Prostate Cancer and Prostatic Diseases
https://doi.org/10.1038/s41391-021-00369-6

ARTICLE

Clinical Research

Conventional radical versus focal treatment for localised prostate cancer: a propensity score weighted comparison of 6-year tumour control

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Received: 27 December 2020 / Revised: 14 March 2021 / Accepted: 15 April 2021

Abstract

Background For localised prostate cancer, focal therapy offers an organ-sparing alternative to radical treatments (radiotherapy or prostatectomy). Currently, there is no randomised comparative effectiveness data evaluating cancer control of both strategies.

Methods Following the eligibility criteria PSA < 20 ng/mL, Gleason score ≤ 7 and T-stage ≤ T2c, we included 830 radical (440 radiotherapy, 390 prostatectomy) and 530 focal therapy (cryotherapy, high-intensity focused ultrasound or high-dose-rate brachytherapy) patients treated between 2005 and 2018 from multicentre registries in the Netherlands and the UK. A propensity score weighted (PSW) analysis was performed to compare failure-free survival (FFS), with failure defined as salvage treatment, metastatic disease, systemic treatment (androgen deprivation therapy or chemotherapy), or progression to watchful waiting. The secondary outcome was overall survival (OS). Median (IQR) follow-up in each cohort was 55 (28–83) and 62 (42–83) months, respectively.

Results At baseline, radical patients had higher PSA (10.3 versus 7.9) and higher-grade disease (31% ISUP 3 versus 11%) compared to focal patients. After PSW, all covariates were balanced (SMD < 0.1). 6-year weighted FFS was higher after radical therapy (80.3%, 95% CI 73.9–87.3) than after focal therapy (72.8%, 95% CI 66.8–79.8) although not statistically significant ($p = 0.1$). 6-year weighted OS was significantly lower after radical therapy (93.4%, 95% CI 90.1–95.2 versus 97.5%, 95% CI 94–99.9; $p = 0.02$). When compared in a three-way analysis, focal and LRP patients had a higher risk of treatment failure than EBRT patients ($p < 0.001$), but EBRT patients had a higher risk of mortality than focal patients ($p = 0.008$).

Conclusions Within the limitations of a cohort-based analysis in which residual confounders are likely to exist, we found no clinically relevant difference in cancer control conferred by focal therapy compared to radical therapy at 6 years.

Introduction

For localised prostate cancer, whole-gland treatments such as radiotherapy or prostatectomy confer excellent long-term cancer control, with 10-year biochemical disease-free survival rates between 65 and 90% [1, 2] and 10-year prostate cancer-specific survival rates of nearly 100% [3–5]. However, these favourable oncological outcomes are often accompanied by detrimental side-effects, most notably urinary leakage requiring pads after prostatectomy, rectal side-effects (bleeding, loose stools, discomfort) following radiotherapy and erectile dysfunction for both types of radical therapies [6–8]. In an effort to avoid over-treatment and its associated morbidity, many low-risk patients can be safely managed with active surveillance [9].

Tissue-preserving focal therapy (FT) has been suggested as 'the middle ground' and has undergone a phased

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Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41391-021-00369-6.

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Published online: 01 May 2021

evaluation over the last 14 years. Early to medium-term outcomes from cohort studies on focal high-intensity focused ultrasound (HIFU), focal cryotherapy and focal brachytherapy have shown pad-free continence rates between 93 and 100% and potency preservation between 58 and 100% with rectal toxicity being rare [10–17].

Randomised comparative effectiveness trials comparing FT to radical therapy are underway, although delivery of such trials may be difficult [18, 19]. If successful, it will take almost a decade before conclusions can be drawn [20]. Awaiting this, the best available evidence comes from cohort-based analyses. This report is a follow-up study to our previously published work [21], comparing cancer control following radical therapy (external beam radiotherapy [EBRT] and laparoscopic radical prostatectomy [LRP]) versus FT, using a propensity score weighted (PSW) analysis.

Materials and methods

Study design and setting

EBRT data were collected from a UK single-centre retrospective registry of patients treated between January 2011 and December 2018. LRP data were collected from a UK multicentre prospective registry between May 2007 and September 2018. FT data were collected from three prospective registries: the focal HIFU HEAT registry, focal cryotherapy ICE registry in the UK and HDR-brachytherapy in the Netherlands, including patients between November 2005 and February 2018. Data collection was approved by local medical research ethics committees and informed consent was obtained from all prospectively followed patients. Our study is compliant with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [22].

