EUROPEAN UROLOGY xxx (xxxx) xxx–xxx

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Original Article

Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries

Alexander Light[a,b,*], *Max Peters*[c], *Archana Gopalakrishnan*[a,b], *Nikhil Mayor*[a,b], *Emma Cullen*[a], *Ranil Johann Boaz*[a,b], *Joseph M. Norris*[a,b], *Samuel Morris*[a,b], *Manit Arya*[a,b], *Mariana Bertoncelli Tanaka*[a,b], *Alan Doherty*[d], *Tim Dudderidge*[e], *Amr Emara*[f], *Mark Emberton*[g,h], *Alistair Grey*[g,h], *Richard Hindley*[f], *Marc Laniado*[i], *Stuart McCraken*[j], *Caroline M. Moore*[g,h], *Raj Nigam*[k], *Mohamed Noureldin*[f], *Clement Orczyk*[g,h], *Arnas Rakauskas*[a,b], *Lucy Simmons*[l], *Jaspal Virdi*[m], *John Withington*[g,h], *Paimaun Zakikhani*[n], *Hashim U. Ahmed*[a,b,†], *Taimur T. Shah*[a,b,†]

[a] *Imperial Prostate, Department of Surgery and Cancer, Imperial College London, London, UK;* [b] *Imperial Urology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK;* [c] *Radiotherapiegroep, Deventer, The Netherlands;* [d] *Department of Urology, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK;* [e] *Department of Urology, Southampton General Hospital, University Hospital Southampton NHS Foundation Trust, Southampton, UK;* [f] *Department of Urology, Basingstoke and North Hampshire Hospital, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK;* [g] *Division of Surgery and Interventional Science, University College London, London, UK;* [h] *Department of Urology, University College Hospital, University College London Hospitals NHS Foundation Trust, London, UK;* [i] *Department of Urology, Wexham Park Hospital, Frimley Health NHS Foundation Trust, Slough, UK;* [j] *Department of Urology, Sunderland Royal Hospital, South Tyneside and Sunderland NHS Foundation Trust, Sunderland, London, UK;* [k] *Department of Urology, Royal Surrey County Hospital, Royal Surrey NHS Foundation Trust, Guildford, UK;* [l] *Department of Urology, Royal United Hospital, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK;* [m] *Department of Urology, Princess Alexandra Hospital, The Princess Alexandra Hospital NHS Trust, Harlow, UK;* [n] *Department of Urology, Princess Royal Hospital, University Hospitals Sussex NHS Foundation Trust, Haywards Heath, UK*

Article info

Article history:
Accepted May 20, 2026

Associate Editor:
Gianluca Giannarini, MD

Statistical Editor:
Andrew Vickers

Abstract

Background and objective: Long-term outcome data for focal therapy using high-intensity focused ultrasound (HIFU) or cryotherapy for nonmetastatic prostate cancer are needed. We report 10-yr cancer control outcomes.
Methods: Patients with nonmetastatic prostate cancer who underwent primary focal HIFU or cryotherapy and had at least 6 mo follow-up were identified from the UK HIFU Evaluation and Assessment of Treatment (HEAT) and International Cryotherapy Evaluation (ICE) prospectively maintained registries. The intervention included up to two focal ablative sessions. The primary outcome was cancer-specific mortality. Secondary outcomes were all-cause mortality, metastasis, local retreatment, radical treatment, and androgen-deprivation therapy (ADT) use.

