The role of minimally invasive ablative therapies in the treatment of primary and radio-recurrent prostate cancer

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I, Taimur Tariq Shah, 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.
Dedication

To my wife, Irene, who has been my rock throughout. Without her patience and understanding this would not have been possible.

To my parents, Tasneem and Tariq Shah, and my brothers, Talal and Talib for their ever-present support.

To my supervisor and mentor, Hashim Uddin Ahmed, who has guided me through the world of academic and clinical urology and given me the freedom to grow and develop my skills as a clinician and scientist.
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Abstract

Focal cryotherapy and High Intensity Focused Ultrasound (HIFU) are emerging treatment modalities for men with prostate cancer both as a primary and radiorecurrent treatment. They aim to treat only the cancer within the prostate using minimally invasive surgical techniques whereby either cold or heat is applied in a focal manner to the cancerous areas whilst sparing adjacent structures. This process leads to control of the cancer whilst minimising treatment related side-effects particularly with regard to urinary and sexual function. My aim in primary disease was to assess the oncological and functional outcomes from focal cryotherapy before performing a comparative analysis of the oncological and functional outcomes against an established surgical treatment, radical prostatectomy. My aim in radiorecurrent disease was to assess outcomes from whole-gland salvage therapy, perform a systematic review on focal salvage therapies before presenting results from the FORECAST trial (FOcal RECurrent Assessment and Salvage Treatment, NCT01883128) and present oncological and functional outcomes in men who underwent focal salvage HIFU and Cryotherapy for both localised and metastatic radio-recurrent prostate.

Primary Disease: An initial systematic review on focal cryotherapy confirmed good oncological outcomes in the short-medium term. When assessing intra-operative ice ball formation, using data from gel model experiments, I found that the -40°C lethal isotherm is approximately 1cm inside the leading edge of the ice-ball. The optimum distance between cryo-needles was 1.5 – 2 cm’s. At distances further apart the ice-balls had either a central core >-40°C or an hourglass shape. Subsequently analysis of a prospective registry-based case-series of 122 consecutive patients confirmed good early oncological control when treating predominantly anterior primary prostate with a 3-year failure free survival of 90.5% [95%CI 84.2-97.3]. Incontinence defined as any was 0/69 (0%) and erectile dysfunction was 5/31 (16.1%). Finally, a propensity score analysis was constructed using a combined focal cryotherapy and HIFU database versus a prospective radical prostatectomy database. After matching there were 246 patients in each arm with low-intermediate risk localised primary prostate cancer. Failure-free survival (95% CI) in the radical prostatectomy compared to focal
therapy groups was 79% (73-86%) vs. 83% (76-90%) at 8 years (adjusted log rank p-value 0.12).

Radiorecurrent Disease: Initial analysis of a 50-patient salvage HIFU showed a 5-year progression-free survival of 31% and 5-year overall survival (OS) of 87%. The main limitation was the adverse event profile with 3/50 (6%) developing a fistula, 27/50 (54%) needing further intervention for bladder outlet obstruction and 8/26 (31%) developing incontinence (any pad-use). A systemic review on focal salvage ablation showed that similar or better oncological outcomes could be obtained with focal salvage treatment with a superior side-effect profile. Results from the FORECAST trial showed that mpMRI for the detection of radiorecurrent disease had a sensitivity of 81% (95%CI 73-88%), specificity 88% (95%CI 73-98%), PPV 96% (95%CI 90-99%) and NPV 57% (95%CI 42-70%). Sensitivity of MRI-targeted biopsy in 87 men was 92% (95%CI 83-97%), specificity 75% (95%CI 45-92%), PPV 94% (95%CI 86-98%) and NPV 65% (95%CI 38-86%). Overall, 4/72 (6%) cancers were missed on systematic biopsies alone and 6/72 (8%) were missed on targeted biopsies alone. Subsequently, 93/181 underwent salvage focal therapy: HIFU (64/93) or cryotherapy (29/93). Probability of return of continence was 84% at 12-months. 73 underwent focal therapy for localised disease. Metastases Free Survival was 80% [95% CI 68 – 88] at 2-years. 20 underwent cytoreductive focal ablation in the presence of nodal/metastatic disease. All were alive at last follow-up. 4/20 had evidence of progression on whole-body imaging.

The programme of work detailed above confirms both the good oncological and functional outcomes that can be achieved from focal therapy in primary and recurrent disease. This evidence provides the basis for future randomised controlled trials and whilst we await the results from these the presented data can be used to guide patients regarding their treatment options.
Impact Statement

The following avenues have been used for dissemination:

1. Academic conference presentations (NCRI national conference, British, European and American Urological and Oncological Societies annual conferences).

2. Peer-reviewed publications (general medical/oncology for primary outcomes specialist urology or radiology for secondary outcomes).

3. Media and Press releases via UCL/UCLH press and media communication departments as well as each of these institutes' and departments’ Twitter and Facebook accounts.

4. Research plans and output will be shared with charities and patient support groups such as Prostate Cancer UK, St Peters Trust, Pelican Foundation, with whom we already have communication channels and links.

The potential impact is:

1. First and foremost there is potential benefit to patients. Prostate cancer is the number one cancer amongst men in the UK and second worldwide. Traditional treatments such as radical prostatectomy, radiotherapy and androgen deprivation therapy have associated morbidity and may not be suitable for all men. Thus, many men are choosing focal ablation. With over 40,000 men a year diagnosed with prostate cancer in the UK alone the potential number of patients that could be impacted is significant, as we may be able to improve their oncological outcomes whilst maintaining a low side-effect profile. This would maintain not only their life expectancy but also quality-of-life. Follow on effects would impact a patients’ family's wellbeing and society in general as both could continue working and thus contribute to society. The NHS would also benefit, as better initial disease control
would reduce the need for further elective and emergency admissions as the disease progresses. The saved funds could be reallocated into other health care services.

2. Policy makers would read my results with interest. NICE (National Institute for Health and Care Excellence) has said that high quality randomised trials are needed. Whilst the results of such trials are awaited we would be providing NICE guidance robust prospective evidence upon which to base future recommendations.

3. Academic institutions would benefit as where possible I plan to make the data open-source. The wider medical community may gain a deeper understanding of the disease process, allowing subsequent trial development.

6. My host institution (UCL/UCLH) and collaborator institutions (Imperial, Southampton, Basingstoke, Brighton, Harlow) have gained further knowledge into the considerations needed when designing a trial for focal therapy, which would subsequently allow application for further research funding.
CONTENTS

1 PRIMARY DISEASE .................................................................................................................. 1-12
  1.1 EPIDEMIOLOGY .................................................................................................................. 1-12
  1.2 TREATMENTS .................................................................................................................... 1-12
    1.2.1 Radical Prostatectomy ................................................................................................. 1-13
    1.2.2 Radiotherapy .............................................................................................................. 1-15
    1.2.3 Brachytherapy .............................................................................................................. 1-16
    1.2.4 Minimally Invasive Ablative Whole Gland Therapies .................................................. 1-17
    1.2.5 Treatment Related Side-effects from Whole Gland Treatments ................................ 1-18
    1.2.6 Minimally Invasive Ablative Focal therapies ............................................................. 1-19
      1.2.6.1 Definition of an Index Lesion and clinically insignificant cancer ............................ 1-20
      1.2.6.1.1 Gleason Grading .............................................................................................. 1-20
      1.2.6.1.2 Tumour Volume and Cancer Significance ......................................................... 1-22
      1.2.6.2 Improvement in prostate cancer diagnostics and disease characterisation .............. 1-22
      1.2.6.3 Clinical Evidence of Focal Therapy in the Primary Disease Setting ...................... 1-25
      1.2.6.3.1 Histological Outcomes after Focal Therapy ..................................................... 1-27
      1.2.6.4 Ideal Candidate for Focal Therapy ........................................................................ 1-33
  2 AIMS, OBJECTIVES AND PATIENT DATASETS .................................................................. 2-35
  3 FOCAL CRYOTHERAPY ......................................................................................................... 3-36
    3.1 Prostate CRYOTHERAPY .................................................................................................. 3-37
    3.2 Systematic Review of Focal CRYOTHERAPY FOR LOCALISED PROSTATE CANCER .... 3-47
    3.3 Optimising CRYOTHERAPY TREATMENT DELIVERY .................................................. 3-53
    3.4 Oncological OUTCOMES FROM Focal CRYOTHERAPY FOR LOCALISED PROSTATE CANCER 3-65
    3.5 Functional OUTCOMES FROM Focal CRYOTHERAPY FOR LOCALISED PROSTATE CANCER 3-85
  4 FOCAL THERAPY PROPENSITY SCORE MATCHED ANALYSIS ........................................ 4-100
    4.1 Introduction and Methods ............................................................................................... 4-100
    4.2 T-stage Analysis ............................................................................................................. 4-106
    4.3 Results and Discussion .................................................................................................. 4-111
  5 FUTURE PERSPECTIVE AND TRIAL DESIGN ................................................................. 5-121
  6 RADIO-RECURRENT PROSTATE CANCER .......................................................................... 6-134
    6.1 How to Define Failure after Radiotherapy ....................................................................... 6-134
    6.2 How to Locate and Diagnose Recurrence ...................................................................... 6-135
    6.3 Treatment ....................................................................................................................... 6-137
    6.4 Metastatic Radiorecurrent Prostate Cancer ..................................................................... 6-138
  7 AIMS, OBJECTIVES AND PATIENTS ............................................................................... 7-147
  8 WHOLE GLAND SALVAGE HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) .......... 8-149
  9 SYSTEMATIC REVIEW – FOCAL SALVAGE THERAPY IN PATIENTS WITH LOCALISED DISEASE .... 9-158
 10 FORECAST (FOCAL RECURRENT ASSESSMENT AND SALVAGE TREATMENT) ........... 10-168
    10.1 Forecast - Focus Group / Patient Involvement ................................................................ 10-169
    10.2 Forecast - Trial Design and Overview .......................................................................... 10-173
    10.3 Forecast - Overall Results ............................................................................................ 10-180
    10.4 Forecast - Prostate MRI and Biopsy Analysis ............................................................... 10-183
    10.5 Forecast - Primary Outcome Analysis ......................................................................... 10-187
    10.6 Forecast - Oncological Outcomes, Localised Disease .................................................. 10-197
    10.7 Forecast - Oncological Outcomes, Nodal or Metastatic Disease ................................. 10-205
    10.8 Forecast - Discussion .................................................................................................... 10-209
 11 FUTURE PERSPECTIVE AND TRIAL DESIGN ................................................................... 10-213
1 Primary Disease

1.1 Epidemiology

In the UK almost 50,000 new cases and over 11,000 deaths occur each year as a result of prostate cancer, making it the commonest cancer and second leading cause of cancer related death in men (1). In comparison, 25,000 lung cancers and 23,500 bowel cancers are diagnosed each year. Fortunately, 80% of men will survive for at least 10 years after their initial diagnosis of prostate cancer.

The incidence of prostate cancer increases with age and post-mortem data demonstrates histological prostate cancer in approximately 30% of all men in their 40s and in up to 90% of men in their 80s - 90s (2). However, the actual incidence peaks at age 65-79 but then drops thereafter, which may be due to a lower rate of PSA testing in this older population (3). The lifetime risk of developing prostate cancer in the UK is 1 in 8, but up to 50% of cases may be low risk and not life threatening (4).

The incidence of prostate cancer has also increased over time with a 68% rise seen in the 45 - 64 age group during the 1990’s. This has been mirrored by a 20% decrease in mortality. The increased uptake of prostate-specific antigen (PSA) testing during this period was likely the reason for the increased incidence. The reasons behind the decrease in mortality are harder to ascertain but may be due to earlier diagnosis along with improvements in available treatments (5, 6).

1.2 Treatments

For some time, radical prostatectomy (RP) and external beam radiotherapy (EBRT) were seen as the only treatment modalities for prostate cancer with watchful waiting being prevalent too. Subsequently evidence from large case series and randomised control trials pointed to the fact that not all prostate cancer needed treatment and that low-risk cancer can be followed up safely and active surveillance protocols were
developed. In an attempt to reduce the treatment related side-effects of radical prostatectomy and radiotherapy, particularly with regards to urinary and sexual function, there was development in the field of minimally invasive therapies such as cryotherapy and HIFU. These have the advantages of treating the cancer within the prostate whilst trying to minimise urinary and sexual side-effects.

1.2.1 Radical Prostatectomy

Prior to widespread PSA testing the SPCG-4 (Scandinavian Prostate Cancer Group) randomised control trial compared watchful waiting with radical prostatectomy (RP). A total of 695 men met the inclusion criteria of age < 75 years, clinical T1 or T2 disease, a life expectancy > 10 years, a PSA of < 50 and a negative bone scan. They were randomly assigned to have either a RP or watchful waiting (WW). Patients were reviewed six monthly for two years and then annually. Those on WW were allowed palliative or symptomatic treatment such as androgen deprivation therapy (ADT) or TURP.

The results have been updated and published on 5 occasions with 23 years of follow-up (median 13.4 years). The original results in 2005 paper showed an increased cancer specific survival of 5.8% in favour of RRP compared to WW (8.6% vs 14.4%) The overall mortality in the prostatectomy group was 23.9% (83 men) compared with 30.5% (106 men) in the WW group. This difference continued to increase over time and the 2014 update quoted a number needed to treat to prevent 1 death as 8. The greatest benefit was seen in those aged <65 years, where the number needed to treat was just 4. Additionally, RRP also conveys a reduction in metastases if performed in older men (7-10). At 23 years median follow-up, a mean of 2.9 extra years of life were gained with radical prostatectomy (11). QoL data from SPCG-4 showed that adverse events and impact on quality of life were high with significant stress and anxiety being more common in those undergoing surgical treatment rather than watchful waiting. For men undergoing radical prostatectomy, incontinence and erectile dysfunction were also frequently reported at 41% and 84%, respectively.
In the early PSA era a US study called the “Prostate Cancer Intervention Versus Observation Trial” (PIVOT) also attempted to determine whether there was any benefit to radical surgery in patients with prostate cancer. It was an RCT assessing radical prostatectomy against observation in localised prostate cancer. A total of 731 men with 50% having T1c disease were randomised to either radical prostatectomy or observation. After a median follow up of 10 years no significant difference in either all cause or cancer specific mortality was seen however subgroup analysis revealed a 7.2% reduction in cancer specific mortality in patients with a PSA level >10ng/mL who underwent radical prostatectomy (12). Further long-term outcomes were published in 2017 and most recently in 2020 which showed a minimal overall survival benefit of surgery after median 18.6 years of follow-up with a hazard ratio of 0.84 [95%CI 0.70-1.00; p= 0.044 and a mean of 1-life year gained. As before the benefit was largely in men with intermediate risk disease (13, 14).

The most recent study to assess the role of radical prostatectomy and radical radiotherapy compared to active monitoring in 1643 men low-intermediate risk cancer was the ProtecT trial (Prostate testing for cancer and Treatment). Similar to PIVOT no cancer specific survival advantage was seen after 10-years median follow-up in patients who underwent radical treatments over active monitoring with only 17 cancer specific deaths in total, although there was a small advantage in terms of metastases free survival (15).

The conflicting results in these three studies is likely due to the fact that they evaluate patients at different stages of the disease and at different time points from the pre-, early- and late- PSA era’s. Patients who undergo PSA screening are much more likely to have clinically impalpable, T1c, disease compared with those who present symptomatically. Therefore, there may be only minimal or even no benefit of offering prostatectomy to low-risk patients, but patients who are at higher risk such as with clinically palpable disease or a PSA > 10 may benefit from radical prostatectomy. Additionally retrospective and cohort reviews have consistently
shown that radical prostatectomy has better treatment outcomes in high risk and advanced disease than other treatment strategies (16, 17).

In terms of surgical method, no significant difference in oncological outcomes has been established between robotic, laparoscopic or open radical prostatectomy and two large series of radical prostatectomy with over 1000 patients in each have shown a 96% biochemical disease free survival (bDFS) at 1 year, 90% at 3 years and 87% at 5 years (18, 19). These values are expectedly lower in higher risk patients with bDFS of 71% at 1 year dropping to 59% at 3 years (20). Yaxley and Coughlin et al also recently published a randomised control trial comparing early outcomes from open versus robotic radical prostatectomy with no differences seen in functional outcomes (90% pad-free and 50% potency) but there was a higher rate of blood loss with open surgery (1338ml vs 443ml, respectively) resulting in a higher transfusion rate of 4% vs 1% and higher post-operative complication rate of 9% vs 4% (21). Apart from a benefit to the surgeon robotic and laparoscopic procedures have consistently been shown to reduce length of stay and have lower blood loss (22). The upfront cost of robotic surgery is higher however in a recent analysis of the out-of-pocket costs associated with robotic and open surgery when compared to open surgery the robotic approach was associated with lower out-of-pocket costs for all studied oncologic procedures (23).

1.2.2 Radiotherapy

The current standard of care is intensity modulated radiotherapy (IMRT) with escalated dosing of 76 – 80Gy and a period of androgen deprivation.

Bolla et al published their RCT on EBRT versus EBRT and ADT in 2010. They randomised 415 with T3-4 prostate cancer and found a 25% improvement in 10 year cancer specific survival (CSS) in patients who received adjuvant ADT (24).

Some oncologists at the time felt that the ADT was having the primary effect rather than the radiotherapy. However subsequently multiple studies have shown that the
addition of radiotherapy to ADT does improve survival over ADT alone. The SPGC-7 study by Widmark et al’s showed a 12% 10 year improvement in cancer specific mortality (CSM) with the addition of flutamide. With a median of 7.6 years follow-up biochemical disease free survival (bDFS) was 82.4% (25).

Other important studies are the PR07 and CHHiP trials. In PR07 ADT was compared to ADT with IMRT and the combination treatment showed a 23% improvement in CSS after 6 years of follow-up (26). CHHiP randomised 3126 men with localised prostate cancer (pT1b-T3a) to conventional (74 Gy delivered in 37 fractions) or one of two hypofractionated schedules (60 Gy in 20 fractions or 57 Gy in 19 fractions). All were given 3-6 months of neoadjuvant androgen deprivation therapy. Their results showed non-inferiority between the standard 74Gy in 37 and 60Gy in 20 regimes with a similar side-effect profile. 5-year biochemical or clinical failure free survival was 88·3% (95%CI 86·0-90·2) versus 90·6% (88·5-92·3), respectively (27). These two studies confirmed that ADT in addition to radiotherapy does in fact improve cancer specific survival and that using a hypofractionated regime consisting of fewer fractions is non-inferior to our standard regime of 37 fractions.

1.2.3 Brachytherapy

Brachytherapy in localised prostate cancer has been in use since the late 80s and has shown similar results to EBRT with a bDFS of between 71 – 96% at 5 years follow-up (28).

It is classically delivered as low dose permanently implanted prostatic seeds (iodine-125 or palladium-103) or more recently as temporary high dose (HDR) Brachytherapy with iridium-192. HDR therapy is normally performed in high risk/T3 disease and is commonly given with a course of EBRT and ADT.

Generally accepted patient selection criteria for low dose brachytherapy include stage cT1-2 with a PSA less than 10 and Gleason 3+3 and 3+4 disease in patients with a prostate volume of <50cc, an IPSS score < 12 and flow rate > 12ml/s (29).
Biochemical disease-free survival at 5-years was 71-95% in a systematic review of 31 studies (28). One of the largest series is by Potters et al who reported results for 1449 consecutive patients having brachytherapy with 61% of patients having T1c disease and 33% T2a disease. After 12 years of follow up the OS was 81% and CSS was 93% (30). It must be noted that there is no RCT comparing brachytherapy to standard of care treatments.

There may also be some benefit in terms of oncological control from using neo-adjuvant androgen deprivation therapy and/or an external beam boost in men with intermediate and high risk disease (31, 32).

1.2.4 Minimally Invasive Ablative Whole Gland Therapies

Cryotherapy uses freezing treatments to induce cell death by dehydration, protein denaturation, ice crystal formation which results in cellular rupture and vascular stasis, thrombi formation and ischaemia. It may also induce an immune response towards the cancerous cells. Whole gland therapy has been used extensively. Bahn et al in 2002 reported a series of 590 patients with a mean follow-up of 5.4 years. Using the ASTRO criteria they reported bDFS of 92% for low risk, 89% for intermediate risk, and 89% for high risk cancer (33). Similar bDFS of 96.4% for low risk, 91.2% for intermediate risk, and 62% for high risk tumours have been reported more recently by Rodriguez et al on 108 patients with a median follow-up of 5 years (34). There are two RCTs comparing whole gland cryotherapy to radical external beam radiotherapy (35, 36). Chin et al randomised 62 men with locally advanced prostate cancer (cT2c-cT3b) to either primary cryoablation or external beam radiotherapy. All patients received neo/adjuvant hormonal therapy for 6 months in total. The trial failed to fully accrue and was closed early. The 8-year biochemical disease-free survival, defined by the Phoenix criterion, was lower in the cryoablation group (17.4% vs 59.1%) (p = 0.01). There was no difference in overall or cancer-specific survival. Donnelly et al conducted a randomized, noninferiority trial comparing cryoablation to external beam radiotherapy in 244 men with newly diagnosed cT1-cT2 prostate cancer. 3-year biochemical disease-free survival, again
defined by the Phoenix criterion, was 76.1% in the cryoablation arm and in 76.3% in the radiotherapy arm. There was no difference in overall or cancer-specific survival. The conflicting results between the two studies can be explained by the higher disease burden in the Chin et al RCT compared to Donnelly et al where all men had localised rather than locally advanced disease. The contrasting results are also likely the reason behind whole-gland cryotherapy not being accepted as a standard of care treatment.

High intensity focussed ultrasound (HIFU) uses focused ultrasound waves to induce mechanical and thermal tissue damage along with cavitation, which results in coagulative necrosis. Whilst there are no comparative studies to speak of, Crouzet et al published a large single center whole gland HIFU study of 1002 patients with T1 or T2 disease who were unsuitable for radical surgery. The 8 year bDFS for low, intermediate and high risk disease patients were 76%, 63% and 57% respectively. The 10 year OS and CSS were 80% and 97% respectively (37). Similar results were seen in German series of 538 patients with 14-years of of follow-up (median 8 years) (38). Systematic reviews of the literature have also confirmed these findings. A review of 31 uncontrolled studies showed a 5-year disease-free survival rates from 61.2 to 95% (39). Despite promising oncological outcomes HIFU in the UK has had a troubled existence due to publication of data from two major cancer centres showing less than ideal results. Both these centres were early in their learning curve and such poor outcomes have not been seen elsewhere (40, 41).

1.2.5 Treatment Related Side-effects from Whole Gland Treatments

All the radical and whole gland treatments have a level of bothersome side-effects particularly with regards to continence and erectile dysfunction (ED). Radical prostatectomy carries early surgical complications which have been significantly reduced by use of the robotic method (21, 22, 42). Continence rates with robotic
radical prostatectomy range between 69 – 92.5% and potency rates range from 50 – 90% at 1 year with an overall prevalence of 52.2% at 1 year (21, 43, 44).

Radiotherapy can cause grade 2 bowel, bladder and lymphatic complications in 22.8% and late grade 3-4 complications in 5% (45). Secondary malignancies of the rectum and bladder are also possible after radiotherapy albeit rarely (46-48). Additionally brachytherapy may result in the need for TURP in up to 8.7% of cases (49).

A meta-analysis of observational studies reviewing ED rates showed 1 year potency rates of 76% (brachytherapy), 60% (brachytherapy + EBRT), 55% (EBRT), 34% (nerve sparing RRP) and 25% (open RRP) (50).

Relatively high side-effects have also limited the potential of whole gland cryotherapy. A Cochrane review by Shelly et al in 2007 found rates of impotence (47 to 100%), incontinence (1.3 to 19%), and urethral sloughing (3.9 to 85%), fistula (0 to 2%), bladder-neck obstruction (2 to 55%), stricture (2.2 to 17%) and pain (0.4 to 3.1%) (51). Similarly whole gland HIFU can lead to adverse events affecting the urinary tract in 0.7–31% of patients, bladder outlet obstruction in 4–51.5% with a urethral stricture rate of 19.4 to 40.4% dependent on whether a suprapubic or urethral catheter was inserted post-operatively (39, 52). A limitation of such data is the wide ranges quoted which are likely due to the quality of data and heterogenous sample sizes of the included studies.

1.2.6 Minimally Invasive Ablative Focal therapies

In an attempt to improve the side-effect profile of whole gland treatments whilst offering oncological control, research started to focus on minimally invasive ablative focal therapies, focal therapy (FT) for short. This focal strategy postulated that targeting only the clinically significant cancerous areas within the prostate may be permissible to prevent disease progression whilst leaving behind clinically insignificant
cancer and also sparing healthy tissue. There were multiple developments that were needed for such treatments to become a reality:

1. Definition of an Index Lesion and clinically insignificant cancer.
2. Improvement in prostate cancer diagnostics and disease characterisation.
3. Evidence on efficacy of ablative modalities.

1.2.6.1 Definition of an Index Lesion and clinically insignificant cancer

Although prostate cancer has often been demonstrated to be multifocal in nature [3] there is evidence that suggest that a solitary index lesion within the prostate drives disease progression and that small and low grade lesions are of limited clinical significance. These small multifocal lesions are often of low grade and volume and may not actually bear the traditional hallmarks of malignancy [8]. Therefore, it may be feasible to treat only the “clinically significant” cancer whilst leaving the “clinically insignificant” cancer behind. The difficulty came when defining clinically insignificant cancer and conversely significant cancer.

1.2.6.1.1 Gleason Grading

One of the most major shifts in prostate cancer happened with new guidance on the histopathological assessment of Gleason Grading. The Gleason score developed in 1966 was one of the earliest methods for categorizing prostate cancer which is determined by the sum of the two highest scoring areas (scored 1-5) within the sample (i.e. 3 + 3 = 6 or 3 + 5 = 8) [53]. It originally ranged from 2-10 however after a 2005 consensus meeting the currently used modified Gleason score was developed [54]. This largely removed scores of 2-4 and effectively made Gleason 6 the lowest pathological risk category. Subsequently a tighter definition for Gleason 6 was agreed on where cribriform pattern 3 was removed and that ill-defined glands with poorly defined glandular lumina should be classified as pattern 4 [55]. These changes meant that there was a decrease in Gleason 6 cancers and an increase in Gleason 7.
disease (56). Re-reviewing 806 radical prostatectomy specimens using these new criteria resulted in 34% of Gleason 6 cancer being upgraded to Gleason 7 (57).

The current group of patients being diagnosed with Gleason 6 disease are a more homogenous group defined pathologically as containing single, well-formed glands which infiltrate along non-neoplastic prostatic acini (58). Keeping in mind this change, even data from studies using the older grading system have shown good outcomes with the 20 year prostate cancer specific mortality being 27% for conservatively managed Gleason 6 disease (59).

More recently the cancerous nature of “True” Gleason 6 disease has been brought into question (60). Hanahan and Weinberg defined six cellular alterations needed to define a cell as malignant (61). These were 1) self sufficiency in growth signals, 2) insensitivity to anti-growth signals, 3) evasion of apoptosis, 4) limitless replicative potential, 5) sustained angiogenesis, and 6) tissue invasion and metastases. A combination of studies has determined that Gleason pattern 3 does not meet these requirements and thus may be almost benign in nature (60).

For instance a re-review of 9554 radical prostatectomy specimens by Eggner et al found that no patient with isolated Gleason pattern 3 died from their disease (62). Similar work by Ross et al has shown that from 14,123 patients who underwent a radical prostatectomy and pelvic lymph node (LN) dissection not a single patient with Gleason 6 disease had a LN metastases (63).

In terms of the focal therapy paradigm this potentially meant that even in cases of multifocality treatment could be delivered to the clinically significant or index lesion. This is beautifully highlighted by Johnson et al who analysed 588 whole mount radical prostatectomy specimens and found multifocality in 63% of cases. However, 75% of these multifocal lesions were Gleason 3+3 (64). Valerio et al had also previously shown that up to 50% of men may be suitable for focal treatment after taking into account clinically insignificant multifocal disease (65).
1.2.6.1.2 Tumour Volume and Cancer Significance

A limitation of using Gleason Grading alone is that it does not take into account tumour volume and multiple studies have shown that tumour volume may better differentiate significant from insignificant cancer (66).

Bostwick et al reviewed studies of tumour size on radical prostatectomy, cystoprostatectomy and autopsy specimens against the risk of capsular invasion, seminal vesicle disease and metastases. They determined that 0.5 cc was a cut-off for a significant volume with a 10% risk of capsular invasion. The risk of invasion and metastases increased with volume and a tumour of 5 cc had a 10% risk of metastases (67).

Using the criteria of < 0.5 cc, < Gleason 7/no pattern 4, up to 25% of tumours found on radical prostatectomy specimens may be deemed insignificant (66).

Originally in 1994, using a more conservative cut-off of ≤0.2 cc for significant disease, Epstein created a set of biopsy criteria to define very-low risk prostate cancer: stage <T1c, no pattern 4, PSA density ≤0.15, ≤2 positive cores and <50% single core involvement (68). These were updated in 2004 when Bastian et al assessed their use in determining organ confined disease and thus suitability for radical treatment in 217 patients with T1c prostate cancer who underwent RP. (69). They found that 91.3% of patients had organ confined disease if they met the criteria. They also advocated a higher number of biopsy cores to more accurately stratify the cancer pre-operatively.

1.2.6.2 Improvement in prostate cancer diagnostics and disease characterisation

Alongside the developments in histological cancer grading improvements were needed in the diagnostic strategy for prostate cancer due to the inherent inaccuracy in random transrectal prostate biopsies (TRUS) that had been the standard practice for many decades.
10 – 12 core transrectal ultra-sound guided (TRUS) biopsy has been the most widely used method for pathological diagnosis. It has several limitations though. Studies reviewing radical prostatectomy specimens show that 20-25% of patients may harbour anterior tumours and these can be missed on a standard TRUS biopsy (70, 71). Also due to the effect of random sampling, when assessing re-biopsy after an initial negative biopsy, 30% of patients are found to harbour a tumour (72). Repeat saturation biopsy, where additional cores are taken by either the transperineal (TP) or trans-rectal route were not found to be significantly different in their cancer yield and either approach appears acceptable for a re-biopsy strategy (72).

In a modern cohort of 552 men with TRUS detected low risk prostate cancer, defined by the D’Amico criteria undergoing radical prostatectomy, Swanson et al found upgrading in 16.9%. Of the remaining 454 patients with Gleason 6 disease, bilateral tumours were found in 70% but 89% of the total tumour volume was from an index lesion. However, only 34% of patients had a tumour nodule of >0.5cc. These results emphasize the need for accurate pre-operative diagnostic procedures in order to accurately determine whether a patient truly has significant versus insignificant prostate cancer (73).

When using a high density 5mm sampling frame transperineal mapping biopsies performed in patients previously shown to having a unilateral low-grade lesion on TRUS biopsies, 23% of cancers were upgraded whilst 60% were found to have bilateral disease (74). Tumours <5mm may be missed and thus the diagnostic accuracy of transperineal biopsy ranges between 90-95% for clinically significant disease when compared to a radical prostatectomy specimens (75-77).

Attempts have been made to determine tumour volume using transperineal biopsy cores. Computational modelling of 107 radical prostatectomy specimens found that using either a total cancer core length (TCCL) of ≥ 10mm or maximum cancer core length (MCCL) of ≥ 6 mm, predicted a tumour volume of > 0.5 cc with a 95%
sensitivity. Using a TCCL of ≥ 6 mm or MCCL of ≥ 4 mm was able to predict a tumour volume of 0.2 cc (78).

These 5mm mapping TP biopsies appear to be the most accurate way to pre-operatively assess disease for both size and volume. However, in order to minimise the number of cores taken, many use systematic transperineal or a saturation transrectal protocol (79).

With the concurrent development of multi-parametric MRI (mpMRI), most contemporary diagnostic strategies have utilised mpMRI and targeted biopsies have been used to diagnose clinically significant cancer.

The two seminal papers in this field were the UK based PROstate MR Imaging Study (PROMIS) and PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not? (PRECISION) studies (80, 81). Within the PROMIS trial 576 biopsy naïve men underwent a blinded pre-biopsy MRI followed by a combined TRUS and 5mm template mapping biopsy. The prevalence of clinically significant disease as defined by any cancer with a maximum cancer core length (MCCL) of >/= 6mm (correlates with tumour volume of 0.5cc or greater) or primary pattern 4 was 40% whilst the presence of any cancer was 71%. Multiparametric MRI correctly identified 213 of 230 clinically significant cancers and missed no cancer of Gleason 4+3 and above. Multiparametric MRI sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were 93%, 41%, 51% and 89% respectively. The PRECISION trial randomised 500 men to either MRI-targeted biopsies or systematic biopsy and found a superior detection of clinically significant cancer in the MRI-targeted biopsy group (38%) versus the systematic biopsy group (26%), P<0.001.

Subsequently, a metanalysis of 42 studies with 7321 patients has confirmed the pooled NPV for biopsy-naïve men to be 90.8% (95%CI 88.1-93.1%) and a metanalysis of 68 paired design studies and 8 RCTs with over 14000 men receiving either or both MRI targeted biopsies and systematic biopsy have confirmed that MRI targeted biopsies detected more clinically significant cancer than systematic biopsy (detection
ratio [DR 1.16 [95% CI 1.09-1.24], p<0.0001] and fewer men with clinically insignificant cancer than systematic biopsy (DR 0.66 [95% CI 0.57-0.76], p<0.0001).

Taken together the developments in the biopsy strategy and the use of multiparametric MRI have improved the detection and localisation of cancer within the prostate which has allowed for a focal ablative approach to become feasible.

1.2.6.3 Clinical Evidence of Focal Therapy in the Primary Disease Setting

Clinical outcome papers started appearing in the mid 2000’s, initially for focal cryotherapy and then focal HIFU. What was clear very early on was that genitourinary function was preserved in the vast majority of men and early disease control appeared promising, leading to numerous prospective developmental trials.

A recent systematic review of 2350 cases of men undergoing focal therapy from 30 studies showed pad-free continence rates of 95-100% and preservation of erectile function in 54-100%. With follow-up ranging from 0 to 11 years, in the primary setting biochemical disease-free survival (bDFS) was 60–83%, whilst post-treatment histological absence of clinically significant cancer ranged from 83-100%. It must be noted that 50% of these men were intermediate or high risk. Valerio et al subsequently reviewed 37 studies with 3230 patients undergoing focal therapy. The rate of significant cancer at control biopsy varied between 0% and 13.4%. Incontinence rate was 0-16.7% and erectile dysfunction occurred in 0-18.5% (82, 83). In the UK, three early phase trials of 20, 41 and 56 men showed that hemi-ablation, focal ablation and index lesion ablation were safe, feasible, conferred low toxicity and acceptable rates of disease control in the short term (16-18).

The most contemporaneous data with regards to focal therapy is on focal HIFU and our group recently presented data from 625 men undergoing focal HIFU. Within this cohort 80 (13%) had low-risk, 491 (81%) had intermediate-risk and 39 (6%) had high-risk disease. Median follow-up was 56 (IQR 33-70) months. Overall re-treatment rate with further FT was 20% whilst transition to radical therapy occurred in 7% and
systemic therapy in 1%. The metastasis-free survival, cancer specific survival and overall survival at five years were 97%, 100% and 99%, respectively. The pad-free continence rate (any pad use) was 97% and preservation of erectile function was 84%. The out-of-field (untreated tissue) de novo disease or progression occurred in only 2-3%, pointing to the safety of leaving untreated tissue and cancers on surveillance after focal therapy and adding more credence to the index lesion concept. (84). Another recent publication was from a French group who reported on 111 patients undergoing hemi-ablation with HIFU for low to intermediate risk prostate cancer (68% low risk, 32% intermediate risk). Their results showed that of the 101 patients with follow-up biopsy, 96 (95%) and 94 (93%) had no clinically significant cancer in the treated or contralateral lobes, respectively. Failure free survival defined as freedom from radical treatment at 2 years was 89%. At 12 months 97% were continent and 78% had preserved erectile functions (85).

Contemporary data on cryotherapy particularly in clinically significant intermediate and high-risk disease appears to be lacking and the largest series is by Ward and Jones on 1160 men from the US Cryo On-Line Database (COLD) registry on focal cryotherapy. Their results showed a biochemical disease-free survival (bDFS) (ASTRO defined) of 75.7% at three-years. Prostate biopsy was generally only performed in those with suspected recurrence in 164/1160 of patients and was positive in 43/164 (26.3%) but in only 3.7% (43/1160) overall. The pad-free continence rate (any pad use) was 98.4% and preservation of erectile function was 58.1%. Rectourethral fistula occurred in only one patient (86). A criticism of this dataset is its historical nature with concerns regarding the completeness of follow-up.

The only RCT in the field of focal therapy randomised 413 men with low risk cancer to either active surveillance or focal VTP. After a median follow-up of 24 months 58% of men had disease progression in the AS arm versus 28% in the VTP arm. With the body of evidence now supporting active surveillance in low-risk disease this cohort are unlikely to meet the modern criteria for clinically significant cancer and thus “active” treatment. This limitation of the study can be attributed to the time period within which it was conceived (2011 and 2013) (87).
The main attraction of focal therapy is that at least in the short to medium term cancer may be well controlled with minimal side-effects to the patients. Repeat procedures are also possible, yet data on this is also lacking, and ultimately the patient may still be eligible for salvage radical whole gland treatments such as radical prostatectomy or external beam radiotherapy.

1.2.6.3.1 Histological Outcomes after Focal Therapy

One of the significant areas of debate relates to how success or failure of focal therapy is assessed, regardless of which ablative modality is being delivered. The arguments for and against various definitions follow a common theme in all studies but consideration must be given to definitions that would allow acceptance and approval of focal therapy. Established PSA follow-up criteria used for whole-gland treatments such as ASTRO, Phoenix and the Stuttgart criteria, are difficult to apply to a patient after focal therapy as the untreated normal prostatic tissue will continue to secrete prostate specific antigen (PSA). PSA kinetics and PSA nadir may play a role as PSA secretion from the cancerous lesion is larger than healthy prostate tissue and Ahmed et al noted an 80% decrease in PSA at 3 months after focal HIFU. This decrease persisted at 12 months (88). The more solid endpoints of metastases and death would require over a decade of follow-up due to the long natural history of even clinically significant prostate cancer. Insisting on such outcomes for changes in clinical practice or regulatory approvals would inevitably stifle innovation. Not only would these findings have limited external validity, reported after 10-15 years, but would be prohibitively expensive and resource heavy. Other outcome measures, such as histological outcomes, are clearly needed.

Below, I aim to first discuss the existing state-of-the-art with respect to histological outcomes after focal therapy and how best to interpret these in clinical practice. The literature is mainly based on the two most widely used modalities of HIFU and cryotherapy.
Histological Changes on Radical Prostatectomy Specimens

HIFU

In one of the very first proof of concept studies, Van Leenders et al assessed the histological changes of unilateral HIFU in men who subsequently underwent a radical prostatectomy 7 – 12 days later. This study was set up in the early evaluation of HIFU using the ablate-excite study model and whilst the investigators did not set out to fully ablate all tissue it did demonstrate that ablation can be achieved. Macroscopically, well demarcated circular and ellipsoid lesions were seen. Microscopically, cell necrosis was seen within the core of the lesion, however and not surprisingly, this was incomplete in 6 out of 9 lesions. Haemorrhage with hyperplastic epithelium and reparative changes were also seen at the borders of the lesion (89).

Napoli et al performed a similar study in five patients with radical prostatectomy performed 7 – 14 days after HIFU treatment. They also found extensive coagulative necrosis but with no viable tumour within or at the boundaries of the treated lesion (90). Subsequently, over time, there is development of fibrosis and elastotic collagen [Figure 1].

Both these studies observed the presence of multi-focal lesions outside of the treated lesion and thus emphasize the need for accurate pre-operative staging and disease localization.

Figure 1. Left image shows a Gleason 3+4 adenocarcinoma. Middle image shows typical changes after HIFU with no discernible glands, viable cells or tumour with presence of fibrosis and elastotic collagen. Right image shows recurrent adenocarcinoma after HIFU.
Cryotherapy

In 1991 Onik et al showed complete coagulative necrosis and accurate visualization of the ice ball under trans-rectal ultrasound (TRUS) in 6 dogs treated with cryotherapy (91). Larson et al examined the effects of exactly this technique for cryotherapy in five patients who were already scheduled to go undergo salvage prostatectomy 2 – 3 weeks later. Histologically squamous metaplasia of glandular epithelium with haemorrhage and a zone of coagulative necrosis and devitalization was seen spreading from a central core (92). However, similar to the HIFU studies, incomplete cell death on occasions has also been noted with cryotherapy (93).

Post-treatment Biopsies

Earlier work with protocol driven TRUS biopsies in 167 out of 176 patients treated with whole-gland cryoablation showed persistent tumour in 38%. However, in this study the exact Gleason grade or volume data and thus clinical significance of the biopsy results was not mentioned (93). Similarly, Crouzet performed post-treatment biopsies in 774 patients from cohort of 1002 patients treated with whole gland HIFU procedures. Overall, 37% of these biopsies were positive (37).

Donnelly et al also performed a randomized control trial (RCT) where 244 men with T2/3 prostate cancer were randomised to either whole-gland cryotherapy or radiotherapy. At a median follow-up of 100 months they found no difference in disease progression between the two groups. They also found a higher number of positive biopsies at 36 months in the radiotherapy arm (28.9% compared to 7.7% with cryotherapy) (36).

Reviewing the results of 8 studies assessing focal cryotherapy, 98/391 (25%) of all post-treatment biopsies were positive (86, 94-100) [Table 1]. No information on grade or location for the 42 positive biopsies from the COLD registry paper by Ward et al was available. Thus, reviewing the results from the remaining papers shows that 86%
(48/56) of positive biopsies were either from an untreated portion of the prostate or met with criteria of insignificant lesions (Gleason 3, ≤2 cores positive).