Patients

Eligibility criteria were: PSA < 20 ng/mL, ≤ISUP 3 and T-stage ≤T2c (National Comprehensive Cancer Network [NCCN] low- to intermediate-risk). Patients with a history of previous prostate cancer treatment were excluded.

Interventions

EBRT

Radiation was administered using intensity-modulated radiotherapy (IMRT) or volumetric modulated arc radiotherapy (VMAT). Until 2013, the indicated protocol for patients with low-risk disease (stage T1-2b, ISUP 1) was 70 Gy in 35 fractions. After 2013, this protocol was changed to 60 Gy in 20 fractions. For patients with a Roach seminal vesicle score [23] >15%, the seminal vesicles were included into the clinical target volume (CTV). Up to 2016, intermediate-risk patients (ISUP 2–3) received 74 Gy in 37 fractions, with the base of the seminal vesicles included in the CTV. From 2016 onwards, this was changed to 72 Gy in 32 fractions. All protocols included a margin of 5 mm (0 mm posteriorly) to the CTV for the planning target volume (PTV). Neoadjuvant short-course (usually 3–6 months) ADT was prescribed for all EBRT patients unless contra-indicated.

LRP

Surgery was performed as a standardised laparoscopic procedure without pelvic lymph node dissection, using unilateral or bilateral nerve-sparing at the discretion of the operating surgeon. If for any reason, surgery had to be delayed, patients received neoadjuvant short-course (usually ≤ 3 months) ADT as a bridging strategy. In case of post-operative adverse pathologic findings (positive surgical margins, upstaging to pT3–4), patients received adjuvant radiotherapy to the prostate bed (66 Gy in 33 fractions) only if they had concomitant PSA progression.

FT

Focal HIFU (Sonablate, Sonacare) was offered to patients with peripheral or posterior tumours or those anteriorly based in which the anterior-posterior height was ≤3.5 cm. Focal cryotherapy (SeedNet or Visual ICE cryotherapy device, Boston Scientific) was the preferred technique in anterior tumours, larger prostates with an anterior-posterior distance of >3.5 cm or those with prostatic calcifications. Focal HDR-brachytherapy (1×19Gy) was performed without restrictions regarding tumour location or prostate size. Detailed descriptions of treatment procedures can be found in previous reports [13, 14, 24]. Salvage or repeat therapy following focal therapy was advised after histological confirmation of recurrent or residual disease. All focal patients had regular PSA monitoring, with an MRI performed in the case of two consecutive PSA rises with no identifiable benign cause. If a lesion of PI-RADS 3 or above was identified the patient underwent biopsy.

Data collection

ISUP grade and maximum cancer core length (MCCL) were determined from either TRUS-guided systematic sampling (LRP patients until 2016, EBRT and focal HDR-brachytherapy patients), MRI-targeted biopsies with peripheral zone sampling (focal HIFU/cryotherapy) or MRI-

targeted biopsies with contralateral sampling (LRP from 2017 onwards). All patients underwent MRI either for staging prior to focal therapy and radiotherapy, or to guide surgical technique regarding nerve-sparing prostatectomy.

Outcome assessment

The primary outcome was failure-free survival (FFS), a composite endpoint of (1) need for local salvage treatment, (2) development of metastatic disease, (3) use of systemic treatment (ADT or chemotherapy) or (4) progression to a watchful waiting (WW) strategy. The secondary outcome was overall survival (OS). Prostate cancer-specific survival could not be assessed, as a causality of death was often difficult to gauge. Salvage treatment was defined as any secondary treatment after EBRT, prostate bed radiotherapy for rising PSA after LRP if there were no adverse pathologic findings and >1 focal re-do or any whole-gland treatment after FT. WW was defined as no intention to treat despite biochemical recurrence after EBRT (PSA nadir + 2 ng/mL) or LRP (PSA > 0.2 ng/mL) or histologically proven recurrence after focal (ISUP ≥ 2 of any length). Prostate biopsies were mostly taken after two consecutive PSA rises and suspected recurrence on mp-MRI, with a small proportion of patients undergoing standard prostate biopsies as part of the FT protocol.

