Focal Salvage HIFU in radiorecurrent prostate cancer

Kanthabalan A.* [1, 2], Peters M* [3], Van Vulpen M [3], McCartan N. [1,2], Hindley R [4], Moore C.M. [1,2], Arya M. [2], Emberton M. [1,2], Ahmed H.U. [1,2,5].

Affiliations:

1. Division of Surgery and Interventional Science, UCL
2. Department of Urology, UCLH NHS Foundation Trust
3. Department of Radiation Oncology, University Medical Centre Utrecht, The Netherlands.
4. Department of Urology, Basingstoke NHS Foundation Trust
5. Division of Surgery, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London

* Both authors contributed equally to this research

Address for correspondence:

Address for correspondence:
Abi Kanthabalan
Urology Research Group
Room 4.23, 4th Floor
132 Hampstead Road, London. NW1 2PS
Email: abramkb7@gmail.com

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Vancouver/ICMJE authorship criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: AK, MP, MvV, NM, RH, CM, ME, HUA

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Abstract

Objective: To assess short to medium term cancer control rates and side effects of focal salvage High Intensity Focused Ultrasound (HIFU).

Materials and methods: A retrospective registry analysis identified 150 men who underwent focal salvage HIFU (Sonablate 500) (November 2006-August 2015). Metastatic disease was excluded using the nodal assessment on the pelvic MRI, a radioisotope bone scan and PET imaging (choline-FDG-PET or Choline PET-CT). In our current clinical practice, metastatic disease must be ruled out by both Choline PET and bone scan. Localisation of cancer was by multi-parametric prostate MRI (T2W, diffusion-weighting, dynamic contrast enhancement) with systematic or template prostate mapping biopsies.

Primary outcome was a composite failure incorporating biochemical failure (BF) and/or positive localised or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases/prostate cancer specific death. Secondary outcome was BF using the Phoenix-ASTRO definition (nadir+2ng/ml). We used Kaplan-Meier analysis and Cox-proportional hazards regression to quantify the effect of the determinants on the endpoints.

Results: Mean age at focal salvage therapy was 69.8 years (SD 6.1) and median PSA pre-focal salvage treatment was 5.5 ng/ml [IQR 3.6-7.9). Median follow-up was 35 months (IQR 22-52). Patients were classified as low 2.7% (4/150), intermediate 39.3% (59/150) and high-risk disease 41.3% (62/150) according to D'Amico classification, prior to focal salvage HIFU.
Composite failure occurred in 61% (91/150) and BF occurred in 51.3% (77/150). The Kaplan-Meier composite endpoint free survival (CEFS) at 3 years was 40% (95% CI 31-50) for the entire group. Kaplan-Meier estimates of CEFS were 100%, 49% and 24% at 3 years in low, intermediate and high D'Amico risk groups pre-salvage, respectively. The Kaplan-Meier biochemical disease free survival (BDFS) at 3 years was 48% (95% CI 39-59) for the entire group. Kaplan-Meier estimates of BDFS was 100%, 61% and 32% at 3 years in low, intermediate and high D'Amico risk groups pre-salvage, respectively. Complications included urine infection (11.3%; 17/150), bladder neck stricture (8%; 12/150), recto-urethral fistula after 1 HIFU procedure (2%; 3/150) and osteitis pubis (0.7%; 1/150).

Conclusion
Focal salvage HIFU confers a relatively low complication and side-effect rate. Composite endpoint free survival and biochemical control in the short to medium term is reasonable, especially in this relatively high risk cohort but still on the lower end compared to current whole gland salvage therapies. Focal salvage therapy may offer disease control in high risk men whilst minimising additional treatment morbidities.

Keywords: Focal salvage HIFU, radiorecurrent prostate cancer

Introduction

Up to half of the patients who have localised prostate cancer treated with radiotherapy may experience biochemical failure (BF) by 5-10 years (1-3) . Due to inadequate patient selection, most patients are treated with androgen deprivation therapy, a palliative treatment strategy which carries significant side-effects (2,4-6) . When curative salvage was possible, whole-gland salvage therapies were usually performed. These salvage therapies include radical prostatectomy (RP), brachytherapy, cryosurgery, and high intensity focused ultrasound (HIFU). Biochemical disease free survival at five years have been reported of up to 82% . However, these therapies carry significant side effects such as urinary incontinence (21-90%), impotence (in those who still have erections) (100%) and rectal injury (9.2%) (2,6).Focal salvage therapy aims to treat the area of recurrent disease rather than the entire prostate gland. A recent review has shown promising biochemical control rates and side-effects of such experimental focal strategies, including strategies considered experimental by the European Assoication of Urology (EAU): cryotherapy and HIFU.

Our aim was to assess cancer control rates and genito-urinary and rectal complications of focal salvage HIFU treatment.

Materials and methods

Patient Selection

Independent prospective academic HIFU registry analysis at two centres (University College London Hospitals and NHS Basingstoke Trust) identified 150 men who underwent focal salvage HIFU (November 2006-August 2015). These patients' records were retrospectively reviewed to obtain data from their external referral centre, on disease localisation, treatment and follow up. Institutional review board exemption was granted by UCH/UCL Joint Research Office. To be eligible for focal salvage HIFU, all patients must have experienced biochemical failure according to the Phoenix definition (PSA nadir + 2.0 ng/ml) before subsequent diagnostic modalities were adopted.

Disease Localization

Before patients are considered for salvage treatment at our institutions, metastatic disease must be ruled out using bone-scan and PET imaging (choline-FDG-PET or

Choline PET-CT) and pelvic MRI for nodal staging. There were no restrictions placed on upper level of PSA or PSA kinetics provided the imaging scans confirmed T3bN0M0 or less. We included T3b provided less than 1cm of the seminal vesicle was involved. Disease was localized using prostate mp-MRI studies. As discussed in our previous paper (7,8), each prostate was divided into four sectors in three sections (base, mid-gland, apex) with the urethra as the anatomical dividing point between right and left and anterior and posterior. Each of the 12 resulting sectors and seminal vesicles were scored using the five-point Likert scale (1, highly likely no tumour; 5, highly likely tumour) . The sequences were evaluated in the following manner. First, the T2 sequences were used to provide morphology and anatomical localisation. DCE played a greater role for the peripheral zone with the additional reference of the DWI scans. A score of 1 or 2 was given if there was no enhancement; a score of 3 was given if symmetrical diffuse enhancement was seen; if there was focal or asymmetrical enhancement ≥3 mm and no abnormality seen on DWI, a score of 4 was given; if there was focal or asymmetrical enhancement ≥3 mm and/or corresponding DWI abnormality in the same anatomical location, a score of 5 was recorded. A similar technique was used to report lesions in the transition zone, with DWI sequences given greater weighting compared with DCE. DCE shows more enhancement of adenomas in this zone, especially after radiotherapy. However, an equivocal score of 3 based on DWI could be upgraded to 4 or 5 if there was an associated obvious DCE abnormality in the same anatomical location .

Patients then had either systematic transrectal ultrasound (TRUS) guided biopsies or transperineal template prostate mapping (TPM) biopsies using a 5-mm sampling frame. The group who had been diagnosed via TRUS biopsy underwent hemi-ablation salvage HIFU when mp-MRI showed a unifocal recurrence at the same site as the positive biopsy. This extended treatment volume was adopted because of insufficient location assessment with systematic TRUS-guided biopsies and the subsequent difficult matching with the recurrence location on MRI.