† These authors are joint senior authors.
* Corresponding author. Imperial Prostate, Department of Surgery and Cancer, Hammersmith Hospital, 72 Du Cane Road, London, W12 0HS. UK.
E-mail address: a.light@imperial.ac.uk (A. Light).

https://doi.org/10.1016/j.eururo.2026.05.007

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

Keywords:
Ablation
Cryotherapy
Focal ablation
Focal therapy
HIFU
Localised
Nonmetastatic
Prostate cancer

Key findings and limitations: A total of 3477 patients (HIFU: *n* = 2897; cryotherapy: *n* = 580) were included from 14 UK centres (2004–2024). A total of 48%, 23%, and 25% had European Association of Urology (EAU) 2025-version favourable intermediate-, unfavourable-intermediate-, and high-risk disease, respectively. Ten-yr cancer-specific mortality was 0.13% (95% confidence interval [CI] = 0.027–0.45%). Ten-yr all-cause mortality and metastases were 12% (95% CI = 8.8–15%) and 3.3% (95% CI = 2.1–4.9%), respectively. Ten-yr ADT use was 14% (95% CI = 11–17%). Ten-yr local retreatment and radical treatment were 33% (95% CI = 30–37%) and 30% (95% CI = 27–34%), respectively, on an intention-to-treat basis. In a post hoc per-protocol analysis, undertaken to estimate outcomes under stricter adherence to the two focal ablative session protocol, patients who underwent radical treatment despite being potentially eligible for a further focal ablative session were censored at the time of radical treatment; 10-yr local retreatment and radical treatment were 13% (95% CI = 11–16%) and 8.9% (95% CI = 6.9–11%), respectively. The observational study design is the main limitation.

Conclusions and clinical implications: Focal therapy using up to two sessions of focal HIFU or cryotherapy could be considered as a first-line treatment for well-selected patients of nonmetastatic prostate cancer alongside radical treatment. Future research priorities should include the development of a dedicated prognostic risk calculator, further prospective assessment of focal therapy for high-risk disease, and improvements in the detection and management of locally recurrent disease.

ADVANCING PRACTICE

What does this study add?
Focal therapy using HIFU or cryotherapy is increasingly used to treat nonmetastatic prostate cancer. Using data from 3477 patients from two nationally mandated UK-based registries, we report promising long-term outcomes following up to two sessions of focal therapy using focal HIFU or cryotherapy, with very few incidences of death or metastases from prostate cancer 10 yr after treatment. These data support focal therapy as a first-line treatment for suitable patients with nonmetastatic prostate cancer.

Clinical Relevance
This study provides the largest contemporary long-term analysis of focal therapy for non-metastatic prostate cancer, reporting oncological outcomes up to 10 years from prospectively maintained national UK registries including more than 3,400 patients treated with focal HIFU or cryotherapy. Its unique scientific value lies in showing very low long-term prostate cancer-specific mortality and metastatic progression rates even in a substantial proportion of unfavourable-intermediate- and high-risk patients, thereby expanding the evidence base beyond the highly selected populations usually included in focal therapy studies. For the community of uro-oncologists, these findings support focal therapy as a potential first-line treatment option in carefully selected patients alongside radical therapies, while also highlighting the need for improved patient selection tools, validated surveillance strategies, and prospective comparative effectiveness trials. Associate Editor: Gianluca Giannarini, MD.

Patient Summary
We looked at how effective focal high-intensity focused ultrasound (HIFU) or cryotherapy is for treating prostate cancer using information from 3477 patients in the UK who had undergone up to two of these treatments. Ten yr after treatment, very few patients had died from prostate cancer and very few had experienced spread of their cancer outside the prostate. Our study suggests that focal HIFU and cryotherapy could be recommended as primary treatments for prostate cancer.

1. Introduction

Focal therapy for nonmetastatic prostate cancer aims to provide adequate cancer control while sparing healthy tissue to reduce genitourinary and rectal toxicity. Its use is increasing globally, driven by better recognition that the toxicity of radical treatments may often not justify the small survival benefit, alongside improvements in localising clinically significant tumours using magnetic resonance imaging (MRI) and targeted biopsy [1–3]. Approximately 50–70% of patients have disease characteristics eligible for focal therapy [4].