Statistical analysis

All analyses were performed using R version 3.5.0. To compare treatments, a PSW analysis was performed using the matching weights approach [25, 26]. Missing data were considered to be missing at random and was imputed upfront with single imputation (mice package). Each patient was assigned a propensity score based on age, PSA, ISUP grade, MCCL, T-stage and year of treatment (VGAM package). Patients were then weighted to correct for imbalances between treatment groups, with more weights applied to patients with equal probabilities of assignment to either treatment group. After weighting, covariates with a standardised mean difference (SMD) < 0.1 were considered sufficiently balanced between treatment groups. Next, a weighted Cox regression analysis was performed to estimate the average treatment effect on hazard of failure and mortality (survey package). To visualise survival over time, PSW-adjusted Kaplan–Meier survival curves were fitted, using a weighted log-rank test to detect differences in FFS and OS (survey package). All analyses were also performed in a three-way setting (EBRT versus LRP versus FT), comparing multiple pairs at once. For all three-way analyses, the significance level was set at $p < 0.017$ (Bonferroni correction). For all two-way comparisons, significance was set at $p < 0.05$.

Results

Overall, 440 EBRT, 390 LRP and 530 FT patients were eligible. Treatment details are summarised in Table 1. Although patients may have had different types of treatment failure, the total number of failures represents each patient's first event. Local salvage treatment after EBRT consisted of

Table 1 Treatment characteristics and outcomes.

	Median (IQR) or number (%)	Missing (%)
EBRT ($n = 440$)		
Neoadjuvant ADT	418 (95%)	5 (1.1%)
Treatment protocol		
60 Gy in 20#	101 (23%)	
70 Gy in 35#	9 (2%)	
72 Gy in 32#	80 (18.2%)	
74 Gy in 37#	243 (55.2%)	
Other	7 (1.6%)	
BED (Gy)	173 (173–180)	
EQD_2 (Gy)	74 (74–77)	
Treatment failure	31 (7%)	
Salvage treatment	2 (0.4%)	
Metastases	7 (1.6%)	
Systemic treatment	10 (2.3%)	
Watchful waiting	17 (3.9%)	
Death	26 (5.9%)	
Follow-up time (months)	41 (21–61)	
LRP ($n = 390$)		
Neoadjuvant ADT	17 (4.4%)	2 (0.5%)
Adjuvant treatment		
EBRT	28 (7.2%)	
EBRT + ADT	12 (3.1%)	
Treatment failure	93 (23.8%)	
Salvage treatment	81 (20.8%)	
Metastases	8 (2%)	
Systemic treatment	19 (4.9%)	
Watchful waiting	2 (0.5%)	
Death	11 (2.8%)	
Follow-up time (months)	77 (45–102)	
Focal therapy ($n = 530$)		
Neoadjuvant ADT	57 (10.8%)	
Type		
Focal HIFU	419 (79.1%)	
Focal cryotherapy	81 (15.3%)	
Focal HDR-brachytherapy	30 (5.7%)	
Treatment failure	113 (21.3%)	
Salvage treatment	71 (13.4%)	
Metastases	13 (2.4%)	
Systemic treatment	6 (1.1%)	
Watchful waiting	32 (6%)	
Death	10 (1.9%)	
Follow-up time (months)	62 (42–83)	

IQR interquartile range, *BED* biologically effective dose, *EQD_2* equivalent dose to 2 Gy fractionation scheme, *ADT* androgen deprivation therapy, *EBRT* external beam radiotherapy, *LRP* laparoscopic radical prostatectomy, *HIFU* high-intensity focused ultrasound, *HDR-brachytherapy* high-dose-rate brachytherapy.

Table 2 Balance assessment before and after applying propensity score matching weights.

	Unweighted		SMD	Weighted		SMD
	Radical	Focal		Radical	Focal	
Age (mean, SD)	66.4 (7.5)	65.7 (7.4)	0.105	66 (7.3)	66 (7.4)	0.001
PSA (mean, SD)	9.6 (4)	7.9 (3.8)	0.441	8.6 (3.5)	8.5 (3.9)	0.022
ISUP grade						
1 (%)	25.4%	28.5%	0.309	31.4%	31.7%	0.011
2 (%)	52.3%	60.6%		56.4%	55.8%	
3 (%)	22.3%	10.9%		12.2%	12.5%	
MCCL (mean, SD)	6.6 (3.9)	6.5 (4)	0.034	6.3 (3.8)	6.3 (3.4)	0.003
T-stage						
T1 (%)	12%	13.8%	0.051	12.7%	12.7%	0.002
T2 (%)	88%	86.2%		87.3%	87.3%	
Year (mean)	2014	2011	1.040	2011	2011	0.026
N or ESS (weighted)	830	530		385.2	376.5	