HIFU Treatment

This has been described in a previous paper (9). In summary using the Sonablate 500 transrectal HIFU device (Sonacare Inc, Sonablate 500, Focus Surgery, Indianapolis, IN, USA), treatment was either focal (quadrant) ablation, hemiablation, or index lesion ablation (Figure 1). Index lesion ablation was performed if there was multifocal cancer; any untreated areas had ≤1 core with

≤3mm Gleason 3 + 3 disease (on TPM) and/or no lesion on mp-MRI. A margin of 5 mm was adopted around the MRI-based tumour delineation.
Following treatment men had either a suprapubic catheter placed for 2 to 6 weeks, depending on individual patient voiding, or a urethral catheter for 7 to 10 days. Men received ciprofloxacillin antibiotics for 7 days postoperatively. Patients with a rise in PSA after primary focal salvage HIFU and a localised recurrence based on mp-MRI and/or TPM-biopsies were eligible for a second focal salvage HIFU treatment.

Follow-Up

Clinical visits occurred every 3 months to record adverse events and the serum PSA level. Validated questionnaires were issued to all men and included the International Prostate Symptoms Score (IPSS), the University of California Los Angeles-Expanded Prostate Cancer Index Composite (UCLA-EPIC) Urinary domain, and the International Index of Erectile Function-5 point scale (IIEF-5) (10,11) . A higher IPSS indicates worsening symptoms, a lower UCL-EPIC score indicates worsening symptoms, and a lower IIEF-5 indicates worsening erectile function.

Any 2 consecutive rises in PSA were investigated using mp-MRI and further biopsies if MRI was positive and/or staging scans including bone-scan or Choline PET/CT or both.

Outcome, measurements and statistical analysis:
Primary outcome was a composite failure rate following 1 or 2 focal salvage HIFU procedures (BF and/or positive localised or distant imaging and/or positive biopsy and/or systemic therapy and/or metastases and/or prostate cancer-related death), The secondary outcome consisted of BF using the Phoenix-ASTRO definition (nadir+2ng/ml) following 1 or 2 focal salvage HIFU procedures, and complications/ side-effects.

We also assessed several factors predicting failure including baseline (before primary radiotherapy) D'Amico risk group, PSA, T-stage, Gleason score, EBRT dose and ADT-use. Factors before focal salvage HIFU included PSA-nadir after primary radiotherapy, T-stage, prostate volume on MRI, Gleason score, Maximum Cancer Core Length (MCCL), PSA, PSA Doubling time (PSADT), ablation type

(hemi/focal/index lesion ablation), ADT-use and residual cancer left untreated. PSA-nadir post focal salvage HIFU was assessed as post-treatment factor.

Statistics

Model development: Cox-proportional hazards regression was used to quantify the effect of the determinants described above on the endpoints. Hazard ratios (HRs) with 95% confidence intervals (CI's) are provided. Factors with $p<0.05$ were included in the multivariable model. The R language environment (version 3.2.1) (available at http://www.r-project.org/) (12) was used for all statistical analyses. A more elaborate description of the statistical methods used is further discussed in the appendix.

Results

150 men had focal salvage HIFU for radiorecurrent prostate cancer between November 2006 and August 2015 (Table 1 and 2). 20.7%, 23.3% and 42.0% had low, intermediate and high risk prior to radiotherapy (14% missing). 96.7% had external beam radiotherapy and 3.3% had external beam radiotherapy with an HDR brachytherapy boost. Radiation doses of 64 Gray in 32 fractions were the most common (n=27). Median time to BF from primary radiotherapy was 80 months (95% CI 72-86 months). Mean age at focal salvage therapy was 69.8 years (SD 6.1) and median PSA pre-focal salvage treatment was 5.5 ng/ml [IQR 3.6-7.9). Prior to focal salvage HIFU metastatic disease was ruled out by bone scan or Choline PET/FDG scan. Some men did have a Choline FDG scan. However this was earlier in the series and clinical practice changed to performing Choline PET-CT instead of Choline FDG scans. All men had an mpMRI and either template prostate mapping (n=104) or TRUS biopsy (N=40) (with one patient undergoing MRI-guided biopsies) (Table 2). From May 2012 onwards, most patients underwent TPM-biopsies (≈85%), while this was approximately 65% before that time. The choice of biopsy was made at the discretion of the treating physician, but a clear temporal trend to more TPM-biopsies is observed.

Low, intermediate and high risk disease using D'Amico classification, was present in 2.7% (4/150), 39.3% (59/150) and 41.3% (62/150) prior to focal salvage HIFU (missing 25. 16,7%). Three forms of ablation were performed (Table 3): focal ablation (55%; 82/150), hemi-ablation (34%; 51/150), and index lesion ablation

(11%; 17/150). 45.3% (68/150) were on ADT (anti-androgen) for their treatment and this was discontinued 6-8 weeks post HIFU. A total of 13 patients received a second focal salvage HIFU procedure for a localised recurrence after primary focal salvage HIFU. The recurrence was based on mp-MRI and TPM-biopsies in 4 patients, TPM-biopsies with negative MRI in 2 patients, only mp-MRI in 4 patients and only TPM-biopsies in 3 patients.

Primary outcome

61% (91/150) met failure by the composite outcome. The Kaplan-Meier composite endpoint free survival (CEFS) at 3 years was 40% (95% CI 31-50) for the entire group. Kaplan-Meier estimates of CEFS was 100%, 49% and 24% at 3 years in low, intermediate and high D'Amico risk groups pre-salvage, respectively. When assessing CEFS in PSA responders (PSA post-treatment ≤0.5 ng/ml) alone, estimated CEFS at 36 months was 67% (95%CI 53-82).

Secondary outcomes

BF occurred in 51% (77/150). The Kaplan-Meier biochemical disease free survival (BDFS) at 3 years was 48% (95% CI 39-59) for the entire group. Kaplan-Meier estimates of BDFS was 100%, 61% and 32% at 3 years in low, intermediate and high D'Amico risk groups pre-salvage, respectively. 43.3% of patients (65/150) were PSA responders; achieving a PSA nadir of ≤0.5, 59.3% (89/150) of men achieved a nadir of ≤1ng/ml. When assessing BF in PSA responders alone (PSA nadir ≤0.5ng/ml), BF occurred in 12% (18/150) and estimated actuarial BDFS at 36 months was 78% (95%CI 67-92). BDFS at 2 years in patients who had re-do HIFU, was 66% (95% CI 43-100%).

The 36-month Kaplan-Meier estimates regarding the primary and secondary outcomes have also been added in Table 6.

Of the patients with biochemical failure, 62 had a mp-MRI in the follow-up, of which 13 were negative. Of the 15 patients without an MRI in the follow-up, 1 died of disease unrelated to prostate cancer or the HIFU treatment, 8 received ADT (3 of which due to metastatic disease on a bone-scan and/or CT and 1 based on positive TPM-biopsies). Of 6 patients follow-up data was insufficient to assess the procedures after BF. Of the 49 patients with a recurrence on mp-MRI, all underwent either pelvic CT or radioisotope bone-scan to exclude metastatic

disease. Patients potentially eligible for a second focal salvage HIFU procedure underwent subsequent TPM biopsies in all but 4 cases.

