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Original Article

Prostate cancer outcomes following whole-gland and focal high-intensity focused ultrasound

Matthew G. Parry[1,2], Arunan Sujenthiran[2,3], Julie Nossiter[1,2], Melanie Morris[1,2], Brendan Berry[1,2], Arjun Nathan[2,4], Ajay Aggarwal[1,5], Heather Payne[6], Jan van der Meulen[1] and Noel W. Clarke[7]

[1]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, [2]The National Prostate Cancer Audit, Clinical Effectiveness Unit, Royal College of Surgeons of UK, [3]Flatiron, [4]University College London, [5]Department of Radiotherapy, Guy's and St Thomas' NHS Foundation Trust, [6]Department of Oncology, University College London Hospitals, London, and [7]Departments of Urology, The Christie and Salford Royal Hospitals, Manchester, UK

Heather Payne, Jan van der Meulen and Noel W. Clarke: Joint senior authors have made an equal contribution to this study and manuscript.

Objective

To report the 5-year failure-free survival (FFS) following high-intensity focused ultrasound (HIFU).

Patients and Methods

This observational cohort study used linked National Cancer Registry data, radiotherapy data, administrative hospital data and mortality records of 1381 men treated with HIFU for clinically localised prostate cancer in England. The primary outcome, FFS, was defined as freedom from local salvage treatment and cancer-specific mortality. Secondary outcomes were freedom from repeat HIFU, prostate cancer-specific survival (CSS) and overall survival (OS). Cox regression was used to determine whether baseline characteristics, including age, treatment year, T stage and International Society of Urological Pathology (ISUP) Grade Group were associated with FFS.

Results

The median (interquartile range [IQR]) follow-up was 37 (20–62) months. The median (IQR) age was 65 (59–70) years and 81% had an ISUP Grade Group of 1–2. The FFS was 96.5% (95% confidence interval [CI] 95.4%–97.4%) at 1 year, 86.0% (95% CI 83.7%–87.9%) at 3 years and 77.5% (95% CI 74.4%–80.3%) at 5 years. The 5-year FFS for ISUP Grade Groups 1–5 was 82.9%, 76.6%, 72.2%, 52.3% and 30.8%, respectively ($P < 0.001$). Freedom from repeat HIFU was 79.1% (95% CI 75.7%–82.1%), CSS was 98.8% (95% CI 97.7%–99.4%) and OS was 95.9% (95% CI 94.2%–97.1%) at 5 years.

Conclusion

Four in five men were free from local salvage treatment at 5 years but treatment failure varied significantly according to ISUP Grade Group. Patients should be appropriately informed with respect to salvage radical treatment following HIFU.

Keywords

cancer outcomes, focal therapy, high-intensity focused ultrasound (HIFU), prostate cancer, routine data

Introduction

National guidelines recommend the radical treatment of patients with clinically significant prostate cancer using surgery or radiotherapy (RT) [1,2]. Typically, these treatments are directed at the whole gland, and they can have significant side-effects, most notably urinary incontinence and erectile dysfunction, with RT also causing proctitis and rectal bleeding [3].

Focal therapies such as high-intensity focused ultrasound (HIFU) aim to reduce treatment-related side-effects whilst maintaining cancer control. There is evidence that HIFU has substantially fewer side-effects than with surgery or RT but there is little comparative data regarding cancer outcomes [4,5]. A study by Guillaumier et al. [6] reported a 5-year failure-free survival (FFS) of 88% in 599 men receiving focal treatment between 2006 and 2015 in England. Cases included in that study were prospectively entered into a clinical

registry covering nine centres. A more recent study using the same clinical registry by Reddy et al. [7] reported that 5- and 7-year FFS was 82% and 69%, respectively, in 1379 men receiving focal treatment between 2005 and 2020. Using the same clinical registry, Shah et al. [8] reported that oncological outcomes 8 years after focal treatment in 501 patients were similar between focal therapy and radical prostatectomy (RP) in patients with low- or intermediate-risk prostate cancer.

