.04 (1.01-1.07)	0.005	**Pre-HIFU PSA (per point increase)**	1.04 (1.01-1.07)	0.004
Gleason Score			**Gleason Score**		
7	1.63 (0.86-3.08)	0.1	7	NS	NS
8-10	3.57 (0.80-16.00)	0.1	8-10	NS	NS
T Stage			**T Stage**		
2	1.24 (0.49-3.15)	0.7	2	NS	NS
3	3.11 (1.13-8.56)	0.03	3	3.06 (1.11-8.44)	0.03

Abbreviations: HR=hazard ratio, HIFU=high intensity focused ultrasound, PSA=prostate specific membrane antigen, NS=not significant. n=22 patients were deleted in the multivariable analysis due to missing data points in the determinants. The total dataset was therefore n=577 with 60 events. There was significant no difference between the patients with and without missing data in the model.

Erectile function was defined by reporting on the proportion of patients who answered on the IIEF-5 questionnaire that they were able to maintain erections sufficient for penetrative intercourse, some, most or all of the time, with or without oral medication

Cox regression was used to determine whether baseline factors could predict failure free survival (FFS). The univariable analysis included age, prostate volume, PSA, Gleason score and clinical T-stage. Multivariable factors with $p<0.05$ were included (Table 4). R version 3.4.2 was used for all statistical analyses. (R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna. Austria. URL https//www.R-project.org/.) The discriminative ability of the model was measured using Harrell's C statistic. The models were recalculated using 2000 bootstrap resamples to account for optimism, after which the c-statistics were adjusted. A C-statistic is comparable to an AUC value for survival models.

Chapter 5

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Focal HIFU in the Treatment of Localised Prostate Cancer - Results

Chapter 5 - Focal HIFU in the Treatment of Localised Prostate Cancer - Results

5.1 Introduction

This chapter provides the results from the independent, academic, prospective focal UK HIFU registry of 625 patients diagnosed with localized prostate cancer and treated with focal HIFU over a period of 10 years. Details of data collection have already been explored in Chapter 4.

5.2 Results

5.2.1. Baseline Characteristics

625 patients were treated with primary focal HIFU for clinically significant non-metastatic prostate cancer, across nine UK centres; 599 with at least 6 months follow-up. 505 (86%) had intermediate or high-risk prostate cancer (Table 5). Median follow-up was 54.2 months (IQR 31.5-68.2).T-staging was solely derived based on histopathology results from the prostate biopsies.

Table 5. Baseline characteristics in patients undergoing focal high intensity focused ultrasound (HIFU) for non-metastatic prostate cancer.

Characteristic	**Group 1** (N=599)
Age, median	66 (SD 7.5)
Pre-HIFU PSA, ng/ml (median, IQR)	7.2 (5.2-10.0) (n=12 missing)
Pre-HIFU PSA ranges, ng/ml, (N, %) **<10** **10-20** **>20**	 440 (75%) 134 (23%) 13 (2%) (n=12 missing)
Pre-HIFU prostate volume, ml, (median, IQR)	37 (28- 47) (n=37 missing)
Pre-HIFU PSA density, ng/ml/ml, (median, IQR)	0.2 (0.1-0.3) (n=46 missing)

Gleason Score, (N, %) **</=6** **=7** **>/=8**	 166 (28%) 327 (55%) 97 (17%) (n=9 missing)
Pre-HIFU T-stage, (N, %) **T1** **T2** **T3a / T3b**	 65 (11%) 432 (75%) 75 (12.5%) / 7 (1.2%) (n=20 missing)
D'Amico Risk Group, (N, %) **Low** **Intermediate** **High**	 78 (13%) 316 (52.8%) 189 (31.6%) (n=16 missing)

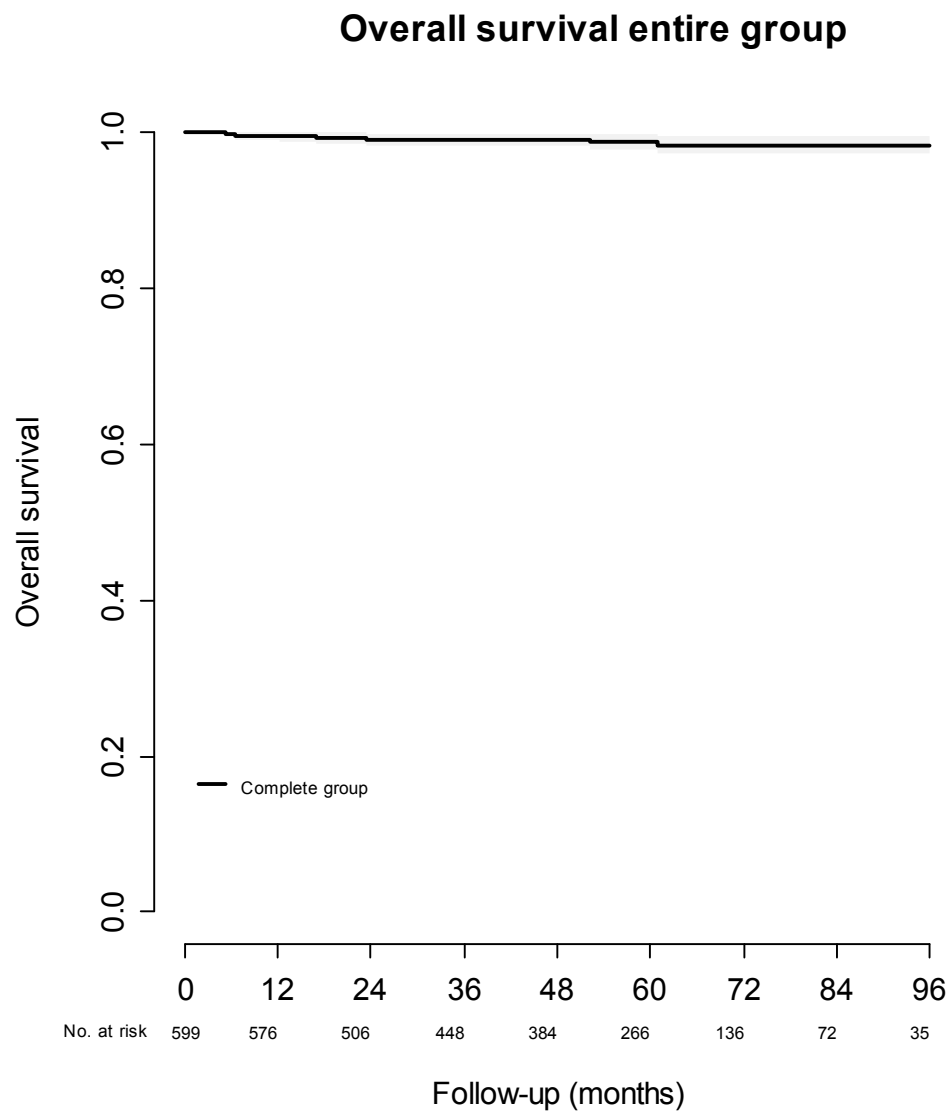
5.2.2 Primary outcomes

Failure free survival (95%CI) at 1, 3 and 5 years was 99% (98-100), 92% (90-95) and 88% (85-91) (Table 6). Kaplan-Meier estimates (95%CI) at 5 years were 96% (91-100), 88% (84-93) and 84% (78-90) for D'Amico low, intermediate and high-risk groups, respectively (*p=0.09*) (Figure 11).

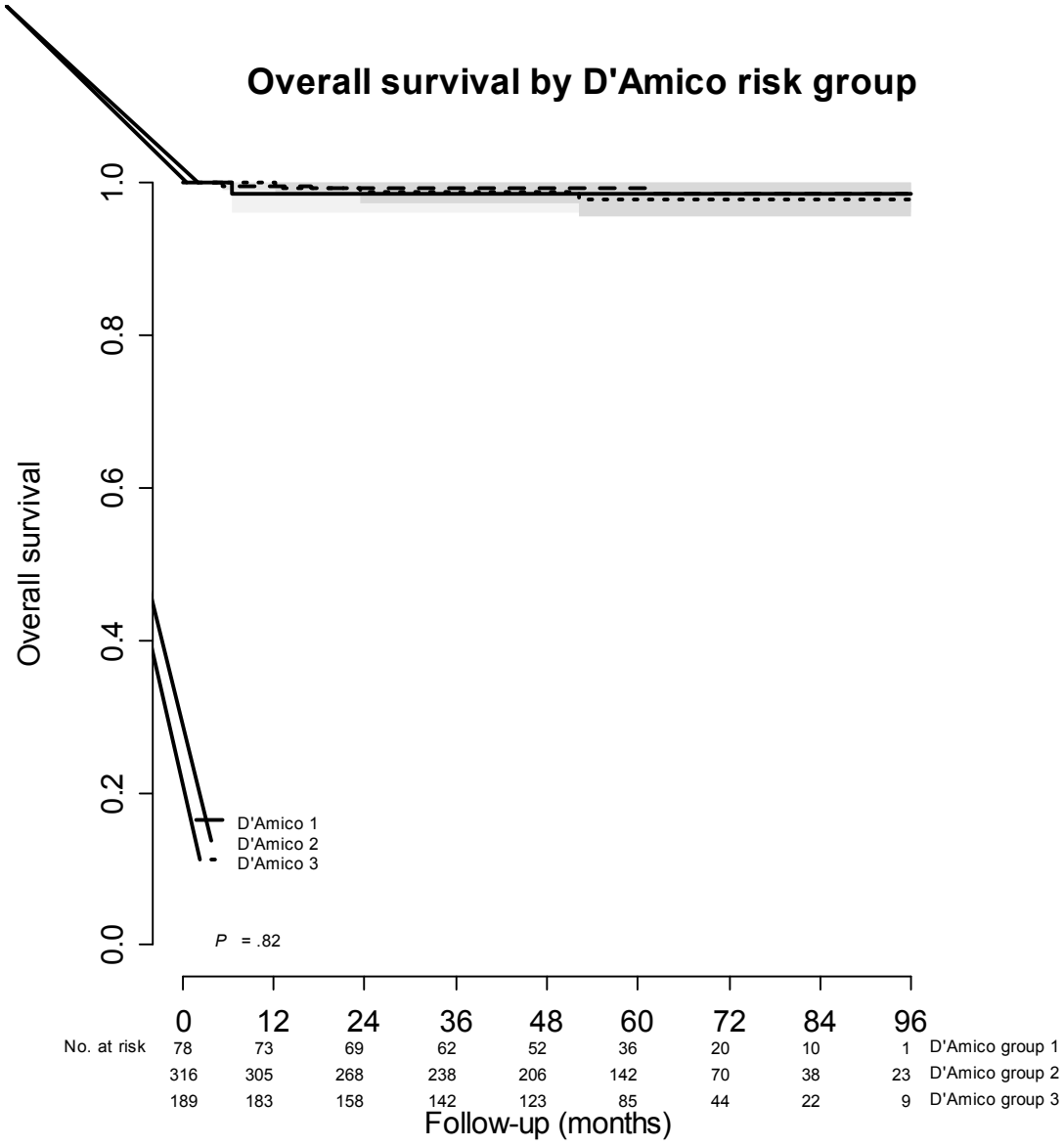
Table 6: Kaplan-Meier estimates of percentage (95%CI) freedom from redo HIFU, survival, metastasis-free and overall failure-free survival (FFS) following focal HIFU therapy in men treated for non-metastatic prostate cancer.

	1 year	**3 years**	**5 years**
Overall survival	100 (99-100)	99 (98-100)	99 (97-99)
By D'Amico Classification			
Low	99 (96-100)	99 (96-100)	99 (96-100)
Intermediate	100 (99-100)	99 (98-100)	99 (97-100)
High	99.5 (98-100)	99 (97-100)	98 (96-100)
P=0.82			
Metastases free survival	99.7 (99-100)	99 (98-100)	98 (97-99)
By D'Amico			
Low	100 (n/a)	99 (96-100)	96 (93-100)
Intermediate	99.7 (99-100)	99 (97-100)	99 (97-100)
High	99.5 (98-100)	98 (96-100)	97 (95-100)
*[p=0.65]**			
Failure free survival	99 (98-100)	92 (90-95)	88 (85-91)
By D'Amico			
Low	99 (96-100)	96 (91-100)	96 (91-100)
Intermediate	99 (97-100)	93 (90-96)	88 (84-93)
High	98 (97-100)	89 (85-94)	84 (78-90)
*[p=0.09]**			
By Gleason score			
≤6	99 (98-100)	95 (92-99)	92 (87-97)
7	99 (98-100)	92 (89-95)	87 (83-91)
≥8	89 (71-100)	89 (79-100)	59 (26-100)
*[p=0.14]**			
By pre-HIFU PSA group			
<10	99.5 (99-100)	95 (93-97)	92 (89-95)
≥10	97 (94-100)	85 (78-91)	77 (69-84)
*[p=0.00002]**			
Free from redo focal HIFU therapy	98 (96-99)	84 (81-87)	75 (71-80)
By D'Amico			
Low			
Intermediate	97 (94-100)	82 (74-92)	78 (69-89)
High	97 (95-99)	88 (85-92)	79 (74-85)
[p=0.02] * log rank test	98 (97-100)	76 (69-83)	68 (61-76)

Figure 11: Kaplan-Meier curves showing overall survival of (a) entire group and (b) by D'Amico risk group.



(a)



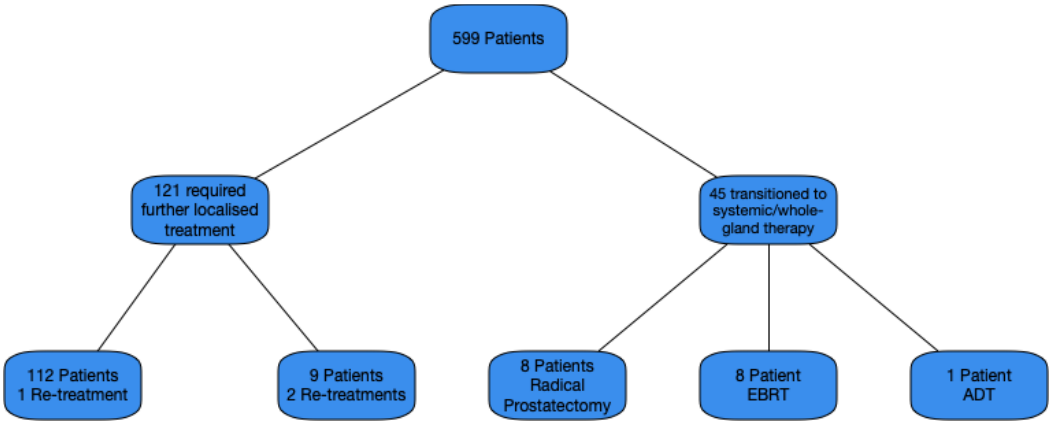
(b)

5.2.3 Secondary outcomes

5.2.3.1 Transition to Further Treatment

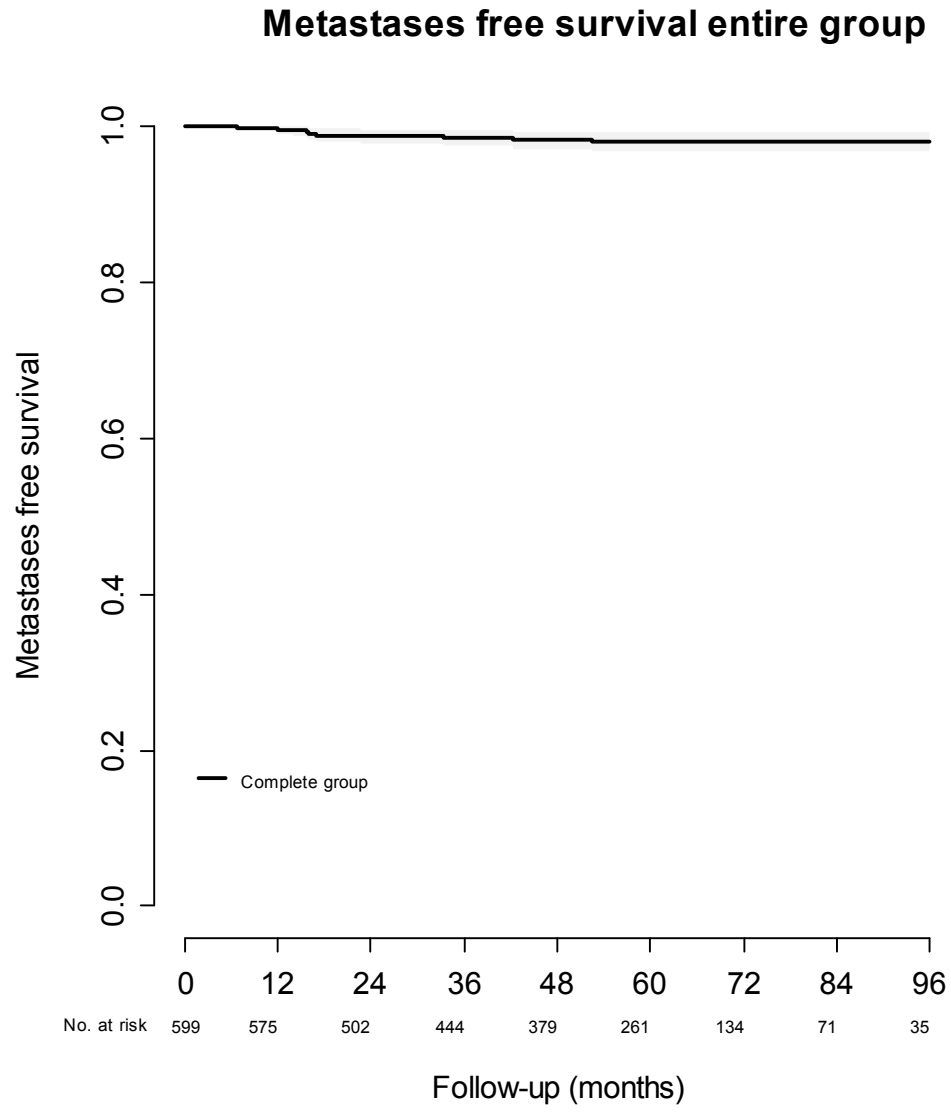
At least one re-treatment with focal-HIFU was given in 121/599 (20%); only one redo-HIFU in 112 patients and two redo-HIFU in 9 (Figure 12). Following focal HIFU therapy, 8/599 (1.3%) transitioned to salvage radical prostatectomy, 36/599 (6%) had salvage external beam radiotherapy and 1/599 (0.2%) was given androgen deprivation therapy, as per Figure 12.