Second, systemic therapy was started in 40.7% (61/150). 6.7% (10/150) had positive biopsy and 9.5% (9/150) developed distant metastases. 2.7% of patients (4/150) died of prostate cancer. Mean time (±SD) to ADT following HIFU was 20 (±15.9) months.

Third, 12% (18/150) underwent biopsy post HIFU. This was positive in 55.6% (10/18). Of these 2/10 underwent salvage radical prostatectomy, 1/10 had ADT and then proceeded to have salvage radical prostatectomy and 3/10 were started on ADT. Overall, further treatment was performed in 14 patients; salvage radical prostatectomy (n=3), EBRT to spinal metastatic disease (n=1), irreversible electroporation (n=1), cryotherapy (n=1), chemotherapy (n=4) and other drug therapy (n=2).

Fourth, there were 9 deaths overall and four were prostate cancer-related. Kaplan-Meier overall survival estimate at 60 months was 92% (95% CI 85-99%). One patient was high risk prior to radiotherapy and had Gleason 3+4 T3b disease prior to focal salvage HIFU. Post-HIFU his PSA continued to rise, he was started on hormones and went on to have further EBRT. The second was intermediate risk prior to radiotherapy and Gleason 4+4 and T3a disease prior to hemi-ablation salvage HIFU. Post-HIFU his PSA nadir was 0.0 ng/ml, he developed BF 15 months later and went on to develop metastases 37 months later following BF. The third patient was high risk prior to radiotherapy and had PSA 4.12 ng/ml, Gleason 4+3, and T3a disease prior to focal salvage HIFU. Post-HIFU his PSA rose to 5.63 ng/ml and he was started on hormones and subsequent chemotherapy 24 months later. The fourth patient was high risk at baseline and had PSA 7.26 ng/ml, Gleason 4+5 and T2b disease prior to hemi-ablation salvage HIFU. Post-HIFU his PSA nadir was 0.11 ng/ml and he developed BF 9 months later and was started on chemotherapy at 54 months.

Complications

Fifth, complications included UTI in 11.3% (17/150), epididymitis in 1.3% (2/150), bladder neck strictures in 8% (12/150), rectourethral fistula after first HIFU in 2% (3/150) and osteitis pubis in 0.7% (1/150). For the men who experienced recto-

urethral fistula, one spontaneously resolved, one is being managed with urinary diversion with SPC and one has been surgically repaired (Table 4).

Sixth, in those with available data from pre and post functional questionnaires (UCLA-EPIC, IPSS and IIEF-5), of those pad-free at baseline, 87.5% (42/48) remained pad-free at 2 years. 70.8% (34/48) were drip-free urinary continent at baseline and 67.6% (23/34) remained drip-free post-operatively at 2 years. Baseline IIEF scores were available for 31 men. 38.1% (12/31) men reported a baseline score >2 for Question 2 of IIEF which meant that erections were mostly sufficient for penetration. 58.3% (7/12) still had score of >2 at follow up (Table 5).

Uni-and multivariable analyses for composite endpoint

In univariable analyses, components that achieved statistical significance for the composite endpoint (CE) included primary Gleason Score 8-10 HR (95% CI) 1.88 (1.06-3.32) p =0.03, time to radiological recurrence HR (95% CI) 0.989 (0.982-0.996, p=0.002), T-stage 3 vs. T stage 1&2 pre-salvage HR (95% CI) 1.70 (1.09-2.65) p=0.02,, pre-salvage PSA HR (95% CI) 1.06 (1.02-1.11 p=0.004), D'Amico pre-salvage high risk vs. low risk HR 2.57 (95% CI 0.89-7.38 P=0.08) and PSA-nadir post-salvage HR (95% CI) 1.26 (1.19-1.32 p<0.0001). In multivariable analyses components that achieved statistical significance for the CE included T-stage 3 vs. T stage 1 & 2 pre-salvage HR 1.96 (1.13-3.39) and PSA-nadir post-salvage HR (95% CI) 1.29 (1.20-1.38) <0.0001.

CEFS at 36 months (Table 6) in those with pre salvage HIFU PSA doubling time (PSADT) ≥12 months was 51%, (95%CI 37-70) vs. 24% (95% CI 14-41) p =0.003 in those with PSADT <12 months (Figure 3.2a) and 51% (95% CI 39-67) vs. 31% (95% CI 21-46 p=0.002) in men with pre-salvage HIFU PSA <5 ng/ml compared to those with pre-salvage HIFU PSA ≥5 ng/ml (Figure 3.2b). For men with MRI volume <25cc rates of composite free survival at 36 months was 48% (95%CI 35-65) vs. 34% (95% CI 24-49 p=0.13) in those with MRI volume ≥25 cc (Figure 3.2c). In men with PSA nadir post salvage HIFU <0.5 ng/ml CEFS at 36 months was 67% (95% CI 53-82) vs. 21% (95% CI 13-33 p<0.0001) in those with PSA nadir ≥0.5 ng/ml (Figure 3.2d).

For the intermediate and high risk D'Amico groups composite-failure free survival at 36 months 49% (95% CI 36-68) and 24% (95% CI 14-40 p=0.006) respectively

(Figure 4a). When the low and intermediate groups were combined, composite-failure free survival at 36 months was 51% (95% CI 38-69) vs. high risk 24% (95% CI 12-38 p=0.001) (Figure 4b).

Since low risk recurrences are uncommon, we have also performed multivariable analysis after excluding low risk D'Amico patients (n=4). Supplementary table 7 reports on the multivariable analysis without D'Amico low risk patients included. For BF, MRI volume and PSA nadir post salvage remain statistically significant with low risk D'Amico patients excluded. For CE, PSA nadir post salvage HIFU remains statistically significant.

Uni-and multivariable analyses for biochemical failure (Phoenix Definition)

In univariable analyses components that achieved statistical significance for BF included primary Gleason Score 8-10 HR 2.06 (95% CI 1.10-3.85 p=0.02), time to radiological recurrence HR (95% CI) 0.988 (0.980-0.995, p=0.002), T-stage 3 vs. T stage 1&2 pre-salvage HR 1.78 (95% CI 1.11-2.87 p = 0.002), MRI volume HR 1.014 (95% CI 1.003-1.025 p=0.01), PSA pre-salvage HIFU had HR 1.07 (95% CI 1.02-1.12 p=0.003), and PSA-nadir after salvage HR 1.26 (95% CI 1.19-1.32 p = <0.0001). In multivariable analyses components that achieved statistical significance for BF included T-stage 3 vs. T stage 1&2 pre-salvage HR 1.99 (1.14-3.46 p=0.02), MRI volume HR 1.014 (95% CI 1.002-1.027 p=0.03) and PSA-nadir after salvage 1.29 (95% CI 1.20-1.38 p = <0.0001).