SMD standardised mean difference, *SD* standard deviation, *PSA* prostate-specific antigen, *ISUP* International Society of Urological Pathology, *MCCL* maximum cancer core length, *N* number of patients, *ESS* effective sample size.

focal HIFU ($n = 2$). LRP patients received either salvage EBRT to the prostate bed ($n = 72$) or EBRT + ADT ($n = 9$). Among FT patients, 17 had a second focal re-do, 29 had salvage whole-gland radiotherapy (EBRT or I-125 brachytherapy), 4 had salvage whole-gland HIFU and 21 had salvage prostatectomy. Mortality was higher in the EBRT group (5.9%) than the LRP (2.8%) and FT (1.9%) groups. Follow-up time ranged from median 41 months (EBRT) to 62 months (focal) to 77 months (LRP).

Two-way analysis

Baseline patient and tumour characteristics are displayed in the 'unweighted' column in Table 2. Missing data was < 2% for all variables except MCCL, which was missing in 5% (focal) and 25% (radical). The most pronounced baseline differences between groups were PSA and ISUP grade, with radical patients presenting with higher PSA than focal patients (mean 10 versus 8) and harbouring higher-grade disease (22% ISUP 3 versus 11%). After PSW, the balance was achieved for all covariates (SMD < 0.1). The remaining effective sample size (ESS), indicating the size of a hypothetical unweighted cohort that would yield similar precision (the larger the better), was ±380 patients per group.

Table 3 displays the Cox-estimated average treatment effect on hazard of failure and mortality after weighting, showing no significant differences between both groups. Figure 1 shows the PSW-adjusted Kaplan–Meier survival curves estimating FFS (Fig. 1A) and OS (Fig. 1B). Overall, the median time to treatment failure was 36 months (IQR 20–62) and the median time to death was 43 months (IQR 25–66). Although there was no clear difference during the first five years of follow-up, FT patients had faster-declining FFS afterwards (6-year FFS 80.3%, 95% CI 73.9–87.3 [radical] versus 72.8%, 66.8–79.8 [focal]; $p = 0.10$). After radical treatment, 6-year OS was significantly lower (93.4%, 90.1–95.2 versus 97.5%, 94–99.9; $p = 0.02$).

Table 3 Estimated average treatment effect on treatment failure and overall mortality.

	Propensity score weighted		
	HR (95% CI)	SE	*p*-value
Treatment failure			
Focal versus radical	1.29 (0.96–1.75)	0.15	0.10
Overall mortality			
Focal versus radical	0.49 (0.22–1.09)	0.41	0.08

HR hazard ratio, *95% CI* 95% confidence interval, *SE* standard error.

Three-way analysis

Results from the three-way PSW-analysis (EBRT versus LRP versus FT) are displayed in Supplementary Table 1 (covariate balance assessment) and Supplementary Table 2 (Cox regression estimates). Balance was achieved for most covariates except for age (mean 66.2 versus 65.3 versus 66.6, SMD 0.161).

Both FT and LRP patients had a higher risk of treatment failure than the EBRT group (both $p < 0.001$), but there was no statistically significant difference between FT and LRP ($p = 0.69$). In terms of overall mortality, the only significant difference was between focal and EBRT patients, with a lower risk of death after FT (HR 0.29, 95% CI 0.11–0.76; $p = 0.008$).

Figure 2 shows the PSW-adjusted Kaplan–Meier survival curves estimating FFS (Fig. 2A) and OS (Fig. 2B) for