In this paper, we report cancer outcomes in patients with clinically localised prostate cancer who had HIFU treatment in the English NHS between 2010 and 2018. Men were identified based on National Cancer Registry data in England. This study is more than twice as large as the previous studies reported by Guillaumier et al. [6] and Shah et al. [8], and is comparable to the study reported by Reddy et al. [7], including most of the patients reported in these earlier studies. A key difference is that we used outcomes derived from linked clinical administrative datasets collected routinely at hospital level, rather than from clinician-reported events in specific HIFU treatment centres.

Patients and Methods

Patient Population

As this study used registry and routine data, there were no a priori sample size calculations. We used English Cancer Registry data [9] and Hospital Episode Statistics (HES) [10], linked at patient level, to follow up men with prostate cancer who were treated with HIFU between 1 January 2010 and 31 December 2018. The International Classification of Diseases, 10th Edition (ICD-10) [11] code 'C61' in the cancer registry data was used to identify men with prostate cancer. The Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, Fourth Revision (OPCS-4) code 'M711' in HES specified their treatment with HIFU but did not specify whether treatment was whole gland or focal. With additional linkage to the National Radiotherapy Dataset (RTDS) [12] the cohort was limited to primary HIFU cases by excluding men who were treated with RT or brachytherapy. The resulting final cohort comprised 1381 men treated in 31 hospitals.

Primary Outcome

Failure-free survival was defined as the avoidance of salvage RP or RT and any prostate cancer-specific death following primary HIFU. Repeat HIFU was not included in the primary outcome measure. The RP cases were identified using the OPCS-4 code 'M61' within HES. Patients receiving RT for prostate cancer were identified within the RTDS if the primary ICD code 'C61' was present. The Office for National Statistics (ONS) provided cause and date of death. Prostate cancer-specific death was defined as any death where prostate cancer was identified on the death certificate as part of the sequence leading to death.

Secondary Outcomes

Our secondary outcomes included prostate cancer-specific survival (CSS) and overall survival (OS). The occurrence of skeletal-related events (SREs) was identified using a coding framework previously developed and validated by the research team [13]. In short, SREs were defined as either a pathological fracture, spinal cord compression, bone surgery or palliative RT based on diagnostic and procedure codes in HES data, and RT codes in the RTDS. We also measured freedom from repeat HIFU defined as the subsequent occurrence of any additional OPCS-4 code for HIFU within HES after the date of primary HIFU ('M711').

Explanatory and Control Variables

The T Stage, N Stage, International Society of Urological Pathology (ISUP) Grade Groups and PSA were identified from the National Cancer Registry data [14]. Age at the time of HIFU was taken from HES based on age at the time of admission.

Statistical Analysis

The data analysis was undertaken using Stata version 15 (StataCorp LLC, College Station, TX, USA). Baseline characteristics are presented as median (interquartile range [IQR]) or proportion, as appropriate. Kaplan–Meier estimates of time-to-event outcomes are described with 95% CIs for all men. Follow-up time was defined as the time from HIFU to 31 December 2018 unless the outcome was observed [15]. For analyses of outcomes that include prostate cancer-specific death, patients who died from other causes were handled as censored observations [16]. For the analysis of freedom from repeat HIFU, patients who underwent radical treatment or who died from any cause were handled as censored observations.

Multivariable Cox regression was used to determine whether baseline characteristics were associated with failure, adjusting for age (as continuous variable), treatment year, ISUP Grade Group and T Stage (the latter three all as categorical variables). A sensitivity analysis was used for men diagnosed from April 2014 for whom we had PSA data. This multivariable Cox regression model was additionally adjusted for PSA. Models were adjusted for clustering of outcomes within hospitals using robust standard errors at the hospital level. Hazard ratios (HRs) were estimated with 95% CIs and Wald tests were used to calculate *P* values. This analytical approach was chosen in order to make our results as comparable as possible to the studies of Guillaumier et al. [6] and Reddy et al. [7].

Missing values for ISUP Grade Group and T Stage were imputed using multiple imputation by chained equations [17]. In all, 10 imputed datasets were created, and Rubin's rules used to combine study estimates. Missing values for PSA were additionally imputed for the sensitivity analysis for men diagnosed from April 2014.