There were significant differences in BDFS (Table 6) at 36 months for men with a PSA doubling time of ≥12 months pre-salvage HIFU; 60% (95% CI 45-79) compared to 30% (95% CI 19-49 p=0.0005) with a PSA doubling time of <12 months (Figure 3a). For those with pre-salvage HIFU PSA <5 ng/ml compared to PSA ≥5ng/ml, BDFS was 62%, (95% CI 50-77) versus 37%, (95% CI 27-53 p=0.0005) respectively (Figure 3b). Men with a prostate volume of <25cc prior to focal salvage HIFU, had a BDFS rate at 36 months of 60% (95% CI 47-77) compared with those with prostate volume ≥25cc; 41%, (95% CI 30-56 p=0.02) Figure 4c). At 36 months those who achieved PSA nadir of <0.5ng/ml had BDFS 78%, (95% CI 67-92) compared with those who achieved a PSA nadir ≥0.5ng/ml; 26%, (95% CI 17-39 p<0.0001) (Figure 4d).

For the intermediate and high risk D'Amico groups BDFS at 36 months was 61% (95% CI 48-79) and 32% (95% CI 20-49 p=0.008) respectively (Figure 3c). When the low and intermediate groups were combined, BDFS rates at 36 months was 62% (95% CI 49-79) vs. high risk 32% (95% CI 20-50 p=0.002) (Figure 3d).

Discussion

In summary, our results show that focal salvage HIFU has potential in the treatment of radiorecurrent prostate cancer. In our relatively high risk cohort, BF occurred in 52% (78/150). The Kaplan-Meier CEFS at 3 years was 40% (95% CI 31-50%) for the entire group and 48% (95% CI 39-59%) for BFFS. The rate of side-effects seems to be lower than that conferred by whole-gland salvage therapies. Bladder neck strictures still occurred relatively frequent in this cohort (n=12 or 8%). Still, this percentage compares favourably to whole-gland salvage HIFU and salvage radical prostatectomy procedures, of which the bladder neck stricture rate is approximately 20% in the reported literature (6). However, the current bladder neck structure rate does compares somewhat unfavourable to other focal salvage series performed so far (6). On the other hand, these series have significantly less patients. Furthermore, due to the more broad patient selection in this study (including patients with seminal vesicle involvement), more extensive disease has potentially been treated, thereby increasing the risk of side-effects. However, only comparative studies could provide a robust estimate of side-effects of different salvage modalities.

Our series therefore potentially reflects higher risk disease than other salvage series. This is observed in the median pre-focal salvage PSA of 5.5 ng/ml in our series. The mean/median PSA ranges from 2.8-5.5 in other focal salvage series reported in the literature (6). However, comparisons regarding D'Amico risk groups is more difficult, since these are usually not provided in the focal salvage series.

It is apparent in this paper that higher risk patients can also benefit from focal salvage HIFU. Even though failure is still common and subsequent treatment initiated, in a substantial amount of patients follow-up whole-gland or systemic treatment can be postponed or prevented and quality of life therefore potentially improved.

Excluding low risk D'Amico patients (n=4) further limits the patient sample and, for this reason coincidental statistical significance cannot be excluded. Therefore, the main statistical analysis was done including the low risk group. Furthermore, MRI-volume and PSA-nadir after salvage remain the most significant and influential factors. As a result, exclusion of low risk D'Amico group does not change factors associated with risk of BF or achieving the CE.

Our study was pragmatic by not limiting the entry criteria for focal salvage HIFU other than to rule out metastatic disease or rule-out significant seminal vesicle invasion. We did not select men on an upper threshold such as PSA or PSA kinetics, we allowed many men with likely micro-metastatic disease to be treated. Our series therefore reflects higher risk disease that other salvage series. As a result, we have been able to more robustly determine the upper limit of what is possible in a focal salvage strategy for future trial design and possible clinical practice.

Also repeat treatment with a second HIFU was not classified as failure, as this was likely due to failure of adequate targeting during initial treatment as opposed to recurrence of disease post first focal salvage treatment. This was therefore classified as a completion of treatment. One of the key attributes for ablative therapies is the repeatability and the literature usually reports outcomes after 1-2 ablative therapies.

Limitations

We had limited information on baseline and post operative erectile and urinary function despite issuing questionnaires to most men. Lack of baseline data may be due to no symptoms at initial consultation and therefore no assessment of symptoms using an objective method. Also as this was not conducted as part of a research trial, patients were not obligated to return questionnaires and this may be the reason for lack of responses. As this functional data was so frequently missing a valid conclusion is hard to link to the outcomes so far. Especially patients with severe deterioration might not have returned the questionnaires, thereby biasing the comparison in a significant way. Further, there is still some debate in the literature about radiation effect, delayed tumour regression and timing of biopsy post radiotherapy. Whilst there is some uncertainty, our team consists of expert uro-pathologists whose published work on clinically significant prostate cancer

using different biopsy strategies primary and radiorecurrent setting (7,13-16) . Our experts only report a Gleason Score when there is minimal radiation effect seen on the biopsies, and so feel that they are able to identify recurrent prostate cancer, when present, in radiation affected tissues with a high degree of accuracy and assign a grade to these.

Nonetheless, focal salvage therapy for men following EBRT provides men with a further chance at cancer control that might avoid systemic therapies (17) and the morbidity of whole-gland salvage surgery or ablation. Salvage radical prostatectomy has been reported to have 5 year BDFS rates of between 47% to 82% (2), complications such as rectal injury (0-28%) (2,18) and rates of incontinence (21- 90%) (2) and erectile dysfunction (80-100%) (2) are high due to fibrosis and poor wound healing due to radiation. A systematic review of salvage focal cryotherapy found biochemical disease-free survival of 50-68% at 3 years, rectourethral fistula rates of 0% and ED occurred in 60-71% (19). BDFS rates following whole gland salvage HIFU are 25-53% (20,21) . Incontinence (10–50 %), erectile dysfunction 66.2–100 % and recto-urethral fistula (3–16 %) have also been reported (20-22) . Overall, functional outcomes are generally poorly reported in the literature due to the retrospective nature of the studies.

A further limitation of the study is that no validated definition for failure is available in the (focal) salvage setting after radiotherapy failure. Therefore, a composite endpoint was chosen as a combined failure definition, incorporating biochemical outcomes, imaging (multiparametric MRI, [Choline-PET]/CT, radioisotope bone scan), biopsy results, systemic therapy initiation and metastatic disease/prostate cancer specific mortality. This definition more clearly reflects failure in the early to medium term after focal salvage since the Phoenix definition is not validated in the focal salvage setting and can be biased due to ADT use before focal salvage, which was present in a substantial amount of patients (n=68).

However, the estimates from the Kaplan-Meier analyses and multivariable analyses are very similar for BF and the CE, potentially indicating the validity of a failure definition based on biochemical outcomes. This is also visible in the verification of BF with mostly MRI (n=51) or biopsies (n=11). However, 13 patients still achieved the composite recurrence outcome without previous BF. In the absence of a clear failure definition, we therefore recommend subsequent imaging and biopsy verification of patients with BF after focal salvage HIFU. Indeed

another limitation of this study is the absence of detailed criteria for response assessment or adoption of subsequent diagnostic modalities in case of disease progression. However, most patients (62/77) with BF received mp-MRI in case of BF after focal salvage HIFU. Results of mp-MRI in the radiorecurrent setting are at least equal, if not better, which is hypothesized to be due to increased contrast of tumour with the surrounding fibrotic prostate tissue. Negative and positive predictive values of up to 90-95% are described (23-27) ,) We have also demonstrated very high negative predictive values of a post-treatment MRI in men treated with focal HIFU who all underwent a biopsy within a clinical trial . To our knowledge, there are no results of mp-MRI and/or biopsies in the setting after both radiotherapy and focal salvage HIFU in the literature.