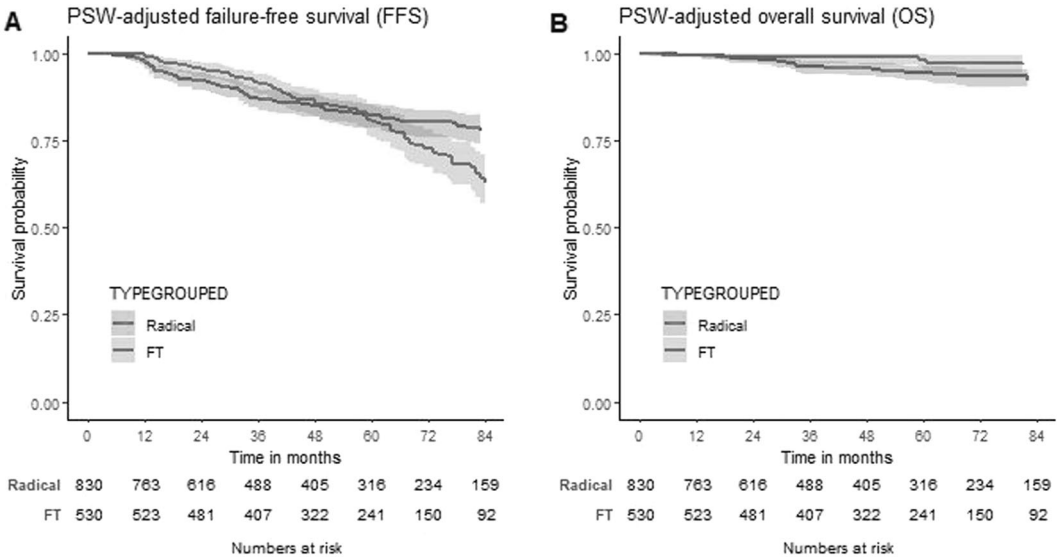

Fig. 1 Two-way propensity weighted failure-free survival (FFS) and overall survival (OS). Kaplan Meier survival curve, displaying propensity weighted FFS (panel **A**) and OS (panel **B**) against time for patients treated with either radical (EBRT or LRP) or focal therapy.

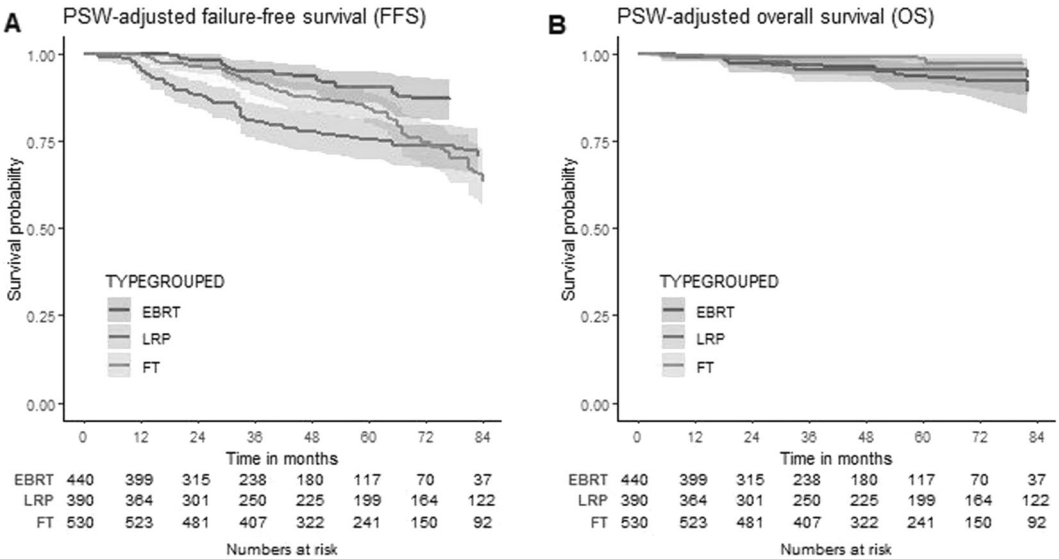

Fig. 2 Three-way propensity weighted failure-free survival (FFS) and overall survival (OS). Kaplan Meier survival curve, displaying propensity weighted FFS (panel **A**) and OS (panel **B**) against time for patients treated with radiotherapy (EBRT), prostatectomy (LRP) or focal therapy (FT).

the three separate treatment groups. After 6 years, the estimated FFS was 87.4% (95% CI 79.9–93.9) in the EBRT group, 73.9% (68–80.9) in the LRP group and 74.4% (68.4–81.5) in the focal group ($p < 0.001$). Estimated 6-year OS was 92.3% (83.5–95.8), 95.3% (88.9–98.3) and 97.5% (94.9–100), respectively ($p = 0.05$).

Discussion

Within the limitations of a cohort-based analysis, our study provides comparative effectiveness data on cancer control showing no clear difference between FT and radical therapies after 6 years of follow-up. Due to the observational nature of the data, systematic baseline differences between groups may affect treatment outcomes. To minimise this effect, we used PSW to equalise the distribution of measured baseline covariates.