Figure 12. Flow diagram showing the total number of patients requiring further re-treatment with focal HIFU and those transitioning to systemic or whole-gland therapy.

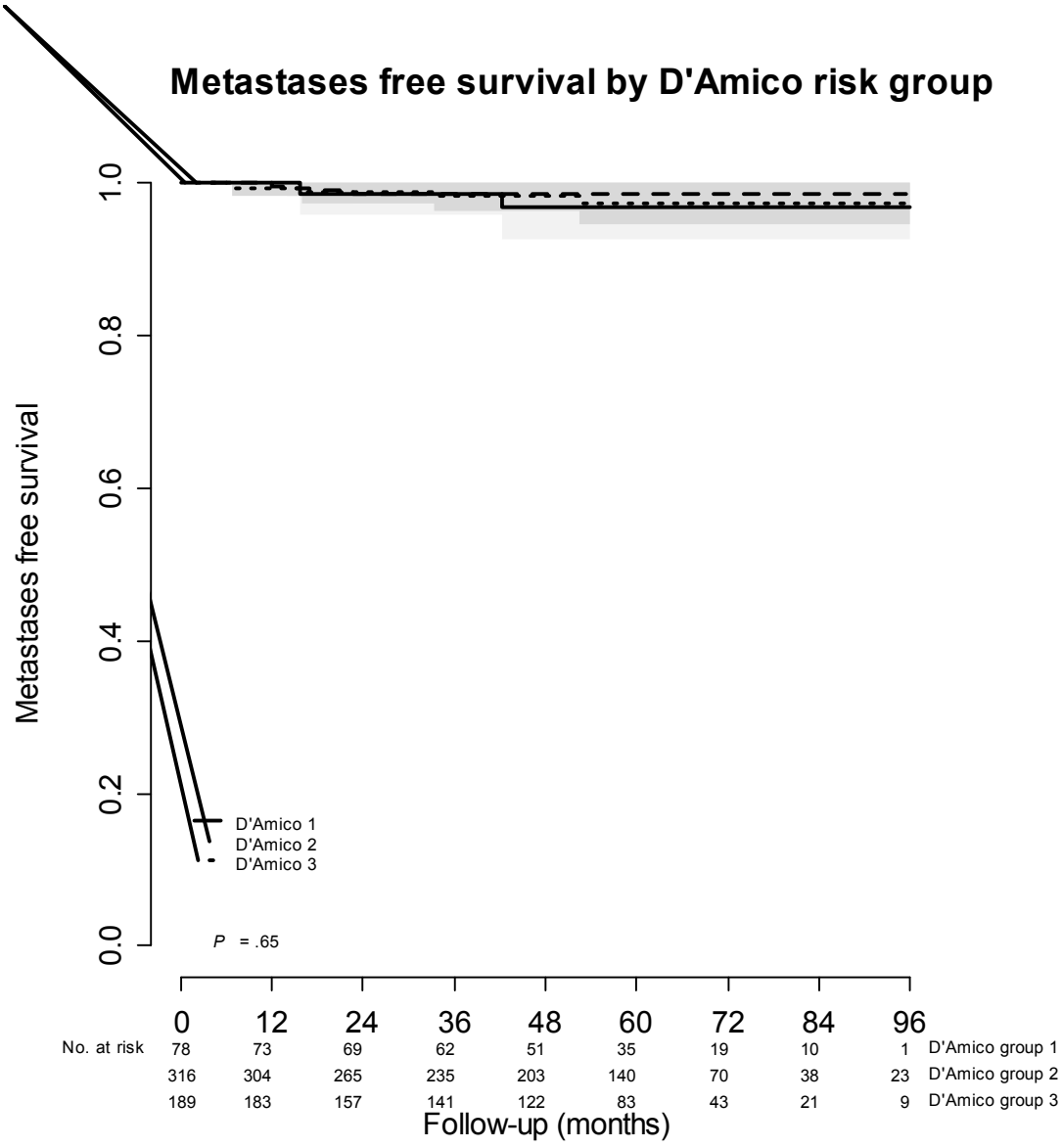


There were 9/599 (1.5%) metastases during the follow-up, of whom 2 had low risk disease, 4 had intermediate risk disease and 4 had high-risk disease; 3 had metastases after the second HIFU treatment. Kaplan-Meier estimates (95%CI) for metastases-free survival at 1, 3 and 5 years was 99.7% (99-100), 99% (98-100) and 98% (97-99), respectively (Figure 13). There were 7/599 (1.2%) deaths, of which none were related to prostate cancer. Kaplan-Meier estimates (95%CI) for overall survival at 1, 3 and 5 years were 100% (99-100), 99% (98-100) and 99% (98-100), respectively.

Figure 13: Kaplan-Meier curves showing metastases free survival of (a) entire group and (b) by D'Amico risk group.



(a)



(b)

5.2.3.2 Post-Focal HIFU Biopsies

Following focal-HIFU 222/599 had biopsies. 111 of these were within our three earlier phase I/II studies[13,14,15] and 111 had for-cause biopsies as a result of rising PSA and/or suspicious mpMRI post focal-HIFU. Overall, 29/599 (4.8%) had histological in-field recurrence on biopsy, whilst 16/599 (2.7%) had histological evidence of out-of-field de novo cancer or progression of untreated low-risk disease. A further 11/599 (1.8%) patients had both in-field and out-of-field disease on biopsy. Figures 14 and 15 show mpMRI pre- and post-focal HIFU in successful primary and re-do treatments.

Figure 14. Dynamic contrast-enhanced MRI changes in successful treatment for localized prostate cancer using focal HIFU. (a) DCE MRI prior to focal HIFU treatment demonstrated localized disease with a lesion in the right peripheral zone of the gland (circled). (b) DCE MRI at 12 months showing fibrotic reaction and no residual prostate tissue in the treated part of the gland.

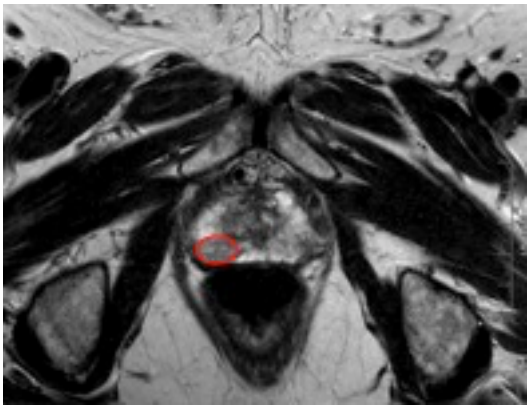


Fig. 14(a)

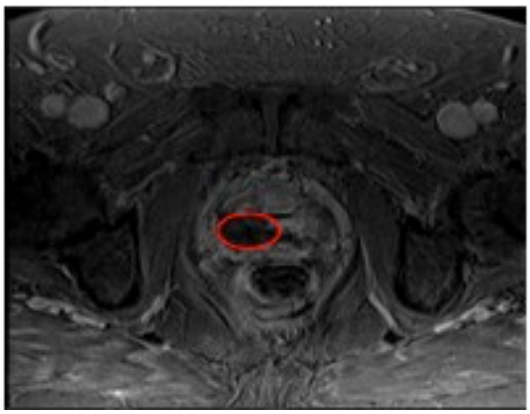
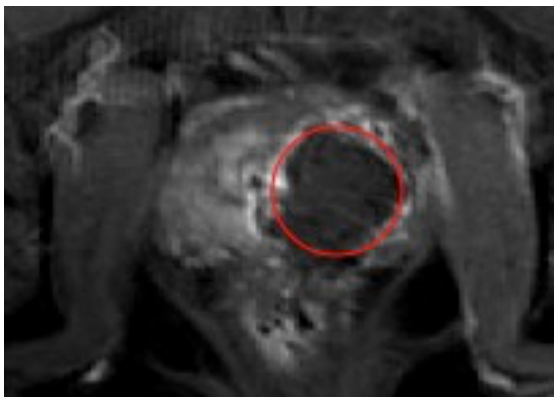


Fig. 14(b)

Figure 15. Dynamic contrast-enhanced MRI changes in successful re-treatment for localized prostate cancer using focal HIFU. (a) DCE MRI 6 weeks after left hemiablation focal HIFU treatment demonstrating treatment cavity poor perfusion in the treated part of the gland (circled). (b) DCE MRI 12 months after hemiablation HIFU treatment demonstrating residual disease at the periphery of the treated cavity. (c) DCE MRI after re-treatment with focal HIFU to the previously treated left prostate gland showing successful, complete treatment.



ure(a)

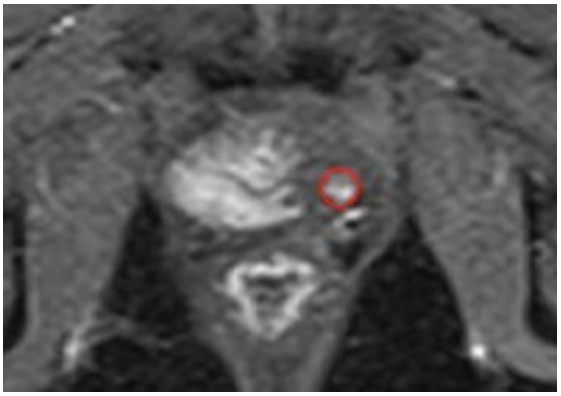


Fig 15(b)

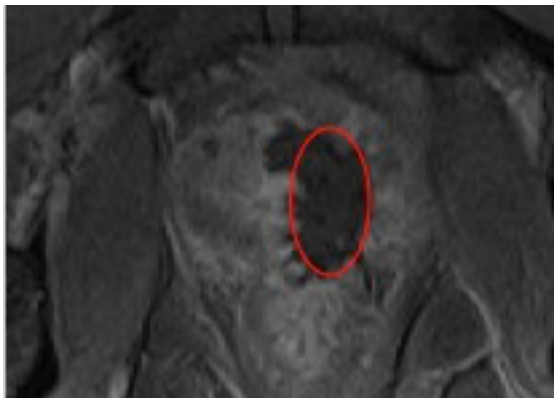


Fig. 15(c)

5.2.3.3 Adverse Events

None had bleeding requiring intervention or transfusion. Within 6 months of treatment, post-operative urinary tract infection and epididymo-orchitis occurred in 53/625 (8.5%) and 12/625 (1.9%), respectively. Endoscopic interventions for lower urinary tract symptoms at any time-point were required in 60/625 (9.6%). There were two (0.3%) recto-urethral fistulae. One healed following urinary diversion using urethral and suprapubic catheters for 6 months but no bowel diversion. The other required open reconstructive surgery due to failure of conservative management (Table 7). The recto-urethral fistulae occurred in patients with high-grade disease with treatment delivered across the midline. These cases occurred in the initial stages of this series, during surgeon's learning curve, which might account for the fistulae formation in these two patients.

It is unlikely that this data is under-reported, as patients were followed-up closely in the immediate post-operative period, and regularly thereafter. In updating the registry data, primary care were contacted for each patient to obtain further information regarding possible adverse events. Once patients were discharged back to primary care, they could be re-referred to the treatment centre.

Table 7: Clavien-Dindo classification of post-HIFU complications

Clavien-Dindo Classification	**Complication**	**Rate**
I	UTI	53/625 (8.5%)
I	Epididymo-orchitis	12/625 (1.9%)
IIIa	Recto-urethral fistula	1/625 (0.1%)
IIIb	Endoscopic procedures for LUTS	60/625 (9.6%)
IIIb	Recto-urethral fistula	2/625 (0.3%)

5.2.3.4 Functional Outcomes

Baseline urinary continence status was recorded in 421 using EPIC Urinary domain questionnaires. At 1-2 years and 2-3 years after focal-HIFU, pad-free status was available in 313 and 247, respectively, at both baseline and follow-up; 304 (97%) and 241 (98%) were pad-free (0 pads), at these two time points, respectively. None required more than 1 pad per day so social continence was achieved in 100%. At 1-2 years and 2-3 years after focal-HIFU, pad-free, leak-free status was available in 250 and 195, respectively, at both baseline and follow-up; 208 (83%) and 156 (80%) were pad-free, leak-free continent, at these two time points, respectively (Table 8).

425 had baseline erectile function recorded through the IIEF-5 questionnaire. At 1-2 years and 2-3 years, erectile function status was available in 165 and 101, respectively, at both baseline and follow-up; 138 (84%) and 87 (86%) maintained erectile function at these two time points, respectively (Table 8).

Table 8. Patient reported outcome measures using validated questionnaires in men undergoing focal HIFU for non-metastatic prostate cancer.

Patient reported outcome measure		**N (%)**	
Follow-up		**1-2 years**	**2-3 years**
Urinary continence (EPIC Urinary domain)	0 pads	304/313 (97%)	241/247 (98%)
	0-1 pads	313/313 (100%)	247/247 (100%)
	No leakage at all	208/250 (83%)	156/195 (80%)
Erectile function (IIEF-5)	Erections sufficient to maintain penetrative sexual activity	138/165 (84%)	87/101 (86%)

5.2.3.5 Multivariate Analyses

The C-statistics are as follows. Model 1: 0.63 (corrected at 0.59), model 2: 0.64 (corrected at 0.60), model 3: 0.66 (corrected at 0.62), model 4: 0.66 (corrected at 0.61), model 5: 0.70 (corrected at 0.65). The third model has the lowest Akaike Information Criterion (AIC) value.