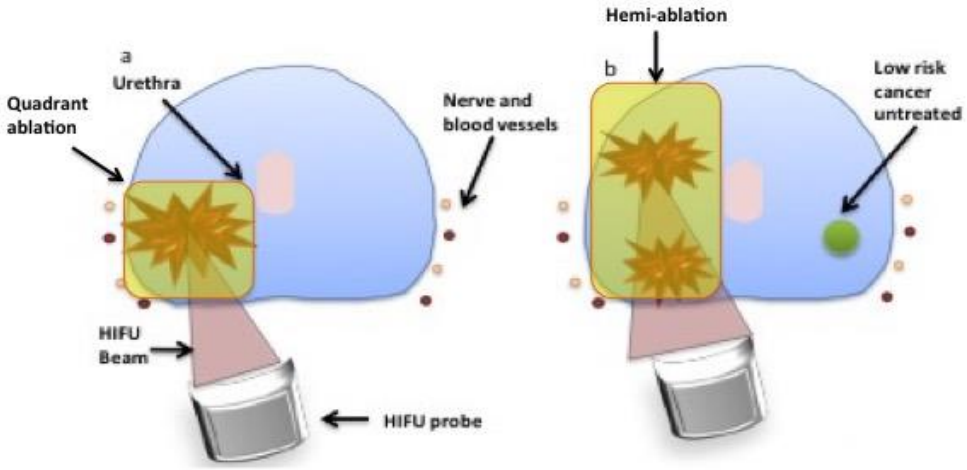
It is quite clear that prospective studies are required. Our FORECAST - Focal Recurrent Assessment and Salvage Treatment for Radiorecurrent Prostate Cancer (28) - study will examine focal salvage cryotherapy and HIFU as well as the role of imaging in ruling out metastatic disease and diagnosing local recurrence. We are also planning comparative studies although these are often difficult to accrue to (29).

Conclusion

Focal salvage HIFU confers a relatively low complication and side-effect rate. Composite endpoint free survival and biochemical control in the short to medium term is reasonable, especially in this relatively high risk cohort, but still on the lower end compared to current whole gland salvage therapies. Focal salvage therapy may offer disease control in high risk men whilst minimising additional treatment morbidities.

Appendix

Figure 1 - Methods of focal ablation



a) Posterior quadrant salvage ablation to a single lesion with focal salvage HIFU

b) Hemi ablation of index lesion to two Index lesions with focal salvage HIFU whilst leaving low risk cancer untreated

Statistical methods

Model development: Missing data was considered at random and handled using multiple imputation by means of the iterative Markov chain Monte Carlo method with a total of 20 iterations (30). Predictor variables used for the imputation procedure were all variables as described above. The outcomes were included as well. Cox-proportional hazards regression was used to quantify the effect of the determinants on the endpoints. Hazard ratios (HRs) with 95% confidence intervals (CI's) are provided. Factors with a p-value on univariable analysis ≤0.05 based on the Wald-test statistic were included in the multivariable model. Proportionality of the cumulative hazard functions was evaluated with Schoenfeld residuals for continuous variables and log-log curves (+ Shoenfeld residuals) for categorical variables. Martingale residuals were used to assess linearity of continuous variables and dfBeta residuals to assess influential outliers. Interactions were not assessed. The R language environment (version 3.2.1) (available at http://www.r-project.org/) [12,31,32] was used for all statistical analyses and population of Kaplan-Meier curves for biochemical disease free survival and freedom from composite end point (using the survival and rms package .

Table 1 - Baseline characteristics at time of radiotherapy

Characteristics before primary radiation treatment	Number	%/IQR/SD	Missing (%)
Primary therapy			
EBRT	145	96.7%	0%
EBRT+HDR-BT boost	5	3.3%	0%
Initial PSA before primary treatment (ng/ml), median (IQR)	13.9	8.9-26.3	10%
D'Amico risk group			14%
1 - High risk PSA 20, Gleason Score ≥8 and T2c-T3a	63	42%	
2 - Intermediate risk PSA 10-20, Gleason Score 7 or T2b disease	35	23.3%	
3 - PSA<10, Gleason Score ≤6 and T1-2a	31	20.7%	
ADT use (cytoreduction/adjuvantly or neo-adjuvantly)	106	71%	1.3%
Abbreviations: EBRT=External beam radiotherapy; HDR=High dose rate; BT=Brachytherapy; PSA=Prostate specific antigen; IQR=Interquartile range; SD=Standard deviation; ADT=Androgen deprivation therapy.			

Table 2 - Pre-focal salvage HIFU characteristics

	Number	%/IQR/SD/ 95% CI	Missing (%)
Age (years) at focal salvage treatment, mean (±SD)	69.8	±6.1	0%
PSA pre-salvage (ng/ml), median (IQR)	5.5	3.6-7.9	0.7%
Radiological T-stage pre-salvage			
T1	11	7.3%	1.3%
T2	102	68%	
T3	35	23.3%	
Gleason grade pre-salvage			
Gleason 2-6	8	5.3%	2.7%
Gleason 3+4	72	48%	
Gleason 4+3	39	26%	
Gleason 8-10	27	18%	
Biopsy type			
TPM biopsies	104	69.3%	3.3%
TRUS-guided biopsies	40	26.7%	
MRI guided	1	0.7%	
D'Amico risk group pre-salvage			
1 - High risk PSA > 20, Gleason Score≥8 and T2c-T3a	62	41.3%	16.7
2 - Intermediate risk PSA 10-20, Gleason Score 7 or T2b disease	59	39.3%	
3 - PSA<10, Gleason Score ≤6 and T1-2a	4	2.7%	
ADT pre-salvage	68	45%	0%

Abbreviations: IQR=Interquartile range; SD=Standard deviation; CI=Confidence interval; Tx=Treatment; TPM=Template prostate mapping; TRUS=Transrectal ultrasound; PSA=Prostate specific antigen.

Table 3 - Outcomes post focal salvage HIFU

	Number	%/IQR/SD/ 95% CI	Missing (%)
Method of ablation			0%
Focal ablation	82	55%	
Hemi-ablation	51	34%	
Index lesion ablation (with residual cancer left untreated)	17	11%	
Composite endpoint (BF, ADT, MRI+, biopsies + systemic treatment + metastases +, prostate cancer specific mortality)	91	60.7%	0%
BF (Phoenix definition)	77	51.3%	0%
PSA-nadir after salvage (ng/ml), median (IQR)	0.67	0.2-1.9	2.7%
Follow-up (months) from salvage, median (IQR)	35	22-52	0%
Death Overall Prostate cancer specific	9 5 4	6% 3.3% 2.7%	0%
Abbreviations: BF=Biochemical failure; ADT= Androgen deprivation therapy; IQR=Interquartile range; PSA=Prostate specific antigen.			