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Number of Patients</th>
<th>Treatment Modality</th>
<th>Biopsy Method for Initial Diagnosis</th>
<th>Protocol or for-cause Biopsy Method</th>
<th>Number of patients with a positive post procedural biopsy / total number of biopsied patients</th>
<th>Biopsy Significance</th>
<th>Subsequent Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargawi 2014</td>
<td>62</td>
<td>Cryo</td>
<td>Template mapping</td>
<td>Protocol 12 month TRUS biopsy</td>
<td>12/62 (19%) 1/12 bilateral 7/12 ipsilateral 4/12 contralateral side</td>
<td>7/8 NS Ipsilateral 3/4 NS contra</td>
<td>AS (5) Re-do cryo (5) RRP (2)</td>
</tr>
<tr>
<td>Bahn 2012</td>
<td>73</td>
<td>Cryo</td>
<td>Doppler TRUS</td>
<td>Protocol and for cause 6 – 12 month TRUS biopsy</td>
<td>12/48 (25%) 1/12 - Ipsilateral 11/12 contralateral side</td>
<td>1/1 NS Ipsilateral 9/11 NS Contralateral</td>
<td>AS (8) Re-do Cryo (1) Brachy (1) ADT (1)</td>
</tr>
<tr>
<td>Ward 2012</td>
<td>1149</td>
<td>Cryo</td>
<td>NA</td>
<td>For Cause TRUS Biopsy</td>
<td>42/162 (26%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Truesdale 2010</td>
<td>77</td>
<td>Cryo</td>
<td>TRUS</td>
<td>For cause TRUS Biopsy</td>
<td>10/22 (45%) 2/10 ipsilateral 7/10 contralateral 1/10 Bilateral</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lambert 2007</td>
<td>25</td>
<td>Cryo</td>
<td>TRUS</td>
<td>For cause or PSA nadir &lt;50% TRUS Biopsy</td>
<td>3/7 (43%) 1/3 ipsilateral 2/3 contralateral</td>
<td>3/3 NS</td>
<td>Re-do Cryo (3)</td>
</tr>
<tr>
<td>Ellis 2007</td>
<td>60</td>
<td>Cryo</td>
<td>NA</td>
<td>Protocol 12 months TRUS biopsy</td>
<td>14/35 (40%) 1/14 ipsilateral 13/14 contralateral</td>
<td>NA</td>
<td>Re-do Cryo (12) Lost to FU (1)</td>
</tr>
<tr>
<td>Onik 2007</td>
<td>55</td>
<td>Cryo</td>
<td>Template mapping</td>
<td>For cause and Protocol 12 months TRUS Biopsy</td>
<td>Protocol 0/26 For cause 4/4 in untreated portion of gland</td>
<td>NA</td>
<td>Re-do Cryo (4)</td>
</tr>
<tr>
<td>Bahn 2006</td>
<td>31</td>
<td>Cryo</td>
<td>Doppler TRUS</td>
<td>Protocol 6 months TRUS biopsy</td>
<td>1/25 (4%) 1/1 in untreated portion of gland</td>
<td>NA</td>
<td>Re-do Cryo (4)</td>
</tr>
</tbody>
</table>

Table 1 – Results from focal cryotherapy studies mentioning post-treatment histological outcomes
Cryo = Cryotherapy; TRUS = Transrectal Ultrasound Guided Biopsy; NA = Not Available; NS = Non significant; ADT = Androgen deprivation therapy; AS = Active Surveillance

Six of these studies mentioned the initial method of diagnosis and only 2 used transperineal mapping biopsies whilst all the others relied on TRUS biopsies for pre-operative planning. The two studies that did use mapping biopsies had a 13 – 19% post procedure positive biopsy rate (94, 99)

Similarly, from the six studies assessing biopsies after focal HIFU, 22% (39/175) were positive (88, 101-105) [Table 2]. Excluding the 4 positive biopsies from the paper by Muto et al, as no data on location or histological grade was available, 63% (22/35) of the positive biopsies were either insignificant or from the untreated part of the gland.
However, results such as these have to be interpreted with caution as they are from a heterogeneous group of for-cause (suspicion of recurrence), protocol-driven, bilateral or targeted biopsies. It would be expected that for-cause biopsies would be more likely to be positive as they are performed for a clinical suspicion of recurrence. However, studies that only conduct for-cause biopsies, means that those with stable PSAs are selectively not subjected to verification biopsies after treatment. If protocol biopsies are performed, then these should be aimed at determining initial treatment success and thus should be targeted at the treated lesion. Additionally, performing biopsies of untreated areas is not assessing treatment success but rather the accuracy of pre-operative assessment.

Table 2 – Results from focal HIFU studies mentioning post-treatment histological outcomes
HIFU = High Intensity Focused Ultrasound; TRUS = Transrectal Ultrasound Guided Biopsy; NA = Not Available; NS = Non-significant; ADT = Androgen deprivation therapy; AS = Active Surveillance

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Number of Patients</th>
<th>Treatment Modality</th>
<th>Biopsy Method for Initial Diagnosis</th>
<th>Protocol or for-cause Biopsy Method</th>
<th>Number of patients with a positive post-procedural biopsy / total number of biopsied patients</th>
<th>Biopsy Significance</th>
<th>Subsequent Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muto 2008</td>
<td>29</td>
<td>HIFU</td>
<td>TRUS</td>
<td>Protocol 6 – 12 months TRUS</td>
<td>3/28 at 6 months 4/17 at 12 months</td>
<td>NA</td>
<td>ADT</td>
</tr>
<tr>
<td>El Fegoun 2011</td>
<td>12</td>
<td>HIFU</td>
<td>NA</td>
<td>Protocol 12 months TRUS</td>
<td>1/12</td>
<td>1/1 NS</td>
<td>Re-do HIFU (1)</td>
</tr>
<tr>
<td>Ahmed 2011</td>
<td>20</td>
<td>HIFU</td>
<td>Template mapping</td>
<td>Protocol 6 months mpMRI + TRUS targeted of treated side only</td>
<td>2/19 ipsilateral</td>
<td>2/2 NS</td>
<td>AS (1) Re-do HIFU (1)</td>
</tr>
<tr>
<td>Ahmed 2012</td>
<td>41</td>
<td>HIFU</td>
<td>Template mapping</td>
<td>Protocol 6 months mpMRI + TRUS targeted of treated side only</td>
<td>9/39 ipsilateral</td>
<td>6/9 NS</td>
<td>AS (5) Re-do HIFU (4)</td>
</tr>
<tr>
<td>Dickinson 2012</td>
<td>88</td>
<td>HIFU</td>
<td>NA</td>
<td>For cause mpMRI + TRUS targeted</td>
<td>20/72 ipsilateral</td>
<td>10/20 NS</td>
<td>NA</td>
</tr>
<tr>
<td>Velthoven 2014</td>
<td>27</td>
<td>HIFU</td>
<td>TRUS + concordance with mpMRI lesion 2 months after biopsy</td>
<td>For cause (Rising PSA)</td>
<td>3/5 contralateral</td>
<td>3/3 Contralateral</td>
<td>Contra-lateral HIFU (3)</td>
</tr>
</tbody>
</table>

Eleven studies mentioned the subsequent management of 62 patients in total who had a positive post-treatment biopsy. 61% (38/62) elected for redo focal therapy, 31% (19/62) chose active surveillance (AS) whilst 8% (5/62) had either external beam radiotherapy (EBRT), radical prostatectomy (RP) or androgen deprivation therapy.
(ADT). The ability to retreat with curative intent without significant additional morbidity is a major advantage of focal therapy over whole gland treatments such as RP or EBRT.

Berge et al recently published the results of 130 patients undergoing a second HIFU procedure of which 19 underwent a second redo session and 1 had a third session. Overall, this group was formed from a cohort of 359 patients and thus represented the 36.2% who needed repeat treatment based on biochemical, histological or imaging (mpMRI) failure. No cancer specific deaths were reported in this group. 56 men (43%) did fail a second time. 40 underwent TRUS biopsy and 22 were positive. Their results also showed that side-effects were not greatly increased with an increase in pad usage from 2.7% to 9% (p<0.001) and no effect on potency (p=0.9) (106). Blana et al had also previously shown a minimal impact on quality of life with a second session of HIFU (107).

A significant portion chose active surveillance (AS) and there is indirect evidence to suggest that this may be an acceptable option for patients with positive post-treatment biopsies. Data from an AS series of 450 patients diagnosed on TRUS biopsy (and therefore approximately 30% of whom would have been true intermediate risk) shows a 10 year cancer specific survival of 97.2% with only 5 deaths. A recent update which now included 993 men with up to 16 years follow-up showed a 15 year actuarial cancer specific survival of 94.3% (108, 109). Another indirect source of evidence are studies assessing the outcomes from patients who have post-radiotherapy positive biopsies. 21-32% of patients may have positive biopsies. The results show that although patients with a positive biopsy have a poorer outcome their 5 year biochemical disease free survival (bDFS) was still high at 83.3% - 93.8% compared to 97.5% for those with a negative biopsy (110). In contrast though, Zelefsky assessed 10 year oncological outcomes and found that the group with positive biopsies had only a 3% PSA relapse free survival and a 69% metastases free survival compared to 59% and 90%, respectively, for patients with negative biopsies. Zelefsky did have a third group of patients who had positive biopsies showing severe treatment effect. This group did not have a significantly different outcome when compared to those with negative
biopsies (111). Thus, a positive biopsy has to be reviewed carefully before a clinical significance can be implied. Similarly, a positive surgical margin after radical prostatectomy does not always convey a poorer outcome (112).

Summary

Research suggests that 1 in 5 of all post-treatment biopsies after focal therapy are positive. However, the majority of these seemed to be from the untreated portion of the gland or met criteria for clinically insignificant disease. The histological outcomes from focal therapy are promising and confirm its effectiveness in the short to medium term. Furthermore, re-treatment is possible whilst maintaining a low side effect profile. Debate is ongoing about the clinical significance of various levels of residual disease after focal therapy and the exact threshold at which to call failure within a patient who has had focal therapy.

1.2.6.4  Ideal Candidate for Focal Therapy

Reviewing the results of three recently published consensus statements discussing many of these issues concerning focal therapy [Table 3] (113-115). All consensus meetings and expert opinions are considered as level 5 evidence and their findings should be considered with this in mind. However, in the absence of high-level evidence, they present important opinions from experts in the field and highlight areas of uncertainty.

Donaldson et al and Van den Bos et al separately discussed inclusion and exclusion criteria and both consensus groups agreed that high volume Gleason 6 (>5mm MCCL) and Gleason 7 disease are the optimal candidates. They discussed the importance of accurate pre-operative assessment using MRI-targeted or fusion biopsy methods prior to offering a patient treatment. They recommend protocol biopsies at 12 months post-treatment and that a rising PSA or suspicious MRI should also trigger a biopsy. The ultimate end point was a negative 12 month biopsy. However, there were differing opinions on whether these should only be targeted or also systematic or whether residual low-grade and low-volume cancer is considered treatment failure.
Donaldson et al mentioned that biopsies should be targeted rather than systematic in order to reduce sampling of untreated tissue, whilst Muller et al (another consensus group) commented that systematic biopsies are useful for surveillance of the untreated gland. Re-treatment was considered acceptable and Donaldson et al commented that overall re-treatment rate should be below 20% since it was argued that retreatment was a positive attribute of the strategy.

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Pre-op Biopsy Strategy</th>
<th>Biopsy End Point</th>
<th>PSA</th>
<th>MRI</th>
<th>Treatment failure</th>
<th>Re-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Bos 2014 Multi-stage Delphi process</td>
<td>3+3 with “substantial cancer”</td>
<td>Clinically insignificant disease (volume &lt;0.5cc)</td>
<td>MRI targeted or Fusion with systematic</td>
<td>Negative 12 month biopsies</td>
<td>3 monthly</td>
<td>Alterations in MRI not sufficient as an end point</td>
<td>Acceptable on one occasion</td>
</tr>
<tr>
<td></td>
<td>3+4</td>
<td></td>
<td></td>
<td>Targeted and systematic</td>
<td>But not sufficient as an end point</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 year life expectancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSA &gt; 15 with caution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donaldson 2014 RAND/UCLA Appropriateness methodology</td>
<td>NCCN Intermediate risk disease</td>
<td>&lt; 5 years life expectancy and those &lt;40 and &gt;80 years with caution WHO performance status 3-4</td>
<td>MRI targeted or template mapping (if no MRI available)</td>
<td>12 month biopsy</td>
<td>Rising PSA may trigger biopsy</td>
<td>Suspicious MRI may trigger biopsy</td>
<td>≤20% retreatment rates</td>
</tr>
<tr>
<td></td>
<td>3+3 with &gt;3-5mm MCCL</td>
<td></td>
<td></td>
<td>Targeted only</td>
<td>Uncertainty about systematic sampling</td>
<td></td>
<td>Cancer in field of equivalent or higher than preoperative grade</td>
</tr>
<tr>
<td></td>
<td>&gt;10 years life expectancy Multifocal disease included (Secondary lesion of Gleason 6, ≤5mm can be left untreated)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low- grade, low-volume (Gleason 6, &lt;3mm) in field is not considered failure</td>
<td></td>
</tr>
<tr>
<td>Muller 2015 Delphi process</td>
<td>12 month biopsy Targeted and systematic</td>
<td>3 monthly</td>
<td>No consensus on role of PSA</td>
<td>1st MRI 6 months post treatment</td>
<td>Suspicious MRI should lead to biopsy Further biopsies after 12 months only if suspicious MRI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 - Consensus Meeting Results
2 Aims, Objectives and Patient Datasets

Building upon the available evidence in the literature I plan to answer the following overarching research questions:

1. What are the outcomes from focal cryotherapy for primary non-metastatic localised prostate cancer?

2. How does focal therapy compare to radical prostatectomy for primary non-metastatic localised prostate cancer?

My main aim will be to develop the evidence base for primary focal therapy with an emphasis on focal cryotherapy. I will present prospective data on focal cryotherapy before presenting a matched analysis comparing both focal HIFU and cryotherapy to radical prostatectomy.

My objectives will be:

1. Assess the evidence base for focal cryotherapy.
2. Evaluate treatment delivery.
3. Develop a prospective study in line with NICE guidance to assess outcomes.
4. Assess the oncological outcomes from focal cryotherapy.
5. Assess the functional outcomes from focal cryotherapy.
6. Assess outcomes from radical prostatectomy in a group of men who would be suitable for focal therapy.
7. Perform a propensity score matched analysis assessing oncological and functional outcomes between focal therapy and radical prostatectomy.
3  Focal Cryotherapy

In this chapter I will discuss the technological aspects of focal cryotherapy followed by a systematic review of the literature, analysis of laboratory data in order to optimise treatment delivery and finally analyse the oncological and functional outcomes from a multicentre, prospective focal cryotherapy database.

In Chapter 3.3 when assessing the ice ball data, I collaborated with the Galil lab in Minnesota. The design of the experiments had already been confirmed prior to my involvement with discussions taking place between my supervisor and Galil. After my discussions with Galil regarding the format of the data I was provided the data. I subsequently planned and conducted the analyses.

In chapters 3.4 and 3.5, I discuss the oncological and functional outcomes from focal cryotherapy. This is based on an early database that I took over from Dr Massimo Valerio. At that stage it had only a handful of patients. I subsequently redesigned the database which I then maintained personally over the course of my PhD. This involved prospectively collecting oncological and functional outcomes. I printed and personally posted PROMs questionnaires and followed these up with the patients. I then processed, cleaned and analysed the data for my thesis. At this point we obtained commercial funding and the database was handed over a database manager and converted into a redcap registry which I also helped design.
Cryotherapy, in which cancer cells are destroyed by freezing temperatures in a minimally invasive procedure, has undergone many technological advances over the last century. The fundamentals of cryotherapy date back to the 19th century. James Arnott (1797-1883), an English physician, applied mixtures of crushed ice and salt (at temperatures of −18° to −24°C) to accessible tumours such as the breast and cervix [3]. He reported that the technique led to a reduction in pain, haemorrhage and tumour size [4]. Although the therapeutic use of freezing temperatures was acknowledged during this period, it was not until the development of better cooling agents that cryotherapy began to evolve into a practical treatment [5].

There was further progress made in the late 1800's when Cailletet and Pictet developed systems that could produce liquified gases such as oxygen, air and carbon monoxide[6]. Their production relied upon the Joule-Thompson effect whereby highly pressurised gasses fall in temperature as they expand through a narrow opening into a lower pressure zone. Campbell White in 1899 was the first person to utilise these refrigerants in his medical practice. The liquid air he used was capable of reaching -190°C and could be applied locally to accessible skin cancers [7]. White noted the "efficacy of liquid air in the treatment of carcinoma" [8]. However, liquid air was hard to obtain and therefore there were limited reports of its uses during this period.

In the first half of the twentieth century, others attempted a range of cryoablation methods. Pusey in 1907 used solid carbon dioxide (-78°C) that could be used on various skin lesions [9]. Furthermore, Lortat-Jacobs in the 1930's passed liquid carbon dioxide through copper tips to treat gynaecological lesions. In 1950, Allington became the first to introduce liquid nitrogen which became widely available after the second world war [10]. It became the choice of cryogen because it was non-explosive, cheap and non-toxic. However, the delivery devices used at the time
offered shallow tissue penetration allowing only a small volume of tissue to be treated.

Modern cryotherapy technologies emerged in the 1960’s. Cooper and Lee developed a cryoprobe system that was able to be used in neurosurgical treatments [11]. The probes consisted of three concentric tubes: the inner tube carried the liquid nitrogen at pressure to the tip, the space of the middle tube allowed the warmed nitrogen gas to leave the tip and the outer tube space acted as a vacuumed insulator to prevent heat loss (figure 1) [12].

---

Figure 1: A simplified diagram of the early cryoprobes developed by Cooper an Lee in the 1960s's [12]. Cold liquid nitrogen was pumped into the system through the central tube. Heat exchange took place at the hollow tip and then warm liquid gas was removed through the middle tube with the help of a vacuum suction. The outer space (lined area) acted as a vacuum to prevent heat loss to unnecessary areas.

In the field of urology, Gonder et al. modified the probes used by Cooper so that they could be used for transurethral treatment in prostatic malignancies [13]. In the following years, Flocks et al. described a similar approach, instead using an open perineal incision in order to directly visualise the prostate [14]. The technology used during this era gave little protection to the surrounding tissue. Liquid nitrogen at
around -200°C was used and only the surgeon’s finger and a small needle-mounted thermocouple helped monitor and protect the rectal tissue [4]. These limitations meant that complication rates, such as urinary fistula formation (14%), and urethral tissue damage, were high (38%) [15] [16]. Thus, cryotherapy fell out of favour. Interest in the technique was renewed in the 1990’s with the introduction of intraoperative transrectal ultrasound (TRUS). This "second-generation" of cryosurgery was introduced by Onik et al. TRUS allowed the ice ball formed during cryotherapy to be visualised so that tumour destruction could be maximised whilst reducing the damage to adjacent tissue such as the bladder, rectum and urethra [17]. Additionally, there were improvements made to the cryosurgical apparatus. There was the introduction of urethral warming devices; a catheter with a double lumen through which heated saline is circulated to reduce damage to the urethra. The cryoprobes were also made thinner (3mm) and the liquid nitrogen was super-cooled to less than -200°C [17]. This allowed for a more efficient heat-transfer and a technique whereby multiple cryoprobes were placed into the prostate under TRUS guidance [18]. During this time, physicians also began to use thermocouples to help monitor the temperatures created within the prostate to protect the surrounding tissue.

Another important advancement in cryosurgery, was the replacement of the original liquid nitrogen systems by "third-generation" argon-based systems in 2001. These argon-based systems utilised the Joule-Thompson effect to cool and circulate argon gas through the cryoprobes at around -186°C [19]. In addition, Helium, which rises in temperature after depressurisation, provides a thawing mechanism that could not be achieved with liquid nitrogen [20]. The transition from liquid nitrogen to gas-based systems allowed the replacement of the larger 2.4-3mm cryoprobes with smaller 17G/1.5mm probes [21]. These "third-generation" systems are able to create ice-balls of predictable size and therefore aid the pre-treatment planning of cryoprobe placement. The development and improvement of cryosurgery has been significant and has helped cryotherapy for prostate cancer become a viable treatment option.
Table 1: Timeline of major developments in cryotherapy technology

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-1800's</td>
<td>First described the benefits of local application of ice mixtures by James Arnott [3].</td>
</tr>
<tr>
<td>1870's</td>
<td>Cailletet and Pictet developed the use of liquified gases such as air, oxygen and carbon monoxide [6].</td>
</tr>
<tr>
<td>1899</td>
<td>First clinical use of liquid air on skin cancers by White [8]</td>
</tr>
<tr>
<td>1907</td>
<td>First clinical use solid frozen carbon dioxide on skin lesions by Pusey [9]</td>
</tr>
<tr>
<td>1930's</td>
<td>Lortat-Jacobs began passing liquid carbon dioxide through copper wires to treat gynaecological lesions</td>
</tr>
<tr>
<td>1950</td>
<td>First use of liquid nitrogen in cryoablation by Allington [10]</td>
</tr>
<tr>
<td>1960's</td>
<td>Cooper and Lee developed a liquid nitrogen cryoprobe that was used in neurosurgical treatment [11]</td>
</tr>
<tr>
<td>1964</td>
<td>Gonder et al. modified the probes used by Cooper for use in prostatic malignancies [13]</td>
</tr>
<tr>
<td>1980-1990's</td>
<td>The &quot;second-generation&quot; of cryotechnology with this introduction of TRUS and improved apparatus such as thinner cryoprobes and urethral warming devices [22]</td>
</tr>
<tr>
<td>2001 onwards</td>
<td>The &quot;third-generation&quot; of cryotechnology with the introduction of gas-based systems and thinner cryoprobes with varied ice-ball formation profiles [19]</td>
</tr>
</tbody>
</table>

Cryobiology

The physiological mechanism by which cryotherapy causes cell death involves many factors. Firstly, close to the cryoprobe, the freezing temperatures are strong enough to induce freezing of the intracellular fluid. This is a lethal event that causes irreversible damage to the cell [7]. Further away from the cryoprobe, the freezing rate is much slower and not all intracellular fluid may freeze. However, there is a dehydration effect caused by the onset of ice formation; the ice formation leads to
water being drawn from the extracellular fluid, leaving behind a hyperosmotic solution. Subsequently, this hyperosmotic solution causes water to leave the cells, resulting in cell shrinkage and damage [21]. Further damage is caused upon thawing; fluid released from the ice melting rushes into the previously hyperosmotic cells causing them to burst [23]. In addition to osmotic damage, ice crystals cause direct cell injury due to shearing forces that disrupt the cells’ highly organised structures [24].

Cryoablation also indirectly aids in tumour destruction by its effect on the vasculature. Marzella et al. examined rabbit ears under microscopy and successfully showed that freezing injury damages the epithelial cells of the microvasculature [25]. This damage leads to increased permeability, oedema and activation of the coagulation cascade [26]. Ultimately this leads to stasis within blood vessels which in turn leads to cell ischemia and necrosis [27].

Following cryoablation, histological examination of the tissue shows a central area of necrosis surrounded by a freeze margin in which cell destruction may be incomplete [28]. Within this margin, apoptosis is an important mechanism to ensure continued cell death. Although the cells integrity remains, it is thought that damage to the mitochondria can signal the activation of cysteine-aspartic-proteases (caspase). These caspases can cleave various proteins that lead to apoptosis (leading to membrane blebbing, genomic fragmentation and cell shrinkage) [29] [30].

Another important aspect in cryosurgery is the concept of "cryo-immunology" which began in the 1970's when Alblin noted that several patients with metastatic cancers showed evidence of regression following cryotherapy. Although the observations recorded were limited, at least one patient had anti-prostatic antibodies within their serum [31]. Over the years, there have been numerous studies showing the significance of the immune system in cryotherapy. Interestingly, the results showed that cryoablation can both increase resistance to tumour re-challenges, but also can have immunosuppressive effects which increase sensitivity to tumour re-challenges [7]. A study by Hanawa et al. attempted to answer why cryoablation may alternate between being immune enhancing and suppressing. The study examined anti-
tumour responses in rats following cryoablation of MRMT-1 tumours in liver tissue. The rats that received full tumour ablation appeared to be more sensitive to subsequent tumour re-challenge than the control group. However, the rats that received partial ablation appeared to have increased resistance to tumour re-challenge [32].

The mechanism behind the mixed immune response is not fully understood. It is thought that the immune response to cryoablation can vary depending upon the mechanism of cell death (danger theory). Following necrosis, there is release of intracellular contents which include pro-inflammatory cytokines in addition to other "danger signals" such as heat shock proteins and uric acid [33]. Firstly, this acts to stimulate the innate immune system with the attraction of natural killer cells (NK cells), macrophages and phagocytes. Furthermore, dendritic cells which are antigen-presenting cells (APCs) process tumour antigens and present them to T cells [34]. This causes activation of multiple anti-tumour immune cells such as CD4+ T cells, CD8+ T cells and B cells. It is thought that this adaptive phase of the immune system may contribute to some of the protective features of cryoablation that has been shown in some studies. However, during apoptosis, there is no such release of intracellular contents and hence no "danger-signals". Instead, the cell displays molecules such as phosphatidylylsersine on its surface which help signal macrophage phagocytosis [35]. Therefore, it is postulated unlike necrosis, apoptosis does not act to provide immune protection to subsequent tumour re-challenges.

There are a number of procedural factors that influence the efficacy of cryotherapy. Firstly, the nadir temperature, which is a main determinant of cell death, has been studied intensively throughout the history of cryotherapy. Research has suggested temperatures that range from -20°C to -70°C [36] [37]. Notably, in vitro and animal studies show that -40°C is a critical temperature at which irreversible cell death occurs [38]. Additionally the physics of water suggest that at close to -40°C all liquid water within a cell would be crystallised leading to the formation of lethal intracellular ice [39]. Furthermore, the rate of cooling and thawing are important. Faster cooling rates are more destructive by increasing the likelihood of intracellular ice formation whereas slowing thawing rates are more destructive by maximising the
solute effects [40] [24]. The number of freeze cycles is also influential in the efficacy of cell death. For example, many in vivo and in vitro studies have shown that a double freeze cycle offers a clear benefit over single cycle therapy [41] [42]. It is widely regarded that producing temperatures of -40°C for a greater than 1 minute using a double cycle protocol leads to complete cell destruction [43].

The Technology

Currently there are two manufacturers that produce prostate cryotherapy systems approved in the USA by the Food and Drug Agency (FDA): Galil Medical Inc. and HealthTronics Inc. The main component of the cryotherapy technology is the cryoablation system. The systems are mobile cryoablation consoles that contain multiple cryoprobe connection channels, thermocouple sockets, argon and helium inlets, and a computer monitor. The system hardware and software are contained within the system. The cryoablation systems have a computerised interface that allow easy visualisation of the gas cylinder, thermocouple and cryoprobe information. Real-time temperature monitoring is shown by the system as well as temperature warnings and timers. The software gives the clinician maximum control over all aspects of the cryotherapy procedure.

There are some small differences between the different systems, but both systems (Visual-ICE ® by Galil and Endocare Cryocare CS® by HealthTronics) utilise the Joule-Thompson effect to achieve their temperature control; both use argon gas to achieve the freezing effect [53] [54]. However, unlike previous models, the latest system by Galil (Visual-ICE®) is now able to thaw without the use of helium and is therefore the only single gas system available (Figure 2). Instead, the I-thaw® cryoprobes use an internal heating system which provides the thawing mechanism. Both Galil and HealthTronics offer systems that can be used in co-ordination with computer tomography (CT) imaging. Currently, Galil are the only manufacturer to produce a whole system (including cryoprobes) to be compatible with MRI imaging techniques (MRI SeedNet® System) [55]. The system requires special installation and setup. The MRI SeedNet® System, junction box and gas cylinders are all placed in a
non-MRI (control) room. Cryoprobe and thermocouple cables from the main system and gas cylinder pipes are extended into the MRI (treatment) room to connect to a SeedNet mobile distribution panel. This setup along with specialised cryoprobes allows the use of cryotherapy within an MRI environment.

![Image of cryoablation system](image)

**Figure 2:** Visual ICE cryoablation system: The most recent cryoablation system available. Currently the only system that can thaw without helium gas. [53]

The cryoprobes are manufactured in a variety of diameters, lengths and freezing ability. The design of the probes vary, but all "third-generation" cryoprobes utilise the Joule-Thompson effect. Highly pressurised argon gas (3000 psi) at ambient temperature is circulated to the cryoprobe tip where it expands into room pressure (15 psi). The expanded gas is then passed to the back of the cryotherapy unit along the outer part of the cryoprobe [19] [Figure 3]. As mentioned earlier, the thawing is achieved either by helium gas or a heating element within the cryoprobe. Although the older liquid nitrogen cryotherapy systems can achieve lower temperatures (super-cooled to -200°C) compared to argon-based systems (-186°C), this does not relate to greater freezing power. However, there appeared to be no difference in size of the ice ball formed by the argon-based systems. Furthermore, argon-based systems also have the advantage of freezing faster and being more responsive to
user inputs (changing between -185°C and +40°C in around 30 seconds) when compared to the 1-2 minute lag time experienced with the liquid nitrogen systems [56].

The different cryoprobes produce ice ball formations of varied shapes, diameters and temperature gradients (Figure 4) [57]. The size of the -40°C isotherm range from 11 x 20mm to 22 x 43mm for the Galil cryoprobes and from 13 x 15mm to 20 x 50mm for the HealthTronics cryoprobes. Besides system design, the main difference between the two manufacturers of cryoprobes is the diameter of the probes. Galil produce a slightly thinner 17 gauge (1.5mm) probes compared to HealthTronics that produce 15 gauge (1.7mm) probes. Another difference, is that HealthTronics produce a V-Probe® that incorporates a variable slider that can create 5 different isotherms from the same probe [58]. In addition to the cryoprobes, the manufacturers also produce thermocouples to monitor the temperatures produced. The most advanced thermocouples are now capable of monitoring multiple temperatures throughout the length of the needle (Multi-point Thermal Sensor® by Galil) [59].

Figure 3: Simplified diagram of the 1.5mm Ice seed cryoprobe by Galil Medical Inc. Compressed argon gas passes though the central channel to reach the stainless steal tip. Significant heat exchange occurs here and then the convective exchange continues along the walls for 12mm, which is thereafter insulated [67].
Figure 4: Galil cryoprobes and isotherm map. Each cryoprobe produced an ice-ball of unique width, diameter and temperature gradient. Also shown in the illustration is the border of each temperature zone.

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3.2 Systematic Review of Focal Cryotherapy for Localised Prostate Cancer

Introduction

Recent improvements in imaging and diagnostic methods have led to a greater emphasis on focal treatment of localized prostate cancer. Data from the Cryo On-Line Database (COLD registry) demonstrates that the number of patients having focal cryotherapy has been rising alongside a decline in whole gland treatment. In 2005, 567 whole gland procedures were performed compared to 475 in 2007. This is in contrast to 168 focal procedures in 2005 compared to 293 in 2007 (86). Therefore, over time there has been a paradigm shift in the treatment of prostate cancer and focal therapies are gaining momentum as the concept becomes popularized.

This chapter aims to perform a systematic review of the literature with regards to focal cryotherapy in the treatment of localized prostate cancer.

Methods

I performed a systematic review of Pubmed/Medline and the Cochrane database using the search terms “cryotherapy OR cryoablation AND Prostate” and “cryoablation prostate”. This yielded a total of 997 Studies.

The inclusion criteria were any paper which included 1) disease characteristics, 2) accurate description of the focal treatment, 3) defined outcome measures and 4) side-effects from treatment.

All abstracts and potential full texts were reviewed to yield 9 papers for primary focal prostate cryotherapy treatment and 2 papers for focal salvage treatment for radiorecurrent prostate cancer.
Results

Primary Treatment

I reviewed 9 studies with a total of 1,582 patients who received focal cryotherapy for primary prostate cancer [Table 1] (86, 95-99, 116, 117). All these studies were case series, and none used controls.

In every study the median age was less than 70 years and when mentioned, the majority of patients had disease with a low risk of progression according to either the National Comprehensive Cancer Network (NCCN) or D’Amico classification (823 patients). However, 759 moderate and high-risk patients were included.

The method of diagnosis and disease characterisation was not always clearly mentioned and thus there was a mix of either trans-rectal (8-12 core) or trans-perineal mapping template biopsy detected tumours.

The American Society for Therapeutic Radiology and Oncology (ASTRO) criterion, which was developed for defining radiotherapy failure in localized prostate cancer, specifies biochemical recurrence as 3 consecutive rises in PSA from the nadir – this was the most commonly used outcome measure. The Phoenix criterion was used by 1 study and defined recurrence as a rise in PSA of 2 ng/ml over the nadir. However, some did use their own definition i.e. PSA rise to higher than pre-operative levels.

Follow-up was of a short to medium term and ranged from 9 – 70 months. At this length of follow-up biochemical disease free survival (bDFS) was between 71 – 93%. No mention was made of any patient in the studies developing either metastases or dying as a result of prostate cancer during the defined follow-up period.

In 7 out of 9 studies metastases free survival (MFS) was 100% and 2 did not mention this outcome. In 8 out of 9, cancer specific survival (CSS) was 100% whilst 1 did not comment on this outcome.
Table 1. Patient characteristics, follow-up duration and outcomes from 9 studies on focal cryotherapy of localized prostate cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Median Age</th>
<th>Diagnostic Method</th>
<th>Patient Characteristics</th>
<th>Pre-op PSA</th>
<th>Median FU</th>
<th>Definition of treatment failure</th>
<th>bDFS</th>
<th>MFS</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargawi 2014 (116)</td>
<td>62</td>
<td>60.5</td>
<td>Trans-perineal template 3D mapping biopsies</td>
<td>L 62 (100%)</td>
<td>NA</td>
<td>28 mo</td>
<td>Higher than pre-op PSA</td>
<td>71%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Barrett 2013 (117)</td>
<td>50</td>
<td>66.5</td>
<td>Trans-perineal template 3D mapping biopsies</td>
<td>L 50 (100%)</td>
<td>6.1</td>
<td>9 mo</td>
<td>PSA Median = 2.5 at 12 mo</td>
<td>NA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bahn 2012 (95)</td>
<td>73</td>
<td>64</td>
<td>TRUS biopsies</td>
<td>L 24 (33%) M 49 (67%)</td>
<td>5.9</td>
<td>3.7 yrs</td>
<td>NA</td>
<td>NA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ward 2012 (86)</td>
<td>1149</td>
<td>67.8</td>
<td>TRUS biopsies</td>
<td>L 541 (47%) M 473 (41%) H 143 (12%)</td>
<td>6.54</td>
<td>21.1 mo</td>
<td>Phoenix</td>
<td>75.7%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Truesdale 2010 (96)</td>
<td>77</td>
<td>69.5</td>
<td>TRUS biopsies</td>
<td>L 44 (57%) M 31 (40%) H 2 (3%)</td>
<td>24 mo</td>
<td>ASTRO</td>
<td>72.7%</td>
<td>NA</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lambert 2007 (97)</td>
<td>25</td>
<td>68</td>
<td>TRUS biopsies</td>
<td>G6 13 (52%) G7 12 (48%) All T1c12%</td>
<td>6.0</td>
<td>28 mo</td>
<td>50% of pre-op PSA</td>
<td>84%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ellis 2007 (98)</td>
<td>60</td>
<td>69</td>
<td>TRUS biopsies</td>
<td>L 40 (66.7%) M 14 (23.3%) H 6 (10%)</td>
<td>7.2</td>
<td>12 mo</td>
<td>ASTRO</td>
<td>80.4%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Onik 2007 (99)</td>
<td>55</td>
<td>NA</td>
<td>Trans-perineal template 3D mapping biopsies</td>
<td>L 26 M 20 H 9</td>
<td>8.3</td>
<td>3.6 yrs</td>
<td>ASTRO</td>
<td>93%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Bahn 2006 (99)</td>
<td>31</td>
<td>63</td>
<td>TRUS biopsies</td>
<td>G6 23 (74%) G7 8 (26%)</td>
<td>4.95</td>
<td>70 mo</td>
<td>ASTRO</td>
<td>92.8%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

All but one study mentioned post-procedural biopsy results [Table 2]. Unfortunately, not all patients opted to have post-procedure biopsies and when these were performed, they were undertaken in patients who were developing biochemical recurrence and thus would be more likely to have positive biopsies. Subsequently, those patients who were found to have either recurrent or residual disease were usually offered a further cycle of cryotherapy. A total of 391 patients underwent a biopsy and positive samples were seen in 4 – 45% of patients. Overall 98/391 (25%)
of biopsies were positive. However, 70% of these were from the contra-lateral, untreated side and were low grade.

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for performing a post-treatment biopsy</th>
<th>Number of patients with a positive post procedural biopsy / total number of biopsied patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargawi 2014 (116)</td>
<td>Standard 12mo TRUS biopsy</td>
<td>12/62 (19%) G3+3 4/12 contralateral side</td>
</tr>
<tr>
<td>Bahn 2012 (95)</td>
<td>Standard 6 – 12mo TRUS biopsy</td>
<td>12/48 (25%) 1/12 - Ipsilateral 8/11 contralateral side +ve had low grade, low volume</td>
</tr>
<tr>
<td>Ward 2012 (86)</td>
<td>Rising PSA TRUS Biopsy</td>
<td>42/162 (26%)</td>
</tr>
<tr>
<td>Truesdale 2010 (96)</td>
<td>Abnormal DRE or biochemical failure TRUS Biopsy</td>
<td>10/22 (45%) 7/10 contralateral side</td>
</tr>
<tr>
<td>Lambert 2007 (97)</td>
<td>Biochemical failure or PSA nadir &lt;50% TRUS Biopsy</td>
<td>3/7 (43%) 3/3 G6 &lt;5% 2/3 contralateral side</td>
</tr>
<tr>
<td>Ellis 2007 (98)</td>
<td>Standard 12mo TRUS biopsy</td>
<td>14/35 (40%) 13/14 from untreated side</td>
</tr>
<tr>
<td>Onik 2007 (99)</td>
<td>Standard 12mo TRUS Biopsy</td>
<td>4/30 (13%) 4/4 in untreated part</td>
</tr>
<tr>
<td>Bahn 2006 (99)</td>
<td>Standard 6mo TRUS biopsy</td>
<td>1/25 (4%) 1/1 in untreated side</td>
</tr>
</tbody>
</table>

Table 2. Outcomes from post-cryotherapy biopsies.

Side-effects were generally well reported [Table 3]. Incontinence ranged from 0 – 3.6% whilst erectile dysfunction (ED) occurred in 0 – 42%. Other side effects of haematuria, strictures and rectal fistulae (0.1%) were very uncommon [Table 3].
Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargawi 2014 (116)</td>
<td>LUTS – average 1.5 point decrease in AUS-SS</td>
</tr>
<tr>
<td></td>
<td>Incontinence – 0%</td>
</tr>
<tr>
<td></td>
<td>ED – 0%</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Barrett 2013 (117)</td>
<td>Incontinence – 0%</td>
</tr>
<tr>
<td></td>
<td>ED – 0%</td>
</tr>
<tr>
<td></td>
<td>Haematuria – 2% (1)</td>
</tr>
<tr>
<td></td>
<td>Stricture – 2% (1)</td>
</tr>
<tr>
<td></td>
<td>Fistula – 2% (1)</td>
</tr>
<tr>
<td>Bahn 2012 (95)</td>
<td>Incontinence – 0%</td>
</tr>
<tr>
<td></td>
<td>ED – 26% (1yr); 14% (2.4yrs)</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Ward 2012 (86)</td>
<td>Incontinence – 1.6%</td>
</tr>
<tr>
<td></td>
<td>ED – 42%</td>
</tr>
<tr>
<td></td>
<td>Retention – 1.1%</td>
</tr>
<tr>
<td></td>
<td>Fistula – &lt;0.01%</td>
</tr>
<tr>
<td>Truesdale 2010 (96)</td>
<td>Mild decrease in AUA-SI and IIEF</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Lambert 2007 (97)</td>
<td>Incontinence – 0%</td>
</tr>
<tr>
<td></td>
<td>ED – 29%</td>
</tr>
<tr>
<td></td>
<td>Retention – 4%</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Ellis 2007 (98)</td>
<td>Incontinence – 3.6%</td>
</tr>
<tr>
<td></td>
<td>ED – 29.4%</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Onik 2007 (99)</td>
<td>Incontinence – 1%</td>
</tr>
<tr>
<td></td>
<td>ED – 15%</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
<tr>
<td>Bahn 2006 (99)</td>
<td>Incontinence – 0%</td>
</tr>
<tr>
<td></td>
<td>ED – 11.9%</td>
</tr>
<tr>
<td></td>
<td>Fistula – 0%</td>
</tr>
</tbody>
</table>

Table 3. Side-effects from focal cryotherapy.
LUTS = Lower urinary tract symptoms
ED = Erectile dysfunction
AUA – SS = American Urological Association Symptoms Score
AUA – SI = American Urological Association Symptoms Index
IIEF = International Index of Erectile Function

Salvage Treatment [Table 4]

Only 2 case series were found which reported on salvage focal cryotherapy (118, 119). Both had small numbers with a combined total of 44 patients and follow-up ranged from 18 - 31 months. bDFS was 89% at 1 year in Eisenberg’s paper but this fell to 50% at 3 years using the ASTRO criteria (119). When they used the Phoenix criterion their bDFS at 3 years was better at 79%. A similar bDFS of 68% was seen by...
De Castro Abreu at 31 months (118). Once again side-effects were low with 0-5% incontinence and ED being the most common side-effect of between 60-71%.

Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Median Age</th>
<th>Diagnostic Method</th>
<th>Patient Characteristics</th>
<th>Pre-op PSA</th>
<th>Median FU</th>
<th>Definition of treatment failure</th>
<th>bDFS</th>
<th>MFS</th>
<th>CSS</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Castro Abreu 2013 (118)</td>
<td>25</td>
<td>61</td>
<td>TRUS + Doppler</td>
<td>T2a/b 20 (80%) T3 a/b 5 (20%)</td>
<td>2.8</td>
<td>31 mo</td>
<td>Phoenix</td>
<td>68%</td>
<td>100%</td>
<td>0%</td>
<td>Incontinence – 0% ED – 71% Fistula – 0%</td>
</tr>
<tr>
<td>Eisenberg 2008 (119)</td>
<td>19</td>
<td>71</td>
<td>TRUS</td>
<td>T2 a/b 19 (100%)</td>
<td>3.3</td>
<td>18 mo</td>
<td>ASTRO</td>
<td>89%</td>
<td>1 yr</td>
<td>50%</td>
<td>Incontinence – 5% ED – 60% Stricture – 5% Prostatic ulcer – 5% Fistula – 0%</td>
</tr>
</tbody>
</table>

Table 4. Outcomes from 2 studies on focal salvage cryotherapy of radio-recurrent prostate cancer.
TRUS = Trans-rectal ultrasound guided
bDFS = biochemical Disease Free Survival
MFS = Metastases Free Survival
CSS = Cancer Specific Survival

Summary

The results show that focal cryotherapy is generally well tolerated with few side-effects and has good short to medium term oncological outcomes for both primary and salvage prostate cancer. Primary focal cryotherapy results compare favourably with the published data on radical prostatectomy, radical radiotherapy and brachytherapy. Results from the primary focal cryotherapy studies show a bDFS between 71 – 93% at follow-ups ranging from 9 – 70 months, suggesting equivalent efficacy to whole gland treatments in the short to medium term. Although long term oncological data on focal salvage cryotherapy is not yet available bDFS was 50 - 68% with a 31 month - 3 years follow-up and side-effects were low with 0-5% incontinence, ED occurring in 60 - 71% and no patient developed a recto-urethral fistula.

There are some limitations to the above systematic review, such as lack of Prospero registration, only one reviewer and no assessment of bias in the studies. I corrected these limitations in my second systematic review in chapter 9.
3.3 Optimising Cryotherapy Treatment Delivery

Introduction

Although there is extensive literature on the clinical outcomes of cryotherapy, largely from single-arm or multi-centre registry studies, there is significantly fewer contemporary data evaluating the dynamics of ice-ball formation using modern equipment. A potential reason for local recurrence may be due to the lack of information regarding ice-ball isotherms (temperature gradient maps) particularly using multi-needle configurations resulting in imperfect and incomplete cancer tissue ablation.

The developing ice-ball normally has a leading edge of 0°C with a colder inner core. This temperature gradient map across the ice-ball is made up of isotherms. Both liquid nitrogen and argon gas systems are theoretically able to produce temperatures close to -190°C. However, it is generally accepted that such low temperatures are not needed for cell death.

Various studies have assessed a so-called “lethal temperature” where complete cell death via coagulative necrosis is expected to occur. The currently accepted temperature beyond which further crystallisation of water does not occur is -40°C (92, 120).

To ensure adequate ice-ball coverage of the target volume at a sufficiently low temperature a surgeon must understand four critical variables for formation of an ice-ball, namely, 1) cryo-needle type, 2) number of cryo-needles, 3) cryo-needle configuration, and 4) duty-cycle percentage (percentage on-off time).

The objective of this chapter was to investigate the interaction of these multiple variables in forming single and multiple isotherm maps, with the aim of improving pre- and intra-operative planning using modern cryo-needles and delivery systems. In order to do this, Galil developed a novel method for accurate testing of ice-ball

3-53
dimensions and isotherms. I subsequently utilised this data in order to assess ice ball parameters with reference to the above-mentioned critical variables.