The first assumption of a PSW analysis is that the set of observed pre-treatment covariates is sufficiently rich such that the propensity score is constructed without missing important unmeasured or unknown confounders [27]. To this end, this study had limitations. We had no data of important characteristics such as PSA doubling time and

robust measurement of tumour volume. Instead, we used MCCL, which appears to be an independent predictor of cancer volume [28]. We also used simplified T-stage categories (stage T1 or T2) due to a large proportion of missing data (40–65%) on sub-classifications of T2. Furthermore, we had no data on comorbidity profiles or socioeconomic status. EBRT patients were more likely to have comorbidities, considering that they were (on average) 5–8 years older and had higher mortality rates than LRP or FT patients. Although we did have data on the history of neoadjuvant ADT, this was not used for the construction of propensity scores because the difference between groups (96% before EBRT versus 4 and 11% before LRP and FT) was too large to achieve sufficient balance. These differences in the use of neoadjuvant ADT are likely to account for the FFS rates favouring EBRT, considering that residual effects of LHRH agonist use are known to continue in ~25% of men for many months after cessation [29, 30].

The second assumption is that each patient has a probability of receiving each treatment and that there are no values of pre-treatment variables that could occur only among patients receiving one of the treatments [27]. We, therefore, chose inclusion criteria (PSA < 20 ng/mL, ≤ISUP 3 and T-stage ≤ T2c) that represent patients who could have been eligible for all treatments. Baseline variables that were used to construct propensity scores (age, PSA, ISUP grade, MCCL, T-stage, and year of treatment) generally have no values that are exclusively seen in one of the treatment groups.

The demonstrated FFS advantage for patients treated with EBRT was most surprising. From randomised comparative trials, there is evidence that at least prostatectomy and radiotherapy are comparable in terms of oncologic outcomes [3, 31]. Although these trials were conducted between 1989 and 2009 and both treatment techniques have markedly improved since updated results from recent observational studies have only confirmed oncologic equivalence [32]. There are several concerns potentially causing biased results in favour of EBRT in our study. First, EBRT data were collected in a retrospective manner, while focal and LRP data were collected prospectively. Second, unknown or unmeasured confounders may have distorted results. Although EBRT patients had higher PSA and higher-grade disease, they may have had smaller tumours or longer PSA doubling time, potentially indicating less aggressive disease. Third, as discussed above, the widespread use of neoadjuvant ADT among EBRT patients may have substantially improved FFS within the available medium length follow-up.

For the focal group, estimated FFS seemed to decline faster beyond six years follow-up in both the three-way and two-way Kaplan–Meier curves. Although this estimation is limited by smaller numbers of patients at risk at later time points, this may reflect the emergence of residual cancer cells in the treated area or de novo lesions emerging in untreated tissue. This requires further research.

We selected patients with NCCN low- to intermediate-risk disease, assuming eligibility for both radical treatment and FT. Besides active treatment, current guidelines however recommend offering active surveillance (AS) to patients with (very) low-risk disease [33–35]. Following general AS eligibility criteria (Gleason score ≤6, clinical T1c or T2a/b and PSA ≤ 10 ng/mL, not taking into account PSA density or number of positive cores) [36], 222/1360 (16.3%) of patients in our study could have been offered AS. This is important because it is generally agreed that FT should only be considered in men who are likely to benefit from active treatment. Nonetheless, the only randomised focal study available compared focal ablation (using vascular targeted photodynamic therapy [VTP]) to AS, randomising 413 men. At four years, they concluded that conversion to radical treatment was less likely in the focal group (24% vs 53%), lowering the risk of treatment-related morbidity [37]. There has been criticism of this study recruiting men with very low-risk disease and not incorporating a confirmatory MRI-targeted biopsy when a lesion was seen prior to randomisation.

As our primary outcome, we studied the composite endpoint treatment failure, consisting of salvage treatment, metastatic disease, systemic treatment or progression to WW. Here, the frequently used endpoint biochemical progression-free survival is of limited value due to the lack of a biochemical failure definition after FT [38]. Although OS is the most valid and reliable endpoint, treatment failure serves as a clinically meaningful surrogate endpoint within the time frame of this study. We considered prostate bed EBRT after LRP as adjuvant treatment (i.e. part of primary treatment) when given as a consequence of rising PSA and positive surgical margins. Before LRP, patients are explained that surgery entails the risk of incomplete resection, which then requires adjuvant radiotherapy. Therefore, we did not consider such adjuvant treatment as a failure. In the same setting, we allowed one focal re-do as part of the initial focal treatment. WW was added to the treatment failure definition to account for the fact that EBRT patients were older and more likely to have comorbidities, potentially preventing them from undergoing salvage treatment upon recurrence.

