Cancer control outcomes following focal therapy using HIFU in 1,379 men with non-metastatic prostate cancer: a multi-institute 15- year experience.

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Abstract

Background

Focal therapy aims to treat areas of cancer to confer oncological control whilst reducing treatment-related functional detriment.

Objective

To report oncological outcomes and adverse events following focal HIFU for treating non-metastatic prostate cancer.

Design, Setting and Participants

Analysis of 1379 patients with 6 months follow-up or greater prospectively recorded in the HEAT registry from 13 UK centres (2005-2020). 5-year follow-up or greater was available in 325 (24%). Focal HIFU therapy used a transrectal ultrasound-guided device (Sonablate, Sonacare).

Outcome Measurements and Statistical Analysis

Failure-free survival (FFS) was primarily defined as avoidance of no evidence of disease to require salvage whole-gland or systemic treatment, or metastases or prostate cancer-specific mortality. Differences in FFS between D'Amico risk groups were determined using log rank analysis. Adverse events were reported using Clavien-Dindo classification.

Results and Limitations

Median (IQR) age was 66 years (60-71) and PSA 6.9ng/ml (4.9- 9.4) with D'Amico intermediate in 65% (896/1379) and high-risk in 28% (386/1379). Overall median follow-up was 32 (17-58) months; for those with >/=5 years follow-up 82 (72-94). 252 had repeat focal due to residual or recurrent cancer; overall 92 patients required salvage whole-gland treatment. Kaplan-Meier 7-year FFS was 69% (64-74%). 7-year FFS in intermediate and high-risk cancers was 68% (95%CI 62-75%) and 65% (95%CI 56-74%) (p=0.3). Clavien-Dindo >2 adverse events occurred in 0.5% (7/1379). Median 10-year follow-up is lacking.

Conclusions

Focal HIFU in carefully selected patients with clinically significant prostate cancer, with 6 and 3 in 10 patients having intermediate and high-risk cancer, has good cancer control in the medium term.

Patient Summary

Focal HIFU treatment to areas of prostate with cancer can provide an alternative to treating the whole prostate. This treatment modality has good medium-term cancer control over 7 years, although 10-year data is not yet available.

Introduction

Treatment of patients with non-metastatic, clinically significant prostate cancer consists of whole-gland approaches using radical prostatectomy or radical radiotherapy (1-3). In patients with intermediate and high-risk disease, radical therapy leads to improvements in both progression-free survival and cancer-specific survival but can confer some treatment-related complications including genitourinary and rectal side-effects (4, 5).

Improvements in diagnostic accuracy and localisation of clinically significant prostate cancer has allowed focal therapy to be considered in carefully selected patients (6). Whilst initially seen as an alternative to active surveillance, it is now arguably seen as a potential treatment modality for patients diagnosed with intermediate to high-risk localised prostate cancer who would otherwise undergo radical therapy (7-10) while minimising treatment-related complications and side-effects (11-13).

Over the last 15 years in the UK, focal HIFU has undergone a programme of health technology evaluation within trials or has been offered as a standard alternative in several centres in which special arrangements included the requirement for prospective registries after multidisciplinary team review and informed consent with written patient information sheets. We report updated multicentre results in patients with non-metastatic prostate cancer, reported in the 'HIFU Evaluation and Assessment of Treatment' (HEAT) registry (14).

Methods

1379 patients with a minimum 6-months follow-up reported within the HEAT registry following focal HIFU between November 2005- July 2020, using the Sonablate (500 and 3G) device (Sonacare Inc., Charlotte, NC, USA) in thirteen centres within the UK, were evaluated. Patients with Gleason Score 6-9 prostate cancer, and radiological stage up to T3bN0M0 were offered focal therapy. This study was exempt from ethics committee approval and the requirement of informed consent of patients were waived as it is a registered audit of clinical outcomes post-surgical intervention by local Research and Development

departments for service and quality assurance. The study was performed in accordance with the declaration of Helsinki.

Patients underwent 1.5 Tesla or 3 Tesla multiparametric MRI (mpMRI) and transrectal or transperineal biopsy. In patients with MRI score (Likert or PIRADS v1 or v2) >/=3, targeted and systematic biopsies were performed; some patients underwent transperineal 5-10mm template mapping biopsies. To ensure suitability for focal therapy, patients with conflicting imaging and histology results underwent further biopsy. Only patients with MRI visible lesions and no high-volume (>/=6mm) Gleason score 3+3=6 or any volume Gleason score >/=3+4=7 disease in areas to be left untreated were considered suitable for focal ablation.