Methods

Multi-Needle TC Matrix Structure
A Multi-Needle ThermoCouple (TC) Matrix fixture was constructed from plastic frames and fine-gauge thermocouple wires to enable the recording of multiple needle configuration isotherms. The exact configuration of the matrix is given in Figure 5. The placement holes allow for a 2-D configuration. The needles can be positioned as desired in the X-Y plane, which is parallel to the plane of temperature measurement (the needles are orthogonal to the measurement plane). The Z-axis (insertion depth) position is fixed to align the centre of the ice ball with the measurement plane. This allowed us to place cryo-needles (each individually controlled) in any 3-D configuration using placement holes that were spaced every 5mm in the X axis and 10mm in the Y axis (similar to a template perineal grid used during cryotherapy) across the matrix.

Figure 5. Assembled Multi-Needle TC matrix. TC Junctions (pink dots) and needle slots (blue dots).

Cryo-Needles
Three types of cryo-needles were evaluated: The IceSphere® and IceRod® were 1.5mm (17G) needles often used for prostate ablation whilst the IceEdge® was a larger 2.4mm (10G) needle often used in larger organs such as for renal ablation (IceEdge®). By varying the diameter, the different needles can produce iceballs of longer or shorter lengths. The IceSphere® differed from the IceRod® by having a shorted
convective exchange region and thus would produce an ice-ball 1.5 cm shorter in length.

Duty cycle describes the percentage of time cryogen gas is flowing through the needle. We tested four duty cycle settings of 100%, 70%, 50% and 20%. In addition, needle configurations with two, three and four needles placed at different spacing was evaluated (1cm, 1.5cm, 2.0cm and 2.5cm).

Previous data reported the length of isotherms measured in gel at 21°C after a standard freezing procedure (121). However, since the body temperature is approximately 37°C, our study was performed in ultrasound gel @ 37°C to mimic the body heat load effect.

The single cryo-needle maximum ice ball diameter at 37°C was 3.4 – 3.6cm for the 17G needles and 4.3 cm for the 10G needle. A smaller inner core of ≤-40°C had a diameter of 1.8cm (17G) and 2.4cm (10G).

*Operating Procedure*

The tested cryo-needles were placed in ultrasound gel at 37°C, with uniform temperature distribution maintained in the gel tank. All needles underwent a simultaneous standard freezing procedure of two 10 minute active argon freeze cycles separated by a 5 minute passive thaw. During the test, the planar temperature distribution at the largest ice plane (middle of the single ice-ball height) was recorded by the multi-needle TC matrix fixture.

The recorded temperature distribution was analysed, to find and calculate the 0°C, -20°C and -40°C isotherms at the centre of the ice ball. The calculation was made using a multi-needle analyser software.
Results

Initial single needle tests assessing duty cycle percentage showed that when duty cycle was decreased to 70% up to a 10% reduction was seen in the maximum ice-ball diameter with an associated 10 - 20% decrease in total volume and area of the -40°C isotherm. This effect was observed particularly with the 17G cryo-needles. As we dropped the duty cycle setting further to 50% an associated 25 – 50% decrease in maximum diameter and a 55 – 75% decrease in volume of the -40°C isotherm was seen. At a setting of 20% none of the cryo-needles were able to produce a -40°C isotherm [Figure 2].

<table>
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<tr>
<th>Duty Cycle</th>
<th>100 %</th>
<th>70 %</th>
<th>50 %</th>
<th>20 %</th>
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<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
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</table>

Figure 2. 17G (IceRod®), single cryo-needle dimensions with respect to duty cycle settings.

Subsequent testing of 2 cryo-needle configurations created either a cylindrical or oblong ice-ball with a maximum -40°C isotherm diameter of 3.1cm (IceSphere®), 4.2cm (IceRod®) and 4.7cm (IceEdge®). The 3 cryo-needle configuration created cylindrical ice-balls until a distance of 2cm where a pyramidal shape developed. The maximum lethal -40°C isotherm diameters were 4.4cm for the two 17G needles and 4.9cm for the 10G needle. Four cryo-needle configurations created larger cylindrical ice balls whose central core only rose above a temperature of -40°C at a distance of 2cm apart, with the lowest duty cycle setting of 20%. The maximum lethal isotherm diameters were 4.7 - 5.0cm for the 17G needles and 6.6cm for the 10G needle.

At a duty cycle setting of 100% all cryo-needle configurations were able to create a confluent central core at distances of up to 2cm apart. Only at the lowest duty cycle setting of 20%, as distance between the needles increased an hour-glass shape (loss
of ice ball confluence) developed with the central core being warmer than the area closest to the cryo-needle. The most efficient distance for cryo-needle placement was 1.5cm for the 17G needles and 2cm for the 10G needle. The multi-needle maps with a spacing of 1.5cm apart with varying duty cycle setting, for the 17G IceRod® needle are shown in Figure 3.

<table>
<thead>
<tr>
<th>Duty Cycle</th>
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<tr>
<td>100 %</td>
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<tr>
<td>[Diagram]</td>
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</table>

Figure 3. 17G (IceRod®), 2 needle (top), 3 needle (middle) and 4 needle (bottom) configurations at a spacing distance of 1.5cm and varying duty cycles. Analysing the various combinations shows that a central core of ≤-40°C develops very consistently at a minimum distance of ~1cm around the perimeter of the cryo-needles. The temperature increases linearly from this point to the ice ball leading edge (0°C), which is a further 0.85 cm to 1.15 cm away. Thus, the -40°C isotherm is approximately 1cm inside the leading edge of the ice ball.

Analysing duty cycle data shows us that, if needed, low duty cycle settings can be used to create small ice balls but in routine practice the optimal is at a duty cycle of 70 - 100%. This maximizes the area of the ice ball and allows consistent core temperatures of ≤-40°C at most configurations and distances.
Discussion

Although numerous groups have tried gel, ex-vivo and in-vivo modelling of the ice ball, to my knowledge this is the first study to investigate so extensively the various ice ball dimensions and isotherms. This is also the first study to assess variations in duty cycle settings.

The results show in all configurations the lethal -40°C isotherm was formed at a distance of 1cm from the cryo-needle/s and the leading edge of the ice ball was approximately a further 1cm away. Single needle performance deteriorates significantly at duty cycle settings of ≤50% whilst multi-needle configurations have a synergistic effect with maximum efficiency noted at distances of 1.5cm apart for the 17G needles and 2cm apart for the 10G needle.

A major consideration when testing ice ball isotherms revolves around the thermal properties of live tissue versus water or gel or ex-vivo tissue. Many studies have used liver tissue and although liver tissue has different thermal characteristics to water it has been shown that ice balls created within 37°C water baths are relatively similar in size to those within the perfused liver (122, 123). Also porcine liver has been shown to be relatively similar to cancerous tissue (124). Additionally, due to the higher water content of human tissue, thermal conductivity should not cause a major problem (120), although this may be different when ablation occurs near large blood vessels or air (lung) due to a heat sink effect (125, 126).

Based on this information we tested in a gel bath maintained at 37°C, which would be similar to but unlikely to precisely mimic in vivo human prostate or renal tissue. However, this model did allow us to test numerous combinations with relative ease whilst trying to maintain in-vivo applicability. Performing 156 individual experiments would have been unfeasible and impractical using porcine models, and thus we felt a gel-based model was the best compromise with the results and principles of ice-ball isotherm formation still relevant for utilization in clinical practice.
Reviewing the results shows that they closely resemble a smaller study by Weld et al in live porcine kidneys (127). They also noted a synergistic effect with multiple cryo-needles and to ensure a 1cm margin more than 1 needle needed to be used. Our data using the 17G IceRod® 2cm apart shows the lethal isotherm defined at -40°C was 1.8cm using 1 needle, 4.4cm using a 3 needle combination and 5cm using a 4 needle combination - this closely resembles their histological ablative dimensions. We also found that the optimum distance between needles to maximize the ice ball area should be 1.5 – 2 cm and studies in live porcine renal tissue have shown a similar result (128).

Previous work by Saliken et al noted that the central core takes longer to fuse and may have lower temperature which needs to be accounted for during clinical practice (129). Our results confirm this finding that when cryo-needles are further apart a central core forms which may not be at or below the lethal temperature of -40°C. Another factor to be considered is the uniformity of the ice ball. Although I did not notice this phenomenon in our experiments, others have found that the lethal temperature is not always uniform around the needles and thus it seems that for accurate in-vivo lethal isoform measurements multiple thermocouples should be routinely used (130). The distance of the leading edge from the lethal isotherm is also important and similar to work by Littrup et al in agar gel phantoms we found that the lethal isotherm is smaller than total ice ball formed (131).

Thus, when applying these results and also data from the reviewed literature into clinical practice there are 4 factors that need to consider when performing cryotherapy, particularly with regards to the treatment field and ice ball configuration. The first is the type of cryo-needle used and with regards to the prostate, the cranio-caudal (base-apex) length of the prostate will ultimately determine the type of needle used. The length of the ice ball should not extend beyond the apex as this may increase the risk of injury to the urethral sphincter.
The results have shown that either small or if needed large ice-balls can be created by varying the remaining three factors: number of cryo-needles, needle configuration and duty-cycle percentage. Using this data set a surgeon can accurately determine pre-operatively which combination of factors he/she needs in order to cover his target lesion.

Similar to the ice-ball length the diameter of the tumour will determine the number of needles needed along with their exact configuration. However, as a general rule I found the optimum distance for cryo-needle placement to be between 1.5 and 2cm. Although the data appears comparable to live porcine experiments, as is not in human tissue, it would be reasonable to use a more conservative distance of 1 – 1.5cm, which would balance ice ball volume and cell kill temperatures. As mentioned previously, manipulation of duty cycle settings can allow further changes in ice-ball size but with low duty cycle settings the risk of incomplete coverage of the tumour by the -40°C isotherm increases and thus in routine practice I feel that a setting of 70 – 100% is most appropriate.

There are, however, some potential limitations to this study which must be highlighted. A gel model at 37°C is not human tissue and the thermal properties may vary. We have also not accounted for variations in vascular anatomy or tested configurations around the urethral warmer during prostatic procedures. However, our data might allow significant pre- and intra- operative decisions to be made in the delivery of cryotherapy for ablation of soft tissue tumors and is the only study of its kind assessing such a large combination of factors. Designing an experimental model to accurately assess all possible combinations of the variables is a challenge. The ideal study would allow real time monitoring of the ice-ball in patients undergoing treatment followed by histological assessment of the treated lesion. However, due to the number of combinations and ethical considerations needed, this scenario is very difficult if not impossible to create. Finally, we also did not assess temperature drop in relation to duration of freeze cycle and used the currently accepted protocol of two 10-minute freeze cycles separated by a 5-minute passive thaw.
We have tried to build an accurate gel model based on the literature and it appears that the results do compare well to other in-vivo studies. Future work will need to focus on modelling ice balls around structures that may lead to a heat sink effect, such as blood vessels and urethral warming catheters. Additionally, there is growing evidence that cryotherapy can lead to both immune stimulatory and inhibitory effects. There may be surgical factors that influence this phenomenon and Urano et al showed that treatment of single rather than multiple lesions within the liver resulted in the largest immune response (132). Additionally a study on a rat breast carcinoma cell line suggested that the immune response decreased at a larger bulk of tissue was frozen (133). Development of animal models in the future, which allow in-vivo testing of numerous ice ball configurations may allow us to gain a further insight into this phenomenon.

**Summary**

I set out to answer four questions: 1) what type of cryo-needle should be adopted? 2) how many needles should be used? 3) which is the best spatial needle configuration? and 4) which is the correct duty-cycle percentage?

To answer questions 1 – 3, the length, diameter and shape of the tumour will ultimately determine the number of needles needed along with their exact configuration. The results show that the -40°C lethal isotherm is approximately 1cm inside the leading edge of the ice-ball. The optimum distance between cryo-needles was 1.5 – 2 cm’s, at duty-cycle settings of 70 - 100%. At distances further apart or with lower duty cycle settings ice-balls had either a central core >40°C or had an hourglass shape. However, considering the results were not within live tissue, I feel that a more conservative distance for cryo-needle placement between 1 and 1.5 cm should be adopted for clinical practice.
To answer questions 4, although the use of low duty cycle settings is possible it runs the risk of incomplete coverage of the tumour by the -40°C isotherm and thus in routine practice I feel that a setting of 70 – 100% is most appropriate.

I have presented a large amount of experimental data on ice ball isotherms, which can aid a surgeon in operative planning with regards to needle placement and duty cycle settings to ensure that the lethal isotherm of -40°C adequately covers the tumour.
## IceSphere, IceRod, IceEdge ice-ball and isotherm dimensions with varying needle configurations at a duty cycle setting of 100%.

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3.4 Oncological Outcomes from Focal Cryotherapy for Localised Prostate Cancer

Introduction

Much of the previously published studies have focused on low-risk patients being offered FT as an alternative to active surveillance (AS). However, multiple consensus groups have highlighted that low-risk patients should not routinely be offered focal therapy and that the ideal patient is one with localised intermediate risk disease (6-8). In this chapter, I report on the cancer control and functional outcomes in patients with intermediate and high-risk prostate cancer, from our prospective, multicentre, focal cryotherapy registry, compliant with the UK’s National Institute of Clinical Excellence (NICE) guidance.

Patients and Methods

Study design

My institution implemented a focal cryotherapy program to complement focal High Intensity Focused Ultrasound (HIFU) (1st October 2013 to 30th November 2016) with data collected prospectively in 5 centres. Ethics committee review exemption was granted by our institution. The database was registered as a clinical evaluation audit and was updated and presented locally every year as recommended by NICE.

Study Coordination

The database was designed by Dr Massimo Valerio and me in excel and all PROMS questionnaires were posted and collated by myself. At the end of my PhD, I helped transfer the database onto the online Redcap database and handed it over to a centralised body for its ongoing delivery.
**Patient Selection**

Pre-operatively, all patients underwent a prostate multi-parametric MRI (mpMRI) followed by either transperineal template mapping or MRI-targeted biopsy with systematic non-targeted sampling. A minority of patients were included on the basis of concordant mpMRI with systematic transrectal ultrasound guided biopsy. The LIKERT MRI grading system was used. Further details are provided in the supplementary information.

All patients were reviewed in a multi-disciplinary team (MDT) meeting. Our general inclusion criteria for focal therapy were patients requiring active treatment with a non-metastatic cancer lesion of Gleason grade group 2 or 3 (Gleason 3+4, 4+3) or high volume Gleason grade group 1 (3+3) disease based on review of imaging and/or maximum cancer core length (MCCL) of ≥6mm. All patients suitable for focal therapy were also offered and counselled about radical treatments. All patients with anterior disease or factors which made focal HIFU unsuitable such as large prostates (anterior-posterior height >3cm) or wide-spread calcifications were considered for focal cryotherapy. There were no limitations on prostate size. Patients with multiple lesions were permitted. When both lesions were clinically significant and if possible, to encompass both into the treatment field then focal cryotherapy was offered. If this was not possible then an alternative treatment modality was recommended to the patient. Bi-focal (bilateral) treatment was permitted for bilateral clinically significant lesions. Ipsilateral and contralateral insignificant disease was permitted. However, treatment for these lesions was not routinely offered providing there was no concordant mpMRI lesion scoring 4 or 5 on the LIKERT grading system. There were no specific exclusion criteria based on tumour size. However, apical lesions invading or abutting the sphincter were excluded.

In the current version of the database the exact method of metastatic workup was not recorded. Our standard protocol was a Nuclear Medicine bone-scan in all patients with Gleason 3+4=7 or any evidence of T3a disease. Further scans to investigate specific findings with a CT Chest abdomen pelvis or alternative whole-
body scans such as Choline PET was rarely carried out and not recorded in the registry as a result.

**MRI Protocol**

These are a *minimum* set of requirements: additional sequences (e.g. 3D isotropic T2 sequences, diffusion tensor imaging, additional ADC maps) are permitted. In addition, improvements in resolution (smaller voxel size or slice width and improved time resolution on the dynamic sequences) can be incorporated after discussion with the lead radiologist.

a) A standard safety questionnaire should be completed.
b) For patients undergoing contrast enhancement: set up IV line in a vein in the antecubital fossa, connected to an automated injector with two syringes (contrast and 20ml saline flush). Contrast and flush should be given at 3ml/s.
c) 20mg buscopan or 1mg glucagon IV to be given just before the start of the scan.
d) T2 sequences:
   Small field of view in 3 planes. The fields of view provided on the standard sequences are enough to cover most prostates. However, if the tips of seminal vesicles and the external sphincter cannot be included on the axial sequence, then the number of slices (and with it the scan time) should be increased. In all cases the slice width should remain at 3mm, with a 10% interslice gap.
e) Diffusion sequences:
   Two sets of sequences are the minimum requirements for the diffusion data. Individual centres are free to do additional sequences (eg for anisotropy).
   i) Multi-b with b values of 0,100,500 and 1000 s/mm². 16 averages using a 3 trace technique. Standard Siemens algorithm for determination of ADC (currently includes b0 with monoexponential decay fitting, but this may be revised)
   ii) b1400 s/mm² with 32 averages. The b value can be higher at 3T (usually 2000).
f) VIBE sequences:
   i) The multi-flip angle VIBE sequence is a relatively quick method for the quantitative determination of T1 relaxation. It is not essential but should be included if possible.
Coverage should be the same as for the dynamic contrast enhanced sequences, and
includes the external sphincter and seminal vesicles as for the T2 axial sequences. If
this cannot be ensured, the priority is to include the prostatic apex: the seminal
vesicle tips are less important, as long as most of the vesicles are included.
Alternative methods of quantifying T1 may be incorporated later.

ii) Dynamic contrast enhancement. Contrast is 0.1mmol/kg of low molecular weight
gadolinium-based contrast: Magnevist or Dotarem (preferred in those with mild
renal impairment), given at 3ml/s. This should be followed by a flush of 20ml Normal
Saline. The infusion is started concurrently with the third dynamic acquisition.
Acquisitions are continued for at least 5 minutes 30 seconds after the start of the
contrast infusion.

**MRI Scan parameters**

<table>
<thead>
<tr>
<th></th>
<th>TR</th>
<th>TE</th>
<th>Flip angle/degree(s)</th>
<th>Plane</th>
<th>Slice thickness (gap)</th>
<th>Matrix size</th>
<th>Field of view /mm</th>
<th>Time for scan</th>
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<td>92</td>
<td>180</td>
<td>Axial, coronal, sagittal</td>
<td>3mm (10% gap)</td>
<td>256x256</td>
<td>180x180</td>
<td>3m 54s (ax)</td>
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<td>2. VIBE at multiple flip angles for T1 calculation (optional)</td>
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<tr>
<td>3. VIBE fat sat</td>
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<td>2.52</td>
<td>15</td>
<td>Axial</td>
<td>3mm</td>
<td>192x192</td>
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<td>Continue for at least 5m30s after contrast</td>
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<tr>
<td>4. Diffusion (b values: 0, 150, 500, 1000)</td>
<td>2200</td>
<td>Min (&lt;98)</td>
<td>5mm</td>
<td>Axial</td>
<td>172x172</td>
<td>260x260</td>
<td>5m 44s (16 averages)</td>
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</tr>
<tr>
<td>5. Diffusion (b=1400)</td>
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<td>Axial</td>
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<td>3m 39s (32 averages)</td>
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Surgical Procedure

All patients underwent standardised focal cryotherapy procedure using either the SeedNet or Visual ICE cryotherapy device (BTG plc, London, UK). The majority of patients underwent a general anaesthetic with a small number undergoing a spinal anaesthetic with sedation. Patients were placed in the lithotomy position with transrectal ultrasound probe for treatment planning based on the tumour location from pre-operative mpMRI and biopsies as previously described (9). Through a square brachytherapy grid with holes spaced every 5mm, transperineal cryoprobe needles were placed 5mm to 15mm apart under ultrasound guidance, according to needles type and ablation strategy. Thermocouples (temperature probes) were placed as close to the centre of the lesion and either in Denonvilliers fascia (for posterior ablations) or in the peripheral zone (for anterior ablations). Flexible cystoscopy was performed to confirm no needles had pierced the urethra or the bladder neck, and subsequently a urethral warmer was inserted over a guide-wire.

During the procedure, real-time ultrasound was used to visualise the growing ice-ball and duty-cycle (gas flow) settings were adjusted to control the ice-ball dimensions (Figure 1 and 2). All patients underwent an initial 10-minute freeze cycle with a target temperature for the cancer lesion thermocouple of -40°C or lower held for at least 3 minutes. Subsequently a 3-minute passive and 3-minutes active thaw was performed followed by a second freeze cycle of similar parameters, times and temperature targets. Following the second cycle an active thaw was performed only until it was possible to remove the needles which allowed for a slow passive thaw to occur naturally [Figure 1]. The margin of the focal cryotherapy was determined by visualisation of the hypoechoic ice-ball edge [Figure 2].

All patients had a urethral catheter placed post-operatively, with a planned removal 7 days later. All were also given aminoglycoside and either penicillin or cephalosporin antibiotics at anaesthetic induction and quinolone antibiotics for 7
days post-operatively. Early in the learning curve some patients underwent a 2-week early MRI with contrast (DCE) to assess the ablation margins [Figure 3].

Figure 1: Temperature graph (above) showing the effect of the two freeze-thaw cycles
Follow-up

Follow-up consisted of serum PSA testing 3 to 6 monthly in the first year (6 monthly thereafter) and mpMRI at 12 months after focal cryotherapy. Subsequently, mpMRI and ‘for cause’ biopsies were performed when a recurrence was suspected due to rising PSA. When there was suspicion of residual or recurrent disease biopsies were targeted to the previous treatment site and to any new lesion/s seen on follow-up MRI. Systematic biopsies were not carried out as standard. In addition, all patients with suspicious MRI were reviewed as part of a MDT meeting and biopsies were offered even with a low PSA if recurrence was confirmed, the case was reviewed in an MDT and potential treatment options (surveillance, further focal therapy, radical or systemic therapy) were discussed with the patient. Up to one further session of cryotherapy was permissible as part of the focal intervention – this could be based on a highly suspicious mpMRI (Likert score 5) in-field residual/recurrent cancer and/or biopsy. Patient reported outcome measures (PROMs) (IPSS, EPIC Urinary, IIEF-15) were sent to patients pre- and post-operatively at 3-monthly intervals for the first year and 6-monthly thereafter. [Figures 4 and 5].
Figure 4. Pre- Cryotherapy MRI images
61-year-old man with a negative DRE and PSA of 10ng/ml with two previous negative TRUS biopsies. Transperineal targeted biopsies confirmed left sided Gleason 3+4 with a maximum cancer core length of 6mm. The patient subsequently left sided focal cryotherapy.
Pre-op MRI Multiparametric MRI showing a 0.8cc left lateral lesion (above).
Top Left: T2 Axial
Top Right: ADC map
Bottom Left: b2000 Diffusion weighted imaging
Bottom Right: Dynamic Contrast Enhanced
Outcome Measures

The primary outcome was failure free survival (FFS), defined as transition to radical, whole-gland or systemic therapy as well as metastases/death as used in our previous reports of focal therapy (10, 11). This is also the primary endpoint used in the PART randomised control trial (RCT) comparing focal High Intensity Focussed Ultrasound (HIFU) with radical therapy (12). Secondary outcomes included histological failure, adverse events (Clavien-Dindo Classification) and functional outcomes (Patient reported outcome measure questionnaires (PROMS): International Index of Erectile Function (IIEF), Expanded Prostate Cancer Index Composite (EPIC) and International Prostate Symptoms Score (IPSS)). I also secondarily evaluated rate of a second focal therapy session within the definition of our composite cancer control outcome as well as cancer-specific, metastases-free and overall survival rates.
Statistical Analyses

Variables with a skewed distribution are presented as medians with interquartile ranges (IQR), normally distributed variables as mean (± standard deviations) and categorical variables as absolute numbers with percentages. Patients who returned questionnaires were compared with ones who did not to assess if any differences existed in these populations. Differences in normally distributed variables were tested with unpaired t-tests, skewed distributed variables with Mann-Whitney U tests and categorical variables with χ² or Fisher’s exact statistic if a frequency in a crosstab cell was <5.

Kaplan-Meier analyses was performed to assess FFS, metastases free survival and overall survival. FFS was stratified for National Comprehensive Cancer Network (NCCN) risk category (Version 3.2018) and Gleason grade groups 1 – 4 (3+3, 3+4, 4+3 and 4+4). Subgroups were compared using the log-rank test statistic. Cox-proportional hazards regression was performed to determine if any factors were associated with requirement for further treatment. Exploratory variables were tested in a univariable manner. Statistically significant factors were subsequently put into the multivariable model. Clinically relevant variables were also added to the model in a multivariable manner. Hazard ratios with 95% confidence intervals (95% CI) were obtained. Separate models with PSA and PSA density were created to assess which model fitted best.

As there were only two patients with low-risk disease these were excluded from our presented analysis. All analyses were performed using IBM SPSS version 25 and R version 3.5.1 (URL https://www.R-project.org/).

Results

Baseline Characteristics and Descriptive Results: Between 1st October 2013 and 30th November 2016, one-hundred and twenty-two consecutive patients underwent primary focal cryotherapy with median follow-up 28 months [IQR 20-37] with 10/122
patients (8%) having less than 12 months follow-up, age 69 years [IQR 65 – 74], pre-operative PSA 11ng/ml [IQR 8-16], prostate volume 45cc [IQR 34-64] and MCCL 8mm [IQR 6-10]. 87 (71%) intermediate-risk and 35 (29%) high-risk. 93% (113/122) patients underwent a TPM biopsy prior to treatment, 2% (2/122) had treatment based on their TRUS biopsy and in 7% (9/122) this information was missing. In addition, 43% (53/122) had undergone a TRUS biopsy in the past. Seventy-six (75%) had anterior ablation, twenty-three (23%) combined posterior and anterior ablation whilst two (2%) had posterior ablation alone [Figure 6 and Table 1].

<table>
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<td>PSA (ng/ml)</td>
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<td>MCCL (mm)</td>
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<tr>
<td>Missing</td>
<td>16</td>
<td>13.1</td>
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Table 1. Baseline characteristics in 122 patients who underwent focal cryotherapy for clinically significant non-metastatic prostate cancer.
Primary outcome: Overall FFS at 3-years was 91% [95% CI 84-97]. When stratified for NCCN risk group 3-year outcomes were 85% [95% CI 71-100] in the high-risk and 93% [95% CI 87-100] in intermediate-risk [Figures 7 and 8]. At last follow-up, 5 underwent radical prostatectomy, 4 radical radiotherapy and 4 were started on systemic therapy. Three of those started on systemic therapy had developed metastatic disease. Four (3%) died of a non-prostate cancer related cause and none of these four had developed metastatic disease.

Figure 7. Kaplan-Meier curve showing failure-free survival (FFS) defined as transition to radical, whole-gland or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant non-metastatic prostate cancer.
Secondary outcomes

At last follow-up, 8 patients underwent a further focal cryotherapy procedure. FFS incorporating further focal cryotherapy at 3-years was 83% [95% CI 75-92]. When stratified for NCCN risk group 3-year outcomes were 68% [95% CI 51-91] in high-risk and 90% [95% CI 83-98] in intermediate-risk [Figures 9 and 10].
Figure 9. Kaplan-Meier curve showing failure-free survival (FFS) defined as transition to any further focal, radical, whole-gland or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant non-metastatic prostate cancer.

Figure 10. Kaplan-Meier curve showing failure-free survival (FFS) defined as transition to further focal, radical, whole-gland or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant non-metastatic prostate cancer (definition 2) stratified for NCCN Risk Category.
Cancer-specific survival, metastases-free survival and overall survival at 3-years was 100% [95% CI 100-100], 98% [95% CI 95-100] and 96% [95% CI 92-100], respectively [Figure 11].

![Figure 11. Kaplan-Meier curve showing metastases-free survival (left) and overall survival (right) in patients undergoing focal cryotherapy for clinically significant non-metastatic prostate cancer.](image)

29/122 patients underwent ‘for cause’ biopsies due to rising PSA and suspicious mpMRI scans with 20 having clinically significant cancer (Gleason grade 3+4=7), one having insignificant cancer (Gleason 3+3=6, 1mm) and 8 had no cancer. Of those with positive clinically significant biopsies (n=21), 9 had infield disease, 9 had out-of-field disease and 3 had both infield and out-of-field disease.

As the decision for radical therapy following focal cryotherapy was based on a discussion with the patient along with clinical parameters, rather than a defined histological criterion, for the purposes of the cox-regression analysis FFS incorporating a further cryotherapy treatment was used in order to determine if any factors predicted the requirement for further treatment. The results demonstrate that baseline PSA density, a bilateral posterior ablation and PSA nadir post-focal were predictors [Table 2]. NCCN risk group was not found to be significantly associated with the composite endpoint (HR 1.97 [95%-CI 0.79-4.91], p=0.14). The multivariable model with PSAD was preferred over the model with PSA (AIC 136
versus 146). Both factors in the final model led to a high VIF between PSAD and PSA (14). Optimism in the final model was approximately 3% (C-statistic decreasing from 0.72 to 0.70).

<table>
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<tr>
<th>Variable</th>
<th>HR</th>
<th>95.0% CI Lower</th>
<th>95.0% CI Upper</th>
<th>Sig.</th>
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<td>1.01</td>
<td>1.04</td>
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<td>Prostate Volume</td>
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<td>PSA Nadir</td>
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<td>1.17</td>
<td>1.83</td>
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Table 2. Cox-regression analysis showing variables which were found to be predictive of transition to further focal, radical, whole-gland or systemic therapy and metastases/death in patients undergoing focal cryotherapy for clinically significant non-metastatic prostate cancer.

Finally, patient reported outcomes (PROMS) questionnaires return rate for 1 pre-op and at least 1- post-op questionnaire was 69/124 (56%) for urinary function and 58/124 (47%) for erectile function. At each time point the return rate was 31/124 at 3 months; 31/117 at 6 months; 30/117 at 9 month and 22/114 at 12 months. Incontinence defined as any pad usage occurred in 4/69 (6%) at 3 months and 0/69 (0%) by 6 months. Baseline median total IIEF-15 score was 33 [IQR 14-56] which dropped to 22 [IQR 13-35] at 3 months, 29 [IQR 15-27] at 6 months, 24 [IQR 15-51] at 9 months and 22 [IQR 9-45] 12 months. Baseline median IIEF-15 Erectile Function subdomain score was 8 [IQR 2-20] which dropped to 5 [IQR 1-8] at 3 months, 6 [IQR 1-15] at 6 months, 7 [IQR 2-18] at 9 months and 4 [IQR 1-17] 12 months. Overall, only 31 patients had pre-op erections sufficient for penetration defined as “erections with sexual stimulation hard enough for penetration a few times over the past 4-weeks” and post-operatively 26/31 (84%) were still potent. As a significant proportion of patients did not return a PROMS questionnaire we compared the baseline characteristics of those that did return a questionnaire to those that did not
and found no statistically significant differences apart from patients who had an initial diagnostic TRUS biopsy were more likely to return a PROMS questionnaire, which could be a type I error.

Other adverse events occurred in 28% (34/122) of patients and included cystoscopic interventions (Clavien-Dindo 3) in 2% (N=2) with none needing bladder neck or prostatic resection, urinary retention managed with a short term catheter in 4% (N=5), urinary tract infections (Clavien-Dindo 2) in 9% (N=11), penile numbness / peno-scrotal swelling in 10% (N=12) (Clavien-Dindo 2), 1% (N=1) had a osteomyelitis of the pubic symphysis managed conservatively with antibiotics (Clavien-Dindo 2) and there were no rectal fistulae (0%).

**Discussion**

In summary, the results show good early-medium term cancer control outcomes with low rates of adverse events and side-effects. At 3-years, 9 in 10 patients being treated with focal cryotherapy for largely intermediate-high risk anterior prostate cancer were free from requiring radical or systemic therapy. No incontinence requiring any pad-use was reported at last follow-up whilst approximately 1 in 6 patients reported erections insufficient for penetration. There were no rectal adverse events.

The data appears to be comparable to alternative energy modalities such as high intensity focused ultrasound (HIFU), irreversible electroporation (IRE) or photodynamic therapy? The use of my definitions for the primary and secondary outcomes may make comparisons with other energy and treatment modalities more difficult but is entirely in keeping with the recently published HIFU series which showed, using the same definition of FFS in a 625 patient multicentre focal HIFU registry, FFS was 92% at 3 years and 88% at 5 years (10). IRE was previously shown to have 33.3% in-field failure within a year when applied to anterior prostate cancer in the NEAT study although others have shown better outcomes with in-field and whole-gland oncological control as high as 97% and 87%, respectively (13, 14).
Photodynamic therapy has been assessed in a RCT published in the Lancet but this was only for very low risk prostate cancer that is normally suitable for active surveillance (15).

For a similar reason direct comparison with other cryotherapy series is difficult but the results do appear comparable to the published series (3). The largest is by Ward and Jones from the US Cryo On-Line Database (COLD) registry on focal cryotherapy in 1160 patients. Their results showed a biochemical disease-free survival (bDFS) (ASTRO defined) of 75.7% at three-years. As in the presented data, prostate biopsy was generally only performed in those with suspected recurrence in 164/1160 and was positive in 43/164 (26.3%) (43/1160 [3.7%] overall). The pad-free continence rate (any pad use) was 98.4% and preservation of erectile function was 58.1% with rectourethral fistula occurring in only one patient (16). The results from my earlier systematic review of 1582 primary focal cryotherapy patients incorporating this COLD-registry data showed bDFS of between 71-93% at 9-70 months follow-up. Incontinence rates were 0-3.6% and ED 0-42% whilst recto-urethral fistula occurred in only 2 patients (3). The use of ASTRO criteria is likely to be flawed however (17, 18).

However, comparisons with reported literature outcomes are limited due to our use of the previously described “a la carte” (19) patient stratified approach to energy selection, whereby focal HIFU was used for glands with mainly posterior tumours or anterior tumours in small glands with cryotherapy used for large glands with anterior tumours or those unsuitable for focal HIFU.

A major strength of the data comes from the fact that the majority of the cohort had intermediate and high-risk prostate cancer risk cancer in contrast to the early cryotherapy cohorts performed in patients with predominately low-risk prostate cancer (20, 21). Almost one-third were NCCN high-risk with some patients having large tumours. More reassuring is that only 2 patients were treated for low-risk disease (though had large volume Gleason 6 cancer, excluded from the analysis) with patients being selected as those needing active treatment rather than active
surveillance. This cohort is in line with current consensus guidelines stating that focal therapy should be directed towards localized intermediate-grade cancer (8). It is increasingly accepted that focal therapy should not be directed toward patients with low-volume Gleason 6 disease who would be suitable for active surveillance. By using mpMRI and targeted biopsies upfront, there is reduced misclassification of low-risk disease and therefore our group does not recommend treatment of low-risk disease unless in extenuating circumstances (high volume Gleason 6, family history, psychological distress to patient on active surveillance). It must be noted that the majority of our patients were deemed high risk due to early T3 disease and/or a PSA over 20 ng/ml. Only two patients had grade group 4 disease which is in keeping with the eligibility criteria for focal cryotherapy. At the study institutions patients with high risk grade group 4 and 5 disease were recommended and underwent whole-gland radical treatments. However, the 95%-CI’s between the NCCN intermediate and high-risk groups are very wide and do overlap and the overall number of events are low. With longer follow-up and a larger cohort tighter estimates can potentially be found.

There are some limitations which also need highlighting. First, there are no defined PSA criteria that are representative of failure. The follow-up strategy is heavily reliant on mpMRI as we have previously shown high negative predictive values of 86%-97% for significant disease post focal therapy (22). This is the main limitation of the study as patients with negative MR (and no specific PSA kinetic pattern) may still harbour clinically significant cancer. Therefore, histological failure could be underestimated. In an ideal setting, 1-year protocol biopsies would have been performed of the ablated area. However, in a routine clinical practice setting this was not possible and from experience is often not accepted by patients in the presence of a low PSA and negative MRI. Second, we used a pragmatic definition of transition to radical or systemic treatment or metastases/death. This takes into account the fact that our focal therapy treatment protocols allow for one further session of focal treatment to either an in-field or out-of-field recurrence. For completeness I also presented a second more conservative definition of failure. Third, it is possible that the true rates of incontinence and erectile dysfunction may
differ as we had incomplete PROM data. However, the figures appear comparable to results in the literature of 0–3.6% incontinence and ED 0–42% (3). Introduction of an online method for collecting questionnaire data may have improved the data retrun. Fourth, due to the low number of failures (events) and large number of variables tested, my Cox-regression model is likely overfitted and limited in its ability to fully assess all the variables which can make interpretation of the HRs difficult, as can be seen with the large HR for ablation pattern. It does however indicate a potential correlation on variables that warrant further exploration in future studies or larger datasets. Fifth, the results are from a highly selected group of patients with predominantly anterior disease. Although this limits generalisability it does indicate that focal cryotherapy in this cohort of patients is a potential treatment option. In addition, one quarter did have both an anterior and posterior ablation.

There is little randomised comparative data on focal therapy, and these will be discussed further in chapter 4. Whilst RCTs on focal therapy compared to radical therapy are piloted, based on the currently available evidence in the literature, it might be reasonable to counsel eligible patients about focal cryotherapy as part of their informed consent.

Summary

Focal cryotherapy used primarily for anterior intermediate and high-risk prostate cancer results in good rates of cancer control and low rates of treatment related side-effects in the medium-term.
3.5  Functional Outcomes from Focal Cryotherapy for Localised Prostate Cancer

Introduction

As discussed in the previous chapter the oncological from focal cryotherapy appear favourable particularly in the short term (2). One of the purported advantages of focal cryotherapy over whole gland radical therapies is the potential for reducing treatment-related impact on urinary and sexual function. However, there is limited prospective data in the literature particularly assessing sexual function following cryotherapy utilizing validated patient reported outcome measures (PROMS) and most importantly reporting on return to baseline function after treatment. We recently highlighted the failure to use validated PROMS to report erectile function outcomes and the use of non-standardised thresholds defining normal function post intervention (3). PROM questionnaire score changes are difficult to interpret and explain to a patient especially as there are no standardised metrics used across all treatment modalities. Therefore, a clinically relevant end point for both the clinician and the patient might be return to baseline function. Although this concept has previously been reported following radical prostatectomy it has not been accepted universally or been assessed in patients undergoing focal therapy (4).

In the previous chapter I reviewed the proportion of men developing erectile dysfunction. In the following chapter using data collected from the same patient cohort, my aim is to determine the impact of focal prostate cryotherapy on urinary and sexual function and assess the return to baseline sexual as measured using the International Prostate Symptoms Score (IPSS) and international index of erectile function (IIEF) 15 questionnaire. I will also determine which factors affect return to baseline function.
Patients and Methods

Study design and patients

As described in chapter 3.4, between October 2013 and November 2016, 122 men underwent focal cryotherapy for clinically significant, intermediate or high risk localised, non-metastatic prostate cancer. As part of our focal cryotherapy program a NICE compliant multicentre prospective registry was maintained on both oncological and functional outcomes across 5 centres. Ethical review board exemption was granted by our institution. I personally administered / posted the questionnaires and was responsible for the collation and analysis.

Data was specifically collected for the following pre-operative and intra-operative variables: Median age; Gleason Score; NCCN Risk Category; T-Stage; Prostate Volume; PSA; Number of positive biopsy cores; Maximum cancer core length (MCCL); Pre-op hormonal use; Ablation pattern (anterior, posterior, unilateral, bilateral); Type of cryotherapy probe used (Ice-Rod, Ice-Seed); Number of cryotherapy probes used.

The International Prostate Symptoms Score (IPSS) and International Index of Erectile Function (IIEF-15) questionnaire data was collected pre-operatively and 3-6 monthly post-operatively. The IIEF-15 data was categorized according to subdomain; erectile function (EF); orgasmic function (OF); sexual desire (SD); intercourse satisfaction (IS); overall satisfaction (OS) and total score.

Procedures

All patients underwent a standard cryotherapy procedure using either the SeedNet or Visual ICE cryotherapy machine. Patients were placed in the lithotomy position with a rectally placed ultrasound (US) probe. Treatment planning was based upon the tumour location from the pre-operative mpMRI and biopsies as previously described (5). All were given aminoglycoside and cephalosporin antibiotics at
anaesthetic induction and quinolone antibiotics for 7 days post-operatively. 11 patients had 3 months pre-operative cytoreductive hormonal use (bicalutamide 50mg once daily) and this was stopped in all cases on the day of surgery.

Primary Outcome

The primary outcome measure for this analysis was defined as the return to baseline function of the International Prostate Symptoms Score (IPSS) and of the IIEF erectile function (EF) subdomain of the IIEF-15 questionnaire.

For IPSS I used the previously described threshold of a 1-point difference from baseline as the definition for return to baseline (6).

For EF the threshold for minimal clinically important differences (MCID) for the IIEF-EF subdomain had previously been established to be 4 with a maximum possible score of 30 (7, 8). I chose to use this same threshold / inferiority limit to define return to baseline function. i.e. if a patient has a post-operative change in their score of -5 they will have been deemed to not have returned to baseline where as a patient with a change in their score of -1 will have been deemed to have returned to baseline. As IIEF data were collected at multiple time-points I chose to use the first time point at which the patient had returned to baseline function for the purposes of the analyses (9).

Secondary Outcome’s

Initially, I assessed whether EF outcomes were corelated with oncological outcomes. For the purposes of this analysis Failure Free Survival (FFS) was defined as a redofocal therapy procedure or transition to radical/systemic therapy or cancer-specific death.

Second, as there are no established thresholds for minimal clinically important differences (MCID) for the total IIEF-15 questionnaire score nor any of the other
subdomains I chose to perform an analysis for the remaining subdomains with varying MCID limits. The maximum total IIEF15 score is 75 whilst for orgasmic function (OF), sexual desire (SD) and overall satisfaction (OS) subdomains is 10 and intercourse satisfaction (IS) subdomain is 15. A 4/30 point change for the EF subdomain equates to a 13% difference. Based on this proportional change for the EF subdomain, I chose to perform a sensitivity analysis for the remaining subdomains with the MCID limits varying between 5-20% with a comparison to the EF subdomain return to baseline outcomes. The following range of values were tested:

1. IIEF-15 has a maximum score of 75 and thus the tested MCID limits were 5, 10 and 15 points.
2. OF, SD and OS have a maximum score of 10 and thus the tested MCID limits were 1 and 2 points.
3. IS have a maximum score of 15 and thus the tested MCID limits were 1, 2 & 3.

Statistical Analyses

1 - Kaplan-Meier (1-KM) analysis was performed to determine time to recovery of sexual function. Second, a cox-regression analysis was performed to assess whether any specific pre-operative or intraoperative variable was associated with post-operative recovery of sexual function (IIEF-EF) for the following variables: pre-operative IIEF score; age; Gleason score; NCCN risk category; T-Stage; Prostate volume; PSA; Number of positive biopsy cores; Maximum cancer core length (MCCL); Pre-op hormonal use; Ablation pattern; Type of cryotherapy probe used and number of cryotherapy probes. Subsequently, as a comparator, a linear regression analysis was also performed comparing IIEF-EF scores during follow-up. As not all patients had returned questionnaires at each time point, for the linear regression the maximum IIEF-EF post-operatively was chosen. Lastly, after performing Kolmogorov-Smirnov, Shapiro-Wilk tests and Q-Q plots which showed that the data was not normally distributed, subsequent paired- Wilcoxon rank-sum tests were performed for the differences between the baseline and post-operative score at each time point. This resulted in 6 tests for IPSS and 36 tests in total for IIEF and with a
Bonferroni correction performed for multiple testing a p-value of <0.0083 (0.05/6) and <0.0014 (0.05/36) was considered statistically significant for IPSS and IIEF, respectively.