Table 4 - Toxicity outcomes

Clavien Grade	Definition	No. of patients (%)
1	Any deviation from the normal intraoperative or postoperative course, including the need for pharmacologic treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy	19 (12.7%)
2	Complications needing only the use of intravenous medications, total intravenous nutrition, or blood transfusion	0 (0)
3a	Complications needing surgical, endoscopic, or radiologic	25 (16.3%)

	intervention under local anaesthesia	
3b	Complications needing surgical, endoscopic, or radiologic intervention under general anaesthesia	16 (11%)
4a	Life-threatening complications requiring intensive care unit management: Single-organ dysfunction	0 (0)
4b	Life-threatening complications requiring intensive care unit management: Multiorgan dysfunction	0 (0)
5	Death of the patients	0 (0)

Table 5 Functional outcomes

Functional outcomes	Pre-focal salvage	Post-focal salvage (6-36) months
IPSS median (IQR)	8 (4-15)	11 (7-18)
Drip free status	67% (50/75)	46% (28/61)
Pad-free status	97% (70/72)	78% (46/59)
IIEF Q2 Score >2 % (n=31)	38% (n=12)	22% (n=7)
IIEFF Score median (IQR)	15 (7-39) (n=54)	13 (7-24) (n=42) (3-72 months)
PDE-5 use	21% (12/57)	24% (11/45)
Abbreviations: IPSS=International prostate symptom score; IIEF=International index of erectile function; PDE-5=Phosphodiesterase type 5 inhibitor.		

Table 6 – Kaplan – Meier estimates for composite endpoint free survival rates (CEFS) and biochemical disease free survival (BDFS) rates at 36 months

	CEFS (95% CI)	BDFS (95% CI)
Entire group	40% (31-50%)	48% (39-59%)
D'Amico low risk	100% (NA)	100% (NA)
D'Amico intermediate risk	49% (36-68%)	61% (48-79%)
D'Amico high risk	24% (14-40%)	32% (20-49%)
D'Amico low +intermediate risk	51% (38-69%)	62% (49-79%)
D'Amico high risk	24% (14-40%)	32% (20-49%)
PSA nadir < 0.5 ng/ml	67% (53-82%)	78% (67-92%)
PSA nadir ≥ 0.5 ng/ml	21% (13-33%)	26% (17-39%)
PSADT ≥ 12 months	51% (37-70%)	60% (45-79%)
PSADT < 12 months	24% (14-41%)	30% (19-49%)
PSA < 5 ng/ml	51% (39-67%)	62% (50-77%)
PSA ≥ 5 ng/ml	31% (21-46%)	37% (27-53%)
Prostatic volume < 25 cc	48% (35-65%)	60% (47-77%)
Prostatic volume ≥ 25 cc	34% (24-49%)	41% (30-56%)

Abbreviations: CEFS=Composite endpoint free survival; BDFS=Biochemical disease free survival; PSA=Prostate specific antigen; PSADT=Prostate specific antigen doubling time.

Supplementary Table 7: Multivariable analysis for biochemical failure and the composite endpoint without D'Amico low risk patients

Determinants BF	HR (95% CI)	p-value	Determinants CE	HR (95% CI)	p-value
MRI volume	1.01 (1.001-1.028)	0.03			
PSA-nadir post-salvage	1.28 (1.19-1.38)	<0.0001	PSA-nadir post-salvage	1.28 (1.19-1.38)	<0.0001

Abbreviations: BF=Biochemical Failure; HR=Hazard Ratio; CI=Confidence Interval; CE=Composite Endpoint; PSADT=PSA-doubling time.

Figure 3 – Composite endpoint free survival (CEFS)