Patients were classified into D'Amico low, intermediate or high-risk disease. Intermediate and high-risk groups underwent radioisotope bone-scan or cross-sectional imaging to rule-out local nodal or distant disease as per local standard of care.

Ablative patterns considered as focal are demonstrated in our previously published study (14). Multiple lesions could be considered for treatment, provided the overall ablation area was in accordance with the maximum permitted ablative pattern. Ablation field was outlined using either intra-operative MRI-TRUS fusion or expert- guided visual-estimation, to allow a minimum of 5mm margin for all MRI visible lesions; this usually led to quadrant or hemi-ablation. Patients were considered not suitable for focal treatment if the tumour abutted the urinary sphincter, urethra, or required ablation adjacent to neurovascular bundles bilaterally. The procedure was performed under antibiotic prophylaxis according to local guidance. A typical regime would entail gentamicin intravenously on induction of anaesthetic and ciprofloxacin continuing for 7 days.

Up to 2 focal therapy sessions were allowed. Use of neoadjuvant and adjuvant androgen deprivation therapy (ADT) within 12 months of focal therapy was used as a temporising or cytoreductive strategy by some physicians, if it was felt that any delays in treatment would be detrimental. Patients underwent a trial without catheter 7-10 days following treatment and were taught how to self-catheterise as a precaution.

Patients were clinically evaluated for signs or symptoms of disease progression or recurrence at all interactions. Recommended follow-up included 3-6 monthly PSA follow-up

in the first year, and 6-monthly thereafter, with mpMRI at 6-12 months. For-cause mpMRIs were performed if consecutive PSA rises over 3 readings without predisposing causes were identified. A transperineal biopsy of typically 3-6 cores with further 6-9 cores systematic sampling was advised if MRI revealed suspicion of recurrent or residual disease; referencing our previous publication demonstrating a negative mpMRI had a negative predictive of 90-96% for significant cancer (cancer core length >/=3mm of any grade or any pattern 4) when compared to protocol mandated biopsy (15).

If a patient declined a for-cause mpMRI or biopsy when clinically indicated, or mpMRI did not indicate the need for biopsy, they continued with PSA surveillance on a 3-6-monthly basis. In cases of continually rising PSA results, the indication for biopsy was re-discussed and often carried out.

If clinically significant cancer defined as >/=3+4 disease occurred in-field (residual disease), or out-of-field (de-novo or progressive disease) was identified, patients were offered repeat focal treatment, radical radiotherapy or radical prostatectomy. Any further treatment including hormone treatment, chemotherapy or palliative treatments were recorded.

Adverse events were identified at all healthcare interactions. Follow-up time for oncological analyses was calculated according to last clinical review evaluating risk of disease recurrence/ progression relative to treatment date and when evaluated overall survival included date of death. Although patients were encouraged to return questionnaires for patient reported outcome measures (PROMS) rates of return were poor and robust analyses of these was not possible.

Primary outcome was failure-free survival (FFS) with failure defined as evidence of cancer requiring whole-gland salvage treatment or third focal therapy treatment, systemic treatment, development of prostate cancer metastases or prostate cancer specific death. Secondary outcomes included a) any retreatment-free survival b) salvage whole-gland and systemic treatment-free survival c) ADT-free survival, d) metastases-free and prostate cancer specific survival, e) overall survival and f) adverse events and complications classified by the Clavien-Dindo system. Secondary analyses compared the above outcomes per

D'Amico risk score, per ISUP group 1-3 and separately for the cohort of patients with at least 5 years follow up.