Missing Data

Baseline data was compared between those who returned a questionnaire and those that did not to determine if there any differences between the two groups.

Results

Baseline Characteristics and Descriptive Results

Median age was 69 years [IQR 65 – 73]; Median pre-operative PSA was 10.4ng/ml [IQR 7.4 – 15.7]; Median prostate volume was 44cc [IQR 31 -60]; Gleason Score: 7 patients (12%) had a Gleason score of 3+3, 41 patients (71%) had a Gleason score of 3+4 and 10 patients (17%) had a Gleason score of 4+3; T-Stage: 43 (74%) were T2, 10 (17%) were radiological T3a and 4 (7%) were T3a, data was missing in 1 (2%) patient; NCCN Risk Category: 39 (67%) were intermediate risk and 19 (33%) were high risk; Median number of positive cores was 6 [IQR 4-9]; Median maximum cancer core length (MCCL) was 7 [IQR 6-10]; 11 patients (19%) underwent pre-operative hormonal use which was stopped on the day of the cryotherapy; Ablation Pattern: 15 (26%) had Anterior Unilateral disease, 27 (47%) had Anterior Bilateral disease, 0 (0%) had Posterior Unilateral disease, 1 (2%) had Posterior Bilateral disease, 12 (21%) had Anterior and Posterior disease and in 3 (5%) the ablation pattern was unknown; Type of cryotherapy probe used: 15 (25%) had Ice Rod Probe, 31 (53%) had Ice Seed Probe, and in 12 (20%) the Probe used was unknown; Median number of cryotherapy probes used was 4 [IQR 4-6].

Of the 58 men, IPSS Questionnaire return was 49/58 at baseline, 38/49 at 3 months, 36/49 at 6 months, 35/49 at 9 months, 30/49 at 12 months, 22/49 at 18 months and 17/49 at 24 months. IIEF Questionnaire return was 58/58 at baseline, 48/58 at 3-
months, 43/58 at 6-months, 39/58 at 9-months, 32/58 at 12-months, 10/58 at 18-months and 21/58 at 24-months.

Analysis of IPSS and Return to baseline function

Baseline median IPSS score was 8 [IQR 6-13] which dropped to 7 [IQR 4-12, p=0.530] at 3 months, 7 [IQR 4-12, p=0.307] at 6 months, 5 [IQR 4-10, p=0.046] at 9 months, 6 [IQR 4-11, p=0.109] 12 months, 6 [IQR 3-10, p=0.107] at 18 months and 7 [IQR 5-7, p=0.820] at 24 months.

39/49 (80%) patients returned to baseline function based on a MCID limit of 1 point. The other 10/49 (20%) men did not return to their baseline function. The actuarial probability of returning to baseline function was 47% at 3-months, 76% at 6-months, 75% at 9-months, 78% at 12-months and 87% at 18- and 24-months with recovery seen up to 18-months post-cryotherapy [Figure 1].

Cumulative incidence for IIEF-EF and IPSS return to baseline

Figure 1. Return to baseline function cumulative incidence plot (probability of returning to baseline function against time). Recovery in IPSS and IIEF-EF continues up to 18- months post-focal cryotherapy.
On Univariable analysis no pre-operative parameter was seen to predict post-operative function.

Analysis of IIEF-EF (Erectile Function) Subdomain and Return to baseline function
Baseline median EF subdomain score was 8 [IQR 2-20, p=0.0014] which dropped to 5 [IQR 1-9, p<0.0014] at 3 months with recovery seen from 6 months onwards, 6 [IQR 1-16, p=0.001] at 6 months, 7 [IQR 1-19, p=0.029] at 9 months, 4 [IQR 1-15, p=0.026] 12 months, 8 [IQR 1-18, p=0.446] at 18 months and 5 [IQR 2-13, p=0.017] at 24 months.

47/58 (81%) patients returned to baseline function based on MCID. The actuarial probability of returning to baseline function was 53% at 3-months, 67% at 6-months, 71% at 9-months, 85% at 12-months and 92% at 18- and 24-months with recovery seen up to 18-months post-cryotherapy [Figure 2]. Overall 5/58 (9%) patients were on PDE5i pre-operatively and a 19/58 (33%) were on PDE5i’s post-operatively. No difference in return to baseline function was seen between the two group with 24-month actuarial probability of returning to baseline function was 90% in those that did not receive PDE5i’s compared to 85% in those that did (p=0.39).

Figure 2. Box and Whisker plots of total score and each subdomain score at each time point with statistically significant p-values from paired Wilcoxon Ranked Sum tests.
On univariable cox-regression the only variable that correlated with erectile function was the pre-operative IIEF score with a Hazard Ratio (HR) of 0.96 [95%CI 0.93 to 0.99, p=0.029). Based on this finding a second model was constructed adjusting for potential confounders such as age, PSA, prostate volume and pre-operative hormone use and no change in the outcome was seen. Pre-operative IIEF-EF score remained a predictor of poorer outcome (HR = 0.96, 95%CI 0.92 to 0.99, p=0.037).

Subsequent linear regression mirrored the findings of the cox-regression analysis with the only variable predicting outcome being pre-operative IIEF-EF score (p=<0.01). For each point increase in pre-operative baseline IIEF-EF score, the mean increase post-operatively was 0.80 (95%CI 0.59–0.88, p < 0.01).

Also, no correlation was seen between return to baseline IPSS function and erectile function (p=1.00).

Secondary Outcomes

Erectile function and correlation with oncological outcomes

When comparing return to baseline function categorised by oncological failure no difference was seen between the two groups (p=0.86). The actuarial probability of returning to baseline function at 24- months was 88% in the group that did not fail compared to 89% in the group that did develop oncological failure.

Analysis of subdomains for return to baseline function

Baseline median total IIEF score was 32 [IQR 14-59] which dropped to 22 [IQR 13-35] at 3 months, 29 [IQR 14-47] at 6 months, 24 [IQR 14-53] at 9 months, 22 [IQR 8-43] at 12 months, 25 [IQR 17-53] at 18 months and 23 [IQR 11-37] at 24 months. Recovery was seen from 9 months onwards.
Baseline median OF score was 7 [IQR 2-9] which dropped to 6 [IQR 2-8] at 3 months, 7 [IQR 3-8] at 6 months, 7 [IQR 3-8] at 9 months, 6 [IQR 2-8] at 12 months, 7 [IQR 5-8] at 18 months and 5 [IQR 3-8] at 24 months. Recovery was seen from 3 months onwards.

Baseline median SD score was 6 [IQR 4-8] which dropped to 5 [IQR 3-6] at 3 months, 5 [IQR 4-7] at 6 months, 6 [IQR 3-7] at 9 months, 4 [IQR 3-6] at 12 months, 6 [IQR 4-7], at 18 months and 4 [IQR 3-6] at 24 months. Recovery was seen from 9 months onwards.

Baseline median IS score was 7 [IQR 0-14] which dropped to 3 [IQR 0-7] at 3 months, 5 [IQR 0-10] at 6 months, 5 [IQR 0-12] at 9 months, 2 [IQR 0-8] 12 months, 5 [IQR 0-13] at 18 months and 4 [IQR 2-7] at 24 months. Recovery was seen from 3 months onwards.

Baseline median OS score was 5 [IQR 4-8] which dropped to 4 [IQR 2-6] at 3 months, 4 [IQR 2-7] at 6 months, 5 [IQR 2-7] at 9 months, 4 [IQR 2-6] 12 months, 4 [IQR 3-7] at 18 months and 3 [IQR 2-6] at 24 months. Recovery was seen from 6 months onwards.

When assessing the total IIEF score, the 24- month probability of returning to baseline function ranged from 75% to 92% based on the tested range of MCID value. Similarly, for the orgasmic function (OF) subdomain score the ranged from 93% to 95%, for the sexual desire (SD) subdomain score the ranged from 85% to 90% for the intercourse satisfaction (IS) subdomain score the ranged from 61% and 67% and for the overall satisfaction (OS) subdomain the range from 83% and 85%. [Figure 3].
Figure 3. Cumulative Incidence curves showing return to baseline function for each IIEF subdomain

Missing Data

As 64/122 patients did not return a post-operative questionnaire, I compared their baseline pre-operative demographics to the remaining cohort and found the two groups to be comparable in terms of age, PSA, prostate volume, tumour stage, grade and MCCL.

Discussion

I have presented data on urinary function and to my knowledge is the first analysis of erectile/sexual function sub-categorised for all the IIEF-15 domains, with return to baseline function as a more pragmatic definition for assessing treatment outcome, in men undergoing primary focal cryotherapy. Briefly summarising the results, the data shows good preservation of function with an overall probability of returning to
baseline function of 87% at 24-months for IPSS and 92% for erectile function (EF), which compares very favourably to the data presented in the previous chapter where a clinical definition for erectile dysfunction was utilised in this same cohort and 84% had erections sufficient for intercourse at 12-months. An important finding from the presented data is that recovery tends to occur from 3 months onwards and can continue up to 18-months post treatment with baseline IIEF-EF score’s being predictive of outcome. When assessing the IIEF-15 subdomains the intercourse satisfaction (IS) subdomain had the poorest outcome with only 61% to 67% returning to baseline function. The results from the other subdomains and the total score were more consistent with those of the EF subdomain.

I used multiple methods to quantify urinary and sexual function based on patient reported IPSS and IIEF-15 questionnaires. However, median changes are difficult to convey to a patient. An outcome measure underreported in the literature is return to baseline function [Table 1]. This accounts for the fact that patients have varying pre-operative baseline function and in our opinion the proportion of men returning to baseline function is the simplest measure to utilise in the consenting and counselling process and is also the most clinically relevant outcome to patient and clinician. Also, if this definition were to be adopted more broadly it would allow for fairer comparisons between the different treatment modalities such as radiotherapy or prostatectomy.

For the erectile function (EF) subdomain, a minimal clinically important difference (MCID) has previously been established and for IPSS assessment I used a definition previously used by others in patients undergoing brachytherapy for localised prostate cancer. Thus, these would be the most robust outcome measures (7). As no MCID value exists for the total IIEF score nor the remaining subdomains, I used varying MCID inferiority limits and thus it is likely that the actual clinically meaningful value lies within the range of presented data. As shown changes in the chosen limits can improve or worsen the proportion deemed to have returned to baseline function. Large scale datasets will need to be utilised in order to validate these limits.
and one can argue that the most pertinent question to ask the patient may be: “do you feel your sexual function has returned to its pre-operative state?”.

<table>
<thead>
<tr>
<th>Study</th>
<th>N=</th>
<th>Erectile Dysfunction Outcomes</th>
<th>Return to Baseline Reported?</th>
</tr>
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<tbody>
<tr>
<td>Barqawi 2018</td>
<td>96</td>
<td>No change in SHIM Score from baseline</td>
<td>No</td>
</tr>
<tr>
<td>(134)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tay 2017</td>
<td>166</td>
<td>ED – 29.5% Physician determined assessment</td>
<td>No</td>
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<tr>
<td>(135)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valerio 2017</td>
<td>23</td>
<td>No change in IIEF-15 Score from baseline</td>
<td>No</td>
</tr>
<tr>
<td>(136)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barqawi 2014</td>
<td>62</td>
<td>No change in SHIM Score from baseline</td>
<td>No</td>
</tr>
<tr>
<td>(116)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrett 2013</td>
<td>50</td>
<td>No change in IIEF-5 Score from baseline</td>
<td>No</td>
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<tr>
<td>(117)</td>
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</tr>
<tr>
<td>Bahn 2012</td>
<td>70</td>
<td>ED – 26% (1yr); 14% (2.4yrs) IIEF-5</td>
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<tr>
<td>(95)</td>
<td></td>
<td></td>
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<tr>
<td>Ward 2012</td>
<td>1160</td>
<td>ED – 42% Physician determined assessment</td>
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<td>(86)</td>
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<td>Truesdale 2010</td>
<td>77</td>
<td>-1.9 point IIEF change at 12 months</td>
<td>No</td>
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<tr>
<td>(96)</td>
<td></td>
<td></td>
<td></td>
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<td>Li 2010</td>
<td>47</td>
<td>ED – 53.2% (3 years) IIEF-15 EF Domain</td>
<td>Yes</td>
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<td></td>
<td></td>
<td></td>
<td>46.8% return to baseline function by 36 months</td>
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<tr>
<td>Lambert 2007</td>
<td>25</td>
<td>ED – 29% Physician determined assessment</td>
<td>No</td>
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<tr>
<td>(97)</td>
<td></td>
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<tr>
<td>Ellis 2007</td>
<td>60</td>
<td>ED – 29.4% Physician determined assessment</td>
<td>No</td>
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<tr>
<td>(98)</td>
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<tr>
<td>Onik 2007</td>
<td>55</td>
<td>ED – 15% Type of questionnaire not mentioned</td>
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<td>(99)</td>
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</tr>
<tr>
<td>Bahn 2006</td>
<td>31</td>
<td>ED – 11.9% Modified Brief Male Sexual Function Index</td>
<td>No</td>
</tr>
<tr>
<td>(99)</td>
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Table 1. Erectile Function and Return to Baseline Function from Focal Cryotherapy as reported by previously published cryotherapy series.
ED = Erectile dysfunction
IIEF = International Index of Erectile Function
SHIM = Sexual Health Inventory for Men
Similarly, the most important question to ask with regards to urinary function would be concerning the use of any pads after focal cryotherapy. However, data from this cohort was presented in the previous chapter showing that only 4 patients developing urinary incontinence which resolved in all after 6 months. This is in keeping with the IPSS data which also showed no great decline in urinary function.

With regards to erectile function, in this cohort, using return to baseline function as the outcome measure 92% returned to their baseline erectile function (EF) by 18-24 months. The reported rates from the radical therapies can be as low as 12% (10). These results highlight the key benefit in terms of erectile function from undergoing focal cryotherapy or in fact focal therapy from any energy modality (11). However, care must be taken when comparing my outcomes with those from radical therapies such as prostatectomy and radiotherapy as a greater than 4-point drop for the EF subdomain does not signify complete loss of erections but signifies a clinically relevant decline (12, 13). This is also highlighted by the fact that not all patients required post-operative PDE5i’s and none were started on second line therapies e.g. Vacuum Erection Devices.

On the multivariable analyses, the pre-operative IIEF-EF score in both the cox- and logistic regression was seen as a strong predictor of outcome. One hypothesis for erectile dysfunction is that ablation can lead to damage to the nerve bundles. Surprisingly the ablation pattern (i.e. anterior, posterior) was not linked to eventual sexual function and neither were the number or type of cryo-needle used. There is much published data from radical prostatectomy series showing that older patients have worse outcomes (17). Although not presented above the linear regression data also showed that increasing age was a significant predictor of poorer outcome however the impact disappeared when adjusted for baseline function. Reassuringly, on multivariable analyses is patients who underwent a short period of oral androgen receptor blockade pre-operatively did not experience any residual effects on urinary or erectile function.
When assessing the subdomains, the most poorly performing subdomain was intercourse satisfaction (IS) and this warrants further exploration with patients in future studies as it may be indicating possible psychological rather than physiological cause of sexual dysfunction, particularly as orgasmic function (OF) and sexual desire (SD) were better maintained. This would not be unreasonable to expect in patients who have received invasive, albeit, minimally invasive prostate cancer treatment, undergone a period of catheterisation and subsequently are living with a diagnosis of cancer. Although much is said about the anatomical reasons for ED after prostate cancer treatment much less is documented on the psychological impact which must not be down played (14). In fact, there is evidence to suggest that enrolment of patients into survivorship programmes for psychosexual health in itself can improve sexual functioning (15, 16).

There are however some limitations that need highlighting. First, is the small sample size which would have impacted on the tightness of the estimates and also upon the multivariable analysis in particular due to the small number of events. Ultimately though these analyses are hypothesis generating and the size of the dataset lacks the power to fully explore all the factors that may impact post-operative sexual function. Another avenue for future research would be to further characterise the volume and location of the ablated tissue to determine if this truly impacts on eventual urinary or sexual function. Second, not all patients returned questionnaires which may lead to a selection bias in the presented outcomes. To ensure validity of the presented data I compared the pre-operative demographics of the cohort of patients that did not return a questionnaire to those that did and found no difference and thus can make the assumption that the outcomes would have been similar across the whole series of 122 patients. Also, the database used was designed and maintained prospectively in a similar manner to prospective clinical trials and only validated patient reported outcomes data rather than subjective data was collected and reported upon. Third, a limitation with regards to the IPSS analysis is that no data was collected on patients starting medical therapy such as a-blocker therapy or 5-alpha reductase inhibitors. These are both potential confounders in the analysis as it is entirely possible that the improvement in IPSS score seen was due to
the use of these medications. Fourth, a factor that may impact on generalisability is the fact that the majority of men had anterior disease and thus the results may not be relevant to those undergoing cryotherapy for posterior tumours. It does however highlight the excellent functional outcomes that can be achieved in this selected cohort of men with localised clinically significant prostate cancer. Finally, a limitation for all analyses using the IIEF questionnaire is that it was initially developed for the drug industry when assessing response to ED therapy. It may not be the most suitable questionnaire for assessment of outcomes post-surgery.

Summary

In men undergoing primary focal cryotherapy there is a high degree of preservation of urinary and erectile function with 87% returning to baseline IPSS function and 92% returning to baseline erectile function with recovery occurring from 3 months onwards and continuing for up to 18-months post focal cryotherapy.

I would also like to make a case that return to baseline function should be the new standard definition when assessing men undergoing treatments for prostate cancer as it allows direct comparisons between treatment modalities regardless on method used to assess pre- and post-operative function and is also the easiest outcome to use when counselling a patient regarding their treatment options.
4 Focal Therapy Propensity Score Matched Analysis

4.1 Introduction and Methods

There have been three propensity score matched analyses assessing oncological and functional outcomes from either focal cryotherapy, HIFU or IRE to whole-gland treatment.

Tay et al showed that using the Phoenix definition of biochemical failure found no statistically significant difference in the 5-year bDFS rate (76.4% whole-gland cryotherapy vs. 70.0% focal cryotherapy, p=0.26). Although there was no difference in incontinence (94.1% vs 95.1%, p = 0.803), erectile function was better preserved in those undergoing focal ablation (29.5% vs 46.8%, p=0.003) (135).

Albisinni et al, matched patients treated with focal HIFU against those undergoing radical prostatectomy and found no significant difference between the two modalities in terms of the need for salvage treatment but with better functional outcomes (137).

Recently, Scheltema et al reported on a comparison of 50 focal IRE patients and 50 radical prostatectomy patients. Again, functional outcomes were superior with focal IRE but 29.5% of patients in the IRE group had residual cancer on 12-month biopsies. Of these only 7 underwent further treatment (three salvage IRE, three salvage RARP, one salvage low-dose rate brachytherapy). In comparison none in radical prostatectomy group experienced biochemical failure at 12-months (138).

Although RCTs in intermediate and high-risk disease are required these may be difficult to recruit to especially considering that many previous trials have struggled to complete when attempting to compare current radical therapy approaches (139). Whilst RCTs on focal therapy compared to radical therapy are piloted I conducted a
propensity score-matched analysis to compare cancer control outcomes of focal therapy to radical prostatectomy.

Research Questions

1. How does focal therapy compare to Laparoscopic Radical Prostatectomy (LRP) in the medium-term with regards to oncological outcomes?

2. How does focal therapy using either focal cryotherapy or focal HIFU compare to Laparoscopic Radical Prostatectomy with regards to functional outcomes?

Patient Population

All consecutive men undergoing either focal HIFU (n=625) or focal cryotherapy (n=122) and laparoscopic radical prostatectomy (LRP) (n=571) between 2007 – 2017 for primary localised non-metastatic prostate cancer had their pre- and post-operative data collected in prospective databases.

The following inclusion/exclusion criteria were applied:

Inclusion criteria

1. PSA <20 ng/ml
2. Gleason score <= 7
3. MRI Stage <= T2c

Exclusion criteria

1. Patients with MRI or clinical T3 disease will be excluded as macroscopic T3 disease is rarely suitable for focal therapy *
2. Within the LRP cohort all men receiving early adjuvant therapy will be excluded**
3. Patients with previous prostate cancer treatment i.e. Radiotherapy or Focal therapy will be excluded.
*Clinical T3 disease is not available on the HIFU database. As per the patient selection criteria for offering focal therapy the assumption will be made that all HIFU patients had clinical T2 disease. As per my analysis detailed below concerning clinical T3 disease in the LRP dataset, patients with clinical T3 disease will also be excluded from the LRP dataset.

** This analysis commenced prior to presentation of the RADICALS trial (ISRCTN40814031) demonstrating no benefit from adjuvant radiotherapy. Therefore, due to some men receiving early adjuvant therapy in the LRP cohort in order to reduce bias all men receiving adjuvant (salvage) therapy within 12 months were excluded from the primary analysis. Additionally, due to the nature of follow-up after FT a failure event within 12-months is very unlikely and thus without the above exclusion further bias could be introduced. Within the secondary analyses all patients undergoing radical prostatectomy were included.

**Intervention**

Focal Cryotherapy or High Intensity Focused Ultrasound (HIFU). All patients underwent focal HIFU (Sonablate, Sonacare Inc, Charlotte, NC, USA) or cryotherapy (SeedNet or Visual ICE, Boston Scientific) as previously described. Cryotherapy was performed in anterior tumours or in larger prostates with an anterior-posterior distance of >3.5cm or those with prostatic calcifications. All other patients with peripheral zone or posterior tumours underwent HIFU.

**Comparator**

Laparoscopic Radical Prostatectomy (LRP). Radical Prostatectomy with unilateral or bilateral nerve-sparing was performed as determined by the operating surgeon and patient tumour characteristics. Lymph node dissection was not routinely performed.
Follow-up and further treatment

In both cohorts, all patients underwent 3-monthly PSA tests for the first year and 6-monthly for 2-years and yearly thereafter. Patients who underwent focal therapy also underwent a multiparametric MRI (mpMRI) at 12-months with biopsies performed if there was suspicion of residual cancer. After the first year post focal therapy, an mpMRI with biopsies as appropriate were used to investigate any rise in PSA over three consecutive readings. If suitable, a further session of focal therapy was offered. Radical therapy was also offered according to patient preference, or in cases of increasing volume or stage of disease or progression to high grade disease. Patients after radical prostatectomy were offered salvage radiotherapy, androgen deprivation therapy or surveillance based on PSA and post-operative pathological findings. In our practice, super-sensitive PSA testing was used, therefore local practise advocated consideration of salvage radiotherapy after radical prostatectomy in the presence of risk-factors for recurrence and a consistently rising post-operative PSA >0.02ng/ml.

Outcome measure

Primary:
The primary outcome was Failure Free Survival (FFS) defined as transition to salvage or systemic therapy.

Up to two focal treatments were allowed as part of the FT intervention

Secondary Outcomes:

- Comparison of FFS with a redo FT and patients receiving early adjuvant treatment in the LRP cohort defined as failure.
- Comparison of functional outcomes between focal therapy and LRP.
- Overall Survival (OS) and Cancer Specific Survival (CSS).
**Matching Criteria**

Matching to occur using the following variables:
- Year of surgery (year)
- Age (years)
- PSA (ng/ml)
- Gleason Grade (3+3, 3+4, 4+3)
- T-stage (will be combined into unilateral (T1c, T2a, T2b) and bilateral (T2c))
  - Combined MRI and biopsy stage in LRP patients and MRI T-stage in HIFU cohort
  - For patients missing formal T-stage in the LRP cohort T2c will be assigned based on Bilateral disease on biopsy
- Maximum cancer core length (MCCL)
- Use of neoadjuvant hormonal therapy

**Missing Data**

Multiple Imputation: Patients with any missing matching variables as outlined above will be excluded.

**Statistical Analyses**

**Baseline**

Continuous data is depicted as mean±sd or median with corresponding interquartile range (IQR), as appropriate. Absolute numbers are depicted with percentages. Differences in continuous variables were tested with the unpaired students’ T-test or Mann-Whitney U test, depending on the data distribution.

**Propensity score**

A propensity score was constructed to correct for baseline imbalances using logistic regression. Nearest neighbour matching without replacement was used and groups were matched 1:2 (one patient receiving prostatectomy for two patients receiving
focal HIFU or focal cryotherapy). The propensity score (i.e. probability of receiving prostatectomy rather than focal HIFU or cryotherapy) was calculated using the following variables: age, use of neoadjuvant ADT, PSA, Gleason grade category, MCCL, tumour stage and year or treatment. Patients outside the range of matched propensity scores were discarded. A caliper of 0.20 of the standard deviation of the logit of the propensity score was used to minimize the differences between the groups in baseline characteristics described above. Missing data was assumed to be missing at random and therefore eligible for imputation. Single imputation was performed to correct for missing data before creation of the propensity score.

**Survival analysis**

Kaplan-Meier analysis was performed on the original dataset, the matched dataset and on the original dataset corrected for the inverse probability of treatment weights (IPTW). The log-rank test was used to ascertain statistical significance of differences in outcomes in the treatment groups.

All analyses were performed using SPSS v25, Stata v16.1 and R version 3.5.2 (http://www.R-project.org). The ‘MatchIt’ and ‘optmatch’ packages were used for propensity score analysis. The ‘mice’ package was using for imputation and the ‘survminer’ package for Kaplan-Meier analyses. The script for the analysis was developed in collaboration with the Utrecht medical centre in the Netherlands.

**Database Coordination**

The focal cryotherapy database was created and updated by me. The focal HIFU database was a collaborative effort over many years. I updated the outcomes prior to analysis. The LRP database was maintained by Mr Mathias Winkler and was updated by me, Annie Kim, Daniel Ball and Deepika Reddy prior to analysis.
4.2 T-Stage Analysis

Introduction and objectives

To be eligible for FT patients needed to have a DRE T-stage of <T3 (locally advanced disease). The LRP cohort had patients with both T2 and T3 disease. As historical data had suggested poor correlation between DRE stage and final pathology stage in order to ensure that I was not unfairly excluding patients I chose to assess the concordance between clinical T-stage to final pathology after laparoscopic radical prostatectomy (LRP). If DRE T-stage did not correlate with final pathology, then I would need to develop an alternative method for patient selection. In addition to the above as data on MRI was also available, I chose to assess the utility of MRI in determining final pathology T-stage.

Methods

All consecutive patients undergoing laparoscopic prostatectomy at a single institution between 2007 – 2017. 571 men underwent LRP with 20% being D'Amico low risk, 43% medium and 37% high risk.

Pre-operative staging data was collected on clinical stage digital rectal examination (DRE), MRI stage and post-operative pathology stage. DRE stage was recorded from a single surgeons’ examination whilst MRI and pathological stage were recorded after institutional multidisciplinary cancer team review (MDT).

First, I assessed concordance between clinical and MRI stage with final pathological stage using cross tabulation, Pearson's Chi2 and Cramer's V statistical tests. Second, I assessed the degree of upstaging seen between DRE and MRI stage.
Results

Digital Rectal Examination (DRE)

DRE stage was available in 571/571 men and was found to have significant concordance with the final pathological stage with a Pearson's Chi2 of $p<0.0001$, (Cramer V value:0.17) indicating weak concordance [Table 1].

<table>
<thead>
<tr>
<th>DRE</th>
<th>T1a</th>
<th>T1b</th>
<th>T1c</th>
<th>T2a/b</th>
<th>T2c</th>
<th>T3</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>T1b</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>T1c</td>
<td>11</td>
<td>3</td>
<td>160</td>
<td>75</td>
<td>21</td>
<td>3</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>T2a/b</td>
<td>8</td>
<td>3</td>
<td>76</td>
<td>36</td>
<td>15</td>
<td>3</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>2</td>
<td>2</td>
<td>20</td>
<td>18</td>
<td>8</td>
<td>1</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>43</td>
<td>26</td>
<td>1</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>8</td>
<td>275</td>
<td>173</td>
<td>71</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Cross-tabulation of DRE vs pathology stage

Magnetic Resonance Imaging (MRI)

All MRI staging data was re-reviewed for T-stage and due to the historical nature of the cohort a definitive diagnosis (T1-T3b) was available in 218/571 patients. Cramer V values were 0.31 for T2 disease and 0.37 for T3 disease indicating a moderate level of concordance with the final pathological stage (Pearson's Chi2, $p<0.0001$) [Table 2 and 3]. For T2 disease MRI had a sensitivity of 51%, specificity of 79%, PPV of 64% and NPV of 69% whilst for T3 disease the sensitivity was 76%, specificity 60%, PPV 70%, and NPV 67%.
Pathology T2 versus MRI T2 Crosstabulation

<table>
<thead>
<tr>
<th>Path T2</th>
<th>MRI T2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99</td>
<td>126</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td>92</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>144</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

Table 2. Cross-tabulation of pathology T2 vs MRI T2 stage

Pathology T3 versus MRI T3 Crosstabulation

<table>
<thead>
<tr>
<th>Path T3</th>
<th>MRI T3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>59</td>
<td>98</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>120</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
<td><strong>218</strong></td>
</tr>
</tbody>
</table>

Table 3. Cross-tabulation of pathology T3 vs MRI T3 stage

Stage Migration

From this cohort of 218 patients with both an MRI and DRE stage documented I found that 36/91 (40%) patients diagnosed with T1 disease on DRE stage were upstaged to T2 on MRI and 44/91 (48%) to T3 on MRI. Similarly, 28/65 (44%) found to have T2 disease on DRE stage were upstaged to T3 on MRI [Figure 1]. Overall 108/156 (69%) patients with T1 or T2 disease on DRE were upstaged based on their MRI [Figure 2].
Figure 1. Upstaging seen on MRI compared to DRE

Figure 2. Multiparametric MRI of an anterior cancer which is T1 on DRE
Summary

Overall, the results show significantly better concordance to final pathology with MRI staging compared to DRE clinical stage.

However, there was a high degree of concordance between DRE T3 stage and Final Pathology and also with T3 disease on MRI. Thus, based on these finding all patients with DRE T3 disease were excluded from the propensity score analysis. A point to note is that this does not account for the unmeasured upstaging that would be seen in the FT cohort as a number of patients with MRI T2 disease may in fact harbour T3 disease. But the assumption was made that clinical T3 disease would have been excluded from the outset in the FT cohort and thus the impact of upstaging would be similar across both groups.
4.3  Results and Discussion

572 radical prostatectomy and 761 focal therapy (626 HIFU, 135 cryotherapy) patients in total were treated. 335 patients in the radical prostatectomy group and 501 patients in the focal therapy group (420 HIFU, 81 cryotherapy) were eligible for analysis. 1-1 propensity score matching resulted in 246 in each group [Figure 1]. With reference to the matching variables patients were well matched, with SMD =/≤0.1 [Table 1].

![Flow diagram demonstrating matching variables and cohort development for the primary outcome](image-url)
### Table 1: Characteristics of RP vs FT prior to matching, and after 1:1 matching and single imputation with calliper 0.20 for the primary outcome (definition 1).

<table>
<thead>
<tr>
<th></th>
<th>RP before matching</th>
<th>FT before matching</th>
<th>p-value</th>
<th>SMD before matching</th>
<th>RP after matching</th>
<th>FT after matching</th>
<th>p-value</th>
<th>SMD after matching</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>N= 335</td>
<td>N= 501</td>
<td></td>
<td></td>
<td>N=246</td>
<td>N=246</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years), mean ± SD</strong></td>
<td>62.1 (±6.1)</td>
<td>65.3 (±7.4)</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>63.4 (±5.6)</td>
<td>63.3 (±6.9)</td>
<td>0.79</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Number of neoadjuvant ADT given</strong></td>
<td>13 (3.9%)</td>
<td>56 (11.2%)</td>
<td>0.0002</td>
<td>0.28</td>
<td>11 (4.5%)</td>
<td>7 (2.8%)</td>
<td>0.47</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>PSA (ng/ml), median (IQR)</strong></td>
<td>7.9 (5.9-10)</td>
<td>7.4 (5.3-10.3)</td>
<td>0.04</td>
<td>0.12</td>
<td>7.9 (6-10)</td>
<td>7.9 (5.5-10.6)</td>
<td>0.59</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Gleason grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+3</td>
<td>132 (39.4%)</td>
<td>135 (26.9%)</td>
<td>0.001</td>
<td>0.27</td>
<td>94 (38.2%)</td>
<td>91 (37.0%)</td>
<td>0.75</td>
<td>0.05</td>
</tr>
<tr>
<td>3+4</td>
<td>169 (50.4%)</td>
<td>310 (61.9%)</td>
<td></td>
<td></td>
<td>128 (52.0%)</td>
<td>135 (54.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+3</td>
<td>34 (10.1%)</td>
<td>56 (11.2%)</td>
<td></td>
<td></td>
<td>24 (9.8%)</td>
<td>20 (8.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage (bilateral)</strong></td>
<td>147 (43.9%)</td>
<td>136 (27.1%)</td>
<td>&lt;0.001</td>
<td>0.66</td>
<td>116 (47.2%)</td>
<td>107 (43.5%)</td>
<td>0.47</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>MCCL (mm), median (IQR)</strong></td>
<td>6 (3-9)</td>
<td>6 (4-8)</td>
<td>0.48</td>
<td>0.04</td>
<td>5 (3-8)</td>
<td>6 (4-8)</td>
<td>0.48</td>
<td>-0.007</td>
</tr>
</tbody>
</table>

**Abbreviations:** RP= radical prostatectomy, FT=focal therapy, ADT= Androgen Deprivation Therapy, PSA= Prostate-Specific Antigen, MCCL= Maximum Cancer Core Length, SMD= standardised mean difference, SD= Standard Deviation, IQR= Inter-Quartile Range
Primary Outcome

As per definition 1, failure-free survival (95% CI) in the radical prostatectomy compared to focal therapy groups was 86% (81-91%) vs. 91% (87-95%) at 3 years, 82% (77-88%) vs. 86% (81-92%) at 5 years and 79% (73-86%) vs. 83% (76-90%) at 8 years, respectively (adjusted log rank p-value 0.12) [Figure 2].

Figure 2. Primary Outcome (Definition 1): Kaplan Meier curve for failure free survival in 1-1 matched patients. Up to two focal therapy treatments were allowed within this definition.
Secondary Outcomes

Additional treatments

39/246 (15.9%) of radical prostatectomy patients underwent salvage radiotherapy. One patient that underwent salvage radiotherapy died of an unrelated cause. After focal therapy, 186/246 (75.6%) required no further treatment; 42/246 (17.1%) underwent a second and 4/246 (1.6%) underwent a third focal therapy session. Whole-gland treatment was carried out in 7/246 (2.8%) after the second focal therapy session with either radiotherapy (n=6; 2.4%) or radical prostatectomy (n=1; 0.4%). Whole-gland treatment straight after the first focal therapy session was carried out in 16/246 (6.5%). No patient that underwent three focal therapy sessions later underwent whole-gland treatment nor had further evidence of recurrence at last follow-up.

Failure free survival (definition 2)

After applying the inclusion/exclusion criteria, 364 patients were eligible in the radical prostatectomy group and 501 patients in the focal therapy group (420 HIFU, 81 cryotherapy). 1-1 propensity score matching resulted in 250 in each group. Patients were well matched according to age, grade, MCCL, stage and neoadjuvant hormones, with SMDs ≤0.1.

Failure-free survival by definition 2 (95% CI) following radical prostatectomy and focal therapy was 76% (70-82%) vs. 82% (77-87%) at 3 years, 73% (67-79%) vs. 71% (64-78%) at 5 years and 70% (64-77%) vs. 63% (55-73%) at 8 years, respectively (adjusted log rank p-value 0.92) [Figure 3].
Freedom from any local salvage, systemic treatment and prostate cancer metastases and mortality

Failure-free survival (95% CI) in which I counted any post-operative radiotherapy after radical prostatectomy as failure in the radical prostatectomy vs. focal therapy cohorts was 76% (70-82%) vs. 93% (90-97%) at 3 years, 73% (68-80%) vs. 88% (84-93%) at 5 years and 71% (65-78%) vs. 86% (80-92%) at 8 years, respectively (adjusted log rank p-value< 0.0001). Metastases-free and overall survival was high in both groups [Figure 5].
Figure 5. Overall Survival

**Functional Outcomes**

Functional outcomes were based on validated patient reported outcome measures (PROMS) (International Index of Erectile Function-5 [IIEF-5], EPIC Urinary domain, International Prostate Symptom Score [IPSS]) for FT, and by clinician assessment following LRP. Urinary continence was defined as no pad usage. Potency was defined as the ability to maintain an erection sufficient for penetrative intercourse, with or without the use of medications. In the FT cohort this was defined as a score of 2-5 on question 2 of the IIEF-5 questionnaire whereas after LRP cohort it was based on physician reporting.
After LRP, all 246 patients had completed continence reports, and 241/246 had potency outcomes reported. After FT, 144/246 patients completed continence PROMs, and 146/246 patients completed potency PROMs. After LRP 212/246 (86.2%) reported pad-free continence compared to 139/144 (96.5%) reporting pad-free continence after FT (p <0.0007). After LRP, 139/241 (57.7%) patients reported being potent compared to 104/146 (71.2%) after FT (p=0.009) [Figure 4].

Figure 4: Continence and Potency rates after focal therapy or laparoscopic prostatectomy
Discussion

The propensity matched comparison of focal therapy and radical prostatectomy in the treatment of non-metastatic prostate cancer shows focal therapy had similar cancer control to radical prostatectomy. This finding was stable across other types of analysis in which either matching criteria or FFS definitions were varied.

The findings contrast those of a recent similar propensity score analysis by Garcia-Barreras et al. who described a repeat focal treatment as failure and found a higher risk of salvage treatment after focal therapy than radical prostatectomy (HR 6.06, 95% CI 3.6-10.2, p <0.001) at 46 months (140). Only 40% of my cohort had Gleason Grade Group 1 compared to 75% in the Garcia-Barreras study. Albisinni et al reported a propensity matched analysis of 55 treated with focal HIFU to 55 undergoing radical prostatectomy. They found no significant difference in need for salvage treatment with median follow-up of 36 months (IQR16-56)(137). A study of 50 focal irreversible electroporation patients compared to 50 radical prostatectomy patients, with only 12 months follow-up and using different failure definitions, showed FFS after focal therapy was higher (138). Although not a directly comparable study, Tay et al showed whole-gland cryotherapy and focal cryotherapy had similar 5-year biochemical disease-free survival rates (135). The Phoenix definition of biochemical failure is used following radiotherapy and has been shown not to be valid following focal therapy (141). In my primary outcome analysis, I excluded patients who received adjuvant radiotherapy after radical prostatectomy and did not use biochemical failure for radical prostatectomy. Had I done so, a higher number of radical prostatectomy failures would be assigned and also would have made comparisons to focal therapy difficult as there are no validated PSA metrics defining focal therapy failure. Recently, Huber et al reported that PSA nadir + 1.5ng/ml after focal therapy may predict failure, but this requires external validation (141).

The presented dataset has some advantages as all men either had mpMRI and targeted/systematic biopsies or template transperineal mapping biopsies prior to
focal therapy. I also used both focal HIFU and focal cryotherapy in a manner that suits the patients’ disease characteristics thus minimising selection bias with longer follow-up and larger numbers than these aforementioned studies. The primary definition that I used is also being used in ongoing RCTs (142, 143). In addition, I conducted a secondary outcome analyses that incorporated any form of treatment after the initial one and still found no statistically significant difference.

There are some limitations. First, there may be some residual confounding variables that the matching process could not account for. Despite diagnostic MRI used in both cohorts, tumour volume was not reported therefore cancer core length was used as a validated surrogate for matching (78). Second, I was unable to adjust for baseline urinary and sexual function, therefore a robust comparison of functional outcomes was not possible. Although functional outcomes for potency and urinary continence were assessed prospectively the outcomes were determined with different methodologies, patients were required to complete formalised questionnaires during FT follow-up, however only a clinician’s subjective assessment of functional outcomes was used in the those who underwent LRP. In terms of pad-usage this is unlikely to create a bias but in the LRP cohort may have led to a higher proportion of men being classified as potent than had a validated PROMs questionnaire been used. However, functional outcomes have been previously reported for focal therapy and radical prostatectomy (21, 83).

The presented study is not a randomised controlled trial. Whilst historical RCTs such as SPCG-4, PIVOT and PROTECT have successfully recruited, many other RCTs have failed to recruit where the interventions are very different as a result of difficulty in maintaining physician and patient equipoise (139). The pilot Partial Ablation versus Radical Therapy (PART) RCT, compared focal HIFU to radical prostatectomy required an extended accrual time than originally intended and the radical arm had approximately 80% compliance (143). The main PART RCT will now compare focal VTP to radical therapy (ISRCTN99760303). The IP4 Comparative Health Research Outcomes of Novel Surgery in prostate cancer (CHRONOS) RCT (clinicaltrials.gov NCT04049747) will aim to randomise men to either radical treatment (radiotherapy,
brachytherapy or prostatectomy) or focal therapy (HIFU or cryotherapy), as well as test neoadjuvant strategies that might improve cancer control after focal therapy (142).

In select patients with non-metastatic prostate cancer, medium term oncological outcomes were similar between focal therapy and radical prostatectomy. Whilst clinicians await the results of RCTs directly comparing focal therapy to radical therapy, comparative data such as these are the best available evidence with which to better counsel patients about their treatment options.
5 Future Perspective and Trial Design

It is accepted that a well-designed RCT is high level evidence upon which treatment decisions can be based. However, designing an appropriate prospective trial to assess the follow-up of patients after focal therapy carries its own challenges. Successfully randomizing men to different surgical treatments in prostate cancer can be challenging.

The initial entry point would be from diagnosis of disease. The methodology for diagnosis is important. Pre-operotive TRUS biopsy has been shown to be inaccurate particularly when assessing patients for focal therapy. For instance, 23% of patients having a template biopsy after a previous TRUS biopsy had upgrading whilst 60% were found to have bilateral disease (74). Systematic transperineal and MRI guided biopsies have been shown to be equally accurate in detecting cancer (144, 145). Thus, a similar principle should be applied to post-treatment biopsies. Most still perform systematic TRUS biopsies after treatment that may under-sample the treated area and lead to detection of insignificant disease from untreated tissue.

To improve upon this ultrasound-MRI fusion techniques have been developed. There seems to be potential benefit of this technique over systematic TRUS biopsies with 67% more significant disease detected, however, the benefit is less clear when comparing cognitive MRI targeting versus a fusion technique (146-148). Wysock et al did not show a significantly increased cancer detection rate between the two techniques but did find improved accuracy for smaller lesions with fusion biopsies (147). Whilst Cool et al showed a 100% increased accuracy for sampling a clinically significant tumour with fusion targeting versus cognitive (148). 5mm transperineal mapping biopsies are arguably still the gold standard though, with up to 95% accuracy when compared to radical prostatectomy specimens (75, 76). Nonetheless, these require a general anaesthetic and due to the higher number of cores taken have a potentially higher side-effect profile.
Subsequently the clinical significance of disease needs to be reviewed before any treatment is offered. Gleason 6 disease has been shown to rarely if ever lead to metastases and thus death (62, 63, 149). Similarly metastases are very rare with tumour volume <0.5cc (67). Combining this data from results from active surveillance series where few deaths occur, it can be reasoned that low volume Gleason 6 disease may not benefit from interventional treatment (108). Thus, the ideal focal therapy candidate is likely to be men with Gleason 7 and above disease or high volume Gleason 6 cancer.