Our study did not have comparative toxicity or patient-reported outcome data. Within randomised trials comparing radiotherapy and prostatectomy, no discernible differences were found in patient-reported quality of life, although the variation of reported symptoms differed [7, 39]. With respect to FT, there is evidence from observational retrospective and prospective studies on different sources of ablative energy, showing that it has a significantly lower impact on genitourinary function [11].

The effectiveness of FT is currently being investigated within randomised clinical trials (RCT). A first feasibility study in the UK (PART) has completed recruitment of 80 patients with either unilateral clinically significant (ISUP 2–3 or >4 mm grade 1) intermediate-risk prostate cancer or dominant unilateral cancer with small contralateral low-risk disease (ISRCTN 99760303). They concluded that it is feasible to randomise patients between prostatectomy and focal HIFU, with an achieved randomisation rate of 50%, although the recruitment period had to be extended and the target lowered from 100 to 80. Compliance in the radical prostatectomy arm was also just under 80% [18]. A follow-up RCT is expected, aiming to randomise 800 patients between radical treatment (prostatectomy, EBRT or LDR-brachytherapy) and focal VTP. Another UK-based RCT (CHRONOS) is currently testing the feasibility of recruiting patients to either an RCT of focal (cryotherapy or HIFU) versus radical therapy (EBRT or low-dose-rate brachytherapy or prostatectomy) or a separate multi-arm multi-stage RCT comparing focal alone to focal with neoadjuvant finasteride or bicalutamide (ISRCTN 17796995).

In conclusion, within the confines and limitations of residual confounding that might be present, we found no clinically relevant difference in 6-year treatment failure-free survival between conventional radical treatments and FT. Awaiting longer follow-up data from cohorts and initial results from RCTs, this study offers an insight into the potential of FT, potentially supporting its use in select patients with localised prostate cancer.

Data availability

De-identified participant data that underlie the results reported in this article are stored in an institutional repository and may be shared upon request to the corresponding author.

Author contributions M.J.v.S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M.J.v.S., M. P., D.R., T.T.S., H.U.A. and A.F. Drafting of the manuscript: M.J.v.S. Critical revision of the manuscript for important intellectual content: M.P., D.R., T.T.S., J.J.W.L., S.M., T.D., S.M., R.G.H., A.E., R.N., R. P., J.V., H.L., C.M., C.O., M.E., M.A., H.U.A., J.R.N.v.d.V.v.Z., M. W. and A.F. Statistical analysis: M.J.v.S. and M.P. Obtaining funding: not applicable. Administrative, technical, or material support: S.R., F. H.-J. Supervision: H.U.A., J.R.N.v.d.V.v.Z., M.W. and A.F.

Compliance with ethical standards

Conflict of interest Dr Peters and Dr van der Voort van Zyp received a research grant from the Dutch Cancer Society. Dr Reddy received a research grant from Prostate Cancer UK and received travel grants from Imperial Health Charity and Sonacare. Dr Shah received funding from Prostate Cancer UK and the St Peters Trust and has received funding in the past for conference attendance from Astellas, Ferring and Galil Medical. Professor Moore receives funding from the National Institute for Health Research, The European Association of Urology Research Foundation, MRC, Cancer Research UK, Prostate Cancer UK, Movember and the Cancer Vaccine Institute for clinical prostate cancer research. She has received advisory board fees for Genomic Health. Professor Emberton's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research Centre. He was awarded NIHR Senior Investigator in 2015. He receives funding from NIHR-i4i, MRC (UK), Cancer Research UK, Sonacare Inc., Trod Medical, Cancer Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. He is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical. Professor Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. He currently receives funding from the Wellcome Trust, Medical Research Council (UK), Prostate Cancer UK, Cancer Research UK, The BMA Foundation, The Urology Foundation, The Imperial Health Charity, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials and studies in prostate cancer. He was a paid medical consultant for Sophiris Biocorp and is still a paid proctor for HIFU, cryotherapy and Rezum water vapour therapy. Dr Winkler received a travel grant and a loan of device from Zicom Biobot. The remaining authors declare no competing interests.

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