Baseline demographics are presented with descriptive statistics in which median and interquartile range, or absolute numbers and proportions were used as appropriate. Failure-free survival as well as other secondary cancer control outcomes, with 95% confidence intervals, were determined using Kaplan-Meier. Log-rank test was used to determine differences in failure rates between patient groups. All analyses were performed using IBM SPSS version 25 (Armonk, NY, USA) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

Baseline Demographics

Overall median (IQR) follow-up was 32 (17-58) months and 82 (72-94) for the 325 patients with >/=5 years follow-up. Median (IQR) follow up for patients with no reported event (n=1218) was 19 (5-43) months, median (IQR) time to failure event was 42 (27-63) months. Median (IQR) age was 66 years (60-71) and PSA 6.9ng/ml (4.9-9.4) [Table 1]. Most patients (65%, 896/1379) had intermediate-risk disease and diagnosed following transperineal biopsy [Table 1, Supplementary-Table 1]. 79% (1093/1379) had ISUP group >/=2 [Table 1]. 13/1379 (0.9%) received either neoadjuvant or cytoreductive ADT. 850/1379 (62%) of patients underwent quadrant ablation [Table-1].

Primary Outcome

The FFS (95%CI) at 7 years was 69% (64-74%), [Table-2] [Figure 1a]. 7-year FFS in intermediate and high-risk cancers was 68% (95%CI 62-75%) and 65% (95%CI 56-74%) (p=0.3) [Figure 1b, Table-2].

Secondary Outcomes

FFS (95% CI) at 7 years for patients with at least 5-years follow-up was 74% (69-80%), with no statistically significant difference demonstrated between intermediate and high-risk disease [Supplementary-Figure 1a-b, Supplementary-Table 2]. Significant differences in FFS

(95% CI) at 7 years between ISUP grade 2 and 3 were identified (p=0.05) [Supplementary Table 3]. In patients followed-up for at least 5 years, 242 reported no failure event. The median (IQR) follow- up of these patients was 82 (71-92) months.

During the first year following treatment 1157 underwent at least 2 PSA tests. Throughout the study period 2224 follow-up mpMRIs were undertaken by 1123 patients; 544 underwent 1 mpMRI, 285 underwent 2, 159 underwent 3, 135 underwent 4 or more mpMRIs. 256 patients did not undergo follow-up mpMRI, only 10 of whom reported treatment failure.

Due to concerns of recurrence or residual disease, 609 patients underwent 853 biopsy sessions, which were performed as either standard of care follow-up biopsies or for-cause biopsies. 401 patients underwent 1 biopsy session post-treatment, 175 patients underwent 2 biopsy sessions, and 33 patients underwent 3 or more biopsy sessions. Overall, recurrent/residual disease was reported in 488 biopsies performed reflecting 403 patients. Subsequently, 352 biopsies performed, representing 314 patients, demonstrated Gleason Grade >/=3+4=7 during their follow-up period [Supplementary-Table-4].

252 patients underwent at least 1 repeat focal therapy session. 225 underwent 1 repeat session, 26 underwent 2 repeat sessions, 1 patient underwent a total of 4 focal therapy sessions. Retreatment-free survival (95% CI) at 7-years was 43% (39-49%) [Supplementary-Table 5, Supplementary-Figure 2A]. Statistically significant differences in retreatment-free survival were observed between D'Amico risk groups (p<0.0001). [Supplementary-Figure-2B, Supplementary-Table-5].

53 patients transitioned to salvage radical prostatectomy and 39 underwent salvage radiotherapy or brachytherapy. Of the 53 undergoing salvage radical prostatectomy, 9 did so after the second focal session. No patient undergoing salvage radical radiotherapy subsequently required any other treatment. Prior to salvage radical radiotherapy, 20 had two focal HIFU sessions and 1 had a whole-gland HIFU session.

Overall, 132 patients underwent salvage local whole-gland or systemic treatment. Salvage whole-gland and systemic treatment-free survival at 7-years was 75% (71-80%) [Supplementary-Figure-2C]. Kaplan-Meier estimates at 7 years are 95% (87-100%), 73% (67-80%) and 73% (65-82%) for low, intermediate and high-risk disease, respectively (p=0.006) [Supplementary-Figure-3D]. There was no statistically significant difference between intermediate and high-risk disease outcomes (p=0.5) [Table-2, Supplementary-Figure 2D].

39 patients received ADT after focal therapy associated with salvage therapy. 7-year ADT-free survival was 92% (89-96%) [Supplementary-Figure-2E], with no statistically significant differences demonstrated between D'Amico risk groups (p=0.1) [Supplementary-Figure-2F, Supplementary-Table-5].