Table 9. Cox regression model for progression free survival based on PSA density, Gleason score and T stage. (n=538)

	HR	p-value	95% Confidence Interval	
Age	1.01	0.70	0.97	1.05
PSA Density				
>0.145 - ≤0.252	0.92	0.81	0.45	1.89
>0.252	1.59	0.16	0.83	3.03
Gleason Score				
7	1.29	0.44	0.67	2.4912
8-10	2.63	0.21	0.57	
T Stage				
2	1.31	0.61	0.46	3.72
3	3.00	0.06	0.96	9.40

Table 10: Cox regression model for progression free survival based on age, PSA density, Pre-HIFU PSA, Gleason score and clinical T stage. (n=538)

	HR	p-value	95% Confidence Interval	
Age	0.99	0.77	0.96	1.03
PSA Density				
>0.145 - ≤0.252	0.80	0.55	0.39	1.67
>0.25	0.96	0.92	0.44	2.10
Pre-HIFU PSA				
>10ng/ml	2.37	0.01	1.20	4.72
Gleason Score				
7	1.31	0.42	0.68	2.52
8-10	2.87	0.18	0.62	13.15
T Stage				
2	1.30	0.62	0.46	3.71
3	3.17	0.05	1.01	9.99

Table 11. Cox regression model for progression free survival based on age, prostate volume, pre-HIFU PSA. Gleason score and T stage (n=538)

	HR	p-value	95% Confidence Interval	
Age	0.99	0.70	0.95	1.03
Prostate Volume				
>31ml - </=43ml	1.50	0.23	0.78	292
>43ml	1.28	0.49	0.64	2.58
Pre-HIFU PSA				
>10ng/ml	2.35	0.003	1.35	4.1
Gleason Score				
7	1.28	0.46	0.66	2.46
8-10	2.61	0.22	0.56	12.1
T Stage				
2	1.38	0.55	0.48	3.95
3	3.54	0.03	1.10	11.28

Table 12. Cox regression model for progression free survival based on age, PSA density, prostate volume, PSA, Gleason score and T stage. (n-538)

	HR	p-value	95% Confidence Interval	
Age	0.99	0.71	0.95	1.03
PSA Density				
>0.145 - ≤0.252	0.86	0.69	0.40	1.82
>0.25	1.24	0.67	0.47	3.26
Prostate Volume				
>31ml - </=43ml	1.63	0.18	0.80	3.32
>43ml	1.48	0.37	0.63	3.50
Pre-HIFU PSA				
>10ng/ml	2.00	0.08	0.93	4.32
Gleason				
7	1.25	0.50	0.65	2.43
8-10	2.60	0.22	0.56	12.08
T Stage				
2	1.39	0.54	0.48	3.98
3	3.53	0.03	1.11	11.26

Table 13. Cox regression model for progression free survival based on age, PSA density, PSA, Gleason score, T stage and post-HIFU PSA nadir (n-524)

	HR	p-value	95% Confidence Interval	
Age	0.99	0.76	0.96	1.03
PSA Density				
>0.145 - ≤0.252	0.92	0.82	0.43	1.94
>0.25	1.17	0.70	0.53	2.55
Pre-HIFU PSA				
>10ng/ml	1.87	0.09	0.91	3.83
Gleason				
7	1.31	0.43	0.68	2.54
8-10	3.26	0.13	0.71	15.00
T Stage				
2	1.16	0.78	0.40	3.35
3	2.92	0.079	0.92	9.27
Post-HIFU PSA Nadir	1.11	0.04	1.01	1.23

Goodness of fit of the models was measured using Harrell's C statistic. The models were recalculated using 2000 bootstrap resamples to account for optimism, after which the C-statistics were adjusted. A C-statistic is comparable to an AUC value for survival models, i.e. discriminative ability of the models. A value 0.7 is usually the border of reasonable discriminative ability. In addition, models were compared with AIC to assess maximum likelihood combined with the amount of utilized parameters by the models.

In clinical terms, the Cox regression analyses above show that PSA and T stage multivariables have an effect on failure. The higher the PSA and T stage, the higher the hazard of failure, which is consistent with our current knowledge, and essentially, are both indicative of disease aggression.

Colinearity was measured using the variance inflation Factor (VIF) in all models. A value between 1 and 4 is generally accepted as indicating moderate correlation for the variable in question. The highest VIF's in the models created are below 4, therefore, we did not exclude the collinear factors from the current models (Table 14).

Table 14: Colinearity between categorical factors measured with the Variance inflation factor (VIF).

	Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.07	1.18	1.17	1.19	1.17
PSA Density					
>0.145 - ≤0.252	1.45	n/a	1.50	1.59	1.56
>0.25	1.45		2.13	3.25	2.09
Prostate Volume					
>31ml - </=43ml	n/a	1.47	n/a	1.69	n/a
>43ml		1.48		2.23	
Pre-HIFU PSA					
>10ng/ml	n/a	1.06	1.61	2.02	1.73
Gleason					
7	1.16	1.16	1.17	1.18	1.17
8-10	1.15	1.17	1.16	1.18	1.16
T Stage					
2	3.38	3.44	3.41	3.45	3.35
3	3.51	3.60	3.53	3.60	3.40
Post-HIFU PSA Nadir	n/a	n/a	n/a	n/a	1.22

5.3 Limitations of this study

We accept that there are some limitations. First, due to the nature of our prospective registry being embedded into clinical care not all patients were routinely biopsied after treatment. We have validated the role of mpMRI for follow-up after focal HIFU compared to prostate biopsy and have shown that the negative predictive value for mpMRI in this setting is 95% or higher for clinically significant prostate cancer.[182] Second, in light of not having a validated and accepted cancer control measure, we considered a clinically meaningful composite outcome measure that reflects the recent Intermediate Clinical Endpoint in Carcinoma of the Prostate (ICECaP) consensus group's findings.[185] Third, validated questionnaire data was not available in all patients, due to our reliance on postal return of questionnaires.

5.4 Discussion

This study shows that following focal HIFU therapy, overall failure-free survival was 89% at 5 years. Metastases-free, cancer-specific and overall survival was 97%, 100% and 99% at 5 years. Only 2% had urinary incontinence requiring 1 daily pad use, none required more than 1 pad per day and 14% suffered erectile dysfunction. Bowel complications were rare (0.3%).

The strengths of our study lie in being large and multicentre with medium term follow-up data prospectively collected in a nationally mandated registry and with independent quality control of data entry against source records. We predominantly treated patients with clinically significant prostate cancer in whom it is widely accepted to require treatment and would otherwise have a higher risk of progression on active surveillance.

The PROTECT trial showed no survival advantage between active monitoring and radical therapy. This trial however, included a population of men recruited from a screening study and was therefore dominated by low risk men, most of which would not benefit from treatment. In the present study, approximately 90% of men had intermediate and high-risk disease and therefore the group is very different to the PROTECT study. Other studies such as SPCG-4 and PIVOT showed that men with intermediate and high-risk disease did benefit from treatment. This study therefore, treated men that required it and not men who would otherwise do well from active surveillance.

Whilst it is accepted that whole-gland radical prostatectomy or radical radiotherapy are effective in treating clinically significant non-metastatic prostate cancer they do so with significant rates of urinary incontinence ranging between 1.5 to 72% after radical prostatectomy, [190,191] and 2 to 42%[192,193,194] after radical radiotherapy, as well as sexual side effects, varying between 26 to 100% in radical prostatectomy and 8 to 85% with external beam radiotherapy.[195] And in the case of radiotherapy, some bowel

toxicity. Focal therapy, by treating known areas of cancer with a margin, aims to preserve prostate tissue and minimize damage to neurovascular bundles, bladder neck, external urethral sphincter and rectum. We have shown that this strategy has low rates of treatment-related side effects and good cancer control in the medium term. Despite the absence of 10 to 15 year follow-up data, we find these results reassuring and acceptable considering that we predominantly offered focal HIFU to patients with intermediate or high-risk cancer.

Most HIFU users have now stopped offering whole-gland HIFU treatment due to the functional outcomes reported in out previous paper. If men require whole-gland treatment based on their disease status, we recommend radical prostatectomy or radiotherapy unless they are unfit or unsuitable for these treatment modalities. We do not see a role for ablative therapy within the whole-gland treatment armamentarium.

Most of our low risk cases were historical when active surveillance for such disease was still questioned and it was deemed appropriate to offer these men focal HIFU as an alternative to radical therapy. Nonetheless, these cases still required a minimum amount of Gleason 6 cancer to qualify. Our UK focal HIFU programme now does not permit focal HIFU treatment in instances of low volume Gleason 6 disease because the probability of such lesions progressing is rare.[196] This stance is in comparison to some other studies that have predominantly treated very low or low risk disease with focal therapy.[197-198]

Whilst long-term data is awaited, randomized comparative studies in patients with intermediate and high-risk cancers are currently being piloted.[29] However, due to previous problems in maintaining physician and patient equipoise in eleven failed randomized comparative trials comparing different interventions for localised prostate cancer this might not be possible to deliver.[199] Even if randomisation could be delivered, the sample size would have to be based on a non-inferiority design that might require

between 2,000 and 8,000 patients recruited, randomised and followed up over 10-15 years, depending on the non-inferiority margin used. Focal therapy has been evaluated using various energy modalities in single-arm retrospective and prospective development studies. Recent systematic reviews of these studies has shown focal therapy to have a minimal impact on the quality of life of patients, and whilst oncological effectiveness is yet to be established, genito-urinary function is well preserved. [142,200]

However, there have been instances of other treatments such as prostate brachytherapy and robotic prostatectomy being approved for clinical use without, or prior to the completion of, randomized comparative studies. Partial nephrectomy for treating renal cancer is another example. Such changes in practice were often based on medium term outcomes from cohort studies because the long natural history of prostate or small renal tumours made it unfeasible to deliver randomised controlled trials. In this context, physicians and healthcare organisations will need to consider whether it is justified to insist on randomized comparative data for focal therapy compared to radical therapy powered on mortality and metastases. On the basis of our data, patients currently diagnosed with prostate cancer that is suitable for focal therapy may prefer to have the option to choose whether they wish to have whole-gland radical therapy or focal therapy.

5.5 Conclusion

Focal therapy using HIFU could be offered to select patients with clinically significant nonmetastatic prostate cancer as it is effective in the medium term in terms of oncological outcomes and has a low probability of urinary and rectal side effects. However, longer-term data is required on maturation of this data set.

Chapter 6

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The Role of Focal HIFU in the Elderly Population

Chapter 6 - Role of Focal HIFU in the Elderly Population.

6.1 Introduction

Prostate cancer is the most common malignancy in men aged >60 years of age. More than half of the men with this diagnosis are aged more than 65 years. And nearly a quarter of men are aged >75 years of age. Therefore, elderly men have the highest prevalence of prostate cancer as well as the highest mortality rate from prostate cancer. Indeed, Scosyrev *et al* examined results from the Surveillance, Epidemiology, and End Results (SEER) database and have shown that compared with men aged 60 to 64 years, men aged 75-79 years were 3.5 times more likely to die from prostate cancer and contributed to twice as many prostate cancer deaths over a period of 8 years.[201]

With the advent of PSA screening and an increase in life expectancy, there is a growing number of men aged >75 years of age that are diagnosed with prostate cancer. Appropriate management in this cohort of patients is controversial. The difficulty lies in balancing the harms of curative treatment against survival benefit and quality of life. To date, the three main treatments offered to these patients are watchful waiting, radical prostatectomy or radiotherapy. This chapter will focus on how focal HIFU might treat this cohort of men with respect to oncological outcomes and the side effects

6.2 Results

The baseline characteristics of the 90 patients treated with focal HIFU between and June 2016 are tabulated below (Table 15). The median follow-up was 30 months (IQR 14-56). 9 (10%) patients were diagnosed with Gleason $\leq$6 disease, 77 (85.5%) had Gleason 7 and 4 (4.4%) were diagnosed with Gleason $\geq$8 disease. 1 patient (1.1%) was diagnosed with stage T1, 62 (68.9%) were diagnosed with stage T2 and 19 (21.1%) and 3 (3.3%) had T3a and T3b disease respectively.

Table 15: Baseline characteristics in 90 patients over 75 years of age undergoing focal HIFU treatment for non-metastatic prostate cancer.

Characteristic	**Group 1** (N=90)
Age, median (IQR)	77.4 (76.3-79.1)
PSA pre-HIFU, median (IQR)	8.4 (6.1-11.5)
Stage	(missing: 5)
T1	1 (1.1%)
T2	62 (68.9%)
T3a	19 (21.1%)
T3b	3 (3.3%)
Gleason Score	
≤6	9 (10%)
=7	77 (85.5%)
≥8	4 (4.4%)
D'Amico Risk Group	
Low	0 (0%)
Intermediate	43 (47.8%)
High	42 (46.7)
Hormones	
Yes	15 (16.7%)
No	75 (83.3%)

6.2.1 Primary outcomes

Since there are no agreed definitions on biochemical PSA failure following focal therapy for localized prostate cancer, again in this data, we look at transition to systemic therapy as an outcome measure. The Kaplan-Meier estimate at 5 years for prostate cancer-specific survival was 100%. Kaplan-Meier estimates (95% CI) at 5 years for metastases free survival and overall survival are 98.5% (95.6-100) and 97% (92.9-199%), respectively (Table 16, Figures 16-18.)

Table 16: Kaplan-Meier estimates of percentage (95%CI) at 5 years follow-up.

Primary outcomes	
Prostate cancer-specific survival	100% (n/a)
Metastases free survival	98.5% (95.6-100%)
Overall survival	97% (92.9-100%)

Figure 16: Kaplan-Meier curve showing Prostate Cancer-specific survival.

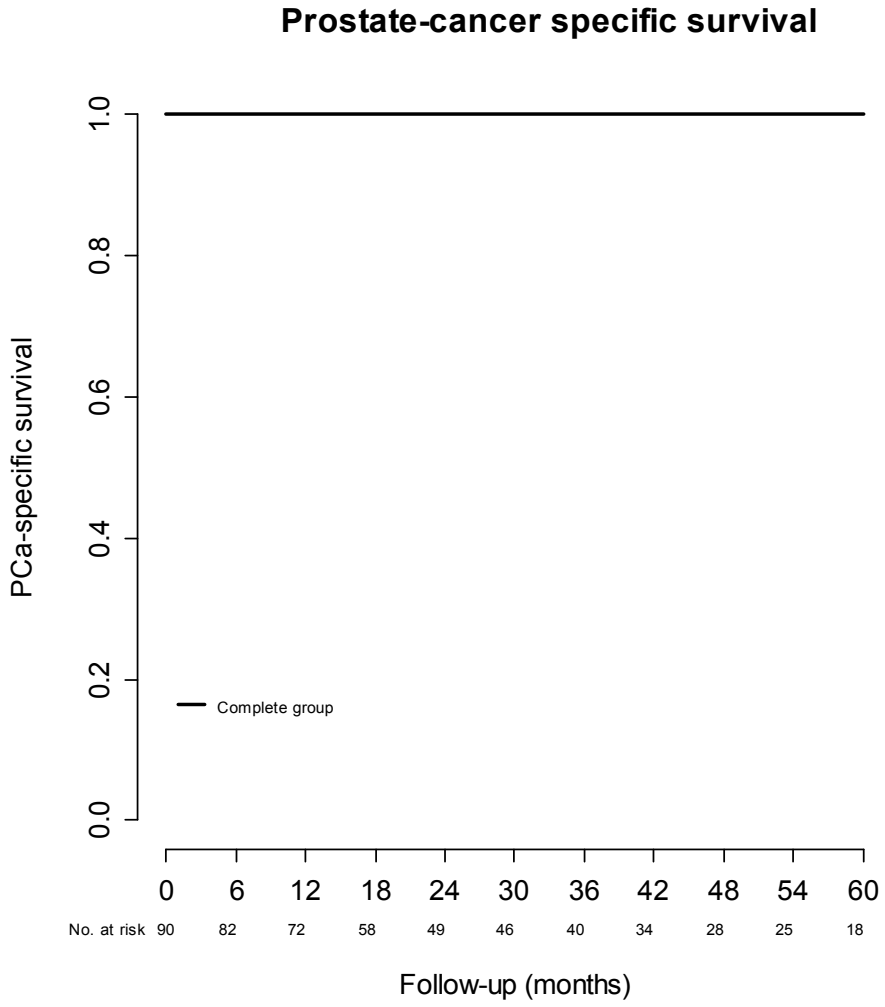


Figure 17: Kaplan-Meier curve showing Metastases-free survival.