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

Prospective cohort studies have demonstrated good cancer control in the short and medium term [5–10]. However, longer-term oncological outcomes following focal therapy remain uncertain. In the UK, focal high-intensity focused ultrasound (HIFU) and cryotherapy have been offered as standard, complementary treatments at select centres over the last 20 yr. Both the UK's National Institute for Health and Care Excellence (NICE) and, more recently, the European Association of Urology (EAU) guidelines require these centres to record treatment outcomes within prospective registries as a condition for offering focal therapy. In the UK, outcomes at 7 and 3 yr for focal HIFU and cryotherapy, respectively, have been published using the nationally mandated HIFU Evaluation and Assessment of Treatment (HEAT) and International Cryotherapy Evaluation (ICE) registries [6–10]. We now report 10-yr cancer control outcomes in patients with nonmetastatic prostate cancer undergoing focal HIFU or cryotherapy.

2. Patients and methods

2.1. Registries

The HEAT and ICE registries are nationally mandated UK registries for focal HIFU and cryotherapy, respectively [8–10]. Prospective data collection is exempt from ethics committee approval and does not require written informed consent, as these registries are deemed institutional audits in the UK.

2.2. Patient cohort

HEAT and ICE were searched on 27 October 2025 for patients who underwent focal HIFU or cryotherapy, respectively, as a primary treatment where a maximum of three-quarters of the prostate received ablation. Patients receiving whole-gland, subtotal, or salvage ablation, patients with nodal or metastatic disease at treatment, and patients with fewer than 6 mo follow-up were excluded. Patients were censored at the date of their last cancer-related investigation.

Patients were counselled pretreatment that the focal intervention included up to two focal ablative sessions to optimise local control, as previously recommended by consensus guidelines, described in prior UK series, and used in previous and ongoing cohort and randomised-controlled trials [8–15]. We have previously shown that a second focal ablative session causes only a minor worsening of genitourinary function [16]. Focal HIFU and cryotherapy were used complementarily; cryotherapy was preferred for anterior lesions, large prostates with an anterior-posterior height of more than 3 cm, and in the presence of widespread prostatic calcifications. HIFU was preferred for posterior lesions or small prostates. Appendix 1 details further information on diagnostic, treatment, and follow-up protocols.

2.3. Outcomes

Outcomes were estimated at 10 yr post-treatment using a competing-risks approach. The primary outcome was prostate cancer-specific mortality, with death from non-cancer causes modelled as a competing risk. The cause of death was determined through case-note review. Secondary outcomes were all-cause mortality, metastasis development, androgen-deprivation therapy (ADT) use, local retreatment, and radical treatment. Mortality was a competing risk to ADT use, local retreatment, and radical treatment. Metastasis development was also a competing risk to local retreatment and radical treatment.

Metastasis was recorded if patients presented with probable nodal, bone, or visceral metastases on whole-body imaging (bone scan, computed tomography [CT], positron emission tomography [PET]/CT, or whole-body MRI), or if metastasis-directed treatment or chemotherapy was required.

To distinguish ADT initiated as a standalone treatment from an adjunct to further local treatment, we excluded ADT started within 2 yr before or 6 mo after any further local treatment. Reasons for ADT initiation were not recorded but included clinician-defined biochemical progression without evidence of local or distant recurrence, treatment of locally recurrent disease due to patient or clinician preference, particularly where patients were older or frailer or had already received further local treatment. Information on whether ADT was combined within doublet or triplet regimens was not recorded.

Local retreatment was recorded if a patient underwent a third focal ablative session, whole-gland ablation, or radical treatment. For local retreatment and radical treatment outcomes, two analyses were conducted: an "intention-to-treat" analysis, which included all incidences of the endpoint, and a "per-protocol" analysis. The latter was a post hoc analysis intended to estimate what outcomes could be under stricter adherence to the two focal ablative session protocol. Patients were censored at the time of radical treatment if they did not meet at least one of the following indications for radical treatment: pre-radical treatment biopsy showing Grade Group 4–5 cancer, Grade Group 2–3 cancer with evidence of simultaneous in- and out-of-field recurrence, Grade Group 2–3 cancer with one previous redo focal ablation session, or at least two previous redo focal ablation sessions. Very few data and guidance exist regarding patient selection for further treatments after focal therapy, and there was probable heterogeneity in how patients were selected for, counselled on, and ultimately chose to have further treatments. The per-protocol analysis attempts to explore how estimates could differ if this process was more standardised. These per-protocol analyses do not account for the possibility that censored patients may have eventually required radical treatment after a hypothetical further focal ablative session.