Overall, 3 patients developed metastases, one of whom subsequently died from prostate cancer. All three patients had T3a disease; two of these had PSA 2.5ng/ml and 0.73ng/ml prior to focal HIFU indicating they might have been PSA non-secretors. 7-year metastases-free and prostate cancer specific survival was 100 (99-100%) [Supplementary-Figure-2G]. Statistically significant differences were observed between D'Amico risk groups (p=0.045) [Supplementary-Figure-2H, Supplementary-Table-5].

During the study period 20 patients were noted to have died from any cause, with overall survival (95%CI) at 7 years being 97% (96-99%), [Supplementary-Figure 2I] with no statistically significant differences observed between D'Amico risk groups (p=0.1) [Supplementary-Table 5, Supplementary Figure- 2J].

Rates of complications with Clavien-Dindo score >2 was 0.5% (7/1379), with most complications either self-resolving or not requiring admission or intervention [Supplementary-Table-6]. A total of 83/1379(6.0%) post-operative complications were noted. Urinary tract infections and epididymo-orchitis were reported in 52 (3.8%) and 11 (0.8%), respectively, one patient required resection of a prostatic abscess and one admitted for subsequent urosepsis. Post-treatment retention was observed in 10 (0.7%) with 3 requiring endoscopic intervention to get catheter free. 1 (0.1%) was treated under spinal anaesthetic, however had incomplete focal treatment due to patient movement; during his

1-year follow-up he required no further retreatment. There were 2 (0.1%) cases of recto-urethral fistulae. One required management with urethral and suprapubic catheters for urinary diversion with subsequent spontaneous fistula healing and the other required reconstructive surgery due to failure of conservative management.

Discussion

To our knowledge this is the largest reported cohort for any form of focal ablative technique. Our multi-centre UK based study demonstrated 69% FFS at 7 years after primary focal HIFU therapy for non-metastatic prostate cancer. Metastases-free survival and prostate cancer specific mortality at 7 years was 100%, and overall survival at 7 years was 97%, and compare similarly to recently published series (16). These outcomes are more clinically relevant as over 90% of our cohort had intermediate to high-risk cancer with modern imaging and biopsy strategies, compared to historical cohorts which had predominantly low risk cancer or diagnosed with transrectal systematic biopsies (16-18). The oncological control demonstrated after focal HIFU is concordant with the rates seen in our earlier paper of 625 patients and continue to reinforce the acceptable medium-term outcomes (14). Approximately one-fifth of cases needed a second session of focal HIFU over 7 years. A second focal therapy treatment appears to be effective and remains part of our focal therapy intervention (19). Patients are counselled that up to two sessions may be required to adequately treat their disease, while preserving at least one neurovascular bundle. Our UK-based group do not advocate the use of third focal HIFU therapy treatment as recurrence or residual disease following two separate sessions would indicate the disease may either be resistant to high temperatures (>70˚C), or the energy can't be delivered to the disease location.

The outcomes observed in this study allow clinicians to better counsel patients with clinically significant prostate cancer who are eligible for tissue preserving strategies. Our recent COMPARE study findings showed that patients were willing to trade small detriments in cancer control in order to return to normal activities quicker, maintain continence and erectile function in both intermediate and high risk cases (20). Our data shows that patients eligible for focal HIFU therapy need not make that compromise.

We have recently reported a propensity matched analysis of focal therapy (HIFU or cryotherapy) in comparison to radical prostatectomy and radical radiotherapy and showed no clinically relevant differences in failure-free survival (21, 22). Nonetheless, randomised controlled trials comparing radical strategies to focal therapy are currently underway to test clinical and patient equipoise, such as IP4-CHRONOS and PART, although if successful at recruiting will take another decade before primary outcomes are known (23, 24).

A strength of our study is that very few low-risk patients were treated, with only 20 (1.5%) having low risk, low volume radiological </=T1c disease treated about a decade ago; this was when our focal programme first started at a time when radical treatment for low-risk disease was considered appropriate and conducted widely. Further, complications following focal HIFU were reported in 6% while serious adverse events were rare; there has previously been concern about rectal injury during HIFU but we have confirmed the low number (0.1%) developing a recto-urethral fistula which matches rates of fistula following radiotherapy or rectal injury following prostatectomy (25). In fact, one of these cases healed with conservative management with catheter diversion of urine. Such outcomes reinforce the safety profile of focal HIFU over time (26, 27). We accept that previous reports of a smaller number of cases observed higher urinary tract infection and retention rates. Patients' notes were reviewed for entry into the registry, so source data was verified in the majority. Lower urinary retention rates may be explained by the move from hemi-gland ablation to quadrant ablation and because patients were often then taught self-catheterisation as a precaution following the initial trial without catheter.