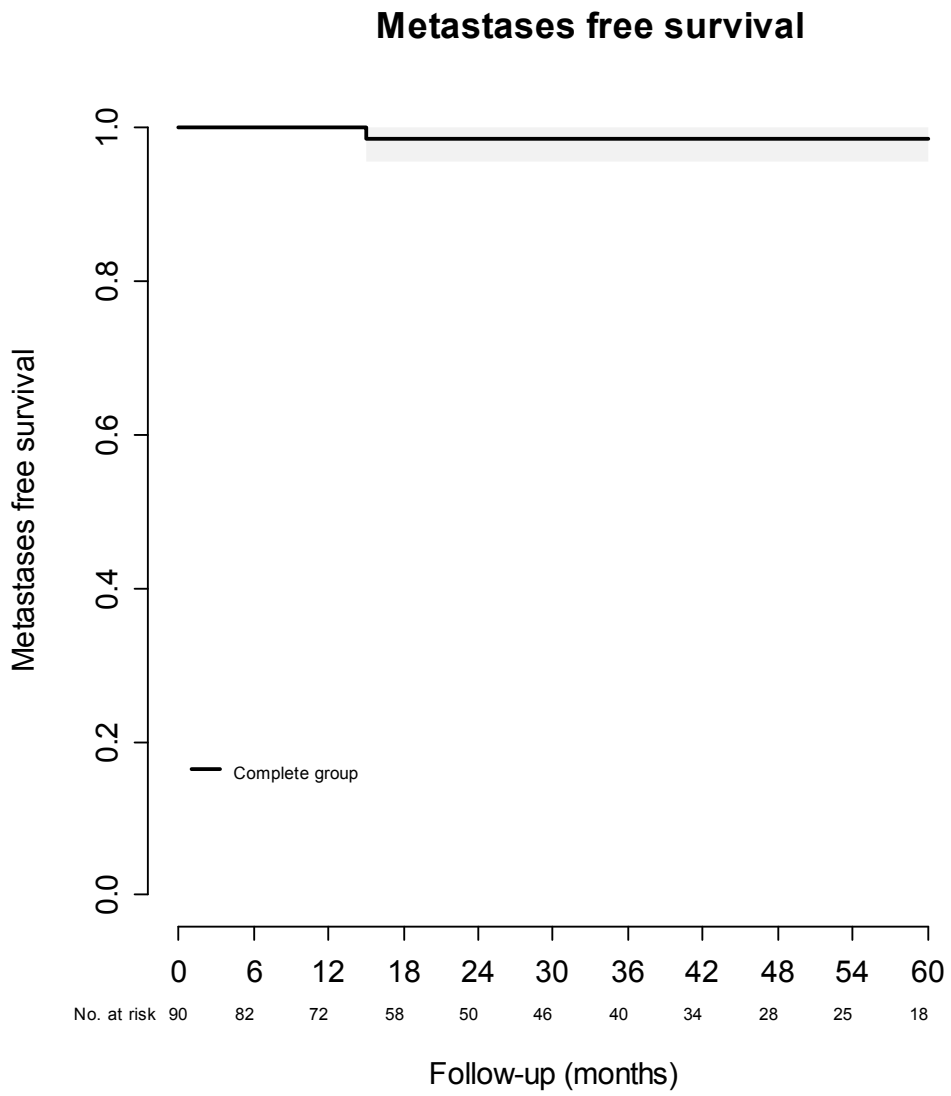
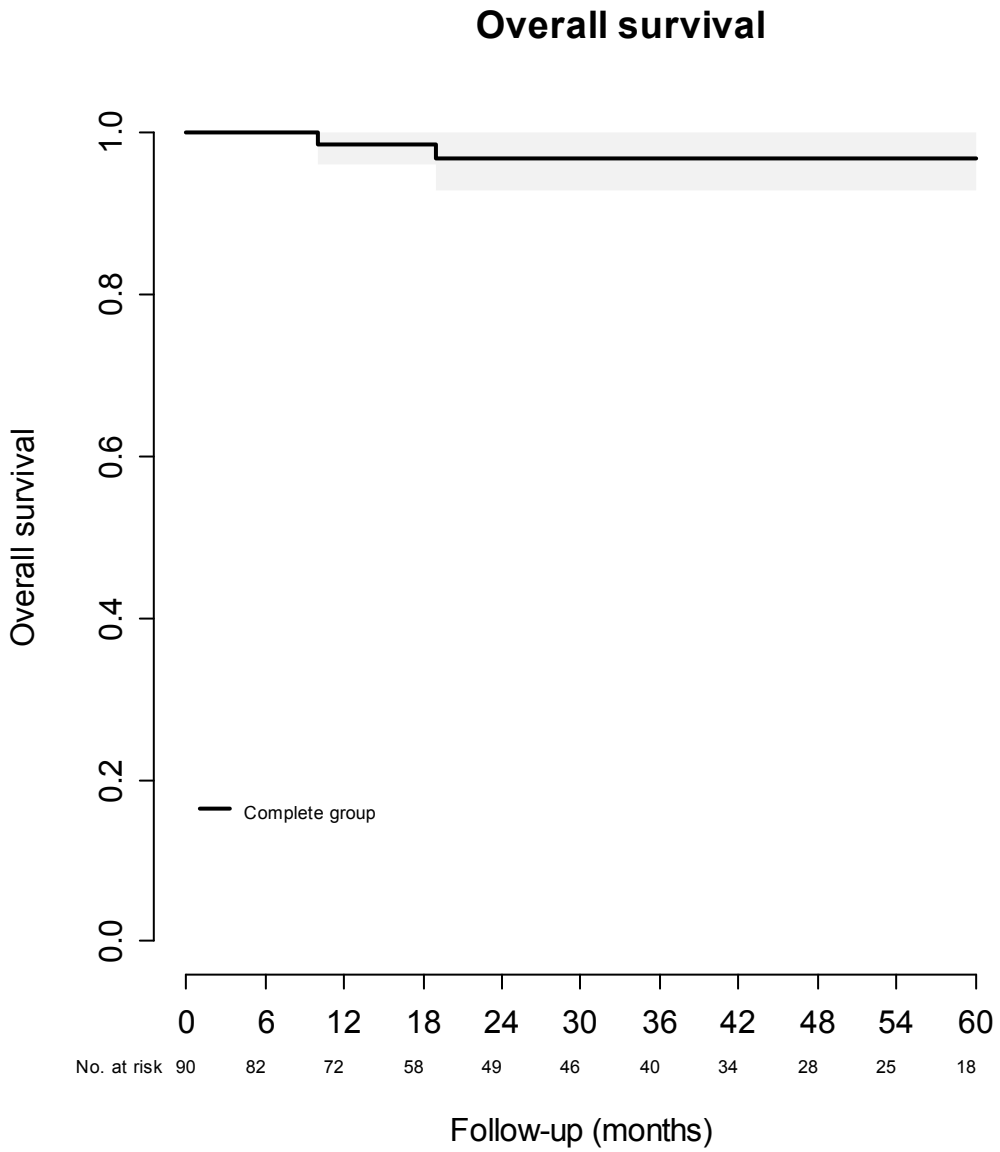


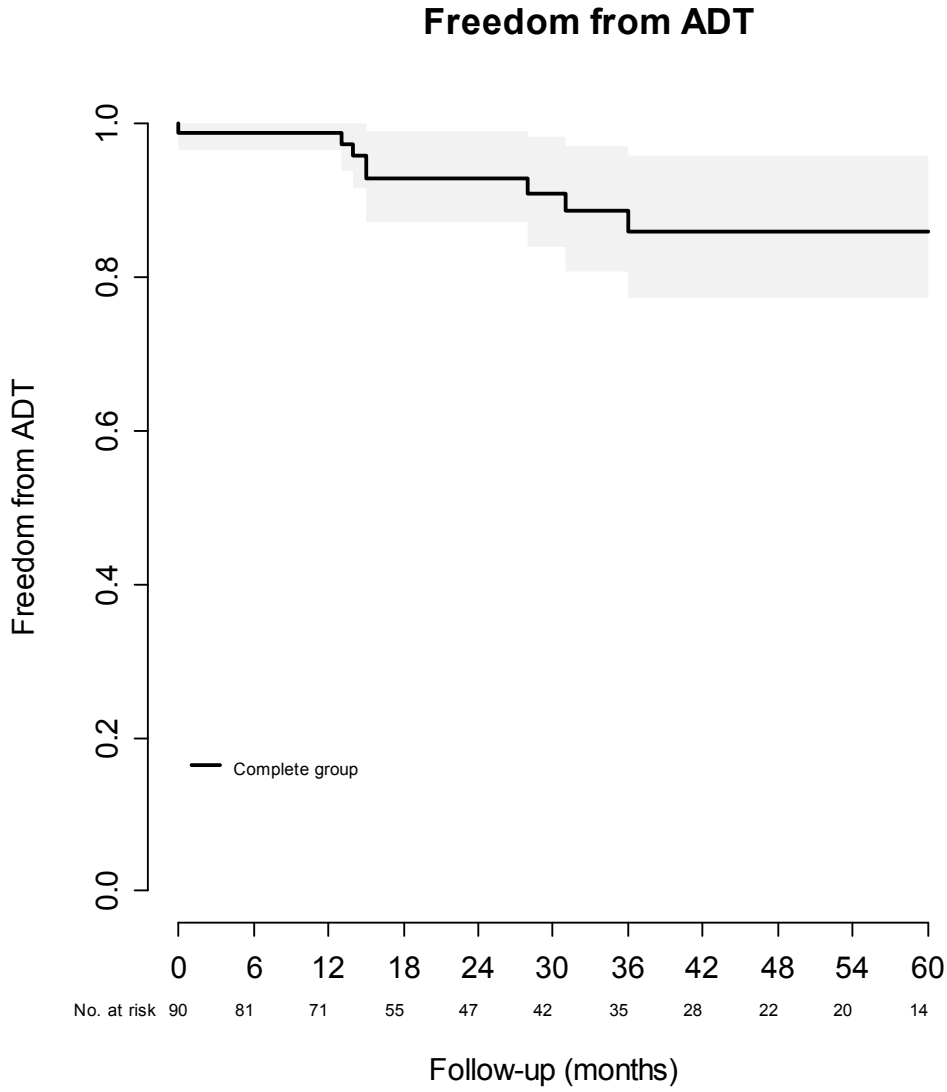
Figure 18: Kaplan-Meier curve showing overall survival.



6.2.2 Secondary outcomes

The Kaplan-Meier curve at 5 years of follow-up of freedom from androgen deprivation therapy was 83.4% (72.9-95.3%) (Figure 19).

Figure 19: Kaplan-Meier curve showing freedom from ADT in the complete group.



Urinary continence was evaluated using EPIC Urinary Continence domain questionnaire with a pad-free definition and a socially continent definition (0-1 pads).

We report on the cohort of patients that completed a baseline EPIC questionnaire. 32 patients had not completed the baseline questionnaires and have therefore been eliminated from the statistical analysis. The p-values were compared to baseline scores using χ^2 or Fisher's exact test. Of the 41 patients that had data for baseline leak-free data, 20 (22.2%) were

leak free at 1-2 years post-focal HIFU and 19 (21.1%) were leak-free 2-3 years post-treatment. Of the 57 patients who completed the pad-free data, the median baseline was 57 (63.3%), 33 (36.7%) and 22 (24.4%) were pad free at 1-2 years and 2-3 years, respectively. The EPIC total baseline median score is 32, and, 81 and 78, at 1-2 years and 2-3 years respectively. The EPIC total score was compared to baseline with the Wilcoxon-signed rank test (Table 17).

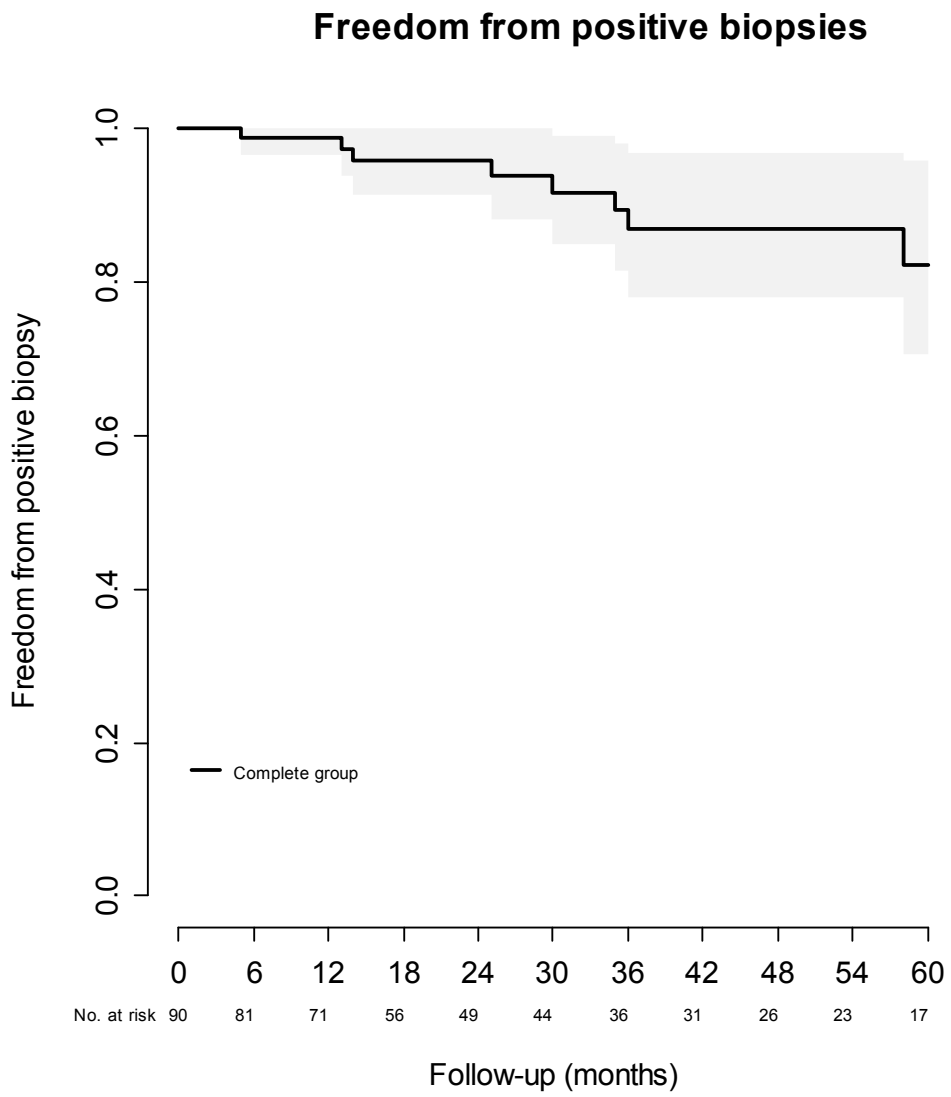
Table 17: The Extended Prostate Cancer Index Composite questionnaire results at 1-2 years and 2-3 years.

EPIC	
Leak free	
Baseline	41 (45.6%) (missing=32)
1-2 years	20 (22.2%) (missing=53) (p=0.06)
2-3 years	19 (21.1%) (missing=63) (p=0.001)
Pad free	
Baseline	57 (63.3%) (missing=32)
1-2 years	33 (36.7%) (missing=53) (p=1)
2-3 years	22 (24.4%) (missing=63) (p=0.05)
EPIC total score	
Baseline, median [IQR]	32 (26-76) (missing=79)
1-2 years, median [IQR]	81 (30-90) (missing=) (p=0.14)
2-3 years, median [IQR]	78 (27-92) (missing=) (p=NA)

In terms of adverse events, 6 (6.7%) patients developed UTI post-operatively, 2 (2.2%) required endoscopic urethral dilation, and a further 2 (2.2%) patients underwent endoscopic incision of the bladder neck secondary to stenosis. None of the patients developed recto-urethral fistula.

Post-operative biopsies were prompted in those patients with a PSA rise. 20 patients underwent post-operative biopsies, of which 8 (8.9%) were negative, 6 (6.7%) had in-field recurrence, 1 (1.1%) had out-of field recurrence and 2 (2.2%) had both. The positive biopsy free survival rate is 76.1% (60.3-96.1%), with a 95% confidence interval (Figure 20).

Figure 20: Kaplan-Meier curve showing freedom from positive biopsies in the complete group.



6.3 Discussion

6.3.1 Screening for Prostate cancer in Elderly Men

The age of PSA screening and the exponential ageing of the population has resulted in an increased prostate cancer detection rate with subsequent concerns of over diagnosis and over treating.[202,203] However, these concerns may be alleviated by the diagnosis of less advanced disease. According to the SEER database, the median age at diagnosis of prostate cancer is 68 years. More than two thirds of prostate cancer specific deaths occur in men aged more than 75 years. 45% of prostate cancer are diagnosed in those over 75 years of age with 50% being low-risk disease according to the D'Amico classification.[204]

PSA screening is mainly offered to younger men. There is as yet, no consensus on offering PSA screening to men over 70 or 75 years of age. Indeed, many PSA screening studies do not, given that most elderly men are more likely to have aggressive and high-risk disease, many argue that PSA screening should not be offered. Currently, the decision lies with the physician and his judgment. Shared decision making between patient and physician should be promoted, taking into account the patient's co-morbidities, expectations, life expectancy and quality of life. Limiting PSA testing in men over 75 years of age may be prohibiting screening in healthy men with otherwise a long life expectancy.