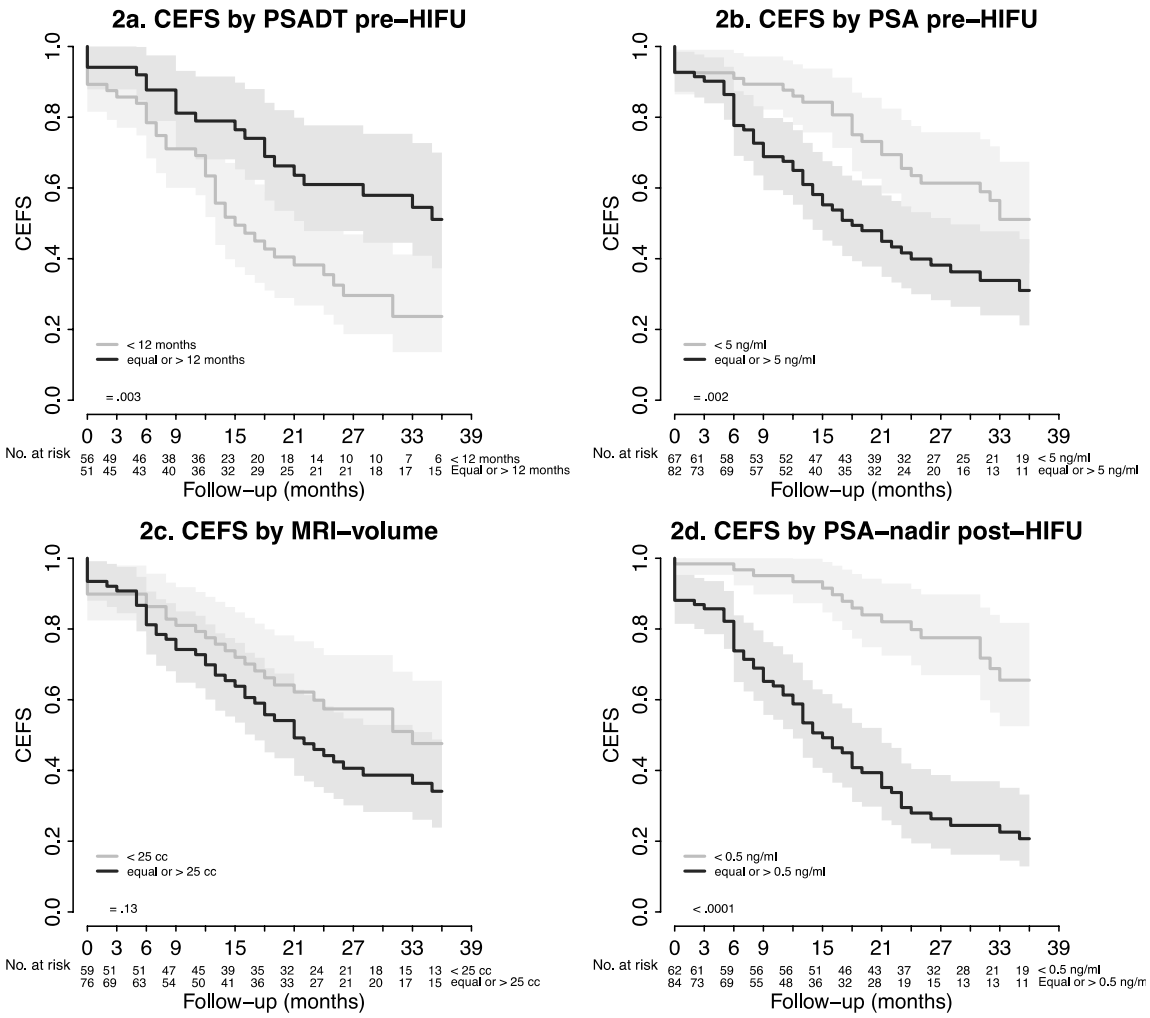


Figure 2a - CEFS for PSA doubling time pre-focal salvage HIFU

Figure 2b - CEFS for pre-focal salvage HIFU PSA

Figure 2c - CEFS by MRI volume

Figure 2d - CEFS for PSA nadir post-focal salvage HIFU

Figure 3 – Biochemical disease free survival (BDFS) rates

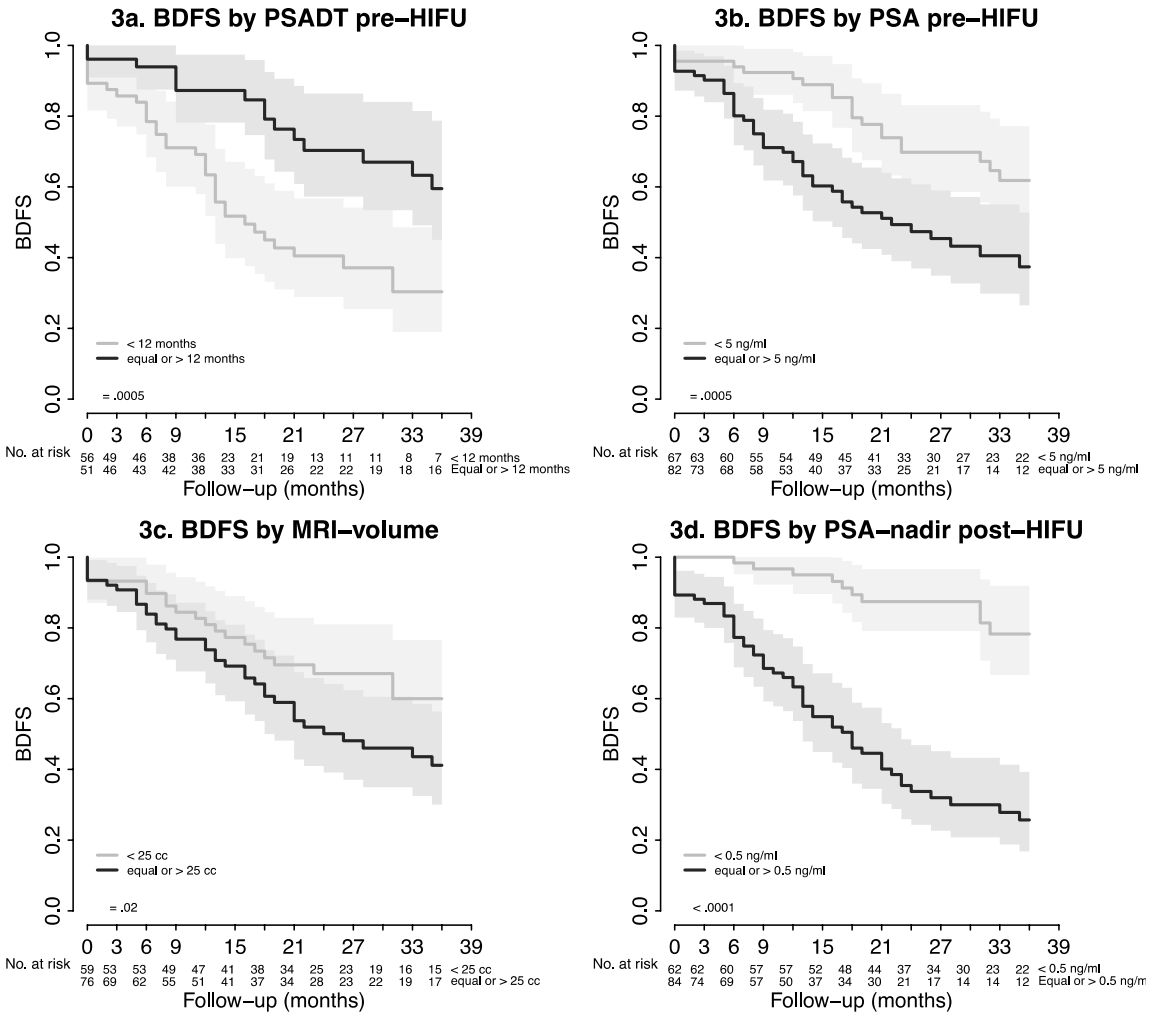


Figure 3a - BDFS for PSA doubling time pre-focal salvage HIFU

Figure 3b - BDFS for pre-focal salvage HIFU PSA

Figure 3c - BDFS by MRI Volume

Figure 3d - BDFS for PSA nadir post-focal salvage HIFU

Figure 4 - Biochemical disease free survival (BDFS) and Composite endpoint free survival (CEFS) according to D'Amico classification pre-focal salvage HIFU