2.4. Statistical analysis

Cumulative incidence plots incorporating a competing-risks approach were created for each outcome.

As a sensitivity analysis, we studied the need for a second focal ablative session, with death, metastasis, and radical or whole-gland ablative treatment as competing risks.

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

A landmark sensitivity analysis was conducted by restricting the cohort to those with at least 7 yr of follow-up and who had not experienced a primary or secondary outcome prior to this, then establishing 10- and 12-yr outcomes, equivalent to 3 and 5 yr after the landmark time, respectively. As the most recent HEAT data evaluated 7-yr outcomes after focal therapy, this 7-yr landmark was chosen to study the occurrence of late events specifically in patients who remained event-free by this timepoint [10]. Given the requirement for 7 yr of event-free follow-up, these estimates should not be interpreted as representative of the overall cohort.

Primary and secondary outcome analyses were also repeated for subgroups based on ablative modality and EAU 2025-version risk groups [17]. These estimates are intended to be descriptive, with formal statistical comparisons between subgroups omitted.

Analyses were performed in R version 4.2.2.

3. Results

3.1. Patient cohort

A total of 3477 patients were included who received focal HIFU (n = 2897) or cryotherapy (n = 580) between 2004 and 2024 at 14 UK centres (Supplementary Fig. 1). Most had EAU favourable-intermediate-risk disease (48%), followed by high-risk (25%) and unfavourable-intermediate-risk disease (23%; Tables 1 and Supplementary Table 1). For patients alive at last follow-up, median follow-up was 3.3 yr (IQR = 1.6–6.1). Of these, 1118 had at least 5 yr' follow-up and 173 had at least 10 yr' follow-up.

Table 1 – Characteristics of included patients

Characteristic	N = 3477[a]
Age (yr)	66 (0, 72)
Unknown	3
PSA (ng/ml)	6.8 (4.9, 9.4)
Unknown	14
PSA density (ng/ml^2)	0.17 (0.11, 0.26)
Unknown	352
Prostate volume (ml)	38 (29, 52)
Unknown	346
T-stage	
T1	136 (4.8%)
T2	2385 (84%)
T3a	297 (10%)
T3b	12 (0.4%)
Unknown	647
Biopsy technique	
Transperineal MRI-targeted ± systematic	1117 (40%)
Transperineal systematic	397 (14%)
Transperineal (strategy unknown)	850 (31%)
Transrectal MRI-targeted ± systematic	56 (2.0%)
Transrectal systematic	85 (3.1%)
Transrectal (strategy unknown)	260 (9.4%)
Systematic (route unknown)	1 (<0.1%)
Unknown	711
Total biopsy cores	18 (12, 28)
Unknown	278
Positive biopsy cores	5 (3, 7)
Unknown	227
Grade Group	
Grade Group 1	380 (11%)
Grade Group 2	2391 (70%)
Grade Group 3	615 (18%)
Grade Group 4	47 (1.4%)
Grade Group 5	7 (0.2%)
Unknown	37
MCCL (mm)	7 (4, 9)
Unknown	351
EAU risk group (2025 version)	
Low-risk	145 (4.3%)
Favourable-intermediate-risk	123 (48%)
Unfavourable-intermediate-risk	767 (23%)
High-risk	837 (25%)
Unknown	105
Neoadjuvant ADT use	226 (6.5%)
Ablative modality	
HIFU	2897 (83%)
Cryotherapy	580 (17%)
Focal treatment pattern	
Quadrant ablation	2008 (58%)
Hemiablation	1,383 (40%)
Hockey stick ablation	86 (2.5%)