These same factors play a role following focal therapy. If a patient's disease has been accurately classified preoperatively then follow-up can consist of imaging and biopsies only targeted to the treated area. As previously mentioned, although various criteria exist for follow-up, all effectively conclude that a rising PSA can be used to guide further investigation for recurrence and timing of the post- treatment biopsy. An additional factor to consider is the use of mpMRI to follow-up treated lesions, and thus trigger a biopsy if residual or recurrent disease is detected.

After focal ablation there is residual inflammation, necrosis and eventual fibrosis. Along with some of the data in our own series, Biermann et al found that detection of grading of cancer in biopsies taken 6 months post HIFU was possible (unlike with radiotherapy); thus it seems reasonable that biopsies can be performed at least as early as 6 months (150).

With respect to mpMRI a consensus meeting found that 77% of panellists felt that this is a reliable tool for follow-up (151). From the series of 118 men who underwent focal HIFU by Dickinson et al, an overall positive biopsy rate was 37% (41/118). Areas under ROC for early and late MRI ranged from 0.65 to 0.76 and 0.77 to 0.85, respectively, with sensitivity, specificity, and negative predictive values of 68% to 91%, 52% to 55%, and 85% to 98% (early MRI), and 63% to 80%, 67% to 73%, and 86% to 97% (late MRI) (152). Overall, there is some evidence to support the use of mpMRI as a method for follow-up, and it appears to form an important part of multi-modal follow-up (153-156).
Subsequently, the clinical significance of post-procedural biopsies needs to be considered. There is limited evidence to suggest that low-grade low-volume residual in-treatment field cancer behaves in a similar way to patients with primary disease of the same pathology. Similarly, there is no data on the natural history of secondary low risk lesions. As mentioned previously the safest option would be to apply the same principles as for AS and follow-up these patients with repeated imaging with biopsies as deemed necessary. From the reviewed cryotherapy and HIFU papers, redo focal treatment and AS appear to be the most common management options selected for patients with positive biopsies.

The final point to consider when designing such a trial is the comparator arm. The two most common radical whole gland treatments are radiotherapy or radical prostatectomy. Only recently have head-to-head results from the PROTECT RCT been published showing equivalence at 10 years in the treatment of largely low risk and some intermediate risk disease. Retrospective reviews have previously shown surgery to have better oncological outcomes, however, even with the best matching, bias can never be fully excluded (15-17, 157).

The role of focal therapy will ultimately help decide the most appropriate comparator arm. I feel that the current role of focal therapy is similar to that of tissue preservation in almost all other solid organ cancers (bar ovarian) in that it leads to a minimal decrease in quality of life for the patient whilst providing acceptable cancer control. At least in the short to medium term the data suggests that focal therapy may be meeting these aims. However, few studies have long-term follow-up and a systematic review showed a varying biochemical disease-free survival of between 86.2% at 8 years and 60% at 5 years (82).

Thus, in the first instance patients with localised intermediate to high-risk disease should be compared to those undergoing radical treatment with either EBRT or RRP. The aim of this study would be to show non-inferiority for short-medium term oncological outcomes with a superior side-effects profile. Repeat treatments are
possible with focal therapy and a second treatment would not be considered a
treatment failure unless there was a significant reduction in the two outcome
measures mentioned.

In addition to the above in order to future proof any potential trial we would need to
further develop and improve on the reported outcomes from focal therapy and reduce
the rate of failure.

Regardless of outwit surgical expertise and learning curve for carrying out focal
therapy, failure can occur due to a number of mechanisms that might be influence
using neoadjuvant and adjuvant strategies. First, the vasculature of the tumour
prevents complete ablation by causing sub-optimal ablative effect (heat-sink effect).
Second, satellite areas of cancer a few millimetres away from the main targeted lesion,
but not detected with MRI or biopsy and outside the normal applied margin of 3-5mm
of ablation, can be left untreated (margin effect). Third, untreated prostate tissue
might harbour clinically significant lesions, missed by MRI and biopsy, which then
progress or micro metastasise (staging effect). Fourth, untreated prostate tissue might
develop de novo clinically significant cancers (field effect) [Figure 1].

Figure 1. Possible causes of failure in patients undergoing focal therapy.
Field Effect: Prostate cancer is commonly noted to be multifocal. One hypothesis for this is an underlying field effect where histologically normal areas of prostate tissue may show genetic and epigenetic changes without histological abnormalities potentially predisposing them to the development of cancer (158). Transcriptome analysis by Kosari et al found that in 37 patients who underwent radical prostatectomy there was significant concordance between cancerous and contralateral benign tissue (159). The field effect may also influence tumour margins as multiple studies have shown that tissue directly adjacent to the tumour exhibits pre-cancerous changes (160, 161). Recent work by Cooper et al using next-generation DNA sequencing in 3 patients post-radical prostatectomy found: 1) In 2 patients somatic mutations in 45% of cells suggesting clonal expansion; 2) Phylogenetic tree analysis showed that benign areas of prostate had mutations and sequence alterations consistent with the field effect; 3) Tumour merging or Intra-prostatic spread of malignant cells may play a part due to multiple clones of the TMPRSS-ERG transgene within the same tumour mass (162). However, it is not known though whether this clonal field effect is due to somatic mosaicism or due another bio-pathological process.

In addition, there is some evidence for the de-differentiation of low risk Gleason 3 prostate cancer and also for its progression into a higher grade (163-165). This has to be balanced against a body of evidence suggesting that low grade prostate lacks the hallmarks needed for cancer progression and indeed progression is rare with histological grade being established early on in the disease process (60, 166, 167).

Thus, the use of neoadjuvant and adjuvant strategies, in combination with focal therapy may reduce the rate of failure: First, hormonal therapies (5-alpha reductase inhibitors, LHRH agonists, anti-androgens, other novel agents [enzalutamide, abiraterone]), which reduce large tumour size, eliminate small low grade tumours and reduce vasculature, might complement focal ablation by reducing the heat-sink and margin effects. Second, as ablation induces an immune response, we could also test immuno-modulatory agents that might potentiate this immune reaction and
impact on residual tumours following the heat-sink effect, as well as potentially impacting on satellite lesions and out-of-field progression/de novo disease. Third, novel agents such as checkpoint inhibitors to potentiate the immune response induced by local ablation, abiraterone and enzalutamide or drugs with links to tumour metabolic pathways such as Metformin might be considered.

With such an array of agents and strategies that could be used, I propose the optimum trial would be a randomised controlled trial using a multi-arm, multi-stage (MAMS) design. This would allow concurrent recruitment to multiple arms with early stop-points for ineffective or highly morbid interventions. Importantly, the MAMS trial design allows arms to be added over time, as and when both novel agents and funding become available, without having to start a new trial altogether; use of existing processes further increases the efficiency of this trial design, enabling seamless recruitment to research questions of interest, and reducing competing trials.

Review of mechanisms of action for neoadjuvant and adjuvant strategies

Anti-androgens (e.g., bicalutamide)

The majority of prostate cancer is androgen dependent with androgens stimulating growth and progression. Androgen deprivation therapy (ADT) using strategies such as an androgen receptor antagonist, a LHRH agonist/antagonist or orchidectomy have been long standing treatments for advanced and metastatic prostate cancer. Although mono-therapy in localised disease has not been shown to improve oncological outcomes, combination therapy with radiotherapy has consistently shown to improve survival (168).

Testosterone and its more potent form di-hydrotestosterone (DHT) are the primary ligands for the androgen receptor (AR). Ligand binding leads to receptor translocation into the nucleus, where it binds DNA on androgen responsive elements
(AREs) within the regulatory regions of target genes. The AR acts as a regulator of G1-S phase progression, able to induce signals that promote G1 cyclin-dependent kinase (CDK) activity, induce phosphorylation/inactivation of the retinoblastoma tumor suppressor (RB), leading to androgen-dependent proliferation. These functions appear to be independent of the AR-induced pro-proliferative TMPRSS2-ETS (ERG, ETV1, or ETV4) fusions occurring in prostate cancer (169).

Use of ADT in animal models has been shown to lead to apoptosis of both tumour and pre-cursor lesions (170). In addition androgen signalling stimulates VEGF secretion leading to tumour neo-angiogenesis (171). Conversely ADT results in down-regulation of VEGF production and vascular regression prior to tumor cell death (172). Data using serial multiparametric MRI has also shown both a reduction in tumour volume of 65% and a reduction in tumour capillary permeability and may be related to a down regulation in VEGF (173). Similar MRI changes have been mirrored by many others with antivascular changes and tissue hypoxia seen as early as 1 month from initiation of ADT (174-177).

Another postulated effect of ADT has been a reduction in micrometastases with work from Pantel et al showing a reduction in cytokeratin positive disseminated tumour cells in 16/21 (76%) patients undergoing ADT (178).

Thus, the combined use of ADT in addition to focal therapy for localised prostate may lead to the disruption of the androgen signalling pathways which in turn would lead to:

1. Shrinkage of the tumour
2. Shrinkage of associated tumour microvasculature.
3. Reduction in micrometastases.

I hypothesize that utilisation of these effects will lead to improved local control by:

1. Improving our surgical margins
2. Reducing the heat sink effect
In addition, as ADT may have an effect on pre-cursor lesions such as High Grade Prostatic Intraepithelial Neoplasia (HGGPIN), use of ADT may lead to a reduction in secondary tumours related to the “field effect” (170).

Common adverse events from long term ADT use include cardiovascular disease (CVD), Insulin resistance, osteoporosis, breast tenderness, gynaecomastia and ED (168, 179-181). However, much of this data is from long term use and from LHRH antagonist treatments which reduce serum testosterone to castration levels. There is very limited data on short term use. Within a trial setting a short 3 month neo-adjuvant course could be utilised with assessments of adverse events and safety during the first phase. An anti-androgen such as Bicalutamide could be used as a monotherapy rather than a LHRH agonist and has been shown not to reduce serum testosterone and has also been shown to lead to a lower rate of ED when compared to castration (182) (183). In addition, Bicalutamide mono-therapy has not been shown to increased CVD events or reduce bone mineral density and although side-effects such as gynaecomastia and breast tenderness are common these resolve on cessation of treatment (184-186).

5-alpha reductase inhibitors (e.g., finasteride or dutasteride)

There are two commonly used types of 5-alpha reductase inhibitors (5ARIs); Finasteride which inhibits type II 5AR in the prostate preventing the conversion of testosterone to the more potent dihydrotestosterone (DHT) and Dutasteride which inhibits both type I and II 5AR enzymes. DHT is a ligand for the androgen receptor (AR) which promotes proliferation of prostate cancer cells. 5ARI’s can be considered a weaker hormonal therapy when compared to the anti-androgens or LHRH agonists described above. Results from the 4 studies presented below (PCPT, REDUCE, REDEEM and MAPPED) show what 5ARI’s may lead to reduction in tumour volume. In addition, 5ARI’s can lead to a reduction in vascularity/micro vessel density primarily through decreased VEGF secretion (187, 188).
Similar to my hypothesis for the neo-adjuvant use of the anti-androgen Bicalutamide, neo-adjuvant use of SARI’s may improve local control by:

1. Improving our surgical margins
2. Reducing the heat sink effect

Two studies have assessed the use of 5a-reductase inhibitors (SARI) for the chemoprevention of prostate cancer.

The initial study called the “Prostate Cancer Prevention Trial” (PCPT) by Thompson et al published in 2003 randomised 18,882 men to either finasteride or placebo. All men at entry were 55 years or older with a normal digital rectal examination (DRE) and a prostate specific antigen (PSA) <3ng/ml and received subsequent yearly PSA and DRE checks. A 6 core biopsy was performed if the PSA rose to 4ng/ml. They released their initial results after 86% of patients had completed 7 years follow-up due to the Drug and Safety Monitoring Committee (DSMA) determining that the objectives had been achieved and further follow-up would not have changed the outcomes. Overall a 25% reduction in prostate cancer was seen (absolute risk reduction of 4%). This was primarily of low grade tumours ≤Gleason 6. However, an absolute 15% increase in Gleason 7 and above tumours was seen in the treatment arm (189).

Possible theories for this phenomenon are either due to a detection bias of biopsy in a smaller gland or that the lower levels of DHT led to de-differentiation and the formation of higher grade tumours. However, finasteride appears to have either treated small low grade tumours or significantly delayed their progression.

A greater proportion of patients underwent for-cause biopsies in the finasteride arm with the difference in rates of high grade tumours present in only this group and not in those who had routine end of study biopsies. In the finasteride arm PSA was multiplied by a factor of 2.3 at 4 years to match those of the placebo arm. Further analysis of the PCPT data set has shown that Finasteride improves the sensitivity and area under the curve (AUC) of PSA in detecting prostate cancer which may lead to
the detection of a greater number of cancers in the finasteride group. The researchers concluded that the increased detection rate of higher grade tumours may have been in part due to improved detection rates using PSA rather than a true induction of high grade tumours and that if finasteride does not reduce the PSA by 50% then there is a higher chance of that man having prostate cancer (190).

Survival data for the patients who developed prostate cancer was published by Thomson et al in 2013 (191). After 18 years follow-up no difference was seen between the placebo and the Finasteride arms with 78% and 78.2% respectively, for all cancers. Thus, even if 5ARIs induce high grade cancer there is no effect on mortality but there is reduced over diagnosis/overtreatment of low-grade cancers. Some have argued though that all these results have shown is that if prostate cancer is detected early enough then treatment is effectively curative. Also, the exact treatment given to the patients and cancer specific survival have never been published. Furthermore 18 years may not be a long enough follow-up to detect a difference in mortality particularly due to the lead-time of prostate cancer.

A second trial, “Reduction of Prostate Cancer Events” (REDUCE), published its data in 2010 (192). It was a randomised, multi-centre, placebo controlled trial. It randomised 6729 men to receive either Dutasteride or placebo with a 4 year follow-up. Patients received a negative baseline 10 core biopsy along with biopsies at 2 and 4 years or biopsies at any time point if clinically indicated. Similar to the PCPT results, REDUCE showed a 22% relative risk reduction in the incidence of prostate cancer with the use of Dutasteride. There was no difference in Gleason 7-10 cancers overall between the groups, however an increase in Gleason 8-10 tumours was seen during years 3-4. They reasoned that this was due to the fact that 141 patients with Gleason 5-7 disease had been initially excluded due to positive baseline biopsies and from surveillance studies, 7% would have been expected to be upgraded on repeat biopsy.
The greater urological community still appears to be split on whether 5ARI’s induce high grade prostate cancer or not. What is clear though is that 5ARI’s are in widespread use and so far there has not been epidemic of high grade prostate cancer.

A third study “Dutasteride in localised prostate cancer management” (REDEEM) randomised 302 men with known low risk prostate cancer (Gleason 5-6, PSA<=11ng/ml, T1a-2a) on active surveillance to either Dutasteride or placebo (193). Progression was defined as either a transition to treatment or pathological upgrading based on Epstein’s criteria. Follow-up consisted of 3 monthly PSA (unblended) and a trans-rectal biopsy at 18 months and 36 months. After 3 years 38% of men in the dutasteride arm had progression of their cancer compared to 48% in the placebo arm. However, although more negative biopsies were seen in the Dutasteride arm (36%) compared to the placebo arm (23%) along with lower biopsy cancer core lengths in those with positive biopsies on Dutasteride, the results from this study have been questioned by some as pathological progression. Overall the two arms showed no significant difference and a difference was seen only when patient choice for transition to treatment was included. This could be accounted for by the relatively small sample size and a hypothesis for the higher percentage of men with negative biopsies in the Dutasteride arm could be due to Dutasteride inhibiting tumour growth leading to shrinkage of tumours. More importantly in contrast to PCPT and REDUCE an increase in high grade tumours was not seen in REDEEEM.

The recently published RCT (MAPPED) demonstrated that this class of drugs has the desired biologic effect. In this randomized, double-blind, placebo-controlled trial, men with early localised prostate cancer on transrectal biopsy who had a Magnetic Resonance Imaging (MRI) visible lesion of >/=0.2ml on T2-weighted sequences were randomized to daily dutasteride 0.5mg or placebo for 6 months. Lesion volume was assessed at baseline, 3 and 6 months, with an image-guided biopsy to the lesion at study exit. The primary endpoint was lesion volume change over 6 months. Forty-two men were recruited between June 2010 and January 2012. In the dutasteride group, the average volumes at baseline and 6 months were 0.55ml and 0.38ml.
respectively, and the average percentage reduction was 36%. In the placebo group, the average volumes at baseline and 6 months were 0.65ml and 0.76ml respectively, and the average percentage reduction was -12%. The difference in percentage reductions between groups was 48% (95%CI 27.4-68.3%. p<0.0001). The most common adverse event was deterioration in erectile function (25% in men randomized to dutasteride, 16% in men randomized to placebo).

Other adverse events from 5ARI’s are uncommon with gynaecomastia and/or breast tenderness occurring in <=2% (194).

*Immune-modulation*

Ablative heat-based destruction of tumour and stromal tissue damages cancer cell membranes but leaves intact tumour-specific antigens / proteins and intracellular cytokines that are subsequently released and stimulate an immune response against sub-lethally damaged or even untreated tissues by the release of pro-inflammatory cytokines, including IL-1β, IL-6 and nuclear factor-κB (NF-κB)-dependent cytokines such as TNFα. These mediators induce the synthesis of vascular adhesion receptors and chemokines that, in turn, initiate recruitment of circulating leucocytes. Early recruits from the innate immune system to an ablated area include granulocytes, monocytes and macrophages, NK cells. These not only have direct effects, but elaborate additional soluble mediators that further modify the local environment. Additionally, these cytokines may lead to increased proliferation of lymphocytes or maturation of antigen presenting cells within the regional draining lymph nodes. There appears to be an apparent lack of infiltration of the ablated tumour by immature dendritic cells, prompting many investigators to combine ablation with methods of attracting dendritic cells (DC).

The nature of the cytokines released, however, would depend upon the presence and composition of lymphocytes within the tumour microenvironment, which may not only vary greatly among tumour types, but also from patient to patient with similar tumours. As a result of the mechanisms discussed, ablation might result in
systemic benefit of local primary cancer ablation. However, the immune response that is stimulated by ablation alone might be too modest. In order to capitalize on the immune potentiating effects of ablation in patients, this response may have to be intensified by using adjuvant immunomodulatory agents to stimulate and boost the response to a clinically effective level. Tanaka 1982, whilst reporting his experiments with the cryoimmune response in animals, first suggested the necessity of augmenting this response for achieving a reliable clinical response. Multiple animal studies have demonstrated an augmented response using a combination of cryoablation with immunomodulators.

In light of the ‘3Es’ hypothesis of cancer (Elimination, Equilibrium and Escape) this treatment could have the effect, if not inducing “Elimination”, of prolonging or helping to restore the “Equilibrium” mode, which should be a clinically acceptable situation (195). It is hypothesised that the combination of boosting the body’s immune responses, in the presence of an increased exposure to tumour antigen, will provide sufficient induction of the immune system to counter further tumour growth.

Thus, ablation either alone or in combination with intensification of the ablative immune response might give us an immunotherapeutic strategy to augment the anti-cancer localized inflammatory response with improved local efficacy.

Summary

The presented body of work highlights the promising outcomes seen with focal therapy and I have highlighted a future research strategy whereby as a medical body we can continue to develop this treatment paradigm further for the benefit of patients. Based on this data I was able to co-lead on a successful grant application from Prostate Cancer UK (PCUK) to run a pilot study called CHRONOS (Comparative Health Research Outcomes of NOvel Surgery in Prostate Cancer) which is comparing the oncological and functional outcomes of focal therapy to radical treatment and also testing neoadjuvant systemic therapy in addition to focal therapy.
6 Radio-recurrent Prostate Cancer

In the UK, around one-third of men with newly diagnosed clinically significant localised prostate cancer undergo radical external beam radiotherapy (EBRT) (4). The incidence of primary treatment with brachytherapy implantation has also increased over the last 20 years (196). Contemporary data suggests a 5-year biochemical failure rate of 10-15% (27).

6.1 How to Define Failure after Radiotherapy

Currently, regular serum PSA measurements are used as the primary strategy in the detection of recurrent disease following treatment with radical radiotherapy. Biochemical failure is defined as the Phoenix criterion of PSA nadir + 2ng/ml, however this was not always the case (197). Originally the American Society for Therapeutic Radiology and Oncology (ASTRO) criterion was developed in 1996 after a consensus meeting to establish a definition of biochemical failure after external beam radiotherapy. Biochemical failure via the ASTRO definition was defined after three consecutive PSA rises from a nadir with the date of failure being back dated to the halfway point between the nadir date and the first rise or any rise that led to salvage therapy. This definition was needed in order to standardise the reporting of radiotherapy outcomes at the time but needed revision due to the fact that it had poor correlation with clinical outcomes and did not take into account the PSA rise seen on cessation of hormone therapy or the benign PSA bounce artefact. Also, back dating led to bias in reporting outcomes especially in patients with inadequate or short follow-up. In 2005 after an ASTRO consensus meeting in Phoenix, the updated Phoenix criterion was introduced. At this meeting various methods and definitions for biochemical failure were reviewed and PSA nadir + 2ng/ml was determined to be most appropriate definition that correlated best with clinical outcomes although PSA nadir +3ng/ml was also considered (2). This definition has been shown to correlate with clinical outcomes such as disease free, metastases free and overall survival with a sensitivity and specificity of 0.64-67 and 0.78-0.84, respectively with a PPV and
NPV of 0.36-0.72 and 0.73-0.95, respectively (198-200). Recent developments in PSMA PET have raised doubt on the adequacy of this definition as recurrences are possible and detectable in patients who have not yet met the definition of biochemical failure (201).

6.2 How to Locate and Diagnose Recurrence

I discussed earlier in my thesis, the role of multi-parametric (mp) MRI in detecting prostate cancer prior to any treatment. The utility of mpMRI following treatment, however, is less certain. In particular, the T2 hypointense changes seen after radiotherapy are nonspecific and may either represent treated non-viable tumour or recurrent disease (202). Furthermore, normal zonal anatomy becomes indistinct following treatment due to prostatic atrophy (203).

Diffusion weighted imaging is sensitive to the microscopic motion of water molecules and allows for non-invasive characterization of biological tissues based on their water diffusion properties. Specifically, the degree of restricted water motion is greater in tissues with a high cell radius and packing, as found in cancers. Apparent Diffusion Co-efficient (ADC) values may be calculated from diffusion weighted images. They may provide a quantitative measure of the degree of diffusion restriction and are often displayed as a parametric map. A decrease in ADC value is thought to reflect decreased free water movement due to an increase in total cell size or number. Conversely, following treatment an increase in water mobility could be expected to occur as a result of cell lysis. Changes in ADC between treated and pre-treated cancerous lesions 1-5 months after radiotherapy have shown potential for use in monitoring response to radiation (204, 205). Initial changes in ADC have been described as early as 1 week following radiotherapy, prior to any change in PSA (206). Image contrast in diffusion-weighted MRI is influenced by a number of microstructural parameters such as cell density, size and shape and can be accounted for by a mathematical model and may also have a role on detecting recurrence.
Kara et al retrospectively reviewed the MRI results of 20 patients undergoing EBRT who also underwent mpMRI and TRUS biopsies at 18 months post treatment. Dynamic contrast enhanced MRI (DCE) was more accurate in detecting prostate cancer recurrence than T2-weighted MRI with a sensitivity and specificity of 93% and 100%, and 86% and 100% respectively (207). Roy et al, Rouviere et al and Haider et al have shown similar findings with DCE-MRI showing improved sensitivity over T2 images alone (208-210).

The role of mpMRI has been evaluated against sextant biopsy in 33 men with rising PSA post radiotherapy. Compared with sextant biopsies, DCE-MRI had significantly better sensitivity (72% [21/29] vs. 38% [11/29]), positive predictive value (46% [21/46] vs. 24% [11/45]) and negative predictive value (95% [144/152] vs. 88% [135/153]) than T2W-MRI. Specificities were high for both DCE-MRI and T2W-MRI imaging (85% [144/169] vs. 80% [135/169]). There was a linear relationship between tumour diameters on DCE-MRI and the percentage of cancer tissue in the corresponding biopsy core (r = 0.9, p < 0.001) (210).

These studies were performed against a reference standard of transrectal ultrasound (TRUS) biopsy. There is a potential for under staging and under grading disease using TRUS. Our department has previously compared template mapping biopsies using a 5mm frame against mpMRI in 13 patients post radiotherapy. ROC analysis showed an area under the curve of 0.77 and 0.89 (211). These results were reviewed again in 2014 and identified 27 men who had undergone mapping biopsies and a mpMRI. The accuracy of mpMRI was 81% compared to 96% for template mapping biopsies (212).

Although these studies do show benefit for mpMRI, particularly the DCE sequences, which has been confirmed in a recent meta-analysis, they all have significant risk of bias with small sample sizes, retrospective designs and lack of blinding. Thus there is a need to formally validate the role of mpMRI in patients with suspicion of recurrence after radiotherapy (213).
There is however some controversy on the timing and histological assessment of post-radiotherapy biopsies. Positive prostate biopsies have been reported in as many as 24–33% of patients after radiotherapy but the accuracy and relevance of systematic post radiotherapy biopsies has generally been reported as being poor (111).

MRI scanning may allow a clearer understanding of disease progression and ultimately diagnosis by enabling targeting of suspicious lesions at biopsy allowing appropriate salvage treatment, but MRI and prostate biopsies only answer part of the diagnostic puzzle. Often patients will harbour metastatic disease and the traditional forms of imaging such as Bone Scan and CT lack the sensitivity to detect distant disease. Newer forms of imaging such as Choline and PSMA PET and Whole-body MRI may prove utility in this context.

6.3 Treatment

Traditional treatment options for these men have been limited and have consisted of either watchful waiting with or without delayed androgen deprivation therapy (ADT) or salvage radical prostatectomy (SRP) in those who are eligible and fit enough for treatment.

Prolonged ADT use can lead to a castrate resistance state after a median of 2 – 3 years. Side-effects include vasomotor complications, sexual dysfunction and gynaecomastia, osteoporosis, metabolic syndrome and depression. Additionally, there may be an association with neurocognitive deficits, thromboembolism, and cardiovascular disease (214). Oncological outcomes after SRP are generally worse than for those undergoing primary treatment with 5-year biochemical disease-free free survival (BDFS) estimated at 48% and cancer specific survival (CSS) of 92%. At 10-years, these fall to 37% and 83% respectively (215). In addition, wound healing after primary irradiation treatment is poor; complications after salvage surgery are common and include urinary incontinence (20-78.1%), anastomotic stricture (0-
41.8%), rectal injury (0-12.5%) and erectile dysfunction (29-100%) (216). Whole gland alternatives to SRP include salvage brachytherapy (SBT), cryotherapy (SCT) and high intensity focused ultrasound (SHIFU) (217, 218). A meta-regression analysis of predominately whole-gland series comparing SRP with SBT, SCT and SHIFU demonstrated no difference in oncological outcomes, but significantly increased rate of urinary incontinence with SRP, supporting the role of minimally invasive ablative therapies for patients with localised recurrence (219).

As I have discussed in Part I of my thesis, there has been a shift towards a more focal ablative approach whereby only the areas of recurrent cancer within the prostate are treated rather than the whole gland. This might provide oncological control whilst limiting functional adverse events and preserving quality of life. Although primary prostate cancer is often multifocal, it has been noted that the largest or highest grade lesion (the index lesion) most likely drives cancer progression in the majority of patients and, after EBRT, the recurrence occurs at this site in 89-100% of patients, suggesting that a radioresistant clone from the original index lesion may be responsible (220, 221). Salvage focal therapy targeting this recurrent lesion may allow satisfactory oncological control whilst avoiding the morbidity of whole gland treatment.

6.4 Metastatic Radiorecurrent Prostate Cancer

There is also a growing body of evidence that patients with metastatic disease may also benefit from local treatment to the prostate and salvage focal therapy in this context may have a role. Currently in the UK approximately 9000 patients with prostate cancer are treated with radiotherapy a year. Subsequently 25% of these will develop biochemical recurrence (rising prostate specific antigen [PSA] blood test); many of these (up to half) have metastases at the time of biochemical failure alongside local disease within the prostate. These men are offered androgen deprivation therapy (ADT) which are hormone tablets or injections. These fail after an average 2-3 years requiring further hormones or chemotherapy. Recent data
suggests that the drop to nadir PSA level after starting ADT is closely correlated with prognosis. The SWOG 9346 trial found that median survival for a patients with a nadir PSA after 7 months of <0.2 ng/ml was 75 months, PSA of 0.2 – 4 ng/ml was 44 months and for a PSA > 4 ng/ml was 13 months (222).

The FORECAST trial (FOcal RECurrent Assessment and Salvage Treatment) at its onset was recruiting patients who develop radio-recurrent prostate cancer. The men in FORECAST who were found to have no metastases would undergo local salvage treatment of the cancer with either heat (HIFU) or cold (cryotherapy). Both of these treatments have been used in early localised non-metastatic prostate cancer and also being evaluated within FORECAST. However, evidence now demonstrates that men with metastatic disease may benefit from treatment to the local tumour as well as systemic therapy. My second aim in men with radiorecurrent cancer was to develop and test a new way of treating men with radiorecurrent metastatic prostate cancer. I review the reasons why in more detail below.

**Scientific Justification**

Cytoreductive treatments where the primary tumour is removed have been shown to lead to regression of metastatic disease in not only animal models but also in human studies of renal cancer, glioblastoma, ovarian, breast and GI malignancies (223).

Specific to urological disease, with regards to metastatic renal carcinoma an EORTC trial showed that radical nephrectomy along with interferon treatment led to a 10 month improved median survival compared to interferon alone. Similar results were seen in a SWOG study and regression of metastases has been noted by others (224-227).

In patients with metastatic colonic cancer, resection of the primary tumour has led to improved response to chemotherapy and resulted in a 22% absolute 2 year survival benefit (228).
A meta-analysis looking into patients with metastatic ovarian cancer found an 11 month improved median survival, if greater than 75% of the tumour was removed compared to when less than 25% was removed (229).

Preclinical

Many theories exist in the role of the primary tumour and its relationship with metastases. The metastatic niche model describes how bone marrow derived haematopoietic cells localize to pre-metastatic sites. Bone marrow derived endothelial and mesenchymal cells have also been suggested as having involvement in the formation of macro-metastases. Mobilisation of these cells results largely from the secretion of VEGF and PIGF by the primary tumour (230).

The classical model of tumour cell shedding and dissemination has also been shown to occur early on and these disseminated cells can be detected in blood (CTC) and bone marrow (DTC) of patients without clinical metastases (231). Lilleby et al also found a poorer outcome from radical treatment in patients with pre-treatment DTC’s with localised prostate cancer (232).

Furthermore a “self-seeding” hypothesis describes the multi-directional interactions of tumour cells between the primary and metastatic sites (233).

Tumour cells may also secrete interleukins, endocrine factors and in the case of prostate cancer, testosterone and di-hydrotestosterone, which may promote metastatic growth and also compete with treatment (234-238).

Thus, removal of the primary tumour may lead to a disruption of these relationships and lead to regression of metastases and thus prolong CSS.
Clinical

External beam radiotherapy (EBRT) is an established treatment for localized prostate cancer. Although performed with curative intent a proportion of patients will develop either biochemical recurrence with a rising PSA signifying local recurrence or distant metastases.

Prostate cancer cells are under the influence of androgens, 90% of which are secreted by the testes and 10% by the adrenal glands. The hypothalamic-pituitary-gonadal axis controls their secretion. Luteinizing hormone secreting hormone (LHRH) from the hypothalamus stimulates the anterior pituitary to secrete luteinizing hormone (LH) which stimulates the Leydig cells of the testes to secrete testosterone.

Treatment of patients with radiorecurrent cancer is the same as for metastatic prostate cancer and has largely been with hormonal manipulation/androgen deprivation therapy by either blockade of the androgen receptor, by disrupting the hypothalamic-pituitary-gonadal axis (LHRH antagonists/agonists) or by preventing secretion with bilateral orchidectomy.

Surgical or chemical castration is the ultimate goal, and data from the SWOG 9346 trial found that median survival for a patients on ADT with a drop in PSA after 7 months of <0.2 ng/ml was 75 months, PSA of 0.2 – 4 ng/ml was 44 months and for a PSA > 4 ng/ml was 13 months (222).

Patients on ADT develop side effects such as loss of libido, hot flushes, gynaecomastia, breast pain, osteoporosis, increased risk of diabetes and cardiovascular disease which can limit their quality of life (QoL).

After 2-3 years patients eventually develop a castrate resistance state where PSA continues to rise despite castrate testosterone levels.
Classically at this stage second line treatment was with chemotherapy (docetaxel). However recently newer treatments such as Abiraterone, Enzalutamide and Cabazitaxel have become available which have been assessed in the pre and post-docetaxel setting.

One of my aims is to delay the time to patients needing chemotherapy/second line treatments.

In 2010 40,975 new cases of prostate cancer were diagnosed and in 2011 there were 10,793 prostate cancer related deaths in the UK. In 2009 a quarter of patients underwent EBRT. Thus, a large proportion of patients will potentially develop radio-recurrent metastatic disease.

Widmark et al/SPCG-7 trail showed that in the group treated with both EBRT and adjuvant androgen blockade at 10 years the biochemical recurrence rate was 25.9% and cancer specific mortality (CSM) was 11.9%. Both outcomes were substantially worse in patients not treated with androgen deprivation therapy (25).

A paper by Zelefsky et al looking at outcomes of 1062 patients treated with EBRT found a metastatic progression rate of 7% at a follow-up of 8 years. The highest probability seen was in the NCCN intermediate and high risk groups of 4.5% and 9.5% respectively. After developing metastases median time to cancer specific death was 3.9 years (17).

One hypothesis for this is the incomplete treatment of the primary tumour using EBRT. This is supported by the fact that post-EBRT prostate biopsies in 339 patients showed persistent tumour in 32%. The absolute 10 year distant metastases free survival (DMFS) rate was 31% lower in patients who had a positive post-EBRT biopsy. Similarly, an 11% absolute decrease in CSM was also seen in this group compared to those with negative post-EBRT biopsies (111).
Similar findings have been shown by Solberg et al when analyzing the SPCG-7 data and found that patients with positive post-EBRT biopsies had a poorer oncological outcome (239).

Although hypothesised, until recently no evidence existed that treatment of the primary tumour may convey a survival benefit in prostate cancer. A retrospective American SEER database review identified 8,185 patients with metastatic disease undergoing either radical prostatectomy (RP), brachytherapy (BT) on no-surgical or radiation treatment (NSR). A 5 year absolute increase in disease specific survival (DSS) of 27.1% was seen with RP and 12.6% with BT over NSR (240). Similar results were seen in a large retrospective Swedish study. The results of 34,515 men treated with either surgery or radiotherapy for their prostate cancer was assessed. Although firm conclusions could not be made, intent to perform radical treatment in patients with metastatic disease led to improved survival (241). Further review of the SEER database showed that the greatest survival benefit in patients whose 3-year CSM was <40%. Thus, adding weight to the argument of early diagnosis and treatment of local disease in metastatic patients (242).

Researchers at the Mayo clinic created a matched cohort of 79 patients each and also found a 40% absolute increase in DSS when lymph node positive patients were treated with RP, lymph node dissection (LND) and orchidectomy versus orchidectomy alone (243). These results have been mirrored by others and there appears to be a 10 year absolute survival advantage of 36%.

STAMPEDE, a multi-arm multi-stage multi-centre UK trial treating advanced or metastatic prostate cancer has recently published data from the treatment arm where local EBRT was used in addition to systemic therapy for men presenting with primary metastatic disease. A survival advantage was seen only in men with low volume metastatic disease (244).

Additionally, case series from the US and Germany have also started testing this hypothesis using radical prostatectomy to treat the local tumour and a number of
prospective trials are underway in the US (MD Anderson, Melbourne) and Sweden (Stockholm). The paper by Heidenreich et al compared 23 patients with metastatic disease who underwent radical prostatectomy against 38 patients who only had ADT. They showed a 12.1 month median improved progression free survival and 11.4% improved cancer specific survival at a median follow-up of 34.5 months (245, 246).

Although trials such as STAMPEDE are treating patients with metastases at initial presentation whilst others are giving salvage local ablation for localized disease, no trials are currently looking into ablative treatment in patients with metastases after previous EBRT.

Ablative therapies may also have additional benefit. Research has shown that cryotherapy itself may lead to an immunological response where the body creates antibodies to the cancer which can attack the metastatic sites.

Early studies showed antibody production against the targeted tissue after cryotherapy (247-249). Additionally, treatment of the prostate in patients with metastatic cancer has been shown to lead to regression of the metastases. As far back as 1972 Ablin et al showed regression of metastases in 6 patients and subsequent animal models confirmed this phenomenon in different tumours treated with cryotherapy (250-254). However this response has not been seen by all and in fact cryotherapy has on occasion been demonstrated to lead to an immunosuppressive effect (255, 256). Interestingly Urano et al showed that the immune response was greatest when only single lesions within the liver were treated rather than multiple (132). Also cryotherapy on a rat breast carcinoma cell line suggested that the larger the bulk of frozen tissue the lesser the immune response (133). These findings attach weight to the concept of focal prostate cryotherapy.

It is suggested that cryotherapy related tissue damage leads to initial activation of the innate immune system (granulocytes, macrophages and NK cells) with a
subsequent acquired response when APCs take up antigen. A humoral or cellular response will then ensue. The immunological response happens largely due to necrosis of tissue with release of pro-inflammatory cytokines and presentation of antigens by dendritic cells to T-cells. Two different populations of T-cells may have opposing effects with CD4 and CD8 cells largely responsible for immune sensitivity. However another population of antagonistic Treg cells may be activated which are responsible for immune suppression (257). Macrophages take up antigen but do not lead to the release of pro-inflammatory cytokines and may actually lead to immuno-suppressive effects (258, 259). The balance between necrosis and apoptosis within a cryoablated lesion may be a reason why not all studies have shown a positive response to cryotherapy, as apoptosis does not generally produce an immune-stimulatory reaction.

Recent focus has been on augmentation of the immuno-stimulatory response whilst inhibiting the immuno-suppressive response seen with cryotherapy. Mono-clonal antibodies against prostate cancer cells are being developed whilst others have used granulocyte-macrophage colony stimulating factor (GM-CSF) or methylated cytosine-guanosine oligodeoxynucleotides (CpG’s) to improve antigen presentation and dendritic cell activation (260-263). Inhibition of Treg cells by cyclophosphamide has also been shown to have potential in metastatic colon cancer mice models treated with local tumour cryotherapy (264).

**Summary**

In the following chapters of my thesis, I aim to evaluate this area further. I will initially present data from a prospective whole gland HIFU dataset to determine whether our reticence about whole-gland ablation is valid and this will be followed by a systematic literature review on the state of focal salvage treatments. I will then discuss the design and outcomes in patients from the NCRN FORECAST trial (FOcal RECurrent Assessment and Salvage Treatment) in which men with radiorecurrent prostate cancer were evaluated with mpMRI and targeted and mapping biopsies and then treated with focal salvage ablation. Finally, I will report on a pilot group of men
from the FORECAST study who underwent local ablation in the setting of metastatic disease as a prelude to test whether they might also benefit from local treatment to the prostate.
7 Aims, Objectives and Patients

The overarching research questions is:

Can we accurately diagnose, localise and then safely and effectively ablate radiorecurrent non-metastatic and metastatic prostate cancer?

The main aim aims are to:

1. Develop the evidence base for focal salvage therapies in localised radiorecurrent disease.
2. Gain insights into the treatment of men with metastatic radiorecurrent cancer.

The objectives are:

1. Assess outcomes from whole gland salvage HIFU from a prospective national registry.
2. Assess outcomes from focal salvage therapy reported in the literature through a systematic literature review.
3. Evaluate the accuracy of mpMRI and MRI-targeted biopsies compared to transperineal mapping biopsies in a paired cohort study embedded within FORECAST
4. Evaluate the safety, functional and early disease control outcomes of focal salvage therapy in men with localised radiorecurrence within the FORECAST study
5. Evaluate the feasibility, acceptability, safety and functional outcomes of focal salvage therapy in men with metastatic radiorecurrence within the FORECAST study

Ethical Approvals

National Health & Care Excellence (NICE) IPG guidance 118 and 424 permits focal
HIFU and focal cryotherapy provided special measures are in place for providing information to patients, consenting, multidisciplinary team (MDT) discussion of all cases and entry of all cases into a registry. The UK Focal Therapy User Group (current Chair, Hashim Ahmed) aims to ensure that high quality training, quality control, data collection and delivery of registry publications occur in the UK whilst also encouraging ongoing research.

The FORECAST trial (FOcal RECurrent Assessment and Salvage Treatment, NCT01883128) was granted ethical approval by the NRES Committee London - City & East. REC reference 13/LO/1401 and IRAS ID 128104.
Whole Gland Salvage High Intensity Focussed Ultrasound (HIFU)

Introduction

As mentioned, the purported advantages of a focal approach to treating radiorecurrent cancer is the improvement seen in functional outcomes and adverse events whilst still offering oncological control. In the lead up to assessing outcomes from focal salvage therapies I analysed a whole gland salvage HIFU dataset for both oncological and functional outcomes in order to determine the context for further evaluation of focal salvage therapy.

Methods

Between 2005 and 2012 50 consecutive men had data collected in our HIFU registry who had undergone whole-gland HIFU following histological confirmation of localized disease after prior EBRT. All underwent bone-scan and pelvic/prostate multi-parametric magnetic resonance imaging (MRI) and cross-sectional CT (with or without choline or FDG positron emission tomography) to rule-out metastases. No upper threshold was applied for risk category, Prostate Specific Antigen (PSA), or Gleason grade either at presentation or at time of failure. Limited data was available on pre-EBRT characteristics including the radiotherapy dose despite approaching referring centres and thus we could not include these in the analyses.

All men underwent a standardized HIFU protocol as previously described and follow-up occurred with 3-monthly clinic visits in the first year followed by 6-monthly thereafter(265). Up to two salvage HIFU re-treatments were permitted as part of the salvage strategy. PSA tests were performed at these visits and patients were asked to complete patient-reported outcome measures (PROM) questionnaires. Routine biopsies were offered, however no patient with a stable PSA opted for these and thus biopsies were performed only if there was a rising PSA. In addition, patients with a rising PSA were offered a multi-parametric MRI (mpMRI) prior to the biopsy.
Progression was defined as a composite outcome of either biochemical recurrence using the Phoenix definition (prostate serum antigen [PSA] > nadir+2 ng/mL) or start of ADT/second-line systemic treatments or development of metastases or cancer-specific mortality.

Statistical Analysis

Variables with a normal distribution are presented as mean (±standard deviation [SD]), skewed distributed variables as medians with interquartile ranges (IQR) and categorical variables as absolute numbers with percentages. Kaplan-Meier analysis was performed to assess the freedom from several outcomes: biochemical failure (PSA nadir+2 ng/mL), development of metastases, initiation of ADT or a combination of these three outcomes as a composite progression endpoint. Statistical differences between subgroups were assessed with the log-rank test. Determinants of the composite progression endpoint were further analysed in univariable analysis with Cox-proportional hazards regression. Hazard ratios with 95% confidence intervals (95% CI) were obtained. Factors taken forward into the multivariable analysis i.e. the nadir value after salvage HIFU, were corrected for other determinants (with p<0.25 from univariable analysis) to assess their independent value in predicting the composite endpoint. Statistical significance was set at p≤0.05. All analyses were performed using SPSS version 25 and the R language environment (version 3.1.2) for statistical computing (using the survival, rms and survMisc packages) (266).