There are limitations. First, despite the considerable time span in which patients were treated our median follow-up was 32 months due to the significant growth in numbers over the last 5 years which inevitably reduce the median. Further patients are lost to follow up or care transferred locally, limiting the long term follow up available within the registry. Second, we recognise that standard of care or protocolised biopsies providing histological confirmation of recurrence or lack of recurrence would be reassuring. The timings for MRI and biopsies after treatment were also dependent upon clinical parameters and patient decision. This reflects real life practice and remains a limitation of observational series reported from registries where patients often do not consent to routine post-treatment biopsies with stable PSA and non-suspicious MRIs. High level evidence in the form of cohort

trials such as INDEX (NCT01194648) will better inform the most appropriate follow-up regimens. Nevertheless, for-cause mpMRI and/or biopsies due to clinical concern remains an accepted management pathway with mpMRI having previously been robustly evaluated (15). Third, we recognise the value in reporting location of recurrence, however our database registry did not capture this variable to a level that we were able to report on. Fourth, the rate of functional PROMS completion was low although we have previously reported PROMS outcomes from our prospective trials which show pad-free continence of 98-99% and erectile function preservation of 85-95% in patients with good baseline function (19, 28-30).

Conclusions

Focal HIFU in carefully selected patients with clinically significant prostate cancer, with 6 and 3 in 10 patients having intermediate and high-risk cancer, has good cancer control in the medium term.

Take Home Message

Focal HIFU is a safe alternative treatment option for patients with intermediate to high risk localised prostate cancer which confers good medium-term cancer control.

Funding and role of funder

Sonacare support the HIFU UK national registry (called HEAT) through an unrestricted grant. No funding source had a role or input into the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Authorship

TS and DR were responsible for data collection, analysis of the data. TS, DR and MP were responsible for production of the first draft and completed the data analysis. All authors were involved in data collection, manuscript preparation/drafting and approval of the final draft. HUA 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. HUA guarantor of the study.

Conflicts of Interest

Ahmed's research is supported by core funding from the United Kingdom's National Institute of Health Research (NIHR) Imperial Biomedical Research Centre. Ahmed currently receives funding from the Wellcome Trust, Medical Research Council (UK), Cancer Research UK, Prostate Cancer UK, National Institute for Health Research (UK), The Urology Foundation, BMA Foundation, Imperial Health Charity, NIHR Imperial BRC, Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed was a paid medical consultant for Sophiris Biocorp in the previous 3 years.

Mark 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. Emberton 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. Emberton is a medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging and Profound Medical.

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.

Shah receives funding from Prostate Cancer UK and the St Peters Trust for clinical research and has received funding for conference attendance from Astellis, Ferring and Galil Medical.

Ahmed, Emberton, Hindley, Moore, Arya and Dudderidge are all proctors for HIFU and are paid for training other surgeons in this procedure. Ahmed and Arya are proctors for cryotherapy and are paid for training other surgeons in this procedure. Emberton is a proctor for Irreversible Electroporation (Nanoknife) and is paid for training other surgeons in this procedure. Ahmed and Hindley are paid proctors for Rezum for the treatment of benign prostate hyperplasia.

Winkler receives a travel grant and previously a loan of device from Zicom Biobot.