The theory behind PSA screening is that mortality from prostate cancer can be theoretically reduced. Two randomized controlled trials look at the benefits of early detection of prostate cancer. The European Randomized Study of Screening for Prostate Cancer (ERSPC) incorporated a total of 182,160 men aged between 50 and 74 years. These were randomly assigned to either PSA screening every four years or to a control group that did not undergo this screening method. They found that the incidence of prostate cancer was 9.6% in the screening group as opposed to 6.0% in the control group. The median follow-up was 11 years. 299 patients died from prostate

cancer-related causes in the screening group and 462 in the control group. Therefore, PSA screening was associated with a 21% relative reduction in prostate cancer mortality and the number needed to screen to prevent one prostate-cancer related death was 1055. It did not however, show any significant difference between the two groups in terms of all-cause mortality. [205]

In the US Prostate, Lung, Colorectal and Ovarian screening trial (PLCO), 76,693 men aged between 55 and 74 years were included with a 10-year follow-up. These men were randomized to either annual PSA testing for 6 years and digital rectal examination for 4 years or to a control group. There was a significant decrease in prostate cancer mortality in the screening group. This group exhibited no co-morbidities and the number needed to screen to prevent one prostate cancer death was 723. The group involving screening in men who had at least, one co-morbidity, showed no reduction in prostate cancer mortality.[206]

Both trials have shown that judicious use of PSA screening can decrease prostate cancer-related mortality. However, they excluded patients over 75 years of age. The National Comprehensive Cancer Network (NCCN) guidelines on prostate cancer early detection does not recommend PSA screening for men >75 years of age.[207]

6.3.2 Histopathology of Prostate Cancer in Elderly Men

Older men tend to be diagnosed with a higher Gleason score as well as a larger total tumour volume. The stage of the tumour has also been found to be higher. With these characteristics, cancer in the elderly population leads to clinically significant disease and contribute to a significant proportion of prostate cancer-related deaths. [201,208,209]

Malignant prostate cells are slow growing and many remain in a latent phase. The pathological characteristics of prostate cancer are closely associated with Gleason score and tumour volume. These determine

capsular penetration, spread to seminal vesicles and lymph nodes.[69,210,211,212] As previously discussed, clinically significant tumours are defined as an index volume of greater than 0.5cm^3 and a Gleason score of 7 or higher.[212,184] Such characteristics may have implications to health outcomes even in the ageing population. Data on the pathological characteristics in elderly men is limited since most men above 75 years of age to do not undergo PSA screening routinely. Delongchamps *et al* have addressed this through their study analyzing 211 autopsied prostate glands of which 74 were from men aged $\geq$70 years of age. 45% of these glands were found to have prostate cancer. Although the difference in the index tumour volume was not significant between the two groups, the total tumour volume was greater in the older group. The Gleason score was also significantly higher in men older than 70 years. The elderly group was also found to have more T3 tumours, and cancer in this group was more commonly clinically significant.[208]

Predicting disease progression seems to be important at predicting life expectancy to determine the appropriate treatment for the individual patient. Elderly men with poorly differentiated disease may benefit from radical curative treatment as the cancer may rapidly progress. An important factor to consider is that older men may be less concerned about the genito-urinary toxicity associated with such treatments than the younger men, mainly due to pre-existing poor function. Alibhai *et al*'s meta-analysis showed that radical prostatectomy resulted in a higher quality adjusted life expectancy than watchful waiting in 75-year-old patients with high-grade disease.[1]

6.3.3 Management of Prostate Cancer in Elderly Men

Diagnosis and management of organ-confined prostate cancer is often controversial, particularly in the elderly population. Disease progression is either slow, or does not occur at all, even without treatment. Many patients die from unrelated causes before the prostate cancer becomes symptomatic or life threatening.

There is, to date, a paucity of data when considering the treatment of prostate cancer in the ageing population. Most clinical trials under-represent this particular cohort of patients.[213,214,215] Our data attempts to address this issue and present the feasibility of focal HIFU for the treatment of localized prostate cancer in the over 75 year age group.

6.3.4 The Ageing Population

The management of cancer in the elderly population is of increasing concern in the public health sector. An ageing population infers a greater number of patients diagnosed with the disease. Indeed, the number of people aged over 75 years is set to increase. Naturally, this will cause dramatic shifts in age distribution and prostate cancer incidence. This has significant implications on hospitalization and the provision of health care. There is an ever-increasing need to address the problems facing clinicians in treating the geriatric population.[216,217]

The post-WW II baby boom has resulted in an ageing population that is more active and healthier than the traditional cohort of elderly patients. Most are functionally independent and have a longer life expectancy. Therefore, they expect and demand curative treatments.[218,219,220]

One argument in favour of curative treatment in the elderly is that its absence can lead to complications impairing the quality of life and subsequent loss of the individual's autonomy. This can, in turn, result in significant additional public health costs.

6.3.5 The Relevance of Comprehensive Geriatric Assessment

The comprehensive geriatric assessment (CGA) is a multidimensional approach to patient evaluation. Specific to individual patients, it helps identify patient's problems. In reaching a management decision, a general overview of the patient should be determined. Estimating life expectancy remains the most challenging part in the decision-making process. There are

to date, no specific guidelines to support physicians in this task. Therefore, a multidisciplinary evaluation and a comprehensive geriatric assessment are crucial to offer a personalized treatment plan. It is considered to be more effective and comprehensive than a standard medical assessment.[203,221,222,223] Physicians should take into consideration the patient's co-morbidities, life expectancy, quality of life, baseline functional status, cognitive function, social situation, age and tumour characteristics.[216,224,225,226,227]

The complexity of this assessment should not be underestimated. This decision framework has to balance the life expectancy against the aggressiveness of cancer.[228] The CGA will help in the decision-making process to finalise the management of prostate cancer in the elderly patient.

Chronological age is a parameter that physicians tend to overemphasize. As a result, physicians are in danger of either over-treating low-risk disease or under-treating healthy elderly men with high-risk disease. [209,229,230,231]

According to Terret *et al*, a comprehensive assessment includes consideration of multiple factors using a variety of validated tools. Dependence was determined using the Katz Activities of Daily Livings (ADLs) scale, the Lawton Instrumental Activities of Daily Living (IADLs) and the Karnofsky Performance Scale (PS). The ADLs appraises daily living activities include bathing, dressing, toileting, transferring, continence and feeding.[232] The IADL assesses more complicated activities required in community residence.[233] The PS deals with performance status.[234] The Folstein Mini Mental State Examination (MMSA) gauges the cognitive status of patients[235] and the Mini Nutritional Assessment (MNA) evaluates the nutritional status.[236] The Performance-Oriented Assessment of Mobility evaluates the risk of falls and physical ability of the patient.[237] The Geriatric Depression Scale evaluates depressive symptoms[238] and comorbidity status was assessed with the Cumulative Illness Rating Scale-Geriatrics (CIRS-CG). This validated tool goes through 14 organ system categories. This paper also

suggests the use of a multidisciplinary team that includes representatives from the geriatric and oncology teams, a pharmacist, dietician, social worker and a physiotherapist.[203]

The multidisciplinary International Society of Geriatric Oncology (SIOG) reached a consensus that older men with prostate cancer should be managed according to their individual health status, rather than their chronological age. By using validated questionnaires and medical assessment, it recommends that patients are classed into three groups: healthy or fit patients who should be offered the same treatment options as younger patients; vulnerable patients with reversible impairment who should receive standard treatment after medical intervention and optimization of health status, and frail patients with non-reversible impairment who should receive adapted treatment.[239]

The comprehensive geriatric assessment is a more comprehensive and reliable way of determining life expectancy of elderly patients, which can greatly aid and improve treatment decision-making. It helps to determine more accurately the physiological age, rather than depend solely on the chronological age.

6.3.6 Current Treatment Options in the Elderly

Considerable controversy surrounds the management of localized prostate cancer in elderly men. The current available treatment options for this group of patients include watchful waiting, radical prostatectomy and radiotherapy. The difficulty in managing this cohort of patients lies in balancing the treatment options available against the benefits of survival and quality of life. Since elderly men are more likely to be diagnosed with high-risk prostate cancer and are more likely to die from the disease than younger men, most will benefit from definitive treatment. However, they are also more likely exhibit co-morbidities, which increase their risk of complications and side effects of therapy. Hence, pre-existing co-morbidities can override treatment options.

In the current practice, a significant proportion of men older than 70 years of age with intermediate or high-risk disease are neither offered nor undergo therapy with curative intent. An older patient, with a short life expectancy, who does not have aggressive disease, may not benefit from curative treatment due to the underlying health issues and the harms experienced from treatment.[228,240,241] A 75-year old man with moderately differentiated tumour is offered radical prostatectomy 3000 times less frequently than a 55-year old man with the same cancer.[241] Indeed, men younger than 60 years of age who are diagnosed with clinically localized disease are 25 times more likely to undergo radical prostatectomy than men 70 years or older.[242]

General anaesthesia in the elderly is associated with increased complications rates. Radical prostatectomy is therefore rarely offered as a curative treatment choice. Radiotherapy has been shown to achieve good results for prostate cancer in the elderly. However there is still paucity of data for this treatment option in the frail elderly patient.

6.4 Conclusion

Elderly men are more likely to die of disease and therefore benefit from treatment. This is evident from Alibhai *et al*'s meta-analysis where radical prostatectomy resulted in a higher life expectancy than watchful waiting in the elderly with high-grade disease. Most elderly men are fully functional, have a good quality of life and they may have a life expectancy of 10 years, depending on their co-morbidities and may well demand curative treatment. Is it fair to deny these men curative treatment simply based on their age? In the absence of curative treatment, watchful waiting too presents complications in terms of quality of life. It also means the loss of the individual's autonomy, and these contribute to higher cost and burden on the public health service.

El Fegoun *et al* published the first series on focal HIFU in the elderly patient cohort. Hemiablation HIFU was performed in a total of 12 patients, 11 of

whom had negative follow-up biopsies. One patient had re-treatment with HIFU and 4 were subsequently treated with androgen deprivation therapy. The recurrence-free survival rate was 90% at 5 years. Low morbidity rates are reported: none experience urinary incontinence, 1 patient suffered from an episode of acute urinary retention and 2 had a urinary tract infection.[243]

The results presented in this chapter have demonstrated that it is indeed feasible and safe to conduct focal HIFU in elderly men with non-metastatic prostate cancer. Prostate cancer-specific survival is 100% at 5 years whilst the metastases free and overall survival are 98.5% and 97% respectively. The side effect profile is therefore acceptably low and the cancer control outcomes reassuringly good in the medium term. As the ageing population grows with men living longer, traditional age cut-offs for PSA screening and for treatment of prostate cancer need to be reconsidered especially as focal HIFU offers a low risk treatment option even if conducted under general anaesthetic.

Chapter 7

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Management of Locally Advanced Prostate Cancer

Chapter 7 – Management of Locally Advanced Prostate Cancer

7.1 Introduction

Locally advanced prostate cancer can be managed with androgen deprivation therapy alone or combined with radiotherapy. Locally advanced prostate cancer, which is defined as high-risk, comprises a category of disease between localized and metastatic disease. It represents a disease status defined by local extension of tumour outside the prostatic capsule and/or invasion into adjacent organs or high PSA levels, with negative metastasis on imaging.[244] Since the likelihood of undetected micrometastases is high, and local tumour is too advanced to eradicate, this disease status is amenably treated with radical local radiotherapy to the prostate combined with lymph node irradiation.[245]

To date, the studies looking at radical treatment of locally advanced and high-risk disease[246-247] clearly show a longer survival benefit with radical treatment (radical prostatectomy or radiotherapy) than those that only receive androgen-deprivation therapy (ADT). Further evidence, from RCTs, supports the use of androgen suppression as adjuvant treatment to radiotherapy, as it has shown to improve survival in this group of men.[248-249]

Indeed, a recent population-based study by Stattin *et al*, looked at men aged less than 80 years of age with stage T4 disease and/or PSA level of 50-200ng/ml, using men with stage T3 disease and PSA level <50ng/ml as controls. The evidence emerging from this study confirms that in men with very high-risk disease, prostate-cancer specific mortality and overall mortality were half as high in those units with the highest exposure to radical local treatment as in the units with the lowest exposure. This strong association suggests that radical local treatment decreases mortality even in men with very high-risk prostate cancer for whom radical treatment had previously been considered ineffective.[250]

To this end, we assessed the association between local cancer control with focal high intensity focused ultrasound (HIFU) and mortality in men diagnosed with stage T3 disease. Does focal HIFU have a role in providing local cancer control in those men diagnosed with high-risk locally advanced disease who would otherwise not be eligible for radical whole-gland treatment based on their age and co-morbidites?

7.2 Results

There were 80 patients identified from our focal HIFU registry that were diagnosed with pathological stage T3 disease. The baseline characteristics are outlined below (Table 18). The median overall follow-up was 52 months. 14 (17.5%) patients had Gleason 6 disease, 63 (78.8%) had Gleason 7 and 3 (3.8%) were diagnosed with Gleason $\geq$8 disease. All 80 patients were categorized into the high-risk D'Amico classification. There were 21 (26.3%) patients who received androgen deprivation therapy in addition to focal HIFU.

Table 18: Baseline Patient Characteristics in 80 patients diagnosed with pathological stage T3 disease.

Characteristic	**Group 1** (N=80)
Mean Age (±sd)	67.6 (7.9)
Mean PSA (±sd)	8.2 (4)
Gleason Score	
$\leq$6	14 (17.5%)
=7	63 (78.8%)
$\geq$8	3 (3.8%)
D'Amico Risk Group	
Low	0 (0%)
Intermediate	0 (0%)
High	80 (100%)
Hormones	
Yes	21 (26.3%)
No	58 (72.5%) (missing: 1)

Primary Outcomes

The prostate-specific survival, overall survival and metastases-free survival were 100%, 98.6% and 95.7% respectively (Table 19, Figures 21 to 23).

Table 19: Kaplan-Meier estimates of percentage (95% CI) at 5 years follow-up.

Primary outcomes	
Prostate cancer-specific survival	100% (NA)
Overall survival	98.16% (96-100%)
Metastases free survival	95.7% (90-100%)

Figure 21: Kaplan-Meier curve showing prostate-cancer specific survival.

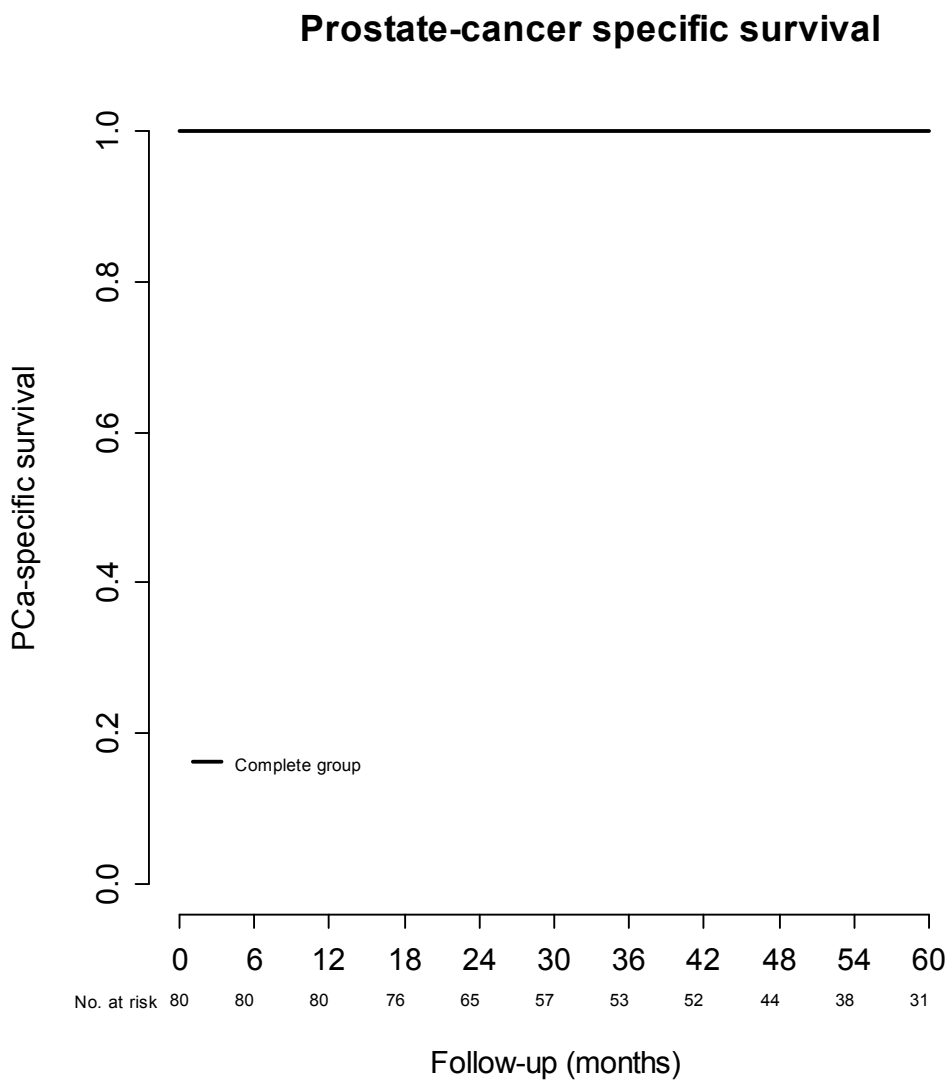


Figure 22: Kaplan-Meier curve showing overall survival.