Results

Baseline Demographics

A total of 1381 men received primary HIFU between 2010 and 2018, with a median (IQR) post-treatment follow-up of 37 (20–62) months. A total of 31 individual hospitals in England were identified as providers of HIFU, with 10 hospitals treating ≥10 patients and five hospitals treating ≥30 patients. One hospital accounted for 62% of all HIFU treatments. In all, 625 (50%) patients had an ISUP Grade Group of 2 and 392 (31%) had an ISUP Grade Group of 1. The median (IQR) age was 65 (59–70) years. Of the men diagnosed since April 2014, 309 (81%) had a PSA level of <10 ng/mL (Table 1).

Primary Outcome

Following primary HIFU treatment, 145 men underwent external beam RT and 111 had a salvage RP during the observed follow-up period (Table 2). The FFS was 96.5% at 1 year, 86.0% at 3 years, and 77.5% at 5 years (Table 2). The FFS varied according to ISUP Grade Group, with the most marked difference between men with Grade Group 1, 2 and 3, and men with Grade Group 4 and 5 (5-year FFS was 82.9% in men with ISUP Grade Group 1, 76.6% in men with Grade Group 2, 72.2% in men with ISUP Grade Group 3, 52.3% in men with Grade Group 4, and 30.8% in men with Grade Group 5; Table 2, Fig. 1).

Using multivariable Cox regression, we found a statistically significant association between increasing ISUP Grade Group and the rate of FFS according to the Wald test ($P < 0.001$). Compared to ISUP Grade Group 2, FFS was statistically significantly lower for ISUP Grade Groups 3 (HR 1.50, 95% CI 1.02–2.20), 4 (HR 3.04, 95% CI 1.58–5.85) and 5 (HR 9.86, 95% CI 4.45–21.87). There was no statistically significant difference in FFS between ISUP Grade Groups 1 and 2 (HR 0.76, 95% CI 0.56–1.03). This was also observed for the sensitivity analysis for men diagnosed from April 2014, where we could also adjust for PSA ($P < 0.001$).

Table 1 Baseline characteristics of the 1381 patients undergoing HIFU.

Characteristic	Value
Age, years, median (IQR)	65 (59–70)
Treatment year, *n* (%)	
2010	98 (7.1)
2011	95 (6.9)
2012	106 (7.7)
2013	148 (11)
2014	147 (11)
2015	200 (14)
2016	216 (16)
2017	227 (16)
2018	144 (10)
ISUP Grade Group, *n* (%)	
1 (Gleason 6)	392 (31)
2 (Gleason 3 + 4)	625 (50)
3 (Gleason 4 + 3)	196 (16)
4 (Gleason 8)	30 (2.4)
5 (Gleason 9 or 10)	16 (1.3)
Missing	122
T Stage, *n* (%)	
1	257 (25)
2	677 (65)
3	102 (9.8)
Missing	345
PSA level (from April 2014), *n* (%)	
≤10 ng/mL	309 (81)
10–20 ng/mL	62 (16)
>20 ng/mL	11 (2.9)
Missing	268

Secondary Outcomes

At 5 years, 21% of men underwent at least one repeat HIFU treatment (187 patients in total: one repeat treatment in 172, two repeat treatments in 13, and three repeat treatments in two; Table 2). Freedom from repeat HIFU at 1 year was 98.6% (95% CI 97.8%–99.1%), at 3 years was 89.1% (95% CI 86.8%–90.9%), and at 5 years was 79.1% (95% CI 75.7%–82.1%).

In total, nine men experienced an SRE and there were 44 deaths, 13 of which were related to prostate cancer (Table 2). The prostate CSS was 99.8% at 1 year, 99.6% at 3 years, and 98.8% at 5 years. The OS was 99.6% at 1 year, 98.2% at 3 years, and 95.9% at 5 years.