Results

Baseline demographics: Median age (IQR), median pre-treatment PSA (IQR), and median Gleason score (range), were 68 years (IQR 64-72), 5.9ng/mL (IQR 2.2-11.3), and 7 (range 6-9), respectively. 33/50 (66%) had localised T1c – T2c disease whilst 17/50 (24%) had radiological T3a/b disease. Median follow-up was 64 months (IQR 49-84). [Table 1]. Twenty (40%) underwent biopsies. These were all non-protocol and were performed for either a rising PSA or high post-treatment nadir. 12/20 (60%) were
positive for significant cancer (Gleason score ≥7), 2/20 (20%) were positive with insignificant cancer (Gleason score = 6) and 6/20 (30%) were negative. Re-treatment occurred in 7/50 (14%) once and 2/50 (4%) had two re-treatments.

Table 1: Descriptive statistics

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Mean/median/n</th>
<th>SD/IQR/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age pre-HIFU, median, (SD)</td>
<td>68</td>
<td>±6</td>
</tr>
<tr>
<td>ADT use, N (%)</td>
<td>31</td>
<td>62%</td>
</tr>
<tr>
<td>PSA pre-HIFU, median, ng/ml, (IQR)</td>
<td>6.3</td>
<td>2.3-10.8</td>
</tr>
<tr>
<td>Nadir post HIFU, median, ng/ml, (IQR)</td>
<td>0.12</td>
<td>0.05-0.83</td>
</tr>
<tr>
<td>No nadir after salvage HIFU, N, (%)</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Progression (Composite), N, (%)</td>
<td>38</td>
<td>76%</td>
</tr>
<tr>
<td>BF, N, (%)</td>
<td>35</td>
<td>70%</td>
</tr>
<tr>
<td>Metastases, N, (%)</td>
<td>12</td>
<td>24%</td>
</tr>
<tr>
<td>Initiation ADT, N, (%)</td>
<td>26</td>
<td>52%</td>
</tr>
<tr>
<td>Death, N, (%)</td>
<td>9</td>
<td>18%</td>
</tr>
</tbody>
</table>

Abbreviations: ADT=Androgen deprivation therapy; SD=standard deviation; IQR=interquartile range; BF=Biochemical failure;

Primary outcomes: Overall 35/50 (70%) experienced biochemical failure, 26/50 (52%) were started on ADT, 12/50 (24%) developed metastases and 9/50 (18%) died (cause of death was not available). Overall, composite progression occurred in 38/50 (76%).

28/50 (56%) patients achieved a PSA nadir of <0.5ng/ml, 15/50 (30%) had a nadir ≥0.5ng/ml and 7/50 (14%) did not achieve a nadir (PSA non-responders). Actuarial 1, 3 and 5 PFS was 72%, 40% and 31%, respectively [Figure 1]. Analysing the results with PSA non-responders removed gave a 1, 3 and 5 year actuarial PFS of 86%, 47% and 37%, respectively. Actuarial 1, 3, and 5 year OS was 100%, 94% and 87%, respectively [Figure 2].
Figure 1. Progression Free Survival and 95% confidence intervals for whole cohort of 50 patients

Figure 2. Overall Survival and 95% confidence intervals for whole cohort of 50 patients
Predictive factors: Univariable and multivariable Cox-regression analysis revealed that the only significant variable for either PFS or OS was post-operative PSA nadir [Table 2]. When comparing patients with PSA nadir <0.5ng/ml, nadir ≥0.5 and non-responders a statistically significant difference in PFS was seen (p<0.0001). 3-year PFS in each group was 57%, 20% and 0%, respectively [Figure 3]. 5-year OS was 96%, 100% and 38%, respectively [Figure 4].

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Univariable (HR, 95%CI [p])</th>
<th>Multivariable (HR, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.94 (0.88-0.99 [p=0.03])</td>
<td>0.96 (0.90-1.01 [p=0.13])</td>
</tr>
<tr>
<td>ADT</td>
<td>2.15 (1.06-4.37 [p=0.04])</td>
<td>1.69 (0.80-3.61 [p=0.17])</td>
</tr>
<tr>
<td>PSA</td>
<td>1.00 (0.97-1.04 [p=0.95])</td>
<td>X</td>
</tr>
<tr>
<td>PSA-nadir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.5 versus &lt;0.5</td>
<td>2.63 (1.22-5.69 [p=0.01])</td>
<td>2.61 (1.19-5.73 [p=0.02])</td>
</tr>
<tr>
<td>no nadir versus &lt;0.5</td>
<td>35.11 (10.64-115.81 [p&lt;0.0001])</td>
<td>28 (8.29-94.53 [p&lt;0.0001])</td>
</tr>
<tr>
<td>NCCN risk group</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(high versus intermediate)</td>
<td>1.22 (0.62-2.40 [p=0.57])</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviation: ADT=androgen deprivation therapy; NCCN=National Comprehensive Cancer Network
Figure 3. Progression Free Survival by nadir status

Figure 4. Overall Survival by nadir status
Secondary outcomes

**Functional Outcomes:** 29 patients completed PROM questionnaires with urinary incontinence (any pad-use) being 11/29 (38%). When assessing IIEF-15 although 29 patients returned at least one questionnaire only 13 patients returned both one pre-operative and one post-operative questionnaire. Reviewing only the results for these patients shows that the majority had pre-existing severe erectile dysfunction with a pre-treatment median IIEF-15 score of 9 (mean = 15.3). Over a 12-month follow-up period there was a non-significant median 3 point (mean 7 point) drop in IIEF-15 score.

Symptoms of bladder outlet obstruction were common and intervention in the form of a bladder neck incision, trans-urethral resection or urethral dilatation was needed in 27/50 patients (54%). Early in the learning curve, between 2005-2007, 2/41 developed a recto-urethral fistula after one salvage HIFU; a further 1/9 developed a fistula after a redo-HIFU. Overall 3/50 (6%) developed a fistula. Two were managed with a diversion or closure along with a salvage radical prostatectomy, whilst one was managed conservatively. In addition, 3/50 (6%) developed osteonecrosis of the pubic symphysis needing prolonged antibiotic treatment.

Discussion

**Summary:** The results show a 5-year PFS of 31%, although OS was high with 87% of men still alive after 5 years. This dropped to 64% at 8 years but is comparable to the survival outcomes of patients undergoing SRP. The results also highlight the discrepancy between disease progression, largely defined by biochemical failure, and survival. It must be noted that there were very few selection criteria for patients undergoing salvage HIFU. In patients who obtain a nadir < 0.5ng/ml 3 year PFS was 57% compared to 20% in those with a nadir > 0.5 ng/ml or 0% in non-responders. Side-effects within this series were also high as with other salvage therapies in this high-risk group.
Limitations: Before discussing the clinical implications, I would like to comment on some of the limitations. First, the sample size was relatively small and this reduces the power of our statistical and multivariable analyses. I was also missing a large amount of data from the initial diagnosis such as radiotherapy dose and thus was unable to use these parameters in the analysis. Second, there was incomplete PROMs data in 42% of patients and thus it is quite possible that the true incontinence and ED rates are higher or lower. However, they appear comparable to results from larger studies such as by Murat, Crouzet and Jones (267-269). Third, there is no PSA criteria that has been validated in this salvage setting to define biochemical failure. I used the Phoenix criteria as the majority of patients had failed EBRT based on this criterion and it is also the most commonly used definition in studies assessing minimally invasive salvage therapies. In addition, I used a more expansive composite outcome to define failure which included clinical progression i.e. metastases/death but also clinician determined need for initiation of second line treatments, regardless of PSA failure, such as ADT. Thus, the PFS outcomes may seem higher than studies that have only reported bDFS. Finally, cause of death was not available, although it is likely that many of these were prostate cancer related as 5/9 had developed metastases whilst 3/9 patients had biochemical failure only and 1/9 had no evidence of progression.

Clinical implications:

My results are in keeping with previously published larger whole-gland salvage HIFU series by Jones et al, Murat et al and Crouzet et al consisting of 100, 167 and 290 patients, respectively (267-269). Jones et al treated 100 men with 78 undergoing a 12-month biopsy, which was negative in 63 (81%). At 1-year 50 men achieved both a negative biopsy and PSA nadir of 0.5 ng/ml or less. Murat et al initially reported a 3-yr PFS of 53%, 42% and 25% for (D’Amico) low, intermediate, and high-risk patients, respectively with a 5-year OS of 84%. Subsequently, Crouzet reported 5-year PFS rates of 45%, 31%, 21% for D’Amico low, intermediate and high-risk prostate cancer, respectively, and a 7-year cancer-specific survival of 79.6%.
However, unlike these studies I did not find, after univariable and multivariable analysis, that any pre-treatment variables were predictors of either progression or survival. In my series only post-operative PSA nadir was seen to be a strong predictor and patients with a nadir >0.5ng/ml (or PSA non-responders) had a poorer prognosis when compared to patients with PSA nadir <0.5ng/ml. These findings could be due to my smaller sample size or may represent the difficulty in accurate risk stratification after radiotherapy and the inability of current imaging modalities to detect micrometastases that have a high prevalence in this group of men.

Summary

Unfortunately, similar to SRP, the poor side-effect profile for whole-gland salvage HIFU has limited its use and recent work has focused on focal therapy of the recurrence. The aim of a tissue-preserving strategy is to achieve similar oncological outcomes with a significantly improved side-effect profile.
Systematic Review – Focal Salvage Therapy in patients with localised disease

Introduction

In order to assess the literature on focal salvage therapy I conducted a systematic review of the literature.

Methods

This study was prospectively registered on the PROSPERO International Prospective Register of Systematic Reviews. Reporting of this review follows recommendations defined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (270).

Eligibility Criteria

English language empirical studies (randomised and non-randomised comparative and non-comparative studies) describing salvage focal (partial gland) treatment of localised radiorecurrent prostate cancer using brachytherapy (sBT), cryotherapy (sCT) and HIFU (sHIFU) were included. Studies describing whole-gland ablation were excluded. Review articles, unpublished studies, case reports, letters, bulletins, comments and conference abstracts were excluded.

Search Strategy

Two researchers performed a systematic review of the Medline and Embase databases for empirical studies (randomised and non-randomised comparative and non-comparative studies) describing salvage focal treatment of localised radiorecurrent prostate cancer up to 23rd April 2019. A hand-search of reference lists of relevant review articles was also undertaken. Search terms included combinations of ‘salvage’, ‘recurrent’ or ‘radiorecurrent’ with each of ‘focal brachytherapy’, ‘focal
cryotherapy’, ‘focal cryoablation’, ‘focal high intensity focused ultrasound’ or ‘focal HIFU’ (for example, ‘salvage AND focal cryoablation’).

Study Selection

Two researchers (CK and TS) reviewed potentially relevant articles for inclusion. The full text of remaining articles was obtained and further screened for inclusion. Small series (n < 10), duplicates, studies with follow up articles and articles not meeting eligibility criteria were excluded. Disparities were discussed to obtain consensus; in cases when agreement could not be reached, a third researcher arbitrated.

Data Items

The primary outcome was biochemical disease free survival, BDFS (as per the ‘Phoenix’ definition- PSA >/= 2ng/ml above the nadir). We also extracted data on rates of metastases, conversion to second line therapies and adverse events (as per the Common Terminology Criteria for Adverse Events.

Quality Assessment

Each study was assessed using the Methodological Index for Non-Randomized Studies instrument, a validated tool designed to assess the quality of nonrandomized comparative and non-comparative surgical studies (271).

Statistical Analysis

As no randomised controlled trials were identified in systematic searching of the literature, a narrative synthesis and not a meta-analysis was performed. All statistical data, including patient demographics and oncological outcomes (e.g. BDFS), are presented as reported directly by the authors of included studies.
Results

The search identified 134 relevant publications. After duplicates, non-English language and ineligible articles were removed, 29 were included for abstract review. Eighteen studies met eligibility criteria; after full text review, 3 were excluded (in all, n < 10). 15 studies (14 case series and 1 comparative study) with a combined total of 628 patients were finally included (figure 1).

---

**Figure 1: Study Selection**

- Literature Search: 118
  - Hand Search: 16
  - n = 134
- Duplicates / non-English language removed
  - (excluded: 38)
- n = 96
- Ineligible removed
  - (excluded: 67)
- n = 29
- Abstract review
  - (excluded: 11)
- n = 18
- Full text screening
  - (excluded: 3)
- Included for final analysis:
  - n = 15
With the exception of 1 study comparing focal and whole-gland sCT (38), all eligible studies were single-arm case series. Only 5 studies were prospective. However, outcome data were complete and measured appropriately. The average Methodological Index for Non-Randomized Studies instrument score was 11.8/16 for non-comparative studies, with the single comparative study scoring 15/24 (Table 1). Primary and secondary outcomes were well reported by all studies. However, there was often heterogeneity in patient selection and treatment protocols (for example, regarding concurrent ADT use).

**Salvage Focal Brachytherapy**

5 case series met inclusion criteria (Table 2) (272-276). Although all studies reported outcomes of focal sBT for radiorecurrent disease, there was heterogeneity in radiation dose. Cohorts were small (n: 12-20). Most studies reported short to mid-term follow up, although one study approached 5-year outcomes (10-56 months). Two- (87-100%) and three-year (61-71.4%) BDFS rates were reasonable. No study reported 5-year rates. Metastasis was uncommon (0-15%); Kunogi et al. reported no metastases after median follow-up of 56 months in 12 patients (274). Rate of conversion to second-line salvage treatment was similarly low (12.3%-30%). The procedure was well tolerated; grade 3 toxicity adverse events were rare, and included urethral stricture (273, 275) and self-resolving haematuria (276).
Table 1: Quality Assessment of Included Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Median Age (Years)</th>
<th>Median Pre-Salvage PSA (ng/mL)</th>
<th>Median Follow Up (Months)</th>
<th>Biochemical Disease-Free Survival</th>
<th>Metastasis</th>
<th>Conversion to second-line salvage therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al.</td>
<td>2012</td>
<td>68</td>
<td>3.5</td>
<td>23.3</td>
<td>100% (2 years); 71.4% (3 years)</td>
<td>0%</td>
<td>13.3% (focal sBT)</td>
</tr>
<tr>
<td>Peters et al.</td>
<td>2014</td>
<td>69</td>
<td>4.7</td>
<td>36</td>
<td>71% (3 years)</td>
<td>15%</td>
<td>30% (ADT-6)</td>
</tr>
<tr>
<td>Kunogi et al.</td>
<td>2016</td>
<td>68</td>
<td>4.09</td>
<td>56</td>
<td>78% (4 years)</td>
<td>0%</td>
<td>16.7% (ADT-1, WW-1)</td>
</tr>
<tr>
<td>Maenhout et al.</td>
<td>2017</td>
<td>69</td>
<td>4.8</td>
<td>10</td>
<td>92% (2 years)</td>
<td>5.9%</td>
<td>na</td>
</tr>
<tr>
<td>Murgic et al.</td>
<td>2018</td>
<td>75</td>
<td>4.1</td>
<td>36</td>
<td>87% (2 years); 61% (3 years)</td>
<td>0%</td>
<td>na</td>
</tr>
</tbody>
</table>

Table 2: Salvage Focal Cryotherapy Outcomes

7 single-arm and 1 comparative trial examining outcomes post focal SCT were included (Table 3) (118, 119, 277-281). There was homogeneity in treatment methodology, with the majority of studies using a hemiablative strategy. Although
most cohorts were small, 3 studies reported outcomes for >50 patients (n: 10-91) (277, 279, 281). Follow-up was short to mid-term (12-37 months).

There was significant variability in reported BDFS rates. At 1-year, BDFS ranged from 48.1% to 95.3%. 3-year (48.1%-72.4%) and 5-year (46.5%-54.4%) rates were more consistent. In their comparative study, De Castro Abreu et al. report 5-year BDFS to be 54.4% in the focal sCT (n=25) and 86.5% in the whole-gland sCT treatment group (n=25) (although no statistical comparison was made due to underlying selection bias and differences in treatment protocols) (38). Rates of metastasis (10-21.3%) and conversion to second-line therapies (40%) were poorly reported, with only Bomers et al. describing patients undergoing further treatment with focal sCT (3 patients) or ADT (1 patient) (n=10) (278). Complications were uncommon; grade 3 adverse events included rectourethral fistula (3.3%-5.5%) (277, 279) and urethral stricture (5.3%-10%) (119, 278). Minor complications included transient haematuria, temporary incontinence and erectile dysfunction (281).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Median Age (Years)</th>
<th>Median Pre-Salvage PSA (ng/mL)</th>
<th>Median Follow Up (Months)</th>
<th>Biochemical Disease-Free Survival</th>
<th>Metastasis</th>
<th>Conversion to second-line salvage therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenberg and Shinohara</td>
<td>2008</td>
<td>19</td>
<td>71 (avg)</td>
<td>3.3 (avg)</td>
<td>18</td>
<td>89% (1 year); 67% (2 years); 50% (3 years)</td>
<td>17.6%</td>
<td>na</td>
</tr>
<tr>
<td>De Castro Abreu et al.</td>
<td>2013</td>
<td>25</td>
<td>61</td>
<td>2.8</td>
<td>31</td>
<td>54.4% (5 years)</td>
<td>0%</td>
<td>na</td>
</tr>
<tr>
<td>†Wenske et al.</td>
<td>2013</td>
<td>55</td>
<td>66</td>
<td>4</td>
<td>37</td>
<td>47% (5 years); 42% (10 years)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Bomers et al.</td>
<td>2013</td>
<td>10</td>
<td>67</td>
<td>3.8</td>
<td>12</td>
<td>na</td>
<td>10%</td>
<td>40% ( focal sCT-3/ ADT-1)</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2015</td>
<td>91</td>
<td>71.1 (avg)</td>
<td>4.8</td>
<td>15</td>
<td>95.3% (1 year); 72.4% (3 years); 46.5% (5 years)</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Overduin et al.</td>
<td>2016</td>
<td>47</td>
<td>66</td>
<td>4.9</td>
<td>24</td>
<td>51% (1 year)</td>
<td>21.3%</td>
<td>na</td>
</tr>
<tr>
<td>Kongnyuy et al.</td>
<td>2017</td>
<td>65</td>
<td>71</td>
<td>4</td>
<td>26.6</td>
<td>48.1% (1 and 3 years)</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

Table 3: Salvage Focal Cryotherapy Outcomes
†Primary Treatment: RT in 80%, Cryotherapy in 20%

Salvage Focal High-Intensity Focussed Ultrasound

3 studies met eligibility criteria (Table 4) (282-284). Treatment strategies varied, and included quadrant-, hemi- and index lesion ablation (with residual cancer left
untreated). The largest cohort (n=150) also had the longest follow up (35 months) (284).

There was heterogeneity in reporting of rates of BDFS. Ahmed et al. split their cohort into patients who achieved a PSA nadir <0.5 ng/mL and those who did not; in the former group BDFS was 86% at 1 year, 75% at 2 years and 63% at 3 years, and in the latter, 55% at 1 year, 24% at 2 years and 0% at 3 years (282). Baco et al. reported BDFS to be 67% at the end of median follow up of 16.3 months (283). Kanthabalan et al. estimate 3-year BDFS to be 48% (284). Rates of metastasis were comparable (5%-12.5%). Conversion rate to second-line treatment was extractable from only one study and was 8% (284). Rates of grade 3 complications were 26% and 27.3% (282, 284). Reported complications included rectourethral fistula (2%-3.6%) (282, 284), bladder neck stenosis (8%) (284), and pubic bone osteitis (0.7% - 4.2%) (283, 284).

Functional outcomes were well described by two studies. Ahmed et al. report a pad-free, leak-free continence rate at 64% and pad-free rate was 87% at last follow up. International Index of Erectile Function (IIEF5) scores worsened from a pre-procedure median of 18 to 13 at 6 months. Concordantly, Kanthabalan et al. note that, of 34 patients who were drip-free continent at baseline, 23 (67.6%) remained drip-free at 2 years. Median IIEF5 score declined from 15 to 13.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Mean Age (Years)</th>
<th>Median Pre-Salvage PSA (ng/mL)</th>
<th>Median Follow Up (Months)</th>
<th>Biochemical Disease-Free Survival</th>
<th>Metastasis</th>
<th>Conversion to second-line salvage therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al.</td>
<td>2012</td>
<td>39</td>
<td>70.5</td>
<td>4.6</td>
<td>17</td>
<td>86% (1 year), 75% (2 years), 63% (3 years) †</td>
<td>5%</td>
<td>na</td>
</tr>
<tr>
<td>Baco et al.</td>
<td>2014</td>
<td>48</td>
<td>68.8</td>
<td>na</td>
<td>16.3</td>
<td>67% (end of follow up)</td>
<td>12.5%</td>
<td>na</td>
</tr>
<tr>
<td>Kanthabalan et al.</td>
<td>2017</td>
<td>50</td>
<td>69.8</td>
<td>5.5</td>
<td>35</td>
<td>48% (3 years)</td>
<td>6%</td>
<td>8% (sRP - 3, irreversible electroporation- 1, sCT- 1, chemotherapy- 4, other drug treatment- 2)</td>
</tr>
</tbody>
</table>

Table 4: Salvage Focal HIFU Outcomes
†Achieved PSA nadir <0.5 ng/mL ‡Did not achieve PSA nadir <0.5 ng/mL
Discussion

In summary, my systematic review shows that, in the treatment of radiorecurrent prostate cancer, focal sBT, sCT and sHIFU all provide acceptable oncological control and have low rates of complications. Salvage focal treatment may represent a viable and less invasive strategy for select patients with localised radiorecurrent disease. Unfortunately, most of the available evidence is level 3 only, and long-term follow up is lacking. Additionally, more robust evaluation of urinary and sexual functional outcomes with validated questionnaires is needed to help inform patient choice.

My systematic search did not return any randomised controlled studies comparing sRP with focal sBT, sCT and sHIFU. The limited available evidence compares sRP with whole-gland sCT and sHIFU treatment (no studies comparing sRP and sBT are available). A retrospective study of 440 men found significantly higher overall mortality rates with sRP (n=99) than whole-gland sCT (n=341) (21.57 vs. 6.14 deaths/100 person years) (285). Conversely, other smaller series have come to different conclusions. Pisters et al. found that sRP (n=42) resulted in a significantly superior 5-year BDFS (66% vs. 42%) and overall survival (95% vs 85%) than whole-gland sCT (n=56) (286), and Vora et al. report similar BCR rates for sRP (16.7%; n= 6) and whole-gland sCT (23.5%; n = 17) (although median follow up times differed; 7.2 vs. 14.1 months) (287). Of note, this latter study reported rates of severe urinary incontinence of 16.7% after sRP and 5.9% after whole-gland sCT. Devos et al. retrospectively compared outcomes of sRP (n= 25) with whole-gland sHIFU (n= 27). Median follow up was similar (43 vs. 45 months). There were no significant differences in estimated 5-year overall survival, cancer-specific survival or metastasis-free survival. However, patients who had undergone sHIFU had better continence at 12 months and experienced fewer Clavien-Dindo ≥3 complications (288). These whole-gland comparisons suggest that sCT and sHIFU may provide comparable oncological and functional outcomes than sRP. Formal comparative studies are needed prior to making firm conclusions regarding the oncological outcomes from focal salvage series however it appears that functional outcomes are superior when compared to the either sRP or whole-gland ablative modalities.
After salvage focal therapy, how do we define biochemical recurrence? Most of the included studies used the ‘Phoenix’ threshold. However, this definition was designed for use post RT in a primary setting; this strategy has not been validated for use in primary FT, let alone in a salvage setting. The use of PSA surveillance after focal therapy is controversial as the untreated tissue may continue to secrete PSA, resulting in a ‘false positive’ biochemical failure (not representative of oncological failure) (141). If the initial PSA reading post focal therapy is high, does this represent recurrence or undertreatment? Ahmed et al. analysed their cohort by ‘responders’ (those who achieved a PSA nadir < 0.5ng/ml/ml) and ‘non-responders’ (those who did not) (282). It has been suggested that, post focal therapy, PSA should reduce by 50% within three months of treatment and remain stable, with recurrence defined as any deviation from this protocol (289). Validation of post focal salvage therapy surveillance strategies is needed.

As ablative technologies develop, it seems inevitable that their use in a salvage focal setting will be explored further. The results suggest that salvage focal treatment provides acceptable oncological outcomes with low rates of adverse events; however, how do we decide between modalities? Unfortunately, to date, there have been no studies comparing focal sBT, sCT and sHIFU or comparisons to sRP or ADT. Choice is likely to depend on both patient and tumour characteristics (such as size and anatomical location).

This systematic review has a number of limitations. Despite a comprehensive search strategy, it is possible we missed some relevant articles. 14 of the 15 included studies were single-arm case series without comparator, and there was lack of standardisation in patient selection (e.g. concurrent ADT use), treatment protocols (e.g. both high and low dose brachytherapy were used) and outcome reporting. Long-term follow up was lacking. Study quality was moderate only. It is not possible to make strong recommendations based on available evidence. Although we did not formally extract urinary and sexual functional outcomes these were poorly reported by studies evaluation sBT and sCT; the patient’s post-treatment quality of life is
undoubtedly a key factor in decision-making. Finally, cost-effectiveness was not evaluated.
10 FORECAST (FOcal RECurrent Assessment and Salvage Treatment)

A prospective phase II trial called FORECAST (FOcal RECurrent Assessment and Salvage Treatment) was developed to recruit men with recurrent cancer after previous radiotherapy. The primary aims were to assess the role of MRI and the functional outcomes after salvage focal therapy and secondarily assess adverse events and oncological outcomes in men with localised disease at the start of trial recruitment. In early 2015, as evidence was emerging that demonstrated that men with metastatic disease may also benefit from treatment to the local tumour in addition to systemic therapy, an ethical amendment was passed which allowed treatment of men with metastatic disease. These patients would be detected in the early stages of FORECAST but not be eligible for local treatment and would receive the current standard of care. Initially a focus group was conducted before a substantial amendment was passed whereby men with metastatic disease were also offered local salvage focal therapy with either HIFU or cryotherapy in addition to any standard of care treatments. The primary outcome assessing functional outcomes was unchanged and will be presented together for both the localised and metastatic cohorts. The adverse events and oncological outcomes will however be presented separately. It is envisaged that the results from FORECAST will eventually lead to the development of a phase II/III randomised controlled trial (RCT) comparing a focal therapy strategy to standard care.

My Role: I came onboard FORECAST as a PhD Fellow after funding for the main study had been obtained. I subsequently was able to obtain further funding from the St Peters Trust. My role in FORECAST consisted of protocol development in particular the amendment related to the treatment of patients with metastatic disease. I was also the trial coordinator and worked closely with the trials unit in opening and subsequently managing new centres. I recruited all but a few of the patients from University College London Hospital (UCLH). Subsequently, I helped build the electronic Macro database and ensured data from all sites was up to date, entered into the Macro database and validated prior to database lock. I performed all the analyses presented in the following chapter myself.
10.1 FORECAST - Focus Group / Patient Involvement

To aid in the development of the trial a focus group was initially undertaken by myself to determine whether men detected in the early stages of FORECAST with metastases would be willing to undergo local treatment in addition to current standard of care therapy.

I wanted to find out whether there are any additional side-effects and also cancer control benefits by treating the cancer inside the prostate in men with metastatic disease which would eventually help develop a future phase III randomised controlled trial (RCT).

I proposed to approach those men who have metastases within FORECAST to determine whether they would participate in a feasibility study where local therapy is added to their standard care.

Other methods of treatment have been suggested in the literature such as surgery with radical prostatectomy, however this carries a significantly higher risk of side-effects and morbidity for the patient and focal salvage therapy in this context may provide similar benefits but with fewer side-effects.

The focus group consisted of 6 patients who had advanced/metastatic prostate cancer was conducted in conjunction with prostate cancer UK (PCUK) in order to determine initial patient acceptability and gauge important opinions on my proposed ethical amendment and study design. 4 patients had previously had radiotherapy as either their primary or secondary treatment. Comments from the group discussion were recorded along with anonymous questionnaires, which the patients returned, by post after the meeting.

Patients were asked specific questions and I have highlighted some of the responses below:
What I think about the number and burden of tests?

“The majority of men who are living with and after prostate cancer will have needed to undergo many forms of testing, some of which in themselves have unpleasant side-effects. My own experience is that one of my key concerns about dealing with cancer is the effect it has on my immediate family. I was fortunate to have had the support of my wife and two daughters to help me through the difficult times and I felt then and still do now, that I would not be deterred by any number or unpleasantness of tests if that meant that I would still be around to help look after them and enjoy being with my family.”

“It would depend on my general state of health at the time but currently I would have no problem in undergoing the above test.”

“Seem tolerable as explained in the presentation.”

“Fine as long as it’s not too painful.”

Would I be happy for further treatment directly to the prostate despite the cancer having spread to other parts of the body?

“I feel that I would be happy to have such treatment. I try to adopt an optimistic approach to life in general and in particular towards important medical decisions that would affect my family. If my medical advisers were able to demonstrate or convince me that a particular course of treatment could result in a longer/more useful life, then I would adopt that path irrespective of any potentially “easier” ways of dealing with the problem.”

“Yes, when you have cancer and there is hope of more treatment then you have to go for this.”
“Yes, if could be explained that this would, on balance, lead to a beneficial outcome.”

“Subject to agreement with spouse...I would be prepared to try it.”

**How do I feel about the potential side-effects of treatment?**

“I am keen for a better solution for survival and for my family without concerns for my own comfort. In other words, the only deterrent that would sway me away from taking this course would be the suggestion of unproven or dangerous treatments likely to result in death.”

“As with any treatment there are side-effects. Being incontinent would be acceptable but colostomy would not.”

“I would probably take the chance.”

“They seem to be no more than other treatments. So that’s acceptable.”

**How would you define treatment success?**

All patients agreed that time to needing secondary treatments as an acceptable outcome.

They also mentioned:

“As my primary definition, prolongation of quality life with my family.”

“Length of life.”

“Reduction in PSA to a constant level.”
“Cancer gone or at least reduced.”

**What other areas of measuring success are important to me?**

All patient agreed that other important measures included “quality of life, pain, shrinkage of cancer areas, avoiding chemotherapy, living longer”

Also mentioned was “removal of fear”, and “maintaining erections and continence”
Objectives

Research Questions:

1. Can we accurately locate and focally treat radiorecurrent prostate cancer?
2. Will men with radio-recurrent metastatic cancer accept focal therapy along with standard care.

Primary

1. To evaluate the accuracy of multi-parametric MRI (mp-MRI) targeted prostate biopsies in identifying areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies (TMP).
2. To determine the urinary incontinence rate (any pad use) of focal salvage treatment for radiorecurrent prostate cancer.

Secondary

1. To determine the complications and side-effect profile of focal salvage therapy to treat the tumour in radiorecurrent localised and metastatic prostate cancer
2. To provide preliminary data on short term disease control outcomes after focal salvage therapy (PSA kinetics, imaging evidence of localised recurrence and metastatic progression and rate of hormone therapy/second line treatments).
3. Feasibility to determine whether patients with radio-recurrent metastatic cancer will accept focal therapy along with standard care.
Overall Study Design

Recruitment occurred from tertiary referrals as well as the local cancer network. Men who had previously undergone any form of radiotherapy were eligible if they were able to have Magnetic Resonance Imaging (MRI), PET-CT, TPM-biopsy, focal salvage therapy and had been advised to undergo further evaluation due to a clinical or biochemical suspicion of recurrent cancer. These men were approached by one of the study team and sent the ethics committee approved patient information sheet. If they were willing to participate in the study, they were asked to attend the screening visit. A minimum of 24hrs was given between the patient being given the patient information sheet and approaching them again. Men were given as much time to think about participation in the study as they need.

Their diagnostic workup consisted of a mpMRI, PET-CT and NM Bone Scan and transperineal mapping and cognitively targeted biopsy of the prostate. Subsequent eligibility for focal salvage therapy was confirmed via a multi-disciplinary team meeting consisting of a urologist, oncologist, radiologist and pathologist. All potential treatment options were offered to the patient including systemic or whole gland therapy such as salvage radical prostatectomy. Patients then underwent a standardised focal therapy procedure (HIFU or Cryotherapy) as previously described.

Follow-up consisted of PSA at 4 week, 3 months, 6 months, 9 months and 12 months post-operatively. At each time point patients were asked to complete an IPSS, EPIC Bladder/Bowel and IIEF15 questionnaire either in person or via post. At 12-months all patients were offered a mpMRI to assess for residual disease. Biopsies and further treatments were offered based on the 12-month MRI findings and PSA kinetics. Trial follow-up for oncological outcomes continued until last patient recruited completed their last 12-month follow-up.
Subject Selection

Inclusion Criteria

1. Previous radiotherapy with or without neo-adjuvant/adjuvant hormone therapy
2. Biochemical failure as determined clinically by treating physician
3. Men considering local salvage treatment for radio-recurrent disease
4. Life expectancy of 5 years or more

Exclusion Criteria

1. Have taken any form of hormones (except 5-alpha reductase inhibitors) within the previous 6 months
2. Unable to have MRI scan as defined by standard care practice
3. Metallic implant likely to cause artefact and reduce scan quality
4. PSA doubling time of 3 months or less
5. PSA value 20ng/ml or greater
6. Any prior local intervention to the prostate (e.g., cryotherapy, HIFU, any other ablative modality, any other radiotherapy, any other prostate injection therapy for symptoms or cancer control)
7. Unable to have general or regional anaesthesia
8. Unable to give informed consent
Trial Flow Diagram

Men with Radio-recurrent Disease

Consent to FORECAST

Excluded at Screening
N = X

Whole-body MRI
Choline PET

Pelvic/Prostate mpMRI
+/- Bone scan/Flair films

Withdrawn
N = X (Not Suitable for focal salvage treatment)
Y (patient withdrew consent)

MR-Targeted Biopsies
Template-prostate Mapping Biopsies

Withdrawn
N = X (Not Suitable for focal salvage treatment)
Y (patient withdrew consent)

Focal Salvage Treatment
+/- Androgen Deprivation Therapy

1 week: Catheter removal
Adverse Events

4 week: Adverse Events, PSA, Questionnaire

3 months: Adverse Events, PSA, Questionnaire

6 months: Adverse Events, PSA, Questionnaire

9 months: Adverse Events, PSA, Questionnaire

12 months: Adverse Events, PSA, Questionnaire, mpMRI +/- Bone Scan +/- Choline PET
Outcomes and Analysis

Primary Outcome

1. Transperineal multi-parametric MRI targeted biopsies compared to Template Prostate Mapping biopsies in the detection of radiorecurrent prostate cancer.

2. Presence of urinary incontinence (any pad usage plus any leakage of urine) as determined by the UCLA-EPIC urinary continence questionnaire, at 12 months, in those men with no urinary incontinence at baseline

Secondary Outcomes

Serious adverse events and other adverse events
- Graded using the National Cancer Institute Common Terminology Criteria (NCI CTC) classification system

Continence
- Time to return of urinary continence (as determined by UCLA-EPIC Urinary domain questionnaire)
- Lower urinary tract symptoms as determined by IPSS and IPSS-QoL scores at 12 months

Sexual
- The presence of severe erectile dysfunction, defined by an inability to have erections sufficient for intercourse, at 12 months, as measured by the IIEF-15 questionnaire (question 2) with or without the use of phosphodiesterase-5 inhibitors, in those with absence of severe erectile dysfunction at baseline
- Time to return of erectile function
Cancer control and disease progression outcomes
- PSA kinetics after focal therapy. Biochemical failure will be defined as PSA + 2ng/ml above the nadir value after treatment.
- Rate of whole-gland therapy or systemic therapy.
- Rate of metastatic progression, overall and disease-specific death.
- Rate of initiating androgen deprivation therapy or second line treatments in patients with metastatic disease

Statistical Analysis Plan

Continuous variables will be presented as medians with interquartile ranges (IQR) or means with standard deviation (SD) and categorical variables as absolute numbers with percentages. Sensitivity, specificity, positive and negative predictive value of Transperineal multi-parametric MRI targeted biopsies compared to Template Prostate Mapping biopsies will be calculated in the detection of 1. Any cancer 2. Gleason \( \geq 3+4 \) AND/OR Maximum Cancer Core Length \( \geq 4 \text{mm} \) in any one biopsy. In addition, a positive MRI will be defined as either 1. Likert 3 and above or 2. Likert 4 and above. Area under the curve (AUC) analysis will be performed for the various definitions. Cumulative incidence analysis will be performed to determine time to recovery of continence. Kaplan-Meier analyses will be performed to assess metastases free survival (MFS) and failure free survival (FFS). Failure Free Survival will be defined as progression to any second line or systemic treatment or the development of metastases. A comparison will be made between baseline risk factors (PSA, T-stage and Gleason grade) to assess differences in MFS. Subgroups were compared using the log-rank test statistic. Subsequently, a cox-regression analysis was performed to assess whether any specific baseline risk factors were associated with MFS. All analyses were performed using Stata version 16.1 (Stata Corp) with the diagt and asdoc packages.
Sample size

To determine whether multi-parametric MRI targeted prostate biopsies can accurately identify areas of radiorecurrent prostate cancer compared to transperineal template prostate mapping biopsies. A minimum N= 81 will need to be biopsied if pA=95% with 90% prevalence of disease.

Currently, we are able to achieve incontinence rates of approximately 40% (any pad-use) following whole-gland salvage therapy. In order to obtain a precision-based estimate on the rate that focal salvage therapy will give rise to, it is estimated that 20% incontinence (any pad use) may occur. Thus 81 men will need to be biopsied, if three-quarters are likely to be suitable for focal salvage therapy, giving N=60 men treated. This gives a 95% confidence interval of +/-10.1%. If incontinence was slightly lower (15%), then the 95% CI would be +/-9.0%. If incontinence was higher (25%), then 95% CI would be +/-11.0%.

Therefore, it is likely that we will need to recruit N=162 of which we estimate 50% will undergo biopsy. In total, with a 10% withdrawal rate, we will need to recruit N=177 in order to meet the minimum numbers required at biopsy.

We will continue to perform template biopsies even once our minimum number of 81 patients has been achieved in order to recruit 60 men for focal salvage treatment.
10.3 FORECAST - Overall Results

Consort Diagram

Overall, there were 3/181 withdrawals for screening failures, 9/181 for metastatic disease prior to the ethical amendment in March 2015, 34/181 for negative biopsies, 29/181 deemed unsuitable for focal therapy, 11/181 patient or investigator decision or other recorded in 3/181. 93/181 underwent salvage therapy: HIFU (64/93) or cryotherapy 29/93. Of these 20/93 patients had multimodal therapy for nodal/metastatic disease.

Tabulation of overall outcome

<table>
<thead>
<tr>
<th></th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening/Inclusion failure</td>
<td>3</td>
<td>1.66</td>
</tr>
<tr>
<td>Prior to Amendment 2 - Positive for metastases</td>
<td>9</td>
<td>4.97</td>
</tr>
<tr>
<td>Negative Biopsies</td>
<td>33</td>
<td>18.23</td>
</tr>
<tr>
<td>Unsuitable for focal therapy</td>
<td>29</td>
<td>16.02</td>
</tr>
<tr>
<td>Withdrawn by Patient or Investigator</td>
<td>11</td>
<td>6.08</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1.66</td>
</tr>
<tr>
<td>Underwent focal therapy</td>
<td>93</td>
<td>51.38</td>
</tr>
<tr>
<td>Total</td>
<td>181</td>
<td>100.00</td>
</tr>
</tbody>
</table>
**Overall Patient Characteristics**

Between April 2014 and January 2018, 181 men were enrolled into the FORECAST trial. 157/181 had previously undergone EBRT, 15/181 brachytherapy, 6/181 brachytherapy with EBRT boost and missing in 3/181. Neo/adjuvant hormone use alongside their primary treatment occurred in 142/181. 29/181 had no hormone use alongside their primary treatment and in 10/181 the data was missing. The most common radiotherapy protocols were 74 Gy in 37 fractions (61/157) and 55 – 60 Gy in 19 – 20 fractions (16/157), however data was missing in 80/157.

Mean time from original diagnosis to enrolment was 7.98 years [SD 3.75]. Mean age at original diagnosis was 63.5 [SD 6.5] years and median PSA was 12ng/ml [IQR 7.8-24]. At original diagnosis 45/181 had Gleason ≤3+3, 88/181 had Gleason 7, 38/181 had Gleason >/= 8 and grade was missing in 18/181.

<table>
<thead>
<tr>
<th>Tabulation of Original Gleason Grade</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;/= Gleason 6</td>
<td>45</td>
<td>26.32</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>88</td>
<td>51.46</td>
</tr>
<tr>
<td>&gt;/= Gleason 8</td>
<td>38</td>
<td>22.22</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The T-stage at original diagnosis was T1 in 15/181, T2 in 51/181, T3 in 80/181, T4 in 2/181 and missing in 33/181.

<table>
<thead>
<tr>
<th>Tabulation of Original T-stage</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>15</td>
<td>10.14</td>
</tr>
<tr>
<td>T2</td>
<td>51</td>
<td>34.46</td>
</tr>
<tr>
<td>T3</td>
<td>80</td>
<td>54.05</td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>1.35</td>
</tr>
<tr>
<td>Total</td>
<td>148</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Mean Age and PSA at enrolment were 71.5 years [SD 6.4] and 4.2ng/ml [SD 4.5]. On re-staging imaging 128/181 had localised disease, 13/181 had N1 disease only, 38/181 had M1+ disease and was missing in 2/181.
Tabulation of stage at time of salvage assessment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0M0</td>
<td>128</td>
<td>71.51</td>
</tr>
<tr>
<td>N1M0</td>
<td>13</td>
<td>7.26</td>
</tr>
<tr>
<td>M1a</td>
<td>15</td>
<td>8.38</td>
</tr>
<tr>
<td>M1b</td>
<td>19</td>
<td>10.61</td>
</tr>
<tr>
<td>M1c</td>
<td>4</td>
<td>2.23</td>
</tr>
<tr>
<td>Total</td>
<td>179</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Multiparametric prostate MRI was performed in 175/181 men and MRI T-stage at enrolment was T1/2 in 144/175, T3 in 27/175 and T4 in 4/175.

Tabulation of MRI T-Stage at time of salvage assessment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2</td>
<td>144</td>
<td>82.29</td>
</tr>
<tr>
<td>T3a</td>
<td>10</td>
<td>5.71</td>
</tr>
<tr>
<td>T3b</td>
<td>17</td>
<td>9.71</td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
<td>2.29</td>
</tr>
<tr>
<td>Total</td>
<td>175</td>
<td>100.00</td>
</tr>
</tbody>
</table>

158/181 underwent prostate mapping +/- targeted biopsies. Mean total biopsy cores were 37.7 SD [16.4] and 126/158 had a positive biopsy for any cancer. Mean total positive cores were 8.9 [SD 7.6]. Mean maximum cancer core length (MCCL) was 7.7 [SD 4.0]. Maximum Gleason grade was 3+3 in 3/124, 3+4 in 18/124, 4+3 in 36/124, 4+4 in 27/124, 4+5 in 24/124 and was not reported in 16/124.

Tabulation of Gleason Score at time of salvage assessment

<table>
<thead>
<tr>
<th>Score</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3</td>
<td>3</td>
<td>2.42</td>
</tr>
<tr>
<td>3+4</td>
<td>18</td>
<td>14.52</td>
</tr>
<tr>
<td>4+3</td>
<td>36</td>
<td>29.03</td>
</tr>
<tr>
<td>4+4</td>
<td>27</td>
<td>21.77</td>
</tr>
<tr>
<td>4+5</td>
<td>24</td>
<td>19.35</td>
</tr>
<tr>
<td>Not reported</td>
<td>16</td>
<td>12.90</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Overall, 155 men underwent a prostate MRI and transperineal mapping (TPM) biopsies. 87 men underwent both a TPM and targeted biopsies.