GG = grade group; MCCL = maximum cancer core length.
[a] Median (Q1, Q3); n (%)

3.2. Prostate cancer-specific mortality

The 10-yr cumulative incidence of prostate cancer-specific mortality was 0.13% (95% CI = 0.027–0.45%; Supplementary Figure 2). One patient had high-risk, Grade Group 5 prostate cancer and underwent focal HIFU with neoadjuvant ADT before developing metastases at 2.9 yr, with death at 3.0 yr. The second patient had unfavourable-intermediate-risk, Grade Group 2 prostate cancer and underwent focal HIFU before developing metastases at 1.2 yr, with death at 4.3 yr.

3.3. Secondary outcomes

The 10-yr cumulative incidence of all-cause mortality was 12% (95% CI = 8.8–15%; 101 events; Fig. 1).

Cumulative incidence plots for other secondary outcomes are shown in Figure 2. The 10-yr cumulative incidence of developing metastasis was 3.3% (95% CI = 2.1–4.9%; 42 events).

A total of 321 patients started ADT for any indication. In 174 patients, this was ADT used alongside further local treatment. Of the remaining 147 patients who received ADT that did not accompany further local treatment, 43 had received a second focal ablative session more than 6 mo previously, 9 had received radical treatment more than 6 mo previously, 29 had developed metastases, and 35 were aged 80 yr or older at the time of starting ADT (Supplementary Fig. 3). The median PSA at ADT initiation was 7.47 ng/ml (IQR = 3.72–12.16), with 46 having a prostate-specific antigen (PSA) ≥10 ng/ml and 17 having a PSA ≥20 ng/ml. A total of 16 patients went on to receive further local treatment more than 2 yr after initiating ADT, which was radical in all. The 10-yr cumulative incidence of ADT use was 14% (95% CI = 11–17%; 136 events).

A total of 511 patients underwent a second focal ablative treatment; the 10-yr cumulative incidence of this was 34% (95% CI = 30–37%; 347 events; Supplementary Fig. 4). A total of 436 patients reached the local retreatment endpoint through undergoing either a third focal ablative treatment (n = 37), whole-gland ablation (n = 8), or radical treatment

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

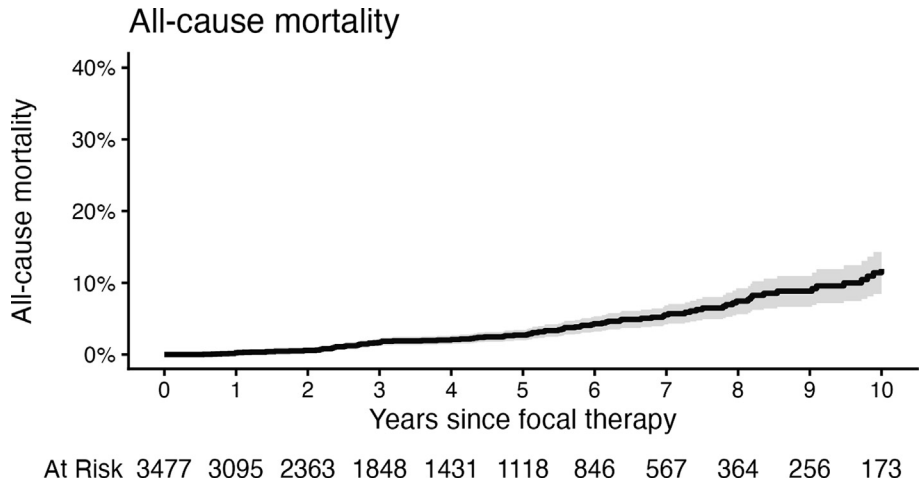

Fig. 1 – Cumulative incidence plot for all-cause mortality. The ten-year cumulative incidence of all-cause mortality was 12% (95%CI 8.8-15%; 101 events).