Discussion

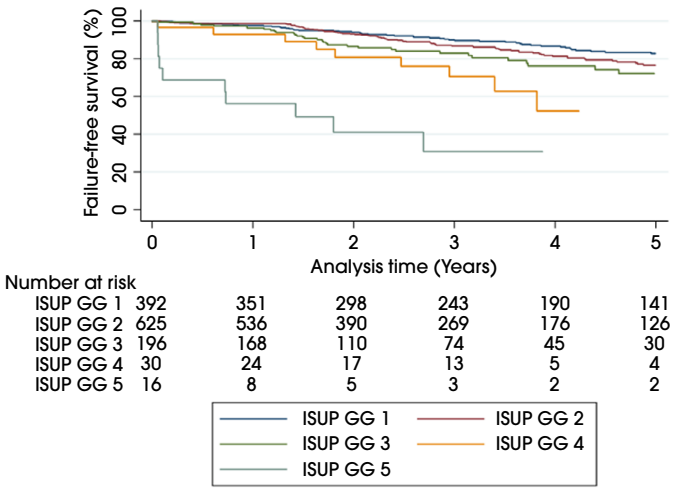
This is one of the largest case series published to date, reporting prostate cancer outcomes following primary HIFU treatment. We aimed to include all men who had HIFU as their primary treatment between 2010 and 2018 in the English NHS. Our results have important implications. First, they indicate overall that about one in every 100 men with this type of prostate cancer will die from their disease, and about one in five men undergoing HIFU will experience treatment failure requiring salvage intervention within 5 years of their primary HIFU treatment. Second, FFS was strongly associated with ISUP Grade Group, with men in the two highest ISUP Grade Groups having poor outcomes. For example, we found that only half of men in ISUP Grade Group 4 and only a third of men in ISUP Grade Group 5 were free from treatment failure at 5 years.

Table 2 Kaplan–Meier estimates of OS, prostate CSS, FFS and freedom from repeat HIFU.

	Kaplan–Meier estimate, % (95% CI)			P*
	1 year	3 years	5 years	
Primary outcome				
FFS	96.5 (95.4–97.4)	86.0 (83.7–87.9)	77.5 (74.4–80-3)	
ISUP GG 1	97.6 (95.5–98.8)	90.0 (86.2–92.8)	82.9 (77.8–86.9)	<0.001
ISUP GG 2	98.7 (97.4–99.4)	86.9 (83.2–89.8)	76.6 (71.2–81.1)	
ISUP GG 3	96.3 (92.4–98.2)	82.9 (75.7–88.2)	72.2 (61.5–80.3)	
ISUP GG 4	93.0 (74.6–98.2)	70.6 (47.3–85.0)	52.3 (24.5–74.2)	
ISUP GG 5	56.3 (29.5–76.2)	30.8 (9.1–56.1)	30.8 (9.1–56.1)	
Secondary outcomes				
Free from repeat HIFU	98.6 (97.8–99.1)	89.1 (86.9–90.9)	79.1 (75.7–82.1)	
ISUP GG 1	97.9 (95.7–98.9)	90.0 (86.1–92.9)	83.5 (78.2–87.6)	0.050
ISUP GG 2	99.3 (98.2–99.8)	89.1 (85.6–91.8)	76.0 (70.0–81.1)	
ISUP GG 3	97.8 (84.0–98.9)	87.7 (80.7–92.3)	72.4 (58.5–82.4)	
ISUP GG 4	93.3 (75.9–98.3)	76.4 (50.4–90.0)	76.4 (50.4–90.0)	
ISUP GG 5	100	100	100	
CSS	99.8 (99.3–100)	99.6 (99.0–99.8)	98.8 (97.7–99.4)	
ISUP GG 1	100	100	99.6 (97.1–100)	<0.001
ISUP GG 2	100	100	99.1 (96.3–99.8)	
ISUP GG 3	100	100	98.9 (92.5–99.8)	
ISUP GG 4	100	100	100	
ISUP GG 5	87.5 (58.6–96.7)	80.8 (51.4–93.4)	80.1 (51.4–93.4)	
OS	99.6 (99.0–99.8)	98.2 (07.2–98.8)	95.9 (94.2–97.1)	
ISUP GG 1	100	99.1 (97.3–99.7)	98.2 (95.6–99.3)	<0.001
ISUP GG 2	99.7 (98.7–100)	98.7 (97.2–99.4)	97.4 (94.9–98.7)	
ISUP GG 3	100	97.8 (93.4–99.3)	93.1 (85.6–96.7)	
ISUP GG 4	96.3 (76.5–99.5)	96.3 (76.5–99.5)	91.0 (67.7–97.7)	
ISUP GG 5	87.5 (58.6–96.7)	73.4 (43.5–89.2)	73.4 (43.5–89.2)	