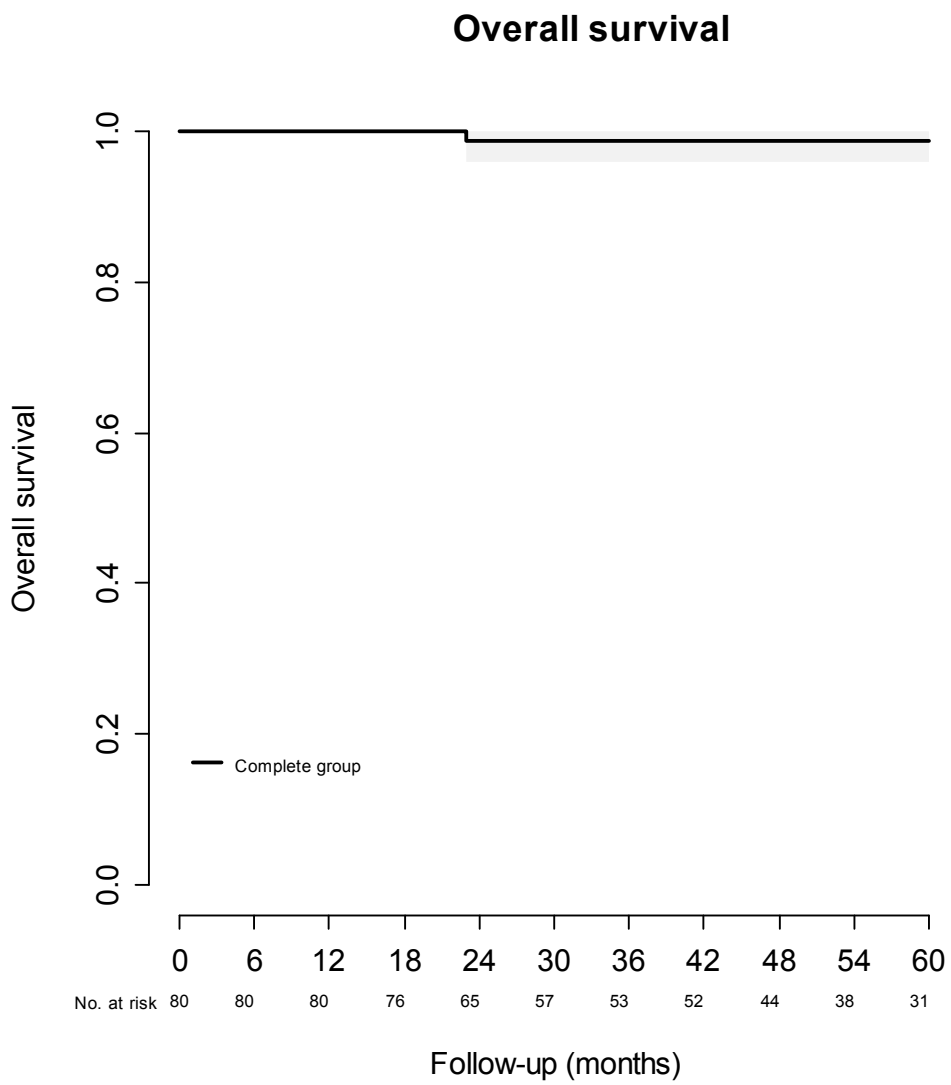
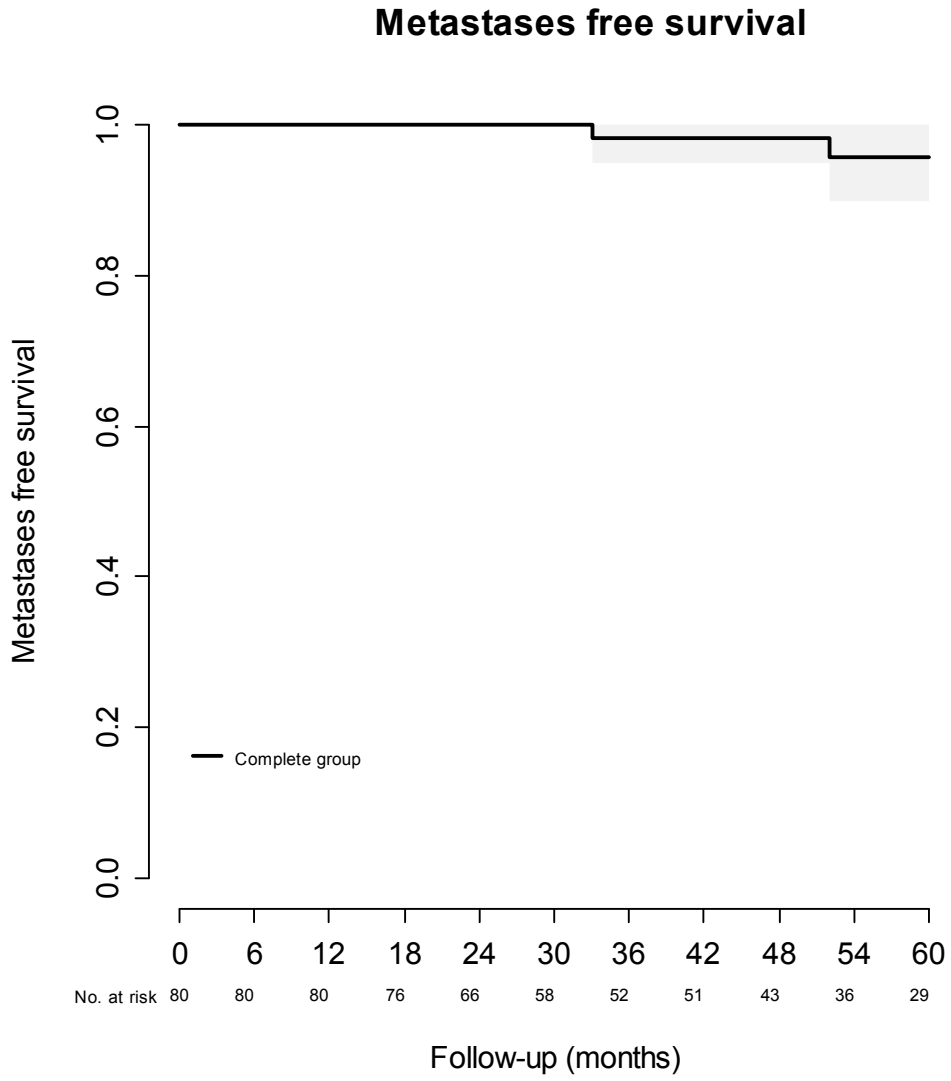


Figure 23: Kaplan-Meier curve showing metastases-free survival.



7.2.2 Secondary Outcomes

The freedom from systemic or whole-gland treatment (ADT, radical prostatectomy and radical radiotherapy) was 75.7%. Freedom from androgen-deprivation therapy was 83.3% (Table 20, Figure 24). A univariable analysis was also carried out which showed that the only significant factors were pre-treatment prostate volume and post-treatment PSA nadir (Table 21).

Table 20: Kaplan-Meier estimates of percentage (95% CI) at 5 years follow-up.

Secondary outcomes	
Freedom from systemic or whole-gland treatment (ADT+RP+RT)	75.7% (65.3-87.8%)
Freedom from ADT	83.3% (74.5-93.2%)

Figure 24: Kaplan-Meier curve showing freedom from systemic or whole-gland treatment.

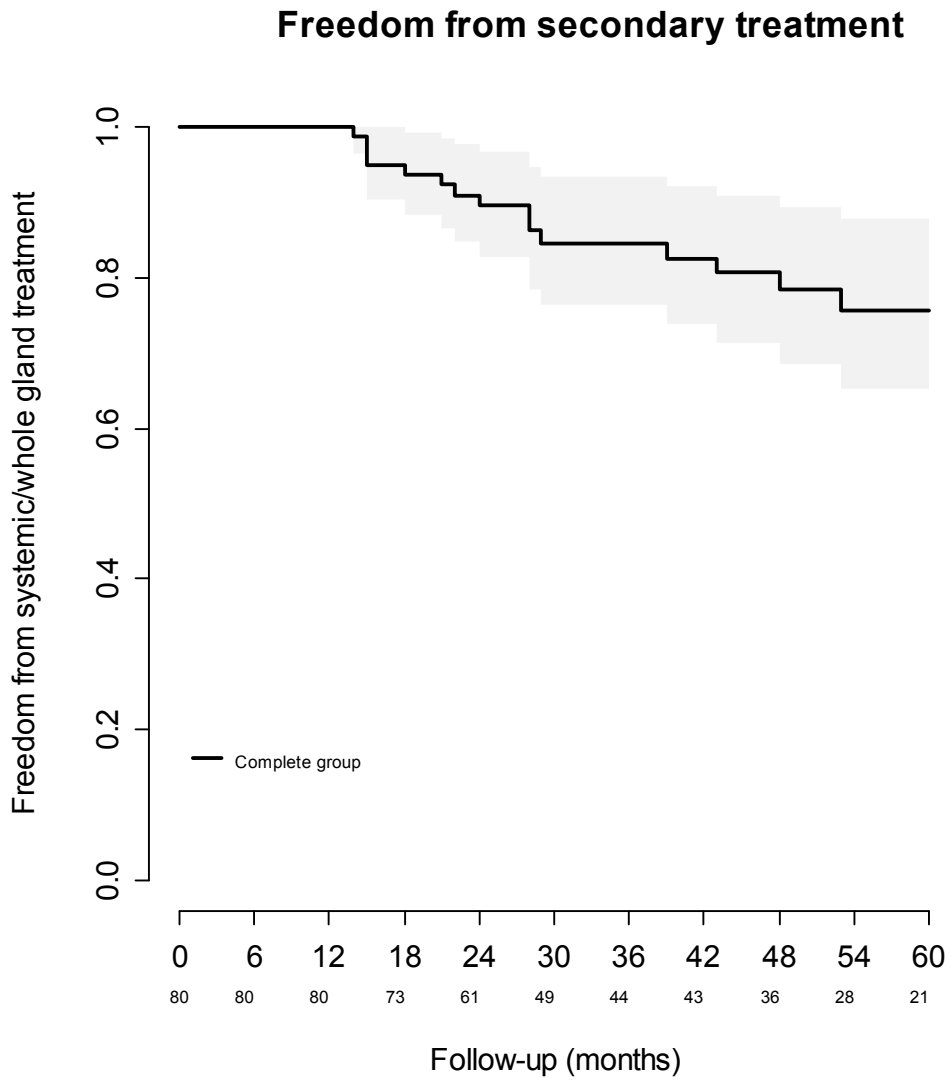
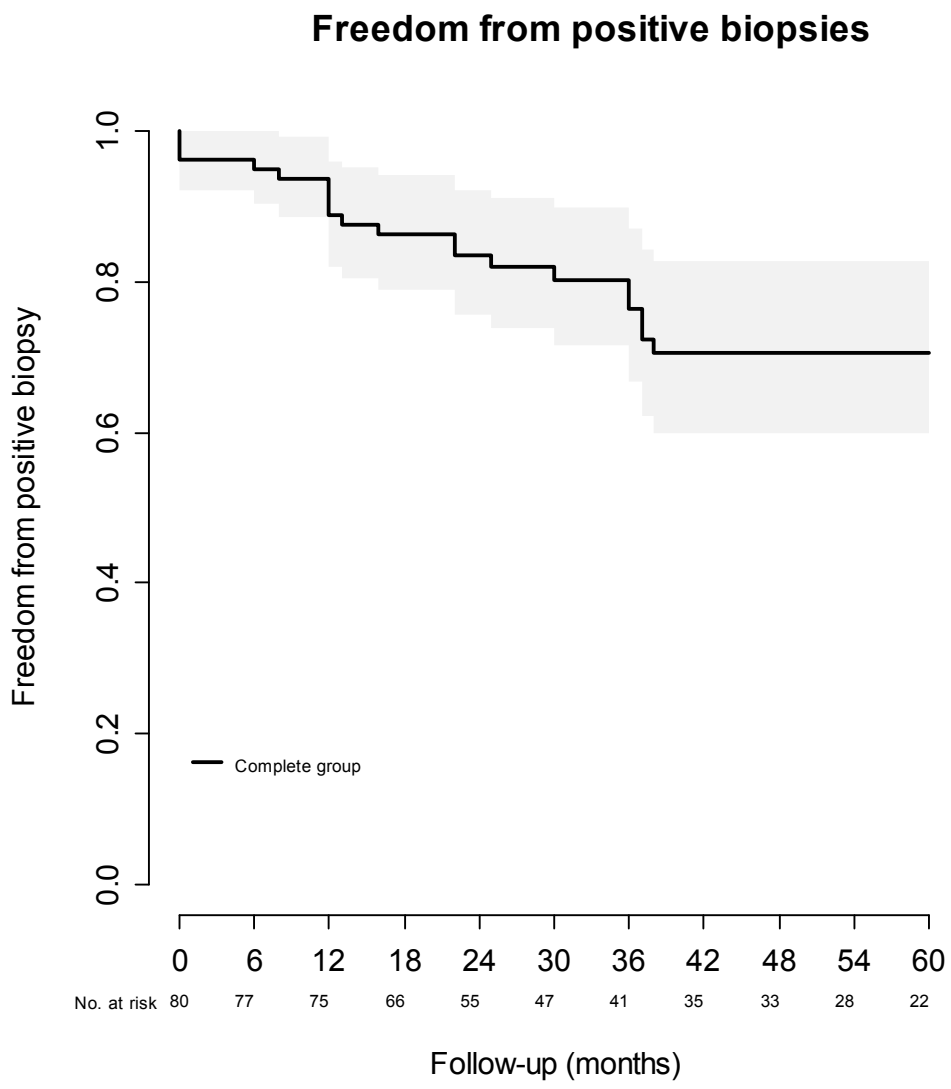


Table 21: The univariable analysis for biochemical failure.

Factor	HR (95%-CI)	p-value
Age	1.00 (0.96-1.05)	0.95 (missing=0)
PSA pre-HIFU	1.00 (0.91-1.09)	0.94 (missing=0)
ADT pre-HIFU	1.61 (0.75-3.44)	0.22 (missing=1)
Pre-HIFU volume	1.016 (1.001-1.032)	**0.04** (missing=2)
HIFU type (Hemi or more versus focal)	1.03 (0.50-2.14)	0.94 (missing=1)
Gleason (<7 vs ≥7)	0.98 (0.37-2.59)	0.97 (missing=0)
MCCL	1.06 (0.94-1.21))	0.34 (missing=12)
Max. %	1.011 (0.997-1.027)	0.13 (missing=11)
Invasion	0.95 (069-1.33)	0.77 (missing=1)
PSA nadir post HIFU	1.23 (1.03-1.46)	**0.02** (missing=5)

A total of 36 (45%) patients had prostate biopsies post-focal HIFU treatment, prompted by a rise in PSA or PIRADS 3, 4 or 5 lesion on multiparametric MRI. Of these, 10 (12.5%) were shown to have in-field recurrence on biopsy, 4 (5%) out-of field recurrence and 6 (7.5%) where shown to have both in-field and out-of field recurrence. 16 (20%) of the total 36 patients had negative biopsies. The positive biopsy free survival was 65.1% (53.2%-79.5%) (Figure 25).