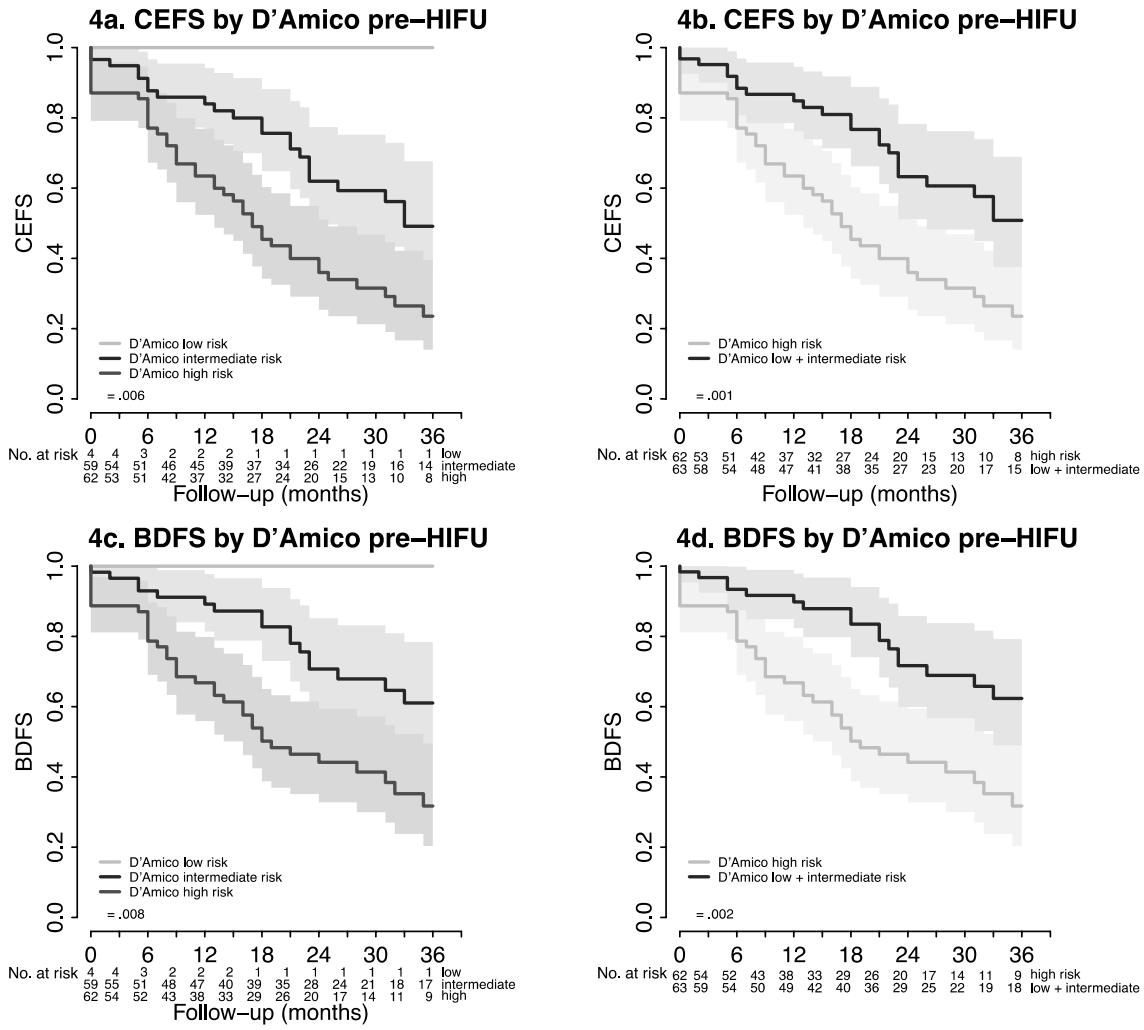


Figure 4a - CEFS by D'Amico risk group pre-focal salvage HIFU

Figure 4b - CEFS by D'Amico low and intermediate combined vs. high risk group pre-focal salvage HIFU

Figure 4c - BDFS by D'Amico risk group pre-focal salvage HIFU

Figure 4d - BDFS by D'Amico low and intermediate combined vs. high risk group pre-focal salvage HIFU

References

1. Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, and Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2013; 85(3):686-92.

2. Chade DC, Eastham J, Graefen M, Hu JC, Karnes RJ et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. Eur Urol. 2012; 61(5):961-71.

3. Zumsteg ZS, Spratt DE, Romesser PB et al. The Natural History and Predictors of Outcome Following Biochemical Relapse in the Dose Escalation Era for Prostate Cancer Patients Undergoing Definitive External Beam Radiotherapy. European Urology. Elsevier BV; 2015;67(6):1009-1016.

4. Tran H, Kwok J, Pickles T, Tyldesley S, and Black PC. Underutilization of local salvage therapy after radiation therapy for prostate cancer. Urol Oncol. 2014; 32(5):701-6.

5. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015; 67(5):825-36.

6. Duijzentkunst DA, Peters M, van der Voort van Zyp JR, Moerland MA, and van Vulpen M. Focal salvage therapy for local prostate cancer recurrences after primary radiotherapy: a comprehensive review. World J Urol. 2016; 34(11):1521-1531.

7. Arumainayagam N, Kumaar S, Ahmed HU, et al. Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy. BJU Int. 2010; 106(7):991-7.

8. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol. 2011; 59(4):477-94.

9. Ahmed HU, Cathcart P, McCartan N, et al. Focal salvage therapy for localized prostate cancer recurrence after external beam radiotherapy: a pilot study. Cancer 2012;118(17):4148-55.

10. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, and Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. Med Care 1998; 36(7):1002-12.

11. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, and Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49(6):822-30.

12. R: The R Project for Statistical Computing [[Internet]]. R: The R Project for Statistical Computing. [cited 2017]. Retrieved from: https://www.r-project.org/

13. Valerio M, Anele C, Charman SC, et al. Transperineal template prostate-mapping biopsies: an evaluation of different protocols in the detection of clinically significant prostate cancer. BJU Int 2016;118(3):384-90.

14. Bott SR, Ahmed HU, Hindley RG, Abdul-Rahman A, Freeman A, and Emberton M. The index lesion and focal therapy: an analysis of the pathological characteristics of prostate cancer. BJU Int. 2010; 106(11):1607-11.

15. Hu Y, Ahmed HU, Carter T, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int. 2012; 110(6):812-20.

16. Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol. 2011; 186(2):458-64.

17. Kanthabalan A, Arya M, Punwani S, et al. Role of focal salvage ablative therapy in localised radiorecurrent prostate cancer. World J Urol. 2013; 31(6):1361-8.

18. Gotto GT, Yunis LH, Vora K, Eastham JA, Scardino PT, and Rabbani F. Impact of prior prostate radiation on complications after radical prostatectomy. J Urol. 2010; 184(1):136-42.

19. Shah TT, Ahmed H, Kanthabalan A, et al. Focal cryotherapy of localized prostate cancer: a systematic review of the literature. Expert Rev Anticancer Ther. 2014; 14(11):1337-47.

20. Murat FJ, Poissonnier L, Rabilloud M, et al. Mid-term results demonstrate salvage high-intensity focused ultrasound (HIFU) as an effective and acceptably morbid salvage treatment option for locally radiorecurrent prostate cancer. Eur Urol. 2009; 55(3):640-7.

21. Uddin Ahmed H, Cathcart P, Chalasani V, et al. Whole-gland salvage high-intensity focused ultrasound therapy for localized prostate cancer recurrence after external beam radiation therapy. Cancer 2012; 118(12):3071-8.

22. Gelet A, Chapelon JY, Poissonnier L, et al. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. Urology 2004; 63(4):625-9.

23. Haider MA, Chung P, Sweet J, Toi A, et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2008; 70(2):425-30.

24. Kara T, Akata D, Akyol F, Karçaaltıncaba M, and Özmen M. The value of dynamic contrast-enhanced MRI in the detection of recurrent prostate cancer after external beam radiotherapy: correlation with transrectal ultrasound and pathological findings. Diagn Interv Radiol. 2011; 17(1):38-43.

25. Roy C, Foudi F, Charton J, et al. Comparative sensitivities of functional MRI sequences in detection of local recurrence of prostate carcinoma after radical prostatectomy or external-beam radiotherapy. AJR Am J Roentgenol. 2013; 200(4):W361-8.

26. Morgan VA, Riches SF, Giles S, Dearnaley D, and deSouza NM. Diffusion-weighted MRI for locally recurrent prostate cancer after external beam radiotherapy. AJR Am J Roentgenol. 2012; 198(3):596-602.

27. Dickinson L, Ahmed HU, Hindley RG, et al. Prostate-specific antigen vs. magnetic resonance imaging parameters for assessing oncological outcomes after high intensity-focused ultrasound focal therapy for localized prostate cancer. Urol Oncol. 2017; 35(1):30.e9-30.e15.

28. Kanthabalan A, Shah T, Arya M, et al. The FORECAST Study - Focal Recurrent Assessment and Salvage Treatment for Radiorecurrent Prostate Cancer. Contemporary Clinical Trials 44 (2015) 175-186

29. Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer? Nat Rev Clin Oncol. 2014; 11(8):482-91.

30. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 338:b2393.

31. Regression Modelling Strategies [[Internet]]. CRAN - Package rms. [cited 2017]. Retrieved from: https://cran.r-project.org/web/packages/rms/index.html

32. CRAN - Package survival [[Internet]]. CRAN - Package survival. [cited 2017]. Retrieved from: https://cran.r-project.org/web/packages/survival/