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References

1. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415-24.
2. Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377(2):132-42.
3. Okamoto K, Okuyama K, Kohno N, Tsugawa T. Clinical outcomes of low-dose-rate brachytherapy based radiotherapy for intermediate risk prostate cancer. J Contemp Brachytherapy. 2020;12(1):6-11.
4. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368(5):436-45.
5. Zhang P, Qian B, Shi J, Xiao Y. Radical prostatectomy versus brachytherapy for clinically localized prostate cancer on oncological and functional outcomes: a meta-analysis. Transl Androl Urol. 2020;9(2):332-43.
6. Lomas DJ, Ahmed HU. All change in the prostate cancer diagnostic pathway. Nat Rev Clin Oncol. 2020;17(6):372-81.
7. Tay KJ, Scheltema MJ, Ahmed HU, et al. Patient selection for prostate focal therapy in the era of active surveillance: an International Delphi Consensus Project. Prostate Cancer Prostatic Dis. 2017;20(3):294-9.
8. Muller BG, van den Bos W, Pinto PA, de la Rosette JJ. Imaging modalities in focal therapy: patient selection, treatment guidance, and follow-up. Curr Opin Urol. 2014;24(3):218-24.
9. Adil Ouzzane NB, Massimo Valerio, Ardeshir Rastinehad, Pierre Colin, Quillaume Ploussard. Focal therapy as primary treatment for localized prostate cancer: definition, needs and future. Future Oncol. 2017;12(8):727-41.
10. Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol. 2015;67(4):771-7.
11. Shah TT, Peters M, Eldred-Evans D, et al. Early-Medium-Term Outcomes of Primary Focal Cryotherapy to Treat Nonmetastatic Clinically Significant Prostate Cancer from a Prospective Multicentre Registry. Eur Urol. 2019;76(1):98-105.
12. Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). 2013;25(8):461-73.
13. Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol. 2007;4(11):632-42.
14. Guillaumier S, Peters M, Arya M, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. Eur Urol. 2018;74(4):422-9.
15. 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- e15.
16. Tourinho-Barbosa RR, Sanchez-Salas R, Claros OR, et al. Focal Therapy for Localized Prostate Cancer with Either High Intensity Focused Ultrasound or Cryoablation: A Single Institution Experience. J Urol. 2020;203(2):320-30.
17. Azzouzi A-R, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer

(CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol. 2017;18(2):181-91.
18. Abreu AL, Peretsman S, Iwata A, et al. High Intensity Focused Ultrasound Hemigland Ablation for Prostate Cancer: Initial Outcomes of a United States Series. J Urol. 2020;204(4):741-7.
19. Lovegrove CE, Peters M, Guillaumier S, et al. Evaluation of functional outcomes after a second focal high-intensity focused ultrasonography (HIFU) procedure in men with primary localized, non-metastatic prostate cancer: results from the HIFU Evaluation and Assessment of Treatment (HEAT) registry. BJU Int. 2020;125(6):853-60.
20. Watson V MN, Krucien N, Abu V, Ikenwilo D, Emberton M, Ahmed HU. Evaluating the Trade-offs Men with Localised Prostate Cancer Make Between the Risks and Benefits of Treatments: The COMPARE Study. J Urol. 2020; 204(2):273-280
21. Shah TT, Reddy D, Peters M, et al. Focal therapy compared to radical prostatectomy for non-metastatic prostate cancer: a propensity score- matched study. Prostate Cancer Prostatic Dis. 2020.
22. van Son MJ, Peters M, Reddy D, et al. Conventional radical versus focal treatment for localised prostate cancer: a propensity score weighted comparison of 6-year tumour control. Prostate Cancer Prostatic Dis. 2021.
23. Reddy D, Shah TT, Dudderidge T, et al. Comparative Healthcare Research Outcomes of Novel Surgery in prostate cancer (IP4-CHRONOS): A prospective, multi-centre therapeutic phase II parallel Randomised Control Trial. Contemp Clin Trials. 2020;93:105999.
24. Hamdy FC, le Conte S, Davies LC, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess. 2018;22(52):1-96.
25. Novara G, Ficarra V, Rosen RC, et al. Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):431-52.
26. Schmid FA, Schindele D, Mortezavi A, et al. Prospective multicentre study using high intensity focused ultrasound (HIFU) for the focal treatment of prostate cancer: Safety outcomes and complications. Urol Oncol. 2020;38(4):225-30.
27. Dosanjh A, Harvey P, Baldwin S, et al. High-intensity Focused Ultrasound for the Treatment of Prostate Cancer: A National Cohort Study Focusing on the Development of Stricture and Fistulae. Eur Urol Focus. 2020.
28. Ahmed HU, Freeman A, Kirkham A, et al. Focal therapy for localized prostate cancer: a phase I/II trial. J Urol. 2011;185(4):1246-54.
29. Ahmed HU, Hindley RG, Dickinson L, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol. 2012;13(6):622-32.
30. Ahmed HU, Dickinson L, Charman S, et al. Focal Ablation Targeted to the Index Lesion in Multifocal Localised Prostate Cancer: a Prospective Development Study. Eur Urol. 2015;68(6):927-36.