The score on the MRI was Likert 1-2 in 13/155 (8%), Likert 3 in 40/155 (25%), Likert 4 in 24/155 (15%) and Likert 5 in 78/155 (50%).

<table>
<thead>
<tr>
<th>Tabulation of MRI Likert Scores</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1.29</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>7.10</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>25.81</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>15.48</td>
</tr>
<tr>
<td>5</td>
<td>78</td>
<td>50.32</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The mean total number of cores taken were 37.7 (SD 16.4), mean positive cores were 8.9 (SD 7.6) and mean MCCL was 7.7 (SD 4.1). Overall 124/158 (78.5%) had a positive biopsy. The Gleason grade was 3+3 in 3/124 (2%), 3+4 in 18/124 (15%), 4+3 in 36/124 (29%), 4+4 in 27/124 (22%), 4+5 in 24/124 (19%) and was not reported in 16/124 (13%).

<table>
<thead>
<tr>
<th>Biopsy Characteristics</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total biopsy cores</td>
<td>158</td>
<td>37.722</td>
<td>16.411</td>
<td>5</td>
<td>117</td>
</tr>
<tr>
<td>Total positive cores</td>
<td>124</td>
<td>8.935</td>
<td>7.623</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>MCCL</td>
<td>117</td>
<td>7.684</td>
<td>4.057</td>
<td>1</td>
<td>21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tabulation of Gleason Scores at TPM +/- Targeted Biopsy</th>
<th>Freq.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3</td>
<td>3</td>
<td>2.42</td>
</tr>
<tr>
<td>3+4</td>
<td>18</td>
<td>14.52</td>
</tr>
<tr>
<td>4+3</td>
<td>36</td>
<td>29.03</td>
</tr>
<tr>
<td>4+4</td>
<td>27</td>
<td>21.77</td>
</tr>
<tr>
<td>4+5</td>
<td>24</td>
<td>19.35</td>
</tr>
<tr>
<td>Not Reported</td>
<td>16</td>
<td>12.90</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Assessment of Prostate MRI at the Whole-gland Level

When assessing the accuracy of MRI in detecting radiorecurrent cancer I compared the two definitions of a positive MRI (Likert 3+ and Likert 4+) with the transperineal mapping biopsy histopathological data. Initially my plan was to also assess two definitions of a positive biopsy namely any cancer or any Gleason 3+4/MCCL 4mm or greater but as there were only 3 out of 124 cases with Gleason 3+3 cancer, I decided to perform all analyses using any cancer as the definition for a positive biopsy.

When Likert 3+ was used as the definition for a positive MRI, sensitivity was 94% (95%CI 88-98%), specificity was 18% (95%CI 7-35%) with an AUC value of 0.56 (95%CI 0.49-0.63) and a PPV of 80% (95%CI 73-87%) and NPV of 46% (95%CI 19-75%). Overall 7/121 (6%) cancers would have been missed using this definition.

<table>
<thead>
<tr>
<th>TPM outcome</th>
<th>MRI Outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>Positive</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>7</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
<td>13</td>
</tr>
</tbody>
</table>

When Likert 4+ was used as the definition for a positive MRI, sensitivity was 81% (95%CI 73-88%), specificity was 88% (95%CI 73-98%) with an AUC value of 0.85 (95%CI 0.78-0.91) and a PPV of 96% (95%CI 90-99%) and NPV of 57% (95%CI 42-70%). Using this definition 23/121 (19%) cancers would have been missed.

<table>
<thead>
<tr>
<th>TPM outcome</th>
<th>MRI Outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>Positive</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>23</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>53</td>
</tr>
</tbody>
</table>

Assessment of Targeted Biopsies

87 men underwent had both a systematic and targeted biopsy. Systematic biopsy was the reference test whilst targeted biopsy was classified as the index test. Overall
disease prevalence (any positive biopsy) was 83% (72/87, 95%CI 73-90%). The individual biopsy characteristics are outlined in the table below.

Systematic and Targeted Biopsy Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic Biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total biopsy cores</td>
<td>86</td>
<td>29.884</td>
<td>10.765</td>
<td>4</td>
<td>55</td>
</tr>
<tr>
<td>Total positive cores</td>
<td>71</td>
<td>7.028</td>
<td>6.164</td>
<td>1</td>
<td>39</td>
</tr>
<tr>
<td>MCCL</td>
<td>71</td>
<td>6.915</td>
<td>3.687</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

| Targeted Biopsy   |     |        |           |     |     |
| Total biopsy cores| 86  | 6.791  | 3.515     | 1   | 18  |
| Total positive cores| 69  | 3.986  | 2.72      | 1   | 14  |
| MCCL              | 69  | 7.493  | 4.002     | 1   | 21  |

Gleason grade was reported by the pathologist in 56 patients. There was only one patient with Gleason 3+3 cancer and overall, the Gleason score was upgraded on systematic biopsy in 11/56 men and on targeted biopsy in 2/56.

Tabulation of Gleason Scores between Systematic and Targeted Biopsy

<table>
<thead>
<tr>
<th>Gleason Score Systematic Biopsy</th>
<th>3+4</th>
<th>4+3</th>
<th>4+4</th>
<th>4+5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3+4</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>4+3</td>
<td>3</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>4+4</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>4+5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>21</td>
<td>11</td>
<td>11</td>
<td>56</td>
</tr>
</tbody>
</table>

Using any cancer as the definition of a positive biopsy the sensitivity of targeted biopsy when compared to systematic biopsy was 92% (95%CI 83-97%), specificity was 75% (95%CI 45-92%) with an AUC of 0.83 (95%CI 0.71-0.95). PPV was 94% (95%CI 86-98%) and NPV was 65% (95%CI 38-86%). Overall, 4/72 (6%) cancers were missed on systematic biopsies alone and 6/72 (8%) were missed on targeted biopsies alone.

Tabulation of Systematic versus Targeted Biopsy (any cancer)

<table>
<thead>
<tr>
<th>Systematic Biopsy</th>
<th>Targeted Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Abnormal</td>
<td>66</td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
</tbody>
</table>

10-18:
Using Gleason 3+4 or a MCCL of $\geq 4$mm as the definition of a positive biopsy the sensitivity of targeted biopsy when compared to systematic biopsy was 86% (95%CI 75-93%), specificity was 65% (95%CI 38-86%) with an AUC of 0.75 (95%CI 0.63-0.88). PPV was 91% (95%CI 81-97%) and NPV was 52% (95%CI 30-74%). Overall, 6/70 (9%) cancers were missed on systematic biopsies alone and 10/70 (14%) were missed on targeted biopsies alone.

<table>
<thead>
<tr>
<th>Systematic Biopsy</th>
<th>Positve</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal</td>
<td>60</td>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>Normal</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
<td>21</td>
<td>87</td>
</tr>
</tbody>
</table>

**Summary**

MRI in the detection of radiorecurrent disease has a sensitivity of 81% (95%CI 73-88%), specificity of 88% (95%CI 73-98%), a PPV of 96% (95%CI 90-99%) and NPV of 57% (95%CI 42-70%). The sensitivity of targeted biopsy was 92% (95%CI 83-97%), specificity was 75% (95%CI 45-92%), PPV was 94% (95%CI 86-98%) and NPV was 65% (95%CI 38-86%).
10.5 FORECAST - Primary Outcome Analysis

Salvage Focal Therapy Cohort Baseline Pre-Salvage Characteristics

Mean age at original diagnosis was 62.6 years [SD 6.560]. Median year of original diagnosis 2008 [IQR 5] with a range from 1988 to 2014. Mean original PSA was 19.4 [SD 22.2]. 81/93 had undergone previous EBRT alone, 8/73 brachytherapy alone, 2/93 had brachytherapy with EBRT boost and was missing in 1/93. Neoadjuvant/adjuvant hormones were used in 69/93. No hormones were used in 17/93 and were missing in 7/93. Gleason grade at original diagnosis was <\= Gleason 6 in 28/93, Gleason 7 in 40/93, Gleason 8 or above in 19/93 and missing in 6/93. T-stage was T1 in 9/93, T2 in 24/93, T3 in 37/93 and missing in 23/93. EBRT Gys ranged from 19 – 37 and fractions from 19-74.

<table>
<thead>
<tr>
<th>Tabulation of Original Gleason Grade</th>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= Gleason 6</td>
<td>28</td>
<td>32.18</td>
<td>32.18</td>
</tr>
<tr>
<td>Gleason 7</td>
<td>40</td>
<td>45.98</td>
<td>78.16</td>
</tr>
<tr>
<td>&gt;= Gleason 8</td>
<td>19</td>
<td>21.84</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>9</td>
<td>12.68</td>
<td>12.68</td>
</tr>
<tr>
<td>T2</td>
<td>23</td>
<td>32.39</td>
<td>45.07</td>
</tr>
<tr>
<td>T3</td>
<td>39</td>
<td>54.93</td>
<td>100.00</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>100.00</strong></td>
<td></td>
</tr>
</tbody>
</table>

Mean time from diagnosis to enrolment was 8.2 years [SD 3.8] with the mean age at enrolment being 70.8 [SD 6.7]. At enrolment the mean PSA was 5.2 [SD 3.4]. ASA grade was 1 in 33/93, 2 in 48/93, 3 in 4/93 and missing in 1/93. All underwent a multi-parametric MRI and transperineal biopsies. Maximum MRI Likert score was 2 in 3/93, 3 in 12/93, 4 in 19/93, 5 in 58/93 and missing in 1/93.
## Tabulation of MRI Likert Scores

<table>
<thead>
<tr>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3</td>
<td>3.26</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>13.04</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>20.65</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>63.04</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>92</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Local staging based on MRI showed that 81/93 had localised disease with 12/93 having locally advanced disease.

## Tabulation of MRI T-Stage

<table>
<thead>
<tr>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2</td>
<td>80</td>
<td>86.96</td>
</tr>
<tr>
<td>T3a</td>
<td>4</td>
<td>4.35</td>
</tr>
<tr>
<td>T3b</td>
<td>6</td>
<td>6.52</td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>2.17</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>92</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Subsequently, 73/93 underwent a 20 zone biopsy with targets and 15/93 underwent a 12 zone biopsy with targets. Mean total biopsy cores was 38.2 SD [15.5]. Mean total positive cores was 7.5 [SD 4.9, missing in 2]. Mean maximum cancer core length (MCCL) was 7.6 [SD 3.9, missing in 6]. Gleason score was 3+3 in 1/93, 3+4 in 15/93, 4+3 in 32/93, 4+4 in 20/93, 4+5 in 13/93 and was not reported in 11/93.

## Tabulation of Gleason Scores

<table>
<thead>
<tr>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+3</td>
<td>2</td>
<td>2.15</td>
</tr>
<tr>
<td>3+4</td>
<td>15</td>
<td>16.13</td>
</tr>
<tr>
<td>4+3</td>
<td>32</td>
<td>34.41</td>
</tr>
<tr>
<td>4+4</td>
<td>20</td>
<td>21.51</td>
</tr>
<tr>
<td>4+5</td>
<td>13</td>
<td>13.98</td>
</tr>
<tr>
<td>Not reported</td>
<td>11</td>
<td>11.83</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>93</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

Assessment of distant disease using choline PET-CT and bone scan showed that 20/93 had evidence of nodal or metastatic disease.
Tabulation of Overall TNM Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Freq</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0M0</td>
<td>73</td>
<td>78.49</td>
<td>78.49</td>
</tr>
<tr>
<td>N1M0</td>
<td>5</td>
<td>5.38</td>
<td>83.87</td>
</tr>
<tr>
<td>M1a</td>
<td>7</td>
<td>7.53</td>
<td>91.40</td>
</tr>
<tr>
<td>M1b</td>
<td>5</td>
<td>5.38</td>
<td>96.77</td>
</tr>
<tr>
<td>M1c</td>
<td>3</td>
<td>3.23</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

64/93 (69%) underwent HIFU and 29/93 underwent cryotherapy (31%). Type of treatment delivered was unilateral in 71/93, bilateral in 16/93 and missing in 5/93. The most common ablation pattern was a hemi-ablation in 37/93. 7/93 underwent either a subtotal or whole-gland ablation. A urethral catheter was inserted in 80/93, suprapubic in 7/93 and missing in 6/93.

Tabulation of Ablation Pattern used for Salvage Treatment

<table>
<thead>
<tr>
<th>Ablation Pattern</th>
<th>Freq</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemi-ablation</td>
<td>29</td>
<td>31.18</td>
</tr>
<tr>
<td>Subtotal hemi-ablation</td>
<td>8</td>
<td>8.60</td>
</tr>
<tr>
<td>Quadrant-ablation</td>
<td>15</td>
<td>16.13</td>
</tr>
<tr>
<td>Dog-leg ablation</td>
<td>13</td>
<td>13.98</td>
</tr>
<tr>
<td>Bilateral/Extended</td>
<td>3</td>
<td>3.23</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1</td>
<td>1.07</td>
</tr>
<tr>
<td>Whole-Gland</td>
<td>6</td>
<td>6.45</td>
</tr>
<tr>
<td>Missing</td>
<td>18</td>
<td>19.35</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Continence

Overall EPIC questionnaire return was 84/93 at baseline, 67/93 at 4 weeks, 63/93 at 3 months, 58/93 at 6 months, 56/93 at 9 months, 45/93 at 12 months.

At baseline 3/84 (3.6%) were wearing a pad. This increased to 30% at 4 weeks and declined to 13% and 18% at 9 and 12 months respectively.
Tabulation of pad-use with all observations included

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4-weeks</th>
<th>3-months</th>
<th>6-months</th>
<th>9-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>84</td>
<td>67</td>
<td>63</td>
<td>58</td>
<td>56</td>
<td>45</td>
</tr>
<tr>
<td>Incontinent (N)</td>
<td>3</td>
<td>20</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Pad-use (%)</td>
<td>3.6%</td>
<td>30%</td>
<td>21%</td>
<td>17%</td>
<td>13%</td>
<td>18%</td>
</tr>
</tbody>
</table>

At last follow-up 15/93 (16%) were still wearing a pad. Probability of return of continence for all those who returned a questionnaire at any time point was 84% at 12-months.

Above: Kaplan Meier Graph and table showing probability of being continent when all observations including those without a baseline questionnaire are used in the analysis.
After excluding those without a baseline questionnaire, at baseline 3/84 (3.6%) were wearing a pad. This increased to 30% at 4 weeks and declined to 12% and 15% at 9 and 12 months respectively. At last follow-up 12/84 (14%) were still incontinent.

<table>
<thead>
<tr>
<th>Total (N)</th>
<th>Baseline 4-weeks 3-months 6-months 9-months 12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinent (N)</td>
<td>3 19 11 8 6 6</td>
</tr>
<tr>
<td>Pad-use (%)</td>
<td>3.6% 30% 19% 15% 12% 15%</td>
</tr>
</tbody>
</table>

Probability of return of continence for all those who returned a questionnaire at any time point was 86% at 12-months.

Above: Kaplan Meier Graph and table showing probability of being continent when only observations for those with a baseline questionnaire are used in the analysis.
Erectile Function

IIEF questionnaire return was 85/93 at baseline, 65/93 at 4 weeks, 63/93 at 3 months, 58/93 at 6 months, 56/93 at 9 months, 47/93 at 12 months.

At baseline there was a high proportion of ED with 52/93 (61%) patients having ED at baseline. ED increased to 54/65 (81%) at 4 weeks with no change over the following months with 40/47 (85%) reporting ED at 12 months.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4-weeks</th>
<th>3-months</th>
<th>6-months</th>
<th>9-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>85</td>
<td>65</td>
<td>63</td>
<td>58</td>
<td>56</td>
</tr>
<tr>
<td>ED (N)</td>
<td>52</td>
<td>54</td>
<td>53</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>ED (%)</td>
<td>61%</td>
<td>83%</td>
<td>84%</td>
<td>83%</td>
<td>84%</td>
</tr>
</tbody>
</table>

When assessing the rate of ED in the 33 patients with adequate function at baseline the proportion reporting new ED was 14/24 (58%) at 4 weeks with no change over the following months and 9/15 (60%) reporting ED at 12 months.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4-weeks</th>
<th>3-months</th>
<th>6-months</th>
<th>9-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N)</td>
<td>33</td>
<td>24</td>
<td>23</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>ED (N)</td>
<td>0</td>
<td>14</td>
<td>13</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>ED (%)</td>
<td>0%</td>
<td>58%</td>
<td>56%</td>
<td>52%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Similarly, overall IIEF-15 score was low at baseline with no change seen over the follow-up period.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>4-weeks</th>
<th>3-months</th>
<th>6-months</th>
<th>9-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median IIEF-15</td>
<td>15</td>
<td>10.25</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>IQR</td>
<td>34</td>
<td>17.57</td>
<td>16.5</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>
Analysis of IIEF subdomains was not conducted due to poor baseline level of overall function leading to a small sample size eligible for analysis.

**IPSS**

Mean IPSS score at baseline was 9.4 [SD 6.1] which increased to 13.4 [SD 7.4] at 4 weeks post-operative before decreasing to 9.7 [SD 5.7] by 12 months.
Box and Whisker plot of IPSS scores at each time point:

IPSS QoL showed a similar trend with an increase at 4 weeks before gradually decreasing.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4-weeks</th>
<th>3-months</th>
<th>6-months</th>
<th>9-months</th>
<th>12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>84</td>
<td>66</td>
<td>63</td>
<td>57</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td>Mean QoL</td>
<td>1.71</td>
<td>2.71</td>
<td>2.70</td>
<td>2.46</td>
<td>2.11</td>
<td>2.20</td>
</tr>
<tr>
<td>sd</td>
<td>1.41</td>
<td>1.49</td>
<td>1.59</td>
<td>1.57</td>
<td>1.36</td>
<td>1.34</td>
</tr>
</tbody>
</table>
Box and Whisker plot of IPSS QoL scores at each time point:

Adverse Events in patients undergoing salvage focal therapy for localised disease

An adverse event was recorded in 15/73 individual patients. The most common adverse events were Visible Haematuria in 6/73, acute urinary retention in 4/73 and worsening radiation proctitis in 4/73. There were 5/73 CTC 3+ adverse events.

<table>
<thead>
<tr>
<th>Related Adverse Event</th>
<th>CTCAE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Haematuria / Haematospermia</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Testicular Swelling</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acute Urinary Retention</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Proctitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>UTI</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Perianal Abscess Drainage</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Urethral Stricture</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unrelated Adverse Events</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Night Sweats</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>TIA</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Polymyalgia Flare</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Biliary Colic / Cholecystectomy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Heart Block</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
Additional urological procedures occurred in 10/73 patients. 3 underwent a cystoscopy, 2 had a dilatation, 3 had a TURP and 1 had a suprapubic catheter inserted.

**Adverse Events in patients undergoing salvage focal therapy for nodal or metastatic disease**

An adverse event was recorded in 7/20 individual patients.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>CTCAE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visible Haematuria</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PR bleeding</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AUR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PR Bleeding</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Additional procedures were performed in 4/20 patients. 1 had cystoscopy alone, 1 had a cystolitholopaxy, 1 had a dilatation and 1 had a TURP.
Patient Characteristics

73 men underwent focal salvage therapy for localised (N0M0) radiorecurrent prostate cancer. 68/73 had previously undergone EBRT and 5/73 brachytherapy with or without an external beam boost. Neo/adjuvant hormone use alongside their primary treatment occurred in 55/73, none in 12/73 and was missing in 6/73. Year of original treatment ranged from 1988 to 2014. Mean time from original diagnosis to enrolment was 7.9 years [SD 3.4]. Mean age and Median PSA at original diagnosis were 63 [SD 6.2] years and 12/ml [IQR 7.7-23]. At the time of their original diagnosis 23/73 had Gleason ≤3+3 disease, 32/73 had Gleason 7 disease, 11/181 had ≥4+4 and the Gleason grade was missing in 7/73. T-stage at original diagnosis was T1 in 7/73, T2 in 21/73, T3 in 29/73 and missing in 16/73. For those who underwent EBRT information was available on 37/68 with a range of Gy’s from 55-74 and fractions from 19-37. Mean Age and median PSA at enrolment were 71 years [SD 6.8] and 4.65ng/ml [IQR 2.5-7.35]. ASA grade was 1 in 25/73, 2 in 38/73, 3 in 4/73 and missing in 1/73.

MRI and Biopsy Characteristics

All men underwent a multiparametric MRI with systematic and targeted biopsies. On MRI 2/73 had an overall Likert score of 2, 8/73 had a score of 3, 15/73 had a score of 4 and 48/73 had a score of 5. The overall score was missing in 2/73.

<table>
<thead>
<tr>
<th>Tabulation of MRI Likert Score</th>
<th>Freq</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>1.37</td>
<td>1.37</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>10.96</td>
<td>12.33</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>20.55</td>
<td>32.88</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>67.12</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Subsequently, 57/73 underwent a 20-zone template and 16/73 underwent a 12-zone template biopsy. Mean number of cores taken were 39.4 [SD 16.4], mean positive cores were 7.9 [SD 4.9, not reported in 1] and mean maximum cancer core length
was 7.9 [SD 4.1, not reported in 5]. Maximum Gleason grade was 3+3 in 1/73, 3+4 in 12/73, 4+3 in 25/73, 4+4 in 17/73, 4+5 in 10/73 and not reported in 7/73.

<table>
<thead>
<tr>
<th>Tabulation of Gleason Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freq.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>3+3</td>
</tr>
<tr>
<td>3+4</td>
</tr>
<tr>
<td>4+3</td>
</tr>
<tr>
<td>4+4</td>
</tr>
<tr>
<td>4+5</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

**Treatment Characteristics**

Data has been presented in an intention to treat manner with 51/73 undergoing salvage HIFU, 21/73 undergoing salvage cryotherapy and 1/73 having an abandoned procedure due to a tight rectum. Two patients received neoadjuvant androgen deprivation therapy pre-operatively. The treatment delivered was unilateral in 51/73, bilateral in 12/73, anterior only in 12/73, posterior only in 31/73 and both anterior and posterior in 8/73. A quadrant ablation was performed in 15/73, hemi or sub-total hemi ablation in 37/73, dog-leg ablation or extended ablation in 17/73, sub-total ablation in 1/73, whole gland ablation in 5/73 and missing in 18/73.

63/73 patient had a urethral catheter inserted post-operatively and 7/73 had a suprapubic catheter inserted. Data was missing in 2/73.

**Oncological Outcomes**

Median follow-up was 856 days [SD 390]. 65/73 underwent a post-operative 12-month MRI. Overall 43/73 (59%) had a negative or equivocal MRI, 18/73 (25%) had a positive MRI for infield disease, 3/73 (4%) had positive out-field disease and 1/73 (1%) had both infield and out-field disease on their MRI. 15/73 (21%) underwent biopsy which was positive in 14/15 (93%) for residual cancer.
Tabulation of Post operative MRI outcomes

<table>
<thead>
<tr>
<th></th>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for recurrence</td>
<td>29</td>
<td>39.73</td>
<td>39.73</td>
</tr>
<tr>
<td>Equivocal out-field recurrence</td>
<td>4</td>
<td>5.48</td>
<td>45.21</td>
</tr>
<tr>
<td>Positive out-field recurrence</td>
<td>2</td>
<td>2.74</td>
<td>47.95</td>
</tr>
<tr>
<td>Equivocal infield recurrence</td>
<td>10</td>
<td>13.70</td>
<td>61.64</td>
</tr>
<tr>
<td>Equivocal infield and positive out-field recurrence</td>
<td>1</td>
<td>1.37</td>
<td>63.01</td>
</tr>
<tr>
<td>Positive infield recurrence</td>
<td>15</td>
<td>20.55</td>
<td>83.56</td>
</tr>
<tr>
<td>Positive infield and equivocal out-field recurrence</td>
<td>3</td>
<td>4.11</td>
<td>87.67</td>
</tr>
<tr>
<td>Positive infield and positive outfield recurrence</td>
<td>1</td>
<td>1.37</td>
<td>89.04</td>
</tr>
<tr>
<td>Missing</td>
<td>8</td>
<td>10.96</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

58/73 had further whole-body imaging. 4/73 underwent a post-operative bone scan which was negative in all 4. 20/73 underwent PET scan of which 10/73 were suspicious for either nodal or metastatic disease. 45/73 underwent WBMRI of which 11 were suspicious for either nodal or metastatic disease.

Overall 15/73 patients had evidence of N1/M+ disease on whole body imaging. Metastases Free Survival (MFS) was 91% [95% CI 82 – 96] at 1-year and 80% [95% CI 68 – 88] at 2-years.
<table>
<thead>
<tr>
<th>Interval</th>
<th>Total</th>
<th>Survival</th>
<th>Error</th>
<th>Error</th>
<th>Std. Corrected [95% Conf. Int.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>64</td>
<td>0.9136</td>
<td>0.0337</td>
<td>0.8177</td>
<td>0.9602</td>
</tr>
<tr>
<td>2-years</td>
<td>38</td>
<td>0.8018</td>
<td>0.0498</td>
<td>0.6836</td>
<td>0.8804</td>
</tr>
</tbody>
</table>

Above: Metastases Free Survival KM graph and table in men with localised radio-recurrent prostate cancer who underwent salvage focal therapy.

23/73 developed biochemical failure defined as a PSA >2ng/ml above the nadir.

Freedom from biochemical failure disease free survival (bDFS) was 90% [95% CI 80 – 95] at 1 year and 68% [95% CI 55 – 78] at 2-years.

![Kaplan-Meier survival estimate](image)

20/73 were started on hormones post-operatively. 2/73 received chemotherapy.

Failure free survival defined as freedom from metastases or systemic therapy was 89% [95% CI 78 – 94] at 1-year and 74% [95% CI 61 – 83] at 2-years. There were no deaths reported during the follow-up period.

Above: Biochemical Disease Free Survival KM graph and table in men with localised radio-recurrent prostate cancer who underwent salvage focal therapy.
10-20

<table>
<thead>
<tr>
<th>Interval</th>
<th>Total</th>
<th>Survival</th>
<th>Std. Error</th>
<th>[95% Conf. Int.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>62</td>
<td>0.8859</td>
<td>0.0380</td>
<td>0.7847 0.9413</td>
</tr>
<tr>
<td>2-years</td>
<td>36</td>
<td>0.7395</td>
<td>0.0552</td>
<td>0.6125 0.8305</td>
</tr>
</tbody>
</table>

Above: Freedom from metastases or systemic therapy in men with localised radiorecurrent prostate cancer who underwent salvage focal therapy.

3/73 underwent SRP, 2/73 underwent SABR and 7/73 underwent a redo focal therapy procedure. Freedom from any second line treatments including redo focal therapy and systemic therapy was 94% [95% CI 86 – 98] at 1-year and 70% [95% CI 56 – 80] at 2-years.
Above: Freedom from any second line treatments including systemic therapy in men with localised radiorecurrent prostate cancer who underwent salvage focal therapy.

Multivariable Analysis

Metastases Free Survival:

Due to the limited number of events a multivariable cox-regression was not possible due to a minimum of 10 events needed per variable. On univariable analysis the only two variables to show an association with subsequent metastases where either the original Gleason grade or the Gleason grade after re-staging biopsies with high grade Gleason 8 and above disease showing much worse outcomes compared to Gleason 7 or below.
Original Gleason Grade:

| Hazard Ratio | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|--------------|-----------|-------|--------|---------------------|
| 3.582623     | 1.425797  | 3.21  | 0.001  | 1.642267 7.815533   |

Above: Cox-regression table and KM Metastases Free Survival probability stratified for original Gleason Grade. Time (days).

Even after adjusting for original PSA and Stage the Gleason score remained a significant predictor for the development of metastatic disease.

| Hazard Ratio | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|--------------|-----------|-------|--------|---------------------|
| 3.773361     | 1.823739  | 2.75  | 0.006  | 1.463275 9.7304    |
| .9839469     | .0137999  | -1.15 | 0.249  | .9572679 1.011369  |
| 1.18152      | .6324059  | 0.31  | 0.755  | .4138447 3.373221  |

Kaplan-Meier survival estimates

Re-staging Gleason Grade:

| Hazard Ratio | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|--------------|-----------|-------|--------|---------------------|
| 2.119542     | .6266808  | 2.54  | 0.011  | 1.187323 3.783686   |
Similarly, after adjusting for PSA and stage the Gleason score remained a significant predictor for the development of metastatic disease.

| t     | Haz. Ratio | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|-------|------------|-----------|-------|-----|----------------------|
| Gleason Score | 2.392059  | .8042068  | 2.59  | 0.009 | 1.237654    4.623221 |
| PSA   | .8817329  | .088033   | -1.26 | 0.207 | .7250239    1.072313 |
| MRI Stage | .8906873  | .3011348  | -0.34 | 0.732 | .4591349    1.727867 |
10.7 FORECAST - Oncological Outcomes, Nodal or Metastatic Disease

**Patient Characteristics**

Overall 51/181 men were diagnosed with having nodal or metastatic disease. 11/51 had negative biopsies, 8/51 were unsuitable for focal salvage therapy, 9/51 were excluded due to screening failure or prior to passing of the ethical amendment and 3/51 were excluded due to patient or investigator choice. Thus, of the 40/51 men who underwent biopsies 20/40 underwent focal salvage therapy for nodal or metastatic (N1M1+) radiorecurrent prostate cancer.

15/20 had previously undergone EBRT and 5/20 brachytherapy with or without an external beam boost. Neo/adjuvant hormone use alongside their primary treatment occurred in 14/20, none in 5/20 and was missing in 1/20. Year of original treatment ranged from 1988 to 2013.

Mean time from original diagnosis to enrolment was 9.15 years [SD 5.1]. Mean age and Median PSA at original diagnosis were 60.9 [SD 7.3] years and 10.1/ml [IQR 6.7-21.4].

At the time of their original diagnosis 4/20 had Gleason ≤3+3 disease, 8/20 had Gleason 7 disease and 8/20 had ≥4+4. T-stage at original diagnosis was T1 in 2/20, T2 in 3/20, T3 in 8/20 and missing in 7/20.

For those who underwent EBRT information was available on 9/15 with a range of 60-74 Grays and 19-37 fractions.

Mean Age and median PSA at enrolment were 70.5 years [SD 6.6] and 4.2ng/ml [IQR 2.6-5.8]. ASA grade was 1 in 8/20 and 2 in 12/20.
MRI and Biopsy Characteristics

All men underwent a multiparametric MRI with systematic and targeted biopsies. On MRI 2/20 had an overall Likert score of 2, 3/20 had a score of 3, 4/20 had a score of 4 and 9/20 had a score of 5. The overall score was missing in 1/20. MRI T-stage was T1/2 in all 20/20.

<table>
<thead>
<tr>
<th>Tabulation of MRI Likert Scores</th>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>20.00</td>
<td>30.00</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>20.00</td>
<td>50.00</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>45.00</td>
<td>95.00</td>
</tr>
<tr>
<td>Missing</td>
<td>1</td>
<td>5.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Subsequently, 16/20 underwent a 20-zone template and 4/20 underwent a 12-zone template biopsy. Mean number of cores taken were 33.5 [SD 10.8], mean positive cores were 5.7 [SD 4.4, not reported in 1] and mean maximum cancer core length was 6.2 [SD 3.1, not reported in 2]. Maximum Gleason grade was 3+4 in 3/20, 4+3 in 7/20, 4+4 in 3/20, 4+5 in 3/20 and not reported in 4/20. 5/20 had N1 disease, 7/20 had M1a disease, 5/20 M1b disease and 3/20 had M1c disease.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3+4</td>
<td>3</td>
<td>15.00</td>
<td>15.00</td>
</tr>
<tr>
<td>4+3</td>
<td>7</td>
<td>35.00</td>
<td>50.00</td>
</tr>
<tr>
<td>4+4</td>
<td>3</td>
<td>15.00</td>
<td>65.00</td>
</tr>
<tr>
<td>4+5</td>
<td>3</td>
<td>15.00</td>
<td>80.00</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>20.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tabulation of TNM stage</th>
<th>Freq.</th>
<th>Percent</th>
<th>Cum.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1M0</td>
<td>5</td>
<td>25.00</td>
<td>25.00</td>
</tr>
<tr>
<td>M1a</td>
<td>7</td>
<td>35.00</td>
<td>60.00</td>
</tr>
<tr>
<td>M1b</td>
<td>5</td>
<td>25.00</td>
<td>85.00</td>
</tr>
<tr>
<td>M1c</td>
<td>3</td>
<td>15.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>
**Treatment Characteristics**

12/20 underwent salvage HIFU and 8/20 undergoing salvage cryotherapy. 8/20 patients received neoadjuvant androgen deprivation therapy pre-operatively.

The treatment delivered was unilateral in 16/20, bilateral in 4/20, anterior only in 5/20, posterior only in 11/20 and both anterior and posterior in 1/20. A quadrant ablation was performed in 3/20, hemi or sub-total hemi ablation in 4/20, dog-leg ablation or extended ablation in 3/20, whole gland ablation in 2/20 and missing in 8/20.

17/20 patient had a urethral catheter inserted post-operatively and data was missing in 3/20.

**Oncological Outcomes**

Median follow-up was 808 days [SD 314]. 16/20 underwent a post-operative 12-month MRI. Overall 14/20 (70%) had a negative or equivocal MRI and 2/20 (10%) had a positive MRI for infield disease.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>negative for recurrence</td>
<td>13</td>
<td>65.00</td>
<td>65.00</td>
</tr>
<tr>
<td>equivocal infield recurrence</td>
<td>1</td>
<td>5.00</td>
<td>70.00</td>
</tr>
<tr>
<td>positive infield recurrence</td>
<td>2</td>
<td>10.00</td>
<td>80.00</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>20.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

16/20 had further whole-body imaging. Over the study period 4/16 had evidence of disease progression on whole-body imaging. The remaining 12/16 had either no change or a reduction in disease volume.
<table>
<thead>
<tr>
<th>Stage</th>
<th>PET done</th>
<th>Bone</th>
<th>Nodes</th>
<th>Visceral</th>
<th>WBMRI done</th>
<th>Bone</th>
<th>Nodes</th>
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Table (Above): Follow-up imaging outcomes in twenty men who underwent focal salvage therapy for nodal or metastatic radiorecurrent prostate cancer

15/20 had been started on hormonal therapy by the end of the follow-up period and of these 3/20 had received Docetaxel chemotherapy. 1/20 had a redo focal therapy for residual disease within the prostate. All 20/20 were alive at last follow-up.
Summarising the results, I found that in the 181 men who had been referred with suspicion of recurrent disease, at enrolment 71% had localised disease whilst 28% had evidence of nodal or metastatic spread. When assessing disease within the prostate 82% had localised disease within the prostate on MRI and on biopsy 80% had pathological evidence of recurrent cancer. Prior to their radiotherapy many would also have been classified as high risk with 22% having Gleason 8 or above cancer and 45% had stage T3 or above. An observation worth noting is that MRI was rarely negative in the enrolled group of men with 84% having either a Likert 4 or 5 lesion. Subsequently, 93 men underwent focal salvage therapy and as per the primary outcome and the probability of being pad-free at 12 months was 84%. The rate of erectile dysfunction was worse with 60% reporting ED at 12-months but this likely highlights the very poor baseline function in this cohort of men. Oncologically, all 93 men were alive after a median follow-up of approximately 2-years and the adverse event rate was low. Of the 73 men with localised disease, 59% had no evidence of disease on their post-operative MRI after one session of focal salvage ablation whilst 20% had evidence of progression to nodal or metastatic disease on whole-body imaging. The only variable to show an association with subsequent metastatic disease was Gleason 8 or above disease on original pre-radiotherapy or pre-salvage re-staging pathology which may indicate the presence of micrometastases prior to treatment. 20 men underwent cytoreductive focal salvage therapy in the presence of metastatic disease. This aspect of the trial confirmed the feasibility of such treatment and all men were still alive at last follow-up with a low rate of adverse events.

There are some limitations to the presented analysis. First and foremost is the non-randomised nature of the study. However, from the outset the aim was to confirm within a phase II trial the functional outcomes previously noted in retrospective datasets from salvage focal therapy and to this degree the aim has been met. The overall rate of adverse events was low with only 3 men having a CTCAE 3 or above adverse event which was related to the intervention. In addition, the probability of
being continent at 12-months was 84% which compares very favourably to the alternative salvage treatment options.

Second, due to the short follow-up, only early oncological outcomes can be reported. As expected, overall survival was 100% but in those that underwent focal therapy for localised disease the 1- and 2-year metastases free survival was 91% and 80% respectively. This likely represents the presence of occult micro metastases at the time of treatment as the vast majority of patients who developed metastases had Gleason 8 or above disease. This also reflects the very broad inclusion criteria for the trial with no restrictions on pre-radiotherapy grade or stage. These criteria are in contrast to international guidelines which recommend salvage radical prostatectomy in men with low-intermediate risk disease. It does raise an important discussion point on stratifying treatment to those with lower risk disease at the onset which unsurprisingly would have a better oncological outcome. It does however deny some men the chance of oncological control with approximately 65% of those with high grade disease being free of metastases at 2-years. These results from FORECAST will be utilised in developing a future RCT which should provide level 1 evidence on the benefit of focal salvage therapy and will be discussed further in chapter 11.

An important discussion point is on which outcome measures are most appropriate to report. Oncological outcomes were only a secondary outcome and thus I reported biochemical failure, freedom from second line treatments, metastases free survival and overall survival. Metastases free survival and overall survival are the most robust outcome measures and allow direct comparison with other studies on salvage therapies. Biochemical failure is a commonly reported outcome measure in the literature but there is no validated threshold in the radiorecurrent cohort and often surrogates such as ADT-free survival are used in the literature (290). In FORECAST we did not stipulate any criteria for starting ADT and some men also went on to have redo focal therapy or salvage radical prostatectomy. Freedom from any second line treatment or systemic therapy was 70% at 2-years.
Notwithstanding the above limitations the major strength from the FORECAST trial actually lies in the fact that it recruited 181 men with no selection criteria at enrolment beyond the ability to undergo further investigations. This represents a generalisable population of men who have developed biochemical failure or have suspicion of recurrent disease. It is the largest prospective trial to assess these men for both localised and metastatic disease with an extensive work-up of imaging and biopsies. It highlights that 28% present with metastases at the time of biochemical failure which are predominantly found on Choline PET scans and that whole-body imaging should not be omitted in these men. The recent development and use of PSMA may have increased the sensitivity for the detection of metastatic disease but was not available at the onset of the trial and in many centres is now standard of care.

The other important finding was that most men had Likert 4 or 5 changes seen on their MRI and 80% of those undergoing biopsies had evidence of cancer. Multiparametric MRI has now become standard of care in primary disease and has been shown to have good utility in selecting men for biopsy at initial presentation with prostate cancer and so it was surprising to find that its performance was not similar in this population of men with recurrent disease after radiotherapy. This is probably due to a significant selection bias whereby only men with suspicion of recurrent disease were being assessed and it is well known that PSA is an important indicator for recurrent disease. In FORECAST the mean PSA at enrolment was 4.2ng/ml [SD 4.5]. In addition to this radiotherapy leads to non-specific T2 changes which can make interpretation difficult. However, when a positive MRI was defined as Likert 4 or 5, MRI had good test performance with an AUC value of 0.85, sensitivity of 81%, specificity of 88%, PPV of 96% and NPV of 57%. In the cohort of men where both targeted and systematic biopsies were performed, targeted biopsies were able to achieve a sensitivity of 92%, specificity of 75%, PPV of 94% and NPV of 65% with an AUC value of 0.83. This meant that 8% of cancers would have been missed if targeted biopsies only were performed but conversely 6% of cancers would have been missed had only systematic biopsies been performed. Taken together the two outcomes on the performance of MRI highlight that it is in fact able
to rule in rather than rule out disease i.e. define which men should have a biopsy rather than which men should not and that targeted biopsies can achieve similar outcomes to systematic biopsy with fewer cores taken (mean 7 vs 30 cores, respectively). This is despite the high prevalence of disease in this patient population. In addition, MRI gives important staging information on the extent of disease. Ultimately though if the highest diagnostic yield is the goal then both systematic and MRI-targeted biopsies should be performed.

Finally, I conducted the first known analysis of focal salvage therapy in men with nodal and/or metastatic disease. The primary aim of this was to assess feasibility and 20 of the 31 potentially eligible men chose to undergo treatment. 7/20 developed an adverse event with only 1 having a CTCAE grade 3+ adverse event. A limitation of this analysis is that no formal evaluation of follow-up imaging was built into the analysis plan. This will be performed post-hoc with aim of utilising this data in developing a future Phase II trial.
Future Perspective and Trial Design

With the increasing number of men receiving radiotherapy and 10-15% developing biochemical failure there is a growing need to develop robust treatment options at the time of recurrence in order to provide oncological control of the cancer whilst still preserving quality of life. As discussed previously, the current treatment options for these men have been limited and generally consist of either watchful waiting (WW) with or without delayed androgen deprivation therapy (ADT) or in a small number, salvage approaches such as radical prostatectomy, ablation and brachytherapy. There is very little prospective research in this field and no level 1 evidence for any interventional treatment option.

Prolonged ADT use can lead to a castrate resistance state and has a significant long-term side-effect profile. Oncological outcomes after salvage radical prostatectomy are encouraging but unsurprisingly, generally worse than for those undergoing primary treatment, with 5-year biochemical disease-free survival (BDFS) estimated at 48% and cancer specific survival (CSS) of 92%. In addition, wound healing can be poor with a higher rate of complications when compared to primary surgery. Never the less, it remains an important treatment option for men with recurrent disease and there is some evidence that robotic approaches to salvage prostatectomy (sRALP) might confer lower complications and side-effects; this is one form of prostatectomy where the greater visual resolution and fine handling of tissue might be a considerable advantage but there is no level 1 comparative data on either the open or robotic approach to standard of care.

Minimally invasive ablative therapies (MIAT) used in a focal manner to treat the areas of recurrent cancer within the prostate rather than the whole gland have also shown promising outcomes by minimising some of the side-effects noted with whole gland therapy. This treatment paradigm makes mechanistic sense as the recurrence is found at the site of the original index lesion in 89-100% of patients. The results from the FORECAST trial have confirmed that high preservation of continence with encouraging early oncological outcomes with an 80% 2-year metastases free
survival. Recently, our group also presented multicentre data at ASCO 2020 on 356 men who underwent either salvage HIFU or salvage cryotherapy with a 75% 6-year failure free survival where failure was defined as any systematic or whole-gland therapy.

However, the role of whole-gland therapy should not be discounted altogether. In patients with high volume, bilateral or locally advanced radio-recurrent disease a focal approach is not feasible and whole gland treatment should be considered.

Whole gland MIAT alternatives to salvage radical prostatectomy include salvage brachytherapy, cryotherapy and high-intensity focused ultrasound but as they target the whole prostate, they tend to have higher rates of complications and side-effects as highlighted by the salvage HIFU analysis in chapter 8.

In my opinion, now is the right time to design, plan and deliver a randomized controlled trial to evaluate modern salvage robotic radical prostatectomy (sRALP) as well as salvage MIAT to standard care.

There are many aspects though that need to be considering when designing any such trial. The point of entry for the patients is likely to be the least contentious issue with biochemical failure after radiotherapy clearly defined by the phoenix criterion. The intervention arms are also relatively straight forward to determine with any treatment modality with robust retrospective or prospective evidence of efficacy included either as focal or whole-gland treatment. In order to simplify these treatments all MIAT could be tested as one group with the other option being salvage RALP.

The aspects of the trial where these is significant uncertainty is:

1. Determining what is standard or care and thus the comparator arm.
2. How to define failure in both the intervention and standard of care arms.
3. The exact trial design.
What is the standard or care for men who develop radiorecurrent disease?