*GG, Grade Group. *Wald tests of the multivariable Cox regression model (with adjustment for age, treatment year, ISUP GG and T Stage) were used to calculate P values testing the hypothesis that each outcome variable at 5 years varied significantly with ISUP GG.*

Fig. 1 Kaplan–Meier curves showing FFS.



A key strength of our study is that it aims to describe outcomes in all patients who were treated in the English NHS in a recent period. Our study includes any patient coded as having HIFU within HES and as such includes all NHS hospitals in England and not just the hospitals that contribute data into a clinical HIFU registry. The accuracy of administrative hospital data has been shown to be high (84%) when compared to clinical documentation and these types of data are widely considered to be sufficiently robust to support its use in research [18].

Also, our data sources are able to identify failure events that occur at local hospitals peripheral to the specialist centre where the HIFU originally took place. This is one potential explanation as to why we report a slightly lower 5-year FFS of 78% compared to 88% reported in the study by Guillaumier et al. [6]. The larger follow-up study of Reddy et al. [7] included 1379 men and reported a 5-year FFS of 82%, which is closer the 5-year FFS that we report, as well as a 7-year FFS of 69%. However, it is unclear to what extent the national coverage of our data explains the differences in FFS between our study and those that make use of a clinical registry, including patients in a selection of hospitals. Our study, based on linked national clinical and administrative hospital data, is not able to explore the origin of these differences.

Another possible explanation for the difference is that the patients in our study included some whole-gland HIFU cases because the procedure code for HIFU does not differentiate between whole-gland and focal HIFU, which is a limitation of the hospital administrative database that we used. However, it is also important to note that our sensitivity analysis, which excluded cases prior to April 2014 by which time whole-gland

HIFU was much less frequently used than focal HIFU in the UK, had similar FFS results as our main analysis.

Other potential reasons for the difference may lie in the different hospitals and time periods that were included. Our study included all NHS hospitals in England, and we captured additional cases that were not included in the clinical registry reported by Guillaumier et al. [6] and Reddy et al. [7]. This said, 1214 of the 1389 patients (87%) included in this paper received HIFU at one of five NHS hospitals that entered patients into the HIFU clinical registry used in the papers of Guillaumier et al. [6] and Reddy et al. [7]. However, it should be noted that in this clinical registry the authors included a small number of patients from four private hospitals that were not included in our study.

Finally, our definition of FFS did not include the avoidance of either systemic therapy or development of metastases as these were not accurately recorded within our datasets. However, as these are rare events within 5 years of diagnosis in patients with prostate cancer who received radical local treatment, we expect that their exclusion had little impact on our results. Furthermore, any effect would have decreased the FFS estimates that we report, further increasing the difference between our results and the studies by Guillaumier et al. [6] and Reddy et al. [7].

With respect to CSS, our results, showing 98.8% survival at 5 years, are consistent with the studies of Guillaumier et al. [6] and Reddy et al. [7]. This is encouraging given there is no evidence to suggest that primary HIFU leads to a detriment in CSS at 5 years. However, according to our data, it is estimated that 21% of patients receiving HIFU as their primary treatment required more than one HIFU treatment, and 22% required salvage treatment or died from their prostate cancer within 5 years. In future studies, linkage of the data from clinical registries with data derived from routinely collected cancer registry and administrative hospital datasets would help to resolve the discrepancies between the data sources.

The reporting of outcomes at 10 years and beyond will be important, given that CSS from localised prostate cancer is high in the short and medium term, irrespective of management, particularly for active surveillance of ISUP Grade Groups 1 and 2 [19–21]. The results from the Partial Prostate Ablation vs Radical Prostatectomy (PART) trial are awaited and will be important for judging the value of HIFU for intermediate-risk prostate cancer [22].