Figure 25: Kaplan-Meier curve showing freedom from positive biopsy.



Urinary incontinence post-focal HIFU treatment in this cohort was evaluated using the EPIC questionnaire. 22 patients were eliminated from the statistical analysis as they had not completed the baseline questionnaires. The p-values were compared to baseline scores using χ^2 or Fisher's exact test.

Of the 50 (86.2%) patients that had data for baseline leak-free data, 41 (93.2%) were leak free at 1-2 years post-focal HIFU and 22 (64.7%) were

leak-free 2-3 years post-treatment. Of the 58 patients who completed the pad-free data, 41 (93.2%) and 31 (91.2%) were pad free at 1-2 years and 2-3 years, respectively. The EPIC total baseline median is 87, and, 91 and 86.5, at 1-2 years and 2-3 years respectively. The EPIC total score was compared to baseline with the Wilcoxon-signed rank test (Table 22). Although some patients were excluded from this analysis as their baseline data was not available, the results show that a high percentage of patients retain their urinary continence status post-operatively, an important factor in maintaining quality of life whilst allowing treatment for the disease.

Table 22: Results from the EPIC questionnaire (p-values compared to baseline scores [χ^2 or Fisher's exact])

Leak free	
Baseline	50 (86.2%) (missing=22)
1-2 years	36 (80%) (p=1.00) (missing=35)
2-3 years	22 (64.7%) (p=0.60) (missing=46)
Pad free	
Baseline	58 (100%) (missing=22)
1-2 years	41 (93.2%) (p=1.00) (missing=36)
2-3 years	31 (91.2%) (p=1.00) (missing=46)
EPIC total score	
Baseline, median [IQR]	87 [84-94] (missing =69)
1-2 years, median [IQR]	91 [85-98] (missing =69) (p=0.06)
2-3 years, median [IQR]	86.5 [70.5-94.5] (missing =66) (p=0.12)

7.2.3 Adverse Events

Urinary tract infections developed post-operatively in 3 (3.8%) patients, and a further patient (1.3%) had epididymo-orchitis. None of these men developed recto-urethral fistulae, and only one patient (1.3%) required endoscopic surgery as treatment for prostatic cavity debris.

7.3 Discussion

Most men with very high risk prostate cancer die from the disease if left untreated.[251] Evidence from various studies report increased survival in those receiving radiotherapy or prostatectomy in addition to ADT. Similar evidence is provided by RCTs comparing combination treatment modalities. Indeed, multimodal treatment in women with locally advanced breast cancer is a well-researched area and as such, has been the accepted standard of care for a significant period.[252]

Patients with clinically detected advanced prostate cancer via PSA testing present controversy, as effectiveness of treatment has yet to be determined. There are no RCTs to date that explore radical treatment in high-risk and locally advanced disease[253,254] and retrospective studies have given conflicting results.[255,256, 257,258] RCTs of androgen deprivation therapy and radiotherapy or radical prostatectomy in men with very high risk disease are as yet, still on going.

The Prostate Testing for Cancer and Treatment (ProtecT) trial compares active surveillance, external-beam radical radiotherapy with or without the use of ADT and radical prostatectomy treatments for PSA-detected clinically localized prostate cancer.[259] Men with locally advanced or metastatic disease were excluded from the ProtecT trial (clinical stage T3-4 and PSA $\geq$20μg/ml). However, these men provided an insight into the outcomes of radical treatment in the context of clinically detected locally advanced disease. This study showed that radical treatment in men with this disease profile had a low rate of prostate cancer death at 7.4 years follow-up. However, those that had non-radical treatment had a lower rate of prostate cancer death.[260]

Left untreated, locally advanced disease often leads to death. Whilst radical treatment increases survival, it is associated with significant genito-urinary morbidity. Focal HIFU offers local control of advanced disease without the decreased quality of life often associated with whole-gland therapy.

This data demonstrates good oncological outcomes in those with locally advanced disease treated with focal HIFU. The prostate-specific survival, overall survival and metastases-free survival were 100%, 98.6% and 95.7% respectively and the positive biopsy free survival was 65.1%, whilst the freedom from systemic or whole-gland treatment was 75.7%.

7.4 Conclusions

Opportunistic PSA testing can identify men with who are asymptomatic with locally advanced and high-risk disease. It is however, vital to assess the balance between longer-term survival and quality of life after treatment. The results here demonstrate that offering early focal HIFU treatment in these cases not only leads to good survival rates, given the high prostate-specific, overall and metastases-free survival in the medium term, but also maintains a low genito-urinary side-effect profile.

Chapter 8

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Discussion and Future Considerations in the Treatment of Prostate Cancer and the role of Focal Therapy

Chapter 8 – Discussion and Future Considerations in the Treatment of Prostate Cancer and the role of Focal Therapy

8.1 Safety Margins versus Functional Outcomes

The general consensus among authors recommend a circumferential safety margin of 4-6mm from the sphincter muscle to ensure incontinence-free outcome.[261] This is further agreed by an expert panel to be 5mm,[141] which is concordant with data showing that mpMRI underestimates tumour volume and that a targeting error in the order of 2-3mm will achieve a positive hit rate of 90-95% of a 0.5ml tumour.[262,263] This safety margin could explain the low rate of incontinence associated with focal HIFU which has been quoted as <1-10%[264,265] and the erectile dysfunction of 5-15%,[266] which is confirmed by data presented in this thesis.

8.2 Types of Energy Modality

The past 10 years or so has seen a surge of interest in focal therapy to treat localized prostate cancer. This has resulted in the development of a range of energy sources, each in various stages of implementation in clinical practice. Each energy source has different limitations and complications. Differences between ablative therapies vary in mechanism of action and tissue damage, delivery and deposition of energy as well as side-effect profile and limitations. Therefore, each of these energy modalities has a different practical application depending on the thermal energy profile as well as tumour characteristics, for example location, volume and grade. Selecting the appropriate treatment modality depending on the location of the index lesion or tumour allows for better oncological and functional outcomes. This may well be the first step towards personalizing treatment for localized prostate cancer. [261]

Early on, these modalities were used to treat the entire prostate gland. However, attitude towards delivery of treatment has shifted over time to providing focal treatment to low-risk patients. This is, in part, due to the growing confidence in the technique by practitioners as well as the

emergence of short to medium term follow-up data.[141]

The “a la carte” approach model described by Sivaraman and Barret proposes the best way to determine the appropriate treatment modality for individual patients is based on tumour location. The anterior prostate gland is easily accessible with transperineal needles, making cryotherapy the more desirable energy source to treat these particular tumours, whereas HIFU would be the better modality to treat posterior tumours, as it has a short focal distance and allows more precise contouring and deposition of thermal energy which is essential given the close proximity to the rectum and lateral neurovascular bundles.[261] Apical cancers can be treated using brachytherapy, cryotherapy and HIFU. Although brachytherapy is a well-known treatment for whole gland radiation, there is limited knowledge in its use within focal therapy. However, it has been shown to have the superior continence rate of the three, hence this approach might be considered best in treating apical tumours.[261,264,266,267]

8.3 Appropriate Candidate Selection

Recent multidisciplinary international consensus meetings have put forward various attributes required for patient selection for focal therapy.

Firstly, there is a general consensus that a life expectancy of >10 years should be foremost in patient selection for focal therapy.

Secondly, there is the disease grade to consider. There is some disagreement as to which disease to offer focal therapy to. Most bodies state that this should be offered to those diagnosed with low or intermediate-risk disease, graded as Gleason 3+3 and Gleason 3+4.

Delivering focal therapy to low volume Gleason 3+3 disease runs the risk of overtreatment, as the 10 to 15-year mortality is very low in these men,[268] which makes them eligible to follow an active surveillance program. Treating such disease with focal therapy moves away from its true purpose

– treating men with clinically significant disease and a higher tumour burden (in terms of volume and grade) than those with very low-risk disease eligible for active surveillance. Focal HIFU should be considered as a less morbid an alternative treatment than whole gland radical surgery or radiotherapy.

Thirdly is the disease localization. Most focal HIFU trials deliver hemiablation treatment to unifocal disease or multifocal disease with low-grade disease on the contralateral side to the index lesion.[269,270,271] Paramount to patient selection is accuracy and precision in mapping the disease within the prostate gland. Imaging in the form of mpMRI offers the most reliable source, in conjunction with transperineal mapping or MRI-US fusion guided biopsies. This is explored in more detail in Chapter 1.

One consideration that must be taken into account with regards to this point is the availability of mpMRI and template or targeted biopsies in hospitals other than tertiary centers. This poses a challenge in the application of focal therapy in the broader aspect, making it more widely available to patients.

One of the future considerations is the standardization of inclusion criteria for focal therapy. These criteria must be established for each thermal modality employed within the umbrella of focal therapy. It is evident that there are wide variations within and between each different ablative modality. In addition, the variability within selection criteria, protocols, oncological and functional outcome points, evaluation and follow-up is wide. This makes it difficult to compare the outcomes from different trials.[142,272]

Personalized medicine may go a step further when considering the natural history of prostate cancer at a molecular and genetic level. There are several questions requiring answers pertaining to the biology and natural history of the individual foci within the prostate gland. Which foci are aggressive and require treatment and which are indolent and unlikely to harm the patient during his lifetime?[273]

8.4 Future Trials in Focal Therapy and Unmet Needs

As per the IDEAL recommendations, focal therapy has been evaluated with trials up to stage 2b. These trials saw patients treated for low risk disease. It is true that the initial stages of trialing focal therapy saw patients with low risk disease being treated. Indeed, most focal therapy trials to date have including men with low-risk disease (low volume Gleason 3+3). The reason was to increase confidence in applying and delivering focal therapy.

We have demonstrated that intermediate- and high-risk disease, graded as high volume Gleason 3+3, Gleason 3+4 or low volume Gleason 4+3 can be treated with focal HIFU, with efficacious oncological and functional results. Other trials with similar supporting evidence have already been published for focal HIFU[123] and focal cryotherapy.[274]

This leads us to the need for more robust, long-term (10 to 15-year) oncological and functional outcome data in the future, as there is paucity of comparative data for focal HIFU. Once the long-term efficacy of focal HIFU is established, the next logical step would be randomized controlled studies comparing focal HIFU against standard practice of active surveillance or radical prostatectomy or radiotherapy. Such data will enable focal HIFU to become standard practice and join the armamentarium available to treat localized prostate cancer. The designing of such studies have been discussed at international multidisciplinary consensus meetings.[269] The inclusion and exclusion criteria according to this meeting are listed below.

Inclusion Criteria

- Serum PSA: <15ng/ml (if >15ng/ml – careful counseling advised)
- Clinical Stage: T1c – T2a
- Pathology: Gleason 3+3 or Gleason 3+4
- Life expectancy: >10years
- Prostate volume: any, HIFU <40ml

Exclusion Criteria

- Previous treatment of the primary cancer within the prostate
- Previous hormone treatment for prostate cancer within 6 months before trial
- Previous radiation to pelvis
- Active urinary tract infection
- PIRADS score <3; equivocal clinically significant cancer
- Extracapsular extension or seminal vesicle invasion
- Lymph node or bone metastasis

8.5 Follow-up after Focal Therapy and Focal HIFU

Oncological follow-up after focal therapy is challenging. A combination of biochemical, histological and radiological results are necessary to ensure evaluation of oncological control of focal HIFU.[91]

8.5.1 Biochemical Follow-up

Part of the evaluation of post-treatment outcome is based on post-HIFU/focal therapy PSA serial measurements. Firstly, focal therapy leaves residual prostate by definition. The volume of prostate left depends on the amount of prostate tissue ablated, and varies between patients depending on the initial prostate volume. The consensus is that ablative treatments should follow one of three patterns: targeted ablation, hemiablation or zonal ablation. Secondly, BPH progression will also contribute to PSA formation. This will vary between individual patients. Hence a PSA nadir must be established for each patient after focal therapy.[114] In fact, PSA nadir has been shown to be a strong predictor of clinical failure following HIFU. Uchida *et al* report on a study involving 115 patients treated with HIFU. The failure rate was 11% in patients with a PSA nadir of 0.0-0.2ng/ml compared with 46% in patients with a PSA nadir of 0.21 – 1ng/ml and 48% in those with a PSA nadir >1.0ng/ml. of note, PSA nadir was strongly associated with both preoperative PSA level and residual prostate volume.[275] Ganzer *et al* also report on PSA nadir following HIFU. The median follow-up in this study was 4.9 years. Treatment failure was defined as per the American Society for

Therapeutic Radiology and Oncology (ASTRO) criteria. Patients in this study were divided into three PSA nadir groups: ≤0.2, 0.21-1 and ≥1ng/ml. treatment failure rates in the three groups were 4.5, 30.4 and 100% respectively. The actuarial disease-free survival at 5 years were 95%, 55% and 0% respectively.[276] Although this data is relevant to whole-gland HIFU, it can be, to some extent, extrapolated to focal HIFU.

Definitions from other therapies have been utilized in an attempt to define biochemical recurrence after focal HIFU and focal therapy. The currently available data sets use the Phoenix (PSA nadir + 2ng/ml)[277] or Stuttgart (PSA nadir + 1.2ng/ml) or ASTRO (three consecutive rises in PSA from nadir) criteria.[278] This has its own limitations as the Phoenix and ASTRO criteria are used in the context of radiotherapy recurrence and the Stuttgart definition relates to patients receiving whole-gland therapy, and have not yet been validated for focal therapy. [109,141,269,142,279]

A consensus has been reached, by an expert panel, on 3 monthly PSA measurements in the first year following focal therapy, then 6 monthly in the second year and annually thereafter. However, the utility of PSA kinetics such as velocity, density and doubling time is also debatable. Indeed, it is not essential to carry out any of these parameters after focal therapy.[269]

Thirdly, there is no level 1 – 3 evidence available to date with regards to an agreed follow-up protocol of patients after focal therapy. Therefore, no consensus on what constitutes biochemical failure has yet been reached. Trial follow-up protocols vary making it difficult to compare oncological outcomes. Biochemical failure has been defined in the current data sets using the Phoenix and/or Stuttgart criteria. Often discussion of treatment failure has centered on the need for re-treatment and transition to radical whole-gland therapies. A proposed follow-up protocol is discussed in further detail in Section 8.5.5.

8.5.2 Imaging Follow-up after HIFU

Integral to evaluating treatment effect is the performance of mpMRI post-focal HIFU. The role of mpMRI in this setting is to assess efficacy of treatment effect on the target area as well as identifying any possible recurrence or residual disease.[280] The sensitivity and specificity of mpMRI are both high.[45] Recent studies have demonstrated that mpMRI can provide useful information regarding the clinicopathological staging of prostate cancer.[281] Cirillo *et al* assess the roles of MRI and magnetic resonance spectroscopy imaging (MRSI) in evaluating the changes in the prostate following HIFU treatment in 10 patients. The images were correlated with histology at biopsy. At 4 months, there was a statistically significant difference between patients responding to treatment and those with persistent disease. MRSI did not seem to add any data of value.[282] Ben Cheikh *et al* presented findings from 15 patients using T2-weighted and DCE sequences for the detection of local tumour recurrence. 13 out of 15 patients were found to have positive biopsies. On T2-weighted images the treated prostate tissue was diffusely hypointense and therefore interfered with interpretation. All 15 cases had suspicious areas on DCE sequences. The sensitivity, specificity, PPC and NPV of T2-weighted MRI post-HIFU treatment were 0.13, 0.98, 0.60, and 0.81 respectively, and 0.70, 0.85, 0.55 and 0.91 respectively for DCE sequences. Therefore, DCE was strongly predictive of positive biopsy results but T2-weighted sequence was not.[283] Kim *et al* on the other hand used a combination of T2-weighted, DCE and DWI sequences in 27 patients who experienced a PSA rise after HIFU therapy. Positive biopsies were found in 33% of patients. The sensitivity, specificity and accuracy values achieved by two independent reporters were 80-87%, 63-68% and 71-72% respectively with DCE sequence and 63-70%, 74-78% and 73% respectively with combined T2-weighted and DWI sequences.[284] The literature available seems to suggest that mpMRI is clinically helpful in the early identification of local recurrence in patients with biochemical recurrence after primary HIFU treatment.