There is very little level 1 evidence on what should happen to patients who develop biochemical failure. The traditional treatment has been ADT and ESMO guidelines do not recommend early ADT for men with biochemical failure unless they have symptomatic local disease, or proven metastases, or a PSA doubling time <3 months. In those needing ADT then intermittent ADT is recommended for men with biochemical relapse after radical radiotherapy as there is an RCT showing its non-inferiority to continuous therapy (291).

The only other RCT in this field was by Duchesne et al who assessed the role of immediate versus delayed ADT in 293 men with biochemical failure of whom 165 had undergone radical radiotherapy (290). Assessing their intervention arm whereby 150 were placed on delayed ADT, 50% were eventually started on ADT at 3-years. Overall 32-42% subsequently developed a castrate resistant state. The rate of GU complications were 27-29%. The trial underrecruited and closed early due to this but its conclusions are in contrast to ESMO guidelines as Duchesne et al showed an advantage to continuous rather than deferred ADT.

EAU guidelines recommend salvage radical prostatectomy (SRP) only in highly selected patients with low comorbidity, a life expectancy of at least ten years, a pre-SRP PSA < 10 ng/mL and biopsy ISUP grade < 2/3, no LN involvement or evidence of distant metastatic disease pre-SRP, and those whose initial clinical staging was T1 or T2. The use of such criteria would indeed select patients who would have the best post-operative oncological outcomes but does deny many men potentially curative treatment albeit at the expense of quality of life. EAU guidelines also do not recommend any MIAT due to their experimental nature which again highlights the current need for a clinical trial that delivers level 1 evidence on salvage interventions.
How should we define failure in both the intervention and standard of care arms?

A potentially suitable outcome measure would be freedom from ADT. An alternative would be biochemical failure as defined by the ESMO guidelines PSA doubling time <3 months.

Various definitions of biochemical failure have been reported in the literature and there is significant heterogeneity in the patient populations. In the largest series of salvage radical prostatectomy by Chade et al utilizing a very strict criteria for BCF of a PSA > 0.1 or 0.2, biochemical disease-free survival (bDFS) at 3-years was approximately 60% and metastases free and overall survival were greater than 90% (215). Not all patients with biochemical failure would have been started on systemic therapy.

Similar results have been seen in patients undergoing salvage brachytherapy with 50-60% bDFS at 3-years and 90% ADT free survival at 3-years (292-294).

Data from FORECAST and from our salvage focal HIFU and cryotherapy registry are comparable with a FFS of 80-81% at 2-3 years which could be as high as 75% at 6-years with an overall survival of 100% at 2-years, 97% at 3-years and 88% at 6-years.

A potential drawback to the using ADT-free survival is that it only works when deferred ADT is the chosen treatment strategy for the standard of care arm. If the deferred use of ADT is not mandated, then neither ADT free survival nor biochemical failure would be suitable. The alternative would be time to castrate resistance. The issue with this as an outcome measure is similar to using arguably the most robust outcome measures of metastases free survival or overall survival. Any trial needs to be feasible and using late outcome measures such as these would require either a very large sample size or very long follow-up thus making the trial potentially unfeasible.
A pragmatic composite outcome would likely be the most feasible solution whilst still being clinically relevant. Progression-free survival could be defined as a composite outcome of biochemical failure or local progression or lymph node progression or development of distant metastases or skeletal-related events or the initiation of systemic therapy including but not limited to ADT, chemotherapy, newer hormonal agents.

Biochemical failure would be defined as a PSADT of < 3 months or an absolute PSA of 10ng/ml or greater and local progression would be defined as the need for symptomatic local control (new long term urinary catheterisation, acute kidney injury, transurethral resection of the prostate/bladder neck incision, treatment for ureteric strictures/bladder neck stenosis, urinary tract obstruction, ureteric stent, nephrostomy, colostomy, fistula, and surgery for bowel obstruction).

**Which trial design should be utilised?**

There are various possible trial designs:

1. **Randomisation to 3-arms**

   This may be difficult to recruit to as all patients would need to agree to and be suitable for salvage RALP and MIAT.

   There is the question of the median age for these men being much older and many surgeons and patients would not accept or be clinically suitable for salvage RALP.

   Further, there are some men with widespread disease that require whole-gland surgical extirpation, potentially with cystectomy, and would be totally inappropriate for MIAT.

   As a result, the selection criteria would mean, very few men being eligible for both intervention arms.
2. Patient preference of which arms they are randomised to.

It is a complex design that requires a large sample size to be adequately powered and to take into account the confounders that usually arise from such preference randomisations. This did occur in the second randomisation of the RADICALS trial (RADICALS-HD) but their sample size was approximately 2500 patients as each comparison needed a separate sample size calculation. In context of radiorecurrent disease it would be (accepting that the fourth 3-arm randomisation of WW/ADT vs sRP vs MIAT is excluded):

A. Deferred ADT vs salvage RALP  
B. Deferred ADT vs MIAT  
C. Salvage RALP vs MIAT

The sample size would still be very large but would allow direct comparisons between the various treatment arms. The eligibility criteria for each randomisation could be varied and patient/clinician preference allowed.

3. Multi-Arm Multi-Stage (MAMS)

A MAMS RCT would have similar issues with regards to patient selection with all men accepting each randomisation. The most well-known MAMS trial in the field of urology is the STAMPEDE trial which has evolved the MAMS design over time. Recently they allowed a metformin arm which had different eligibility criteria to the other arms. The key would be to ensure that the differing characteristics would not imbalance the arms and make the interim endpoint much more difficult to directly compare especially between salvage RALP and MIAT.
4. 2 arms with a mixed intervention arm

Deferred ADT vs Salvage RALP or MIAT. This is a pragmatic design and could have 1:2 or 1:3 allocation between SOC and intervention arm but might reduce generalisability. No robust comparison is possible between salvage RALP and MIAT. There may be bias according to site and surgeon, but this does reflect a natural equipoise. The ultimate problem is that we cannot state that the mechanism of action of the interventions are the same so if the study was successful, was it the salvage RALP or the MIAT that was the true driver of the delta. Subgroup analyses might help but the subgroups would have inherent residual confounders (disease, site, surgeon, oncology biases) and thus any conclusions would attract criticism.

5. Preference randomisation with two paired RCTs

Deferred ADT vs Salvage RALP and Deferred ADT vs MIAT
This design would be of parallel RCTs as per the CHRONOS trial in men with primary disease, and one that reflects the design for PACE. It allows independent recruitment into either study and gives a degree of patient/clinician preference to the treatment. It fits with local site and physician equipoise. No direct comparison between salvage RALP and MIAT would be possible but if both are successful then it gives us the ability for guideline change for each.

Based on the above I feel that the two paired RCT design would be most appropriate, but all trial designs have their pros and cons.

Ultimately, the two parameters that will need to be met are:
1. Ability to recruit to and thus deliver the study.
2. Design that is acceptable to funding bodies.
11 Closing Remarks

Despite the publication of prospective robust data such as those presented in my thesis and from other institutions around the world the pace of change towards offering men focal therapy has been slow and has created controversy with heated debates on either side. Neither NICE nor international guideline committees (EAU, AUA) currently recommend focal therapy in men with localised prostate cancer outside of a clinical trial or prospective registry. In some ways the focal therapy paradigm mirrors that of active surveillance and prostate MRI with both also having had to overcome barriers to wide-spread adoption.

The arguments for and against focal therapy haven’t changed significantly over time. Opponents would argue prostate cancer is multifocal with field change seen at the genomic level and thus is not suitable, whilst proponents would argue that multifocality usually comprises of a clinically significant index lesion with smaller low risk clinically insignificant lesions seen in some, with only the index lesion driving cancer progression.

Multifocality in itself is not a new concept being found in breast, thyroid and liver cancer to name a few. It is also found in urological cancers with 5-10% having multifocal lesions in renal cancer and 30-50% in those with bladder cancer. Yet the concept of tissue preserving surgery is standard practice in both those malignancies. For comparisons sake partial nephrectomy for T2 renal cell carcinoma has a recurrence rate of 3 – 16%, G3 Ta bladder transitional cell carcinoma treated with transurethral resection has a recurrence rate of 30 - 50% whilst intermediate risk prostate cancer treated with only one session of focal therapy has a recurrence rate of 20-30%. What is most surprisingly, considering that high-risk non-muscle invasive bladder cancer has a 20% rate of progression despite intravesical BCG, overall a 5-year cancer specific mortality of 11% and 65% cancer specific mortality in those that do progress, is that we are not routinely offering radical cystectomy to all these patients at the onset of disease (295, 296). In comparison, high risk prostate cancer
managed with non-curative intent, is associated with 10-year cancer specific mortality rate of 28% (297).

I understand that radical cystectomy has a significant adverse event profile and my argument is purposely flippant but the second most cited reason by opponents is that there is no level 1 evidence on the efficacy of focal therapy. As another example we as a urological community have adopted the practice of partial nephrectomy based on extensive non-randomised data despite the issue of multifocality and local recurrence rate and the fact that the only RCT in the field showed a survival advantage in favour of radical nephrectomy (298).

With regards to prostate cancer, although we now have RCT evidence on the substantial functional improvements seen with focal therapy from the PART trial there is still no level 1 evidence on its oncological outcomes (143). Proponents would argue that level 1 evidence on many of our radical treatments did not exist until very recently, yet we used robust non-randomised data to guide our clinical decisions. To date there is only one randomised comparison between radical surgery and radiotherapy which was published in 2016 and only applies to low-intermediate risk disease (15). Similarly, the only RCT published comparing robotic to open surgery was also only published in 2016 (42). Our oncology colleagues have performed better in providing level 1 evidence for radiotherapy, but these trials were often against androgen deprivation therapy or to other forms of radiotherapy and so do not aid us when making comparisons between the various treatment modalities. Numerous trials between prostate cancer treatments have failed to recruit and there is a very high probability that we may never see an RCT comparing focal therapy to the established radical treatments (139). Using the need for level 1 evidence as our benchmark to recommend treatment we would potentially deny many thousands of men a year treatment that would preserve their quality of life whilst still treating their cancer. Results from the COMPARE (COMparing treatment options for ProstAte cancer) study confirmed that men were willing to trade 6.99% absolute decrease in survival to have active surveillance over definitive therapy. They were also willing to trade 0.75% absolute decrease in survival for a 1-month reduction in time to return
to normal activities and 0.46% for a 1% absolute improvement in urinary and 0.19% for a 1% absolute improvement in sexual function. Men with high risk disease were willing to trade 3.10% absolute decrease in survival for a 1-month reduction in time to return to normal activities and 1.04% for a 1% absolute improvements in urinary and 0.41% for a 1% absolute improvement in sexual function (299).

Another often cited argument is the inadequate length of follow-up in the focal therapy series. I have presented 8-year outcomes from the combined focal therapy cohort and have shown no disadvantage in terms of overall survival when compared to radical prostatectomy. Presumably 8-years of follow-up is too short to see any advantage from either treatment but again this highlights that even in the medium term there is no harm to the patient. With regards to salvage disease the FORECAST data confirms that 80% of men with recurrent cancer are free of metastases at 2-years whilst avoiding the significant side-effects of radical surgery or hormone manipulation.

I have to be clear here that focal therapy is not the only treatment that should be offered to men with prostate cancer and neither is it suitable for all men but in the post-Montgomery era, men that are eligible should be at least allowed to make an informed decision regarding treatment of their prostate cancer. My aim here is also not to argue for the cessation of the pursuit to obtain level 1 evidence but it is more of a call to arms to the urological and oncological community to utilise the evidence that is presented but also to use this as an impetus to actually successfully recruiting to trials that are presented in the future. I have outlined two research strategies for both primary and recurrent disease and the wide-spread support of the uro-oncological community will be vital in their success.
12 Publications from Thesis

**Publications related to my thesis and their abstracts:**


Histological Outcomes after Focal High Intensity Focused Ultrasound and Cryotherapy (300)

Taimur T. Shah [1,4], Veeru Kasivisvanathan [1,3,4], Alex Freeman [5], Mark Emberton [1, 2, 3] Hashim U. Ahmed [1, 3]

1. Division of Surgery and Interventional Science, UCL, London, UK
2. NIHR UCLH/UCL Comprehensive Biomedical Research Centre, London, UK
3. Department of Urology, UCLH NHS Foundation Trust, London, UK
4. Department of Urology, Whittington Hospital NHS Trust, London, UK
5. Department of Histopathology, UCLH NHS Foundation Trust, London, UK

Abstract

Focal therapy has increasingly become an accepted treatment option for patients with localised prostate cancer. Most follow-up protocols use a mixture of protocol biopsies or “for cause” biopsies triggered by a rising PSA. In this paper we discuss the histological outcomes from these biopsies and their use in guiding subsequent management and trial development.

Research suggests that 1 in 5 of all post-treatment biopsies after focal therapy are positive. However, the majority of these seemed to be from the untreated portion of the gland or met criteria for clinically insignificant disease. The histological outcomes from focal therapy are promising and confirm its effectiveness in the short to medium term. Furthermore re-treatment is possible whilst maintaining a low side effect profile.

Debate is ongoing about the clinical significance of various levels of residual disease after focal therapy and the exact threshold at which to call failure within a patient who has had focal therapy.
Modern Prostate Cancer Management

Taimur Shah [1, 2], Manit Arya [1, 2], John D Kelly [1, 2]

Chapter 11, Recent Advances in Surgery—37

1. Division of Surgery and Interventional Science, UCL, London, UK

2. Department of Urology, UCLH NHS Foundation Trust, London, UK

No Abstract Available

Publisher JP Medical Ltd, 2015
ISBN 9351526984, 9789351526988
Technological aspects of delivering cryotherapy for prostate cancer (301)

Benjamin Lau 1, Taimur Tariq Shah 1,2,3, Massimo Valerio 1,2, Hashim Uddin Ahmed 1,2, Manit Arya 1,2,4

1) Division of Surgery and Interventional Science, University College London, London, UK
2) Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK
3) Whittington Hospital, London, UK
4) Barts Cancer Institute, Queen Mary University of London, UK

Abstract

Since the era of prostate specific antigen (PSA) testing, there has been a stage and grade migration seen with prostate cancer along with a reduction in mortality. Subsequently, concerns have been raised about the over treatment of patients following the diagnosis of localized prostate cancers. Cryotherapy, in which extremely low temperatures induce cell death via multiple mechanisms, has seen a drastic improvement in its technology since the 1800s. Such advances have improved oncological outcomes while reducing complication rates. Furthermore, technological advances have allowed the development of focal cryotherapy which aims to reduce morbidity associated with more radical whole-gland therapies. There is growing evidence that focal cryotherapy provides good oncological and morbidity rates when compared with traditional radical/whole-gland therapies.
Focal Cryotherapy of Localised Prostate Cancer: a Systematic Review of the Literature (302)

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Abstract
Radical/whole gland treatment for prostate cancer has significant side-effects. Therefore focal treatments such as cryotherapy have been used to treat localized lesions whilst aiming to provide adequate cancer control with minimal side-effects. We performed a systematic review of Pubmed/Medline and Cochrane databases’ to yield 9 papers for primary focal prostate cryotherapy and 2 papers for focal salvage treatment (radio-recurrent). The results of 1582 primary patients showed biochemical disease-free survival between 71–93% at 9–70 months follow-up. Incontinence rates were 0–3.6% and ED 0–42%. Recto-urethral fistula occurred in only 2 patients. Salvage focal cryotherapy had biochemical disease-free survival of 50–68% at 3 years. ED occurred in 60–71%. Focal cryotherapy appears to be an effective treatment for primary localized prostate cancer and compares favorably to radical/whole gland treatments in medium-term oncological outcomes and side-effects. Although more studies are needed it is also effective for radio-recurrent cancer with a low complications rates.
Modeling cryotherapy ice-ball dimensions and isotherms in a novel gel based model to determine optimal cryo-needle configurations and settings for potential use in clinical practice. (303)

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Abstract

Objective: To gain a better understanding of ice ball dimensions and temperature isotherms relevant for cell kill when using combinations of cryo-needles we set out to answer 4 questions: (1) what type of cryo-needle? (2) how many needles? (3) best spatial configuration? and (4) correct duty cycle percentage?

Methods: We conducted laboratory experiments to monitor ice ball dimensions and create multi-needle planar isotherm maps for 17G and 10G cryo-needles using a novel multi-needle thermocouple fixture within gel at body temperature. We tested configurations of 1-4 cryo-needles at duty cycles of 20%-100% with 1-2.5 cm spacing.

Results: Analysis of various combinations shows that a central core of ≤-40°C develops at a distance of ~1 cm around the cryo-needles. Temperature increases linearly from this point to the ice ball leading edge (0°C), which is a further ~1 cm away. Thus, the -40°C isotherm is approximately 1 cm inside the leading edge of the
ice ball. The optimum distance between cryo-needles was 1.5-2 cm, at duty cycle settings of 70%-100%. At distances further apart or with lower duty cycle settings, ice balls either had a central core >-40°C or had an hourglass shape.

**Conclusion:** In answer to questions 1-3, tumor length, diameter, and shape will ultimately determine the number of needles and their configuration. However, we propose a conservative distance for cryo-needle placement between 1 and 1.5 cm should be adopted for clinical practice. In answer to question 4, using low duty cycle settings runs the risk of incomplete -40°C isotherm coverage of the tumor, and thus in routine practice we suggest that settings of 70%-100% are most appropriate.
Early-Medium term outcomes of primary focal cryotherapy to treat non-metastatic clinically significant prostate cancer from a prospective multicentre registry. (304, 305)

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ABSTRACT

BACKGROUND:
Focal cryotherapy can be used to treat patients with clinically significant non-metastatic prostate cancer to reduce side-effects.

OBJECTIVE:
Early-medium-term cancer control and functional outcomes.

DESIGN, SETTING, AND PARTICIPANTS:
A prospective registry-based case-series of 122 consecutive patients undergoing focal cryotherapy between 1/October/2013-30/November/2016 in 5 UK centres. Median follow-up was 27.8 months [IQR 19.5-36.7]. Thirty-five (28.7%) had NCCN high-risk and eight-seven (71.3%) intermediate-risk. Risk and zonal stratification included multiparametric magnetic resonance imaging (mpMRI) with targeted and systematic biopsies, or transperineal mapping biopsies.

INTERVENTION:
Focal cryoablation of MR visible tumours.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS:
Follow-up involved PSA monitoring, mpMRI, and for-cause biopsies. Primary outcome was failure-free-survival (FFS), defined as transition to radical, whole-gland or systemic therapy or metastases/death. Secondary outcomes included adverse events and functional outcomes.

RESULTS AND LIMITATIONS:
Eighty (65.6%) had anterior ablation, twenty-three (19.7%) combined posterior and anterior ablation whilst two (1.6%) had posterior ablation alone (SeedNet or Visual-ICE, BTG plc). Median age was 68.7 years [IQR 64.9-73.8] and pre-operative PSA 10.8ng/ml [IQR 7.8-15.6]. Overall FFS at 3-years was 90.5% [95%CI 84.2-97.3]. When stratified for NCCN risk group, 3-year outcomes were 84.7% [95%CI 71.4-100] in high-risk and 93.3% [95%CI 86.8-100] in intermediate-risk. At last follow-up, incontinence defined as any pad use was 0/69 (0%) and erectile dysfunction (defined as erections insufficient for penetration) was 5/31 (16.1%). Limitations include lack of long-term outcomes.

CONCLUSIONS:
Focal cryotherapy primarily for anterior intermediate and high-risk prostate cancer results in good rates of cancer control and low rates of treatment related side-effects.

PATIENT SUMMARY:
In this multicentre study of 122 patients undergoing focal cryotherapy for medium to high risk prostate cancer, at 3 years, no patient died from their cancer whilst failure-free survival, was approximately 90%. No patient needed to wear pads for urine leakage although 16% had erection problems.
Assessment of return to baseline urinary and sexual function following primary focal cryotherapy for non-metastatic prostate cancer (306)

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Abstract

Background
The oncological outcomes in men with clinically significant prostate cancer following focal cryotherapy are promising although functional outcomes are under reported.

Objective
To determine impact of focal cryotherapy on urinary and sexual function, specifically assessing return to baseline function.

Design/Setting/Participants
Between October 2013-November 2016, 58 of 122 men underwent focal cryotherapy for predominantly anterior clinically significant localised prostate cancer within a prospective registry returned patient reported outcome measure questionnaires included International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF-15).

Intervention
Standard cryotherapy procedure using either the SeedNet or Visual-ICE cryotherapy system.

Outcome Measurements and Statistical Analysis
Primary outcome was return to baseline function of IPSS score and IIEF-Erectile Function (EF) subdomain. Cumulative incidence and cox-regression analyses were performed.

Results and Limitations
Probability of returning to baseline IPSS function was 78% at 12-months and 87% at both 18 and 24-months with recovery seen up to 18-months. For IIEF (Erectile Function domain), the probability of returning to baseline function was 85% at 12-months and 92% at both 18 and 24-months with recovery seen up to 18-months. Only the pre-operative IIEF-EF score was associated with poor outcome (HR 0.961, 95%CI 0.925 to 0.999, p=0.04). Main limitation was that only half the patients returned their questionnaires.

Conclusion
In men undergoing primary focal cryotherapy there is a high degree of preservation of urinary and erectile function with return to baseline function occurring from 3 months and continuing up to 18-months post focal cryotherapy.
**Patient Summary**

In men who underwent focal cryotherapy for prostate cancer approximately 9 in 10 returned to their baseline urinary and sexual function.
Magnetic resonance imaging-transrectal ultrasound fusion focal cryotherapy of the prostate: A prospective development study (136)

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Abstract

Objectives: The use of software-based magnetic resonance-transrectal ultrasound fusion to deliver focal therapy may increase the precision of treatment. This is a prospective development study assessing the feasibility of Magnetic resonance imaging-transrectal ultrasound (MRI-TRUS) fusion focal cryotherapy.

Methods and materials: Consecutive patients undergoing focal cryotherapy were included in an academic registry (December 2013-June 2014). MRI-TRUS fusion focal cryotherapy was offered to men with visible clinically significant prostate cancer (Galil SeedNet system). Eligibility was determined by multiparametric MRI (mpMRI), and transperineal template mapping or targeted biopsies. A rigid fusion platform (Biojet) was used with the operator ensuring the ice ball covered at least the lesion. Adverse events were scored using the NCICTC V4. Genitourinary toxicity was assessed using patient-reported outcome measures (IPSS, IIEF-15, and UCLA-EPIC). Early contrast-enhanced MRI and mpMRI at 6 to 12 months were used to assess extent of lesion ablation.

Results: Of 23 patients scheduled, 5 did not have image fusion owing to surgeon preference. Overall, 18 patients undergoing image fusion cryotherapy had median age of 68 (interquartile range [IQR]: 65-73) years and median preoperative prostate-specific antigen = 9.54 (5.65-16)ng/ml. In all, 13 (72.2%) and 5 (27.8%) patients had intermediate and high-risk cancer, respectively. In total, 10 adverse events were reported with one of these as serious (grade 3) because of admission for hematuria requiring wash out only. There was no difference in the IIEF-15 between baseline and study end (P = 0.24). The IPSS remained stable (P = 0.12), whereas the UCLA-EPIC tended to improve (P = 0.065). The prostate-specific antigen level significantly decreased at 1.8 (1.04-2.93) ng/ml (P<0.001). Both early and late mpMRI showed no residual disease in the treated area. In 2 men, radiological progression of known contralateral disease was observed; both underwent focal high intensity focused ultrasound.

Conclusion: MRI-TRUS fusion focal cryotherapy is feasible in most patients and seems to accurately guide ablation demonstrated by posttreatment imaging. Additional studies are needed to determine efficacy using postcryotherapy biopsy.
Evaluation of functional outcomes after a second focal high-intensity focused ultrasonography (HIFU) procedure in men with primary localized, non-metastatic prostate cancer: results from the HIFU Evaluation and Assessment of Treatment (HEAT) registry (307)

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Abstract

Objectives: To assess change in functional outcomes after a second focal high-intensity focused ultrasonography (HIFU) treatment compared with outcomes after one focal HIFU treatment.

Patients and methods: In this multicentre study (2005-2016), 821 men underwent focal HIFU for localized non-metastatic prostate cancer. The patient-reported outcome measures of International Prostate Symptom Score (IPSS), pad usage and erectile function (EF) score were prospectively collected for up to 3 years. To be included in the study, completion of at least one follow-up questionnaire was required. The primary outcome was comparison of change in functional outcomes between baseline and follow-up after one focal HIFU procedure vs after a second focal HIFU procedure, using IPSS, Expanded Prostate Cancer Index Composite (EPIC) and International Index of Erectile Function (IIEF) questionnaires.

Results: Of 821 men, 654 underwent one focal HIFU procedure and 167 underwent a second focal HIFU procedure. A total of 355 (54.3%) men undergoing one focal HIFU procedure and 65 (38.9%) with a second focal HIFU procedure returned follow-up questionnaires, respectively. The mean age and prostate-specific antigen level were 66.4 and 65.6 years, and 7.9 and 8.4 ng/mL, respectively. After one focal HIFU treatment, the mean change in IPSS was -0.03 (P = 0.02) and in IIEF (EF score) it was -0.4 (P = 0.02) at 1-2 years, with no subsequent decline. Absolute rates of erectile dysfunction increased from 9.9% to 20.8% (P = 0.08), leak-free continence decreased from 77.9% to 72.8% (P = 0.06) and pad-free continence from 98.6% to 94.8% (P = 0.07) at 1-2 years, respectively. IPSS prior to second focal HIFU treatment compared to baseline IPSS prior to first focal HIFU treatment was lower by -1.3 (P = 0.02), but mean IPSS change was +1.4 at 1-2 years (P = 0.03) and +1.2 at 2-3 years (P = 0.003) after the second focal HIFU treatment. The mean change in EF score after the second focal HIFU treatment was -0.2 at 1-2 years (P = 0.60) and -0.5 at 2-3 years (P = 0.10), with 17.8% and 6.2% of men with new erectile dysfunction. The rate of new pad use was 1.8% at 1-2 years and 2.6% at 2-3 years.

Conclusion: A second focal HIFU procedure causes minor detrimental effects on urinary function and EF. These data can be used to counsel patients with non-metastatic prostate cancer prior to considering HIFU therapy.
Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (IP4-CRONOS): A prospective, multi-centre therapeutic phase II parallel Randomised Control Trial (308)

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Abstract

Introduction: Focal therapy (FT) targets individual areas of cancer within the prostate, providing oncological control with minimal side-effects. Early evidence demonstrates encouraging short-medium-term outcomes. With no randomized controlled trials (RCT) comparing FT to radical therapies, Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (CHRONOS) will compare the cancer control of these two strategies.

Patients and methods: CHRONOS is a parallel phase II RCT for patients with clinically significant non-metastatic prostate cancer, dependent upon clinician/patient decision, patients will enrol into either CHRONOS-A or CHRONOS-B. CHRONOS-A will randomize patients to either radical treatment or FT. CHRONOS-B is a multi-arm, multistage RCT comparing focal therapy alone to FT with neoadjuvant agents that might improve the current focal therapy outcomes. An internal pilot will determine the feasibility of, and compliance to, randomization. The proposed definitive study plans to recruit and randomize 1190 patients into CHRONOS-A and 1260 patients into CHRONOS-B.

Results: Primary outcome in CHRONOS-A is progression-free survival (transition to salvage local or systemic therapy, development of metastases or prostate-cancer-related mortality) and in CHRONOS-B is failure-free survival (includes the above definition and recurrence of clinically significant prostate cancer after initial FT). Secondary outcomes include adverse events, health economics and functional outcomes measured using validated questionnaires. CHRONOS is powered to assess non-inferiority of FT compared to radical therapy in CHRONOS-A, and superiority of neoadjuvant agents with FT in CHRONOS-B.

Conclusion: CHRONOS will assess the oncological outcomes after FT compared to radical therapy and whether neoadjuvant treatments improve cancer control following one FT session.
PSA nadir as a predictive factor for biochemical disease-free survival and overall survival following whole-gland salvage HIFU following radiotherapy failure (309)

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Abstract

Background: Treatment options for radio-recurrent prostate cancer are either androgen-deprivation therapy or salvage prostatectomy. Whole-gland high-intensity focused ultrasound (HIFU) might have a role in this setting.

Methods: An independent HIFU registry collated consecutive cases of HIFU. Between 2005 and 2012, we identified 50 men who underwent whole-gland HIFU following histological confirmation of localised disease following prior external beam radiotherapy (2005-2012). No upper threshold was applied for risk category, PSA or Gleason grade either at presentation or at the time of failure. Progression was defined as a composite with biochemical failure (Phoenix criteria (PSA>nadir+2 ng ml(-1))), start of systemic therapies or metastases.

Results: Median age (interquartile range (IQR)), pretreatment PSA (IQR) and Gleason score (range) were 68 years (64-72), 5.9 ng ml(-1) (2.2-11.3) and 7 (6-9), respectively. Median follow-up was 64 months (49-84). In all, 24/50 (48%) avoided androgen-deprivation therapies. Also, a total of 28/50 (56%) achieved a PSA nadir <0.5 ng ml(-1), 15/50 (30%) had a nadir ≥0.5 ng ml(-1) and 7/50 (14%) did not nadir (PSA non-
responders). Actuarial 1, 3 and 5-year progression-free survival (PFS) was 72, 40 and 31%, respectively. Actuarial 1, 3 and 5-year overall survival (OS) was 100, 94 and 87%, respectively. When comparing patients with PSA nadir <0.5 ng ml(-1), nadir ≥0.5 and non-responders, a statistically significant difference in PFS was seen (P<0.0001). Three-year PFS in each group was 57, 20 and 0%, respectively. Five-year OS was 96, 100 and 38%, respectively. Early in the learning curve, between 2005 and 2007, 3/50 (6%) developed a fistula. Intervention for bladder outlet obstruction was needed in 27/50 (54%). Patient-reported outcome measure questionnaires showed incontinence (any pad-use) as 8/26 (31%).

Conclusions: In our series of high-risk patients, in whom 30-50% may have micrometastases, disease control rates were promising in PSA responders, however, with significant morbidity. Additionally, post-HIFU PSA nadir appears to be an important predictor for both progression and survival. Further research on focal salvage ablation in order to reduce toxicity while retaining disease control rates is required.
A systematic review of salvage focal therapies for localised non-metastatic radiorecurrent prostate cancer (310)

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Abstract

Although radiotherapy to the prostate for cancer is effective, recurrence occurs in 10-15% within 5 years. Traditional salvage treatments for men with radiorecurrent prostate cancer comprise of watchful waiting (WW) with or without androgen deprivation therapy (ADT) or radical prostatectomy (RP). Neither strategy provides ideal therapeutic ratios. Salvage focal ablation is an emerging option. We performed a systematic review of the Medline and Embase databases for studies reporting outcomes of focal salvage brachytherapy (sBT), cryotherapy (sCT) or high-intensity focused ultrasound (sHIFU) for radiorecurrent prostate cancer (conception to April 2019). Results were screened for inclusion against predetermined eligibility criteria. Certain data were extracted, including rates of biochemical disease-free survival (BDFS), metastasis, conversion to second-line therapies and adverse events. Of a total 134 articles returned from the search, 15 studies (14 case series and 1 comparative study) reported outcomes after focal sBT [5], sCT [7] and sHIFU [3]. Cohort size varied depending on intervention, with eligible studies of sBT being small case series. Median follow-up ranged from 10 to 56 months. Although pre-salvage demographics were similar [median age range, 61-75 years; prostate-specific antigen (PSA) range, 2.8-5.5 ng/mL], there was heterogeneity in patient selection, individual treatment protocols and outcome reporting. At 3 years, BDFS ranged from 61% to
71.4% after sBT, 48.1-72.4% after sCT and 48% after sHIFU. Only studies of sCT reported 5-year BDFS, which ranged from 46.5% to 54.4%. Rates of metastasis were low after all salvage modalities, as were conversion to second-line therapies (although this was poorly reported). Grade 3 adverse events were rare. This systematic review indicates that salvage focal ablation of radiorecurrent prostate cancer provides acceptable oncological outcomes and is well tolerated. Unfortunately, there is heterogeneity in the study design of existing evidence. Level 1 research comparing salvage focal therapies to existing whole-gland strategies is needed to further establish the role of these promising treatments.
The FORECAST study - Focal recurrent assessment and salvage treatment for radiorecurrent prostate cancer (311)

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Abstract

Background: One-third of men may experience biochemical failure by 8 years following radical radiotherapy for localised prostate cancer. Over 90% of men are started on androgen deprivation therapy (ADT) which is non-curative and confers systemic side-effects. Focal salvage therapy (FST) limits collateral tissue damage and may improve therapeutic ratios. In order to deliver FST, distant disease must be
ruled-out and intra-prostatic disease must be accurately detected, localised and characterised.

Aim: FORECAST - Focal Recurrent Assessment and Salvage Treatment - is a study designed to evaluate a novel imaging-based diagnostic and therapeutic complex intervention pathway for men who fail radiotherapy.

Methods: Men with biochemical failure following radical prostate radiotherapy, prior to salvage therapy will be recruited. They will undergo whole-body multi-parametric MRI (WB-MRI), choline PET/CT, bone-scan and pelvic-mpMRI and then MRI transperineal-targeted biopsies (MRI-TB) and Transperineal Template Prostate Mapping Biopsy (TPM). Those suitable for FST will undergo either high intensity focused ultrasound (HIFU) or cryotherapy.

Results: Primary outcome measures: a) the accuracy of WB-MRI to detect distant metastatic disease; b) accuracy of prostate mpMRI in local detection of radiorecurrent prostate cancer; c) detection accuracy of MRI-TB; and d) rate of urinary incontinence following FST.

Conclusion: Focal salvage therapy may confer lower rates of morbidity whilst retaining disease control. In order to deliver FST, intra- and extra-prostatic disease must be detected early and localised accurately. Novel diagnostic techniques including WB-MRI and MRI-TB may improve the detection of distant and local disease whilst reducing healthcare burdens compared with current imaging and biopsy strategies.
Localising occult prostate cancer metastasis with advanced imaging techniques (LOCATE trial): a prospective cohort, observational diagnostic accuracy trial investigating whole-body magnetic resonance imaging in radio-recurrent prostate cancer (312)

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Abstract

Background: Accurate whole-body staging following biochemical relapse in prostate cancer is vital in determining the optimum disease management. Current imaging guidelines recommend various imaging platforms such as computed tomography (CT), Technetium 99 m ($^{99m}$Tc) bone scan and $^{18}$F-choline and recently $^{68}$Ga-PSMA positron emission tomography (PET) for the evaluation of the extent of disease. Such approach requires multiple hospital attendances and can be time and resource intensive. Recently, whole-body magnetic resonance imaging (WB-MRI) has been
used in a single visit scanning session for several malignancies, including prostate cancer, with promising results, providing similar accuracy compared to the combined conventional imaging techniques. The LOCATE trial aims to investigate the application of WB-MRI for re-staging of patients with biochemical relapse (BCR) following external beam radiotherapy and brachytherapy in patients with prostate cancer.

Methods/design: The LOCATE trial is a prospective cohort, multi-centre, non-randomised, diagnostic accuracy study comparing WB-MRI and conventional imaging. Eligible patients will undergo WB-MRI in addition to conventional imaging investigations at the time of BCR and will be asked to attend a second WB-MRI exam, 12-months following the initial scan. WB-MRI results will be compared to an enhanced reference standard comprising all the initial, follow-up imaging and non-imaging investigations. The diagnostic performance (sensitivity and specificity analysis) of WB-MRI for re-staging of BCR will be investigated against the enhanced reference standard on a per-patient basis. An economic analysis of WB-MRI compared to conventional imaging pathways will be performed to inform the cost-effectiveness of the WB-MRI imaging pathway. Additionally, an exploratory sub-study will be performed on blood samples and exosome-derived human epidermal growth factor receptor (HER) dimer measurements will be taken to investigate its significance in this cohort.

Discussion: The LOCATE trial will compare WB-MRI versus the conventional imaging pathway including its cost-effectiveness, therefore informing the most accurate and efficient imaging pathway.

Trial registration: LOCATE trial was registered on ClinicalTrial.gov on 18th of October 2016 with registration reference number NCT02935816.
Cytoreductive treatment strategies for de novo metastatic prostate cancer (313)

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Abstract

In the past decade, a revolution in the treatment of metastatic prostate cancer has occurred with the advent of novel hormonal agents and life-prolonging chemotherapy regimens in combination with standard androgen-deprivation therapy. Notwithstanding, the use of systemic therapy alone can result in a castrate-resistant state; therefore, increasing focus is being placed on the additional survival benefits that could potentially be achieved with local cytoreductive and/or metastasis-directed therapies. Local treatment of the primary tumour with the established modalities of radiotherapy and radical prostatectomy has been explored in this context, and the use of novel minimally invasive ablative therapies has been proposed. In addition, evidence of the potential clinical benefits of metastasis-directed therapy with ionizing radiation (primarily stereotactic ablative radiotherapy)
is accumulating. Herein, we summarize the pathobiological rationale for local cytoreduction and the potentially systemic immunological responses to radiotherapy and ablative therapies in patients with metastatic prostate cancer. We also discuss the current evidence base for a cytoreductive strategy, including metastasis-directed therapy, in the current era of sequential multimodal therapy incorporating novel treatments. Finally, we outline further research questions relating to this complex and evolving treatment landscape.
13 Grants, Prizes and Invited Talks

13.1 Grants


St Peters Trust, Joint-Lead Application, Ahmed and Shah: “Liquid Biopsy – using cell free DNA (cfDNA) and circulating tumour cells (CTC’s) - in the diagnostic and treatment pathway for high risk radiorecurrent prostate cancer” - £32K July 2015 – January 2018

13.2 Prizes

Best trainee presentation at BSOT conference, Leeds January 2020

BASO – The Association of Cancer Surgery: Trainee Poster 1st Prize November 2018
Propensity Score-Matched Comparison of Focal High Intensity Focused Ultrasound (HIFU) to Laparoscopic Radical Prostatectomy (LRP) for Clinically Significant Localised Prostate Cancer
Supervised Prize to Daniel Hall, FY1

BASO – The Association of Cancer Surgery: Trainee Poster Prize Runner up November 2018
T-Stage Migration by Routine Pre-Biopsy MRI Staging May Affect Risk Assessment with Current Risk Classification Systems
Supervised Prize to N Hyun Kim, FY1

13.3 Invited Talks and Lectures

Role of additional non-targeted prostate biopsies
Shah TT
BSOT Conference, Leeds, January 2020

Prostate Cancer and Focal Therapy
Shah TT
Invited Lecture, Leverkusen, January 2020
Prostate Cancer and Focal Therapy - Case Based MDT Presentation
Shah TT
Session Chair, Focal Therapy Masterclass, London, April 2019

Focal Cryotherapy
Shah TT
Invited Lecture, Focal Therapy Masterclass, London, April 2019

Imaging in Prostate Cancer. MRI prior to biopsy.
Shah TT
Invited Lecture: Brennpunkt Urologie, Zurich October 2018

T-stage migration with routine MRI staging may impact on risk assessment with current risk calculators
Taimur T Shah, Max Peters, Enrique Gomez-Gomez, Hashim U. Ahmed, Mathias Winkler
Moderator Poster: American Urological Association (AUA) Annual Conference, San Francisco, May 2018

Predictors of poor functional outcomes after focal high intensity focused ultrasound (HIFU)
Shah, Taimur; Peters, Max; Gomez-gomez, Enrique; Miah, Saiful; Guillaumier, Stephanie; Arya, Manit; Afzal, Naveed; Dudderidge, Tim; Hosking-Jervis, Feargus; Hindley, Richard; Lewi, Henry; McCartan, Neil; Moore, Caroline; Nigam, Raj; Ogden, Chris; Persad, Raj; Shah, Karishma; Virdi, Jaspal; Emberton, Mark; Ahmed, Hashim; Winkler, Mathias
Moderator Poster: American Urological Association (AUA) Annual Conference, San Francisco, May 2018

Propensity Score-Matched Comparison of Focal High Intensity Focused Ultrasound (HIFU) to Laparoscopic Radical Prostatectomy (LRP) for Clinically Significant Localised Prostate Cancer
Shah, Taimur; Peters, Max; Gomez-gomez, Enrique; Miah, Saiful; Guillaumier, Stephanie; Arya, Manit; Afzal, Naveed; Dudderidge, Tim; Hosking-Jervis, Feargus; Hindley, Richard; Lewi, Henry; McCartan, Neil; Moore, Caroline; Nigam, Raj; Ogden, Chris; Persad, Raj; Shah, Karishma; Virdi, Jaspal; Emberton, Mark; Ahmed, Hashim; Winkler, Mathias

Podium Presentation: Royal Society of Medicine (RSM), Malcolm Copcoat Prize Presentation; London, April 2018

Cryotherapy for anterior prostate cancer
Shah TT
Invited Lecture at Symposium: 10th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer will take place at the Grand hotel Huis Ter Duin in Noordwijk, The Netherlands, February 11-13, 2018

Transperineal Prostate Biopsy
Shah TT
Invited Lecture: 7th ESUR MRI Prostate course. Copenhagen, June 2017

Primary focal cryotherapy: A prospective multicenter UK registry study of 135 patients
Moderated Poster: British Association of Urological Surgeons (BAUS) Annual Conference, Glasgow 2017

The Effect on Sexual Function from Primary Focal Cryotherapy for Localised Prostate Cancer
Moderated Poster: BAUS Academic Meeting, January 2017
Primary focal cryotherapy in the treatment of predominantly high volume anterior, intermediate and high-risk localized prostate cancer: A prospective multicenter UK registry study of 102 patients
Taimur T. Shah, Feargus Hosking-Jervis, Neil McCartan, Benjamin Thomas, Massimo Valerio, Manir Arya, Hashim U. Ahmed
Moderated Poster: BAUS Academic Meeting, January 2017

Primary focal cryotherapy in the treatment of predominantly high volume anterior, intermediate and high-risk localized prostate cancer: A prospective UK registry study of 102 patients
Taimur T. Shah, Feargus Hosking-Jervis, Neil McCartan, Benjamin Thomas, Massimo Valerio, Manir Arya, Hashim U. Ahmed

Technological Advancements in Focal Cryotherapy
Shah TT
Invited Lecture: China Forum on Ablative Therapy, Tianjin, August 2016

Development and internal validation of a multivariable prediction model for biochemical failure after focal salvage high intensity focused ultrasound for locally recurrent prostate cancer: presentation of a risk score for individual patient prognosis.
Moderated Poster: British Association of Urological Surgeons (BAUS) Annual Conference, Liverpool, June 2016

Primary focal cryotherapy in the treatment of predominantly anterior and high volume intermediate and high-risk localized prostate cancer in the UK
Taimur T. Shah, Benjamin Thomas, Massimo Valerio, Hashim U. Ahmed, Manir Arya
Focal Cryotherapy
Taimur T. Shah, Benjamin Thomas, Massimo Valerio, Hashim U. Ahmed, Manit Arya
Invited for breakout session: British Association of Urological Surgeons (BAUS)
Annual Conference, Manchester, June 2015

Image guided evolution of clinical practice in urology
Shah TT
Invited Lecture: Medical Imaging Computer Summer School (MediCSS), UCL London,
August 2015

Focal cryotherapy in the treatment of localised prostate cancer: early outcomes
Taimur T. Shah, Benjamin Thomas, Massimo Valerio, Hashim U. Ahmed, Manit Arya
Focal therapy conference, Amsterdam, June 2015

Whole gland HIFU in the treatment of radiorecurrent prostate cancer
Taimur Shah, Abi Kanthabalan, Neil McCartan, Yomi Fatola, Alex Freeman, Manit Arya, Mark Emberton, Hashim U. Ahmed
14 References


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