Given our findings, that one fifth of men receiving primary HIFU will require local salvage treatment within 5 years, it is clear that patient selection for HIFU is key, and our results highlight the importance of patient preference and appropriate counselling at initial treatment planning.

A further aspect that needs consideration is the side-effect profile after primary HIFU treatment. Reports indicate that focal therapy has a minimal impact on quality of life and that genitourinary function is well preserved [4,5], consistent with the results of the study by Guillaumier et al. [6], which showed that 98% of men were pad-free and 80% were pad-free, leak-free at 2–3 years. However, a study using HES data of 1742 HIFU patients treated between 2007 and 2018 in the English NHS reported that the occurrence of urethral strictures following HIFU was 10% and 1.3% developed a urinary fistula (without specifying the duration of follow-up) [23]. This study also investigated further treatments after HIFU and reported that for patients with at least 5 years of follow-up, 18% had salvage treatment (either RT, surgery, or both), within 5 years of the primary HIFU treatment. Its results are more in line with the 5-year FFS of 78% reported in our study and the FFS of 82% reported by Reddy et al. [7], rather than the FFS of 88% reported by Guillaumier et al. [6].

In conclusion, our analysis of linked routinely collected national data found that the 5-year FFS after primary HIFU in England is 78%, which is lower than that reported by other series using clinical registries. Patients should be appropriately informed about the possible need for repeat HIFU and salvage treatment, the rate of which is linked to cancer grade. Further follow-up beyond 5 years is required to fully judge the impact of HIFU on cancer control in the longer term.

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Author Contributions

Designed the work: Matthew G. Parry, Jan van der Meulen. Analysed and interpreted data: Matthew G. Parry, Julie Nossiter, Melanie Morris, Ajay Aggarwal, Heather Payne, Jan

van der Meulen, Noel W. Clarke. Drafted article: Matthew G. Parry, Jan van der Meulen. Provided critical revision: All authors. Approved final version to be published: All authors.

Ethics Approval and Consent to Participate

This study was exempt from NHS Research Ethics Committee approval because it involved analysis of pseudonymised linked data collated for the purpose of service evaluation as part of the National Prostate Cancer Audit.

Disclosure of Interests

Arunan Sujenthiran is an employee of Flatiron Health, an independent subsidiary of the Roche group, and holds stock in Roche. Heather Payne has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Janssen, Sanofi Aventis, Takeda, Ipsen, Ferring, Sandoz, and Novartis. Jan van der Meulen reports a contract with the HQIP for the provision of the National Prostate Cancer Audit (www.npca.org.uk) funded by the HQIP (www.hqip.org.uk). Noel W. Clarke has attended and received honoraria for advisory boards, travel expenses to medical meetings, and served as a consultant for AstraZeneca, Astellas, Bayer, Janssen, Sanofi Aventis, Takeda, Ipsen and Ferring.

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Data Availability Statement

The cancer registry data used for this study are based on information collected and quality assured by Public Health England's National Cancer Registration Service (www.ncras.nhs.uk). Access to the data was facilitated by the Public Health England's Office for Data Release. HES were made available by the NHS Digital (www.digital.nhs.uk); all rights reserved. Matthew G. Parry had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Data are not available to other researchers as it uses existing national datasets.

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Correspondence: Matthew George Parry, The National Prostate Cancer Audit, The Clinical Effectiveness Unit, Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London WC2A 3PE, UK.

e-mail: mparry@rcseng.ac.uk

Abbreviations: CSS, cancer-specific survival; FFS, failure-free survival; HES, Hospital Episode Statistics; HIFU, high-intensity focused ultrasound; HQIP, Healthcare Quality Improvement Partnership; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; ISUP, International Society of Urological Pathology; OPCS-4, Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures, Fourth Revision; OS, overall survival; RP, radical prostatectomy; RT, radiotherapy; RTDS, Radiotherapy Dataset; SRE, skeletal-related event.