8.5.3 Histology post-focal HIFU

Histological changes on radical prostatectomy specimens after HIFU treatment have shown the macroscopic changes to be well demarcated, and ellipsoid in nature. Microscopically, cell necrosis was seen within the core of the lesion. Haemorrhage with hyperplastic epithelium and reparative changes were also seen at the borders of the lesion.[285] A similar study was performed by Napoli *et al* showing that extensive coagulative necrosis, with no viable tumour, was found within or at the boundaries of the treated lesions. Over time, there was development of fibrosis and elastic collagen.[286]

Focal HIFU trials vary widely in their post-treatment biopsies protocols and are poorly reported. Therefore, the international multidisciplinary consensus on trial design recommends that the absence of clinically significant disease at 12 months post- focal therapy should be considered as the primary end-point.[269] A separate consensus meeting confirms that the optimal time for re-biopsy after focal treatment is at 1 year, ideally performed in a targeted manner as previously untreated tissue could easily be inadvertently sampled. No consensus has yet been reached on biopsies of the untreated gland post-focal therapy.[141]

8.5.4 What Parameters Should Prompt Re-intervention?

Recurrence/progression of tumour or de novo disease arising after primary treatment can be re-treated with the same energy modality.[280] The data presented in this thesis establishes that re-treatment with HIFU is both efficacious and feasible, although tumour grade, volume and location should be taken into consideration. As discussed in the above section, post-operative biopsies assess both the treated and untreated areas. Polascik *et al* define treatment success if no residual cancer is found in the treated area, or small volume of Gleason 3+3 or small volume ($<0.2cm^3$/5mm in diameter) of Gleason 3+4 is found. Indeed, an expert panel from 2015 has agreed that Gleason 3+3 in the treated area with a cancer core length of $\leq$3mm, 1 year after primary focal therapy treatment, is an acceptable reduction in tumour volume and does not require further treatment. They

have also agreed that Gleason 3+4 or 4+3 represents residual disease that warrants further treatment, and hence is considered as treatment failure. The expert panel also agreed that retreatment rates of <20% were acceptable whereas transition to whole-gland therapy should be considered as failure of focal therapy.[141]

8.5.5 Proposed Follow-up Protocol for focal HIFU

A standardized follow-up schedule following focal HIFU treatment is currently non-existent. Based on the evidence from this data, follow-up of focal HIFU patients should include 3- monthly PSAs during the first year of follow-up, followed by six monthly PSAs over the following two years. This would allow sufficient time for a PSA nadir to be reached and PSA levels to be monitored thereon.

Imaging in the form of mpMRI should be done at 6 and 12 months post-operatively and thereafter, prompted if and when PSA levels start to rise above the PSA nadir prior to considering prostate biopsies. Although the negative predictive value of mpMRI is high, targeted transperineal prostate biopsies should be carried out at 12 months, with 4 cores taken from the margin of the treated area and 1 or 2 cores taken from the centre. Prostate biopsies should thereafter only be carried out as 'for-cause' after mpMRI.

However we must consider the fact that focal HIFU treatment and follow-up should be taken case for case and hence we are moving into an era of individualized treatment for non-metastatic prostate cancer.

8.6 Other Focal Ablative Therapies of the Future

8.6.1 Irreversible electroporation

Irreversible electroporation (IRE) is a novel technique where tissue is ablated through non-thermal effects. Electroporation involves a significant increase in the electrical conductivity across a cell membrane, by an externally applied electric field. The high-energy direct current causes the

lipid bilayer in the cell membrane to lost its integrity, creating nanopores, which increase the permeability of the cell membrane, losing cellular homeostasis, resulting in subsequent cell death. This phenomenon is dynamic and depends on the electric field strength and tissue properties.[287,288] This type of needle ablation has been attempted in other solid organ cancers too, namely renal[289] and hepatic.[290,291] Promising data has been seen with IRE in the prostate.[292] For example, Valerio *et al* carried out a pilot study on 45 patients, 34 as primary treatment and 11 as salvage treatment. Three men had high-risk disease whilst 31 and 11 men intermediate-and low-risk disease respectively. 28 patients had available follow-up and all achieved urinary continence whilst of the 25 men that were potent preoperatively, 96% maintained their potency.[293] Recently van den Bos *et al* assessed the effects of IRE on prostate tissue on histopathological examination. Of 16 patients who underwent IRE with subsequent radical prostatectomy, the ablation zone microscopically consisted of fibrotic necrosis and fibrotic tissuewith no viable cells visible and precise targeting.[294] Ongoing studies will determine the clinical utility of focal IRE.

8.6.2 Radiofrequency Ablation

Radiofrequency ablation applied via electrodes inserted via the transperineal route can induce thermal energy to the prostate.

Further potential ablative technologies include the use of magnetic nanoparticles that can be injected into the tumour within the prostate gland and produce heat on activation by electromagnetic stimulation.[295,296,297]

8.6.3 High-Dose Rate Brachytherapy

Little is known about high-dose rate brachytherapy (HDR-BT) as a focal treatment. However, the advantage of brachytherapy seeds is the rapid deceleration in radiation dose and subsequent effects to a few millimetres around the radiation seeds. Therefore, only cancer cells closely adjacent to the seeds are killed, allowing precise targeting and preserving important

structures to preserve the genito-urinary function. The functional outcomes reported to date show incontinence rates of 0-8% and maintenance of erectile function of 3.9% to 71%.[298,299] Oncological and further functional results from focal brachytherapy are eagerly awaited in the near future.

8.6.4 MR-guided High Intensity Focused Ultrasound

MR-guided high intensity focused ultrasound (MRg-HIFU) is a method that aims to improve treatment planning, develop robust models of tissue properties that influence and determine thermal ablation and detect the formation of coagulative necrosis through relative changes in tissue property. One of the challenges of delivering HIFU treatment is the monitoring of tissue heating intra-operatively complicated by the inter-patient variability in tissue properties and acoustics. These properties also change throughout treatment delivery and sonication time. Once denaturation ensues, tissue dynamics alter, which in turn, affects the acoustic properties of the prostate gland. Key to obtaining precise ablation is the ability to detect such changes, allowing alterations in the delivery and deposition of thermal energy accordingly, is key to obtain precise ablation. Therefore, accurate control of temperature control and distribution is paramount for complete treatment of desired gland volume, whilst preserving functional surrounding structures. Important to treatment planning is the determination of patient anatomy, including acoustic pressure, temperature and thermal dose field predictions.[300] These vary from patient-to-patient as well as throughout treatment delivery and sonication time.[301] The study by Johnson *et al* has validated MRgHIFU as a noninvasive technique that can measure differences in temperature and tissue dynamics during HIFU sonication. We look to the future for trials involving the *in vivo* application of this device before and during HIFU delivery.[300]

8.6.5 Immunotherapy and HIFU

Immunotherapy for treating prostate cancer is another field currently under investigation. Indeed, several recent studies have looked at the potential of

HIFU to initiate an immune response.[114] Hu *et al* demonstrated tumour-infiltrating lymphocytes (TILs) along the margins of HIFU-ablated areas in human breast cancer. The number of tumour-infiltrating CD3, CD4, CD8, CD4/CD8, B lymphocytes and natural killer cells were significantly increased with HIFU treatment.[66] Wu *et al* are another group also examining the effects of HIFU on systemic anti-tumour immunity in cancer patients. A total of 16 patients with solid cancers were treated with HIFU. The results showed a significant increase in the population of CD4 lymphocytes. In addition, the ratio of CD4/CD8 lymphocytes increased.[302] The same group also presented findings from another study, involving 23 patients with breast cancer treated with HIFU then submitted to modified radical mastectomy. The breast cancer specimens were stained for cellular molecules, and a number of tumour antigens were identified which could provide a potential antigen source that stimulates anti-tumour immune response.[303] Furthermore cells damaged by HIFU may trigger the activation of dendritic cells playing a role in anti-tumour response stimulation. The dendritic cell activation was more pronounced when the tumour cells themselves were mechanically lysed by focused ultrasound treatment.[304]

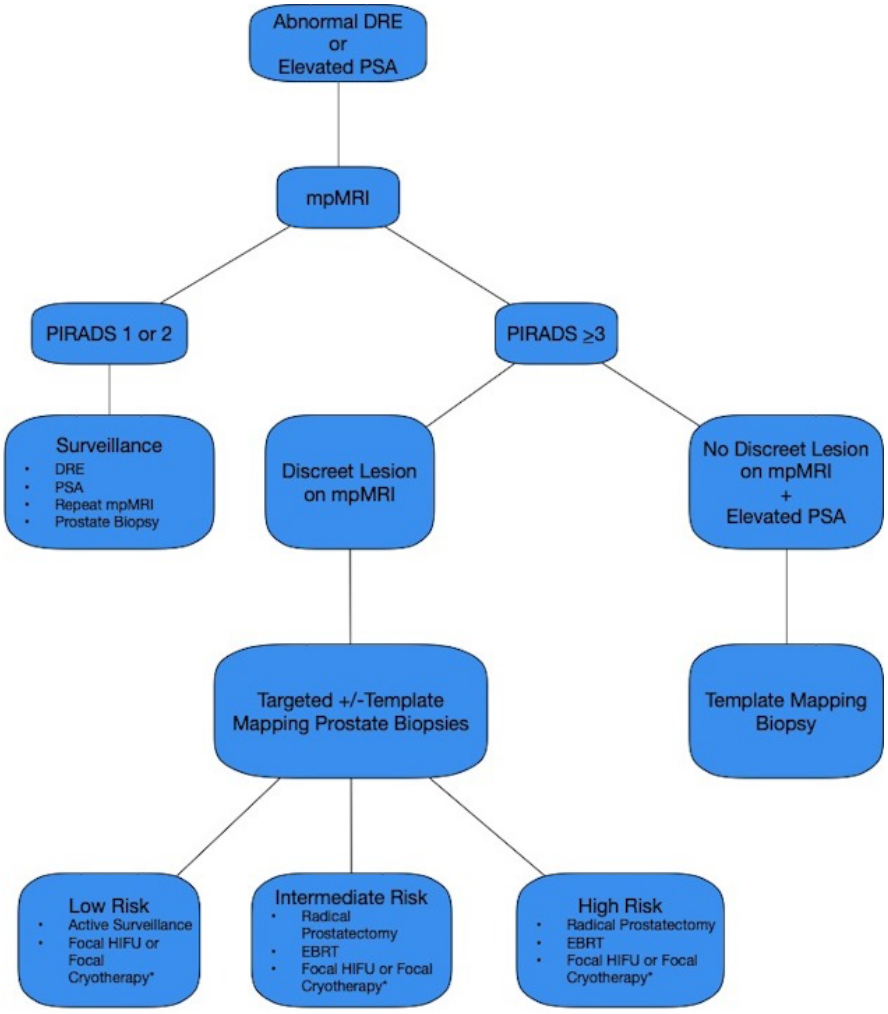
8.7 Conclusions

Focal therapy is widely used in the treatment of both breast[305] and kidney cancer.[306] Focal therapy for localized prostate cancer is a powerful approach offering cancer control with limited morbidity. Although there are a number of ablative sources available for use as focal therapy, HIFU and cryotherapy are the most studied and published. There are no medium or long term data available for focal HIFU. This thesis presents the first medium-term outcomes for focal HIFU in the largest study to date.

Focal therapy is as yet, an evolving landscape, and a controversial topic, for various reasons. Firstly, although the data we have to hand is promising, long-term efficacy data on the functional and oncological outcomes of focal HIFU is eagerly awaited. We should be looking at composite medium-term outcomes as primary outcomes for focal therapy, rates of local and systemic

salvage treatment, whilst longer-term outcomes should also include rates of metastases and mortality. As previously mentioned, this will provide more robust evidence that would enable focal HIFU to take its place within the treatment pathway for localized prostate cancer, and available for dissemination to non-tertiary centres. The data presented in this thesis is of medium-term and needs time to mature into the long-term data that we need, as do other focal HIFU datasets previously published. Figure 26 shows where focal HIFU should be placed in the treatment pathway for prostate cancer.

Figure 26: Proposed treatment pathway for prostate cancer.



* For anteriorly placed tumours, recommend focal cryotherapy. For posteriorly placed tumours, recommend focal HIFU.

Secondly, in order for this to be achieved, a definition of failure of focal HIFU should be established via a consensus meeting, as well as guidelines for appropriate candidate selection for focal HIFU, and a pre-defined follow-up protocol for each energy modality of focal therapy. This will in turn, lead to a consistency in delivering focal HIFU treatment – of paramount importance prior to disseminating focal HIFU to non-tertiary centres.

Thirdly, we need a randomized controlled study, comparing efficacy of focal HIFU versus current standard treatment for localized prostate cancer. However, it will provide the definitive efficacy data necessary to establish focal HIFU within the armamentarium available in treating localized prostate cancer.

Appendix

1. Outputs from Research

1.1 Publications - Peer-Reviewed Journals

A Multi-centre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Non-metastatic Prostate Cancer. **Guillaumier S**, Peters M, Arya M, Afzal N, Charman S, Duderidge T, Hosking-Jervis F, Hindley RG, Lewi H, McCartan N, Moore CM, Nigam R, Ogden C, Persad R, Shah K, van der Meulen J, Virdi J, Winkler M, Emberton M, Ahmed HU. Eur Urol. 2018.

The Effects of Focal Therapy for Prostate Cancer on Sexual Function: A Combined Analysis of Three Prospective Trials. Yap T, Ahmed HU, Hindley RG, **Guillaumier S**, McCartan N, Dickinson L, Emberton M, Minhas S. Eur Urol. 2015.

Harnessing the Immunomodulatory Effect of Thermal and Non-Thermal Ablative Therapies for Cancer Treatment. Bastianpillai C, Petrides N, Shah T, **Guillaumier S**, Ahmed HU, Arya M.Tumour Biol. 2015.

Letter to the Editor Morgan R. Pokorny, Maartende Rooij, Earl Duncan, et al. Prospective Study of Diagnostic Accuracy Comparing Prostate Cancer Detection by Transrectal Ultrasound-Guided Biopsy Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in Men Without Previous Prostate Biopsies. Shanmugabavan Y, **Guillaumier S**, Ahmed HU. Eur Urol. 2015.

1.2 Publications – Book Chapters

Focal Therapy of Prostate Cancer: An Emerging Concept for a Minimal Invasive Staged Therapy. In *Focal Therapy for Prostate Cancer*. Springer 2015. **Guillaumier S**, Ahmed HU, Emberton M.

High Intensity Focused Ultrasound for Prostate Cancer. In *Interventional Urology.* Springer 2016. **Guillaumier S**, Ahmed HU, Emberton M.

1.3 International Presentations

A Multi-Centre Focal HIFU Registry Experience for the Treatment of Localised Prostate Cancer.

BAUS Annual Meeting, 2016

Localized prostate Cancer – The Focal HIFU Registry Experience

EUSC Annual Meeting, 2016

Focal HIFU for Treatment of Localised Prostate Cancer: A Multi-centre Registry Experience

AUA Annual Meeting, 2016

Medium Term Outcomes Following Focal HIFU for the Treatment of Non-Metastatic Prostate Cancer: A UK Registry Analysis of 625 Cases.

EAU Annual Meeting, 2016

Does Focal High Intensity Focused Ultrasound Have A Role in Treating Localised Prostate Cancer in the Elderly?

GU ASCO Annual Meeting, 2015

High Intensity Focused Ultrasound in The Treatment of Localised Prostate Cancer: Focal Salvage Transition Rates.

SIU Annual Congress, 2014

High-Intensity Focused Ultrasound in the Treatment of Localised Prostate Cancer: Salvage Transition Rates.

AUA Annual Meeting, 2014

Erectile Dysfunction following Focal Therapy using HIFU: An Anlaysis of Risk Factors for Developing ED from a Combined Analysis of Three Prospective Trials. **AUA Annual Meeting, 2014**

Is Focal High Intensity Focused Ultrasound Feasible in Treating Localised Prostate Cancer in the Elderly?
BAUS Academic Urology, 2014

High-Intensity Focused Ultrasound in the Treatment of Localised Prostate Cancer: A Registry Experience.
Focal Therapy for Kidney and Prostate Cancer, 2014

1.4 National Presentations

High Intensity Focused Ultrasound: A Treatment for Localised Prostate Cancer.
Specialist Urological Registrars Group, 2014

Dedications

To my mother and father, whose unflinching support and love is the backbone of my life.

To my sister, Christina, and brother-in-law, Ronald, whose faith and trust in me kept me going.

To my aunt, Josephine, who is my second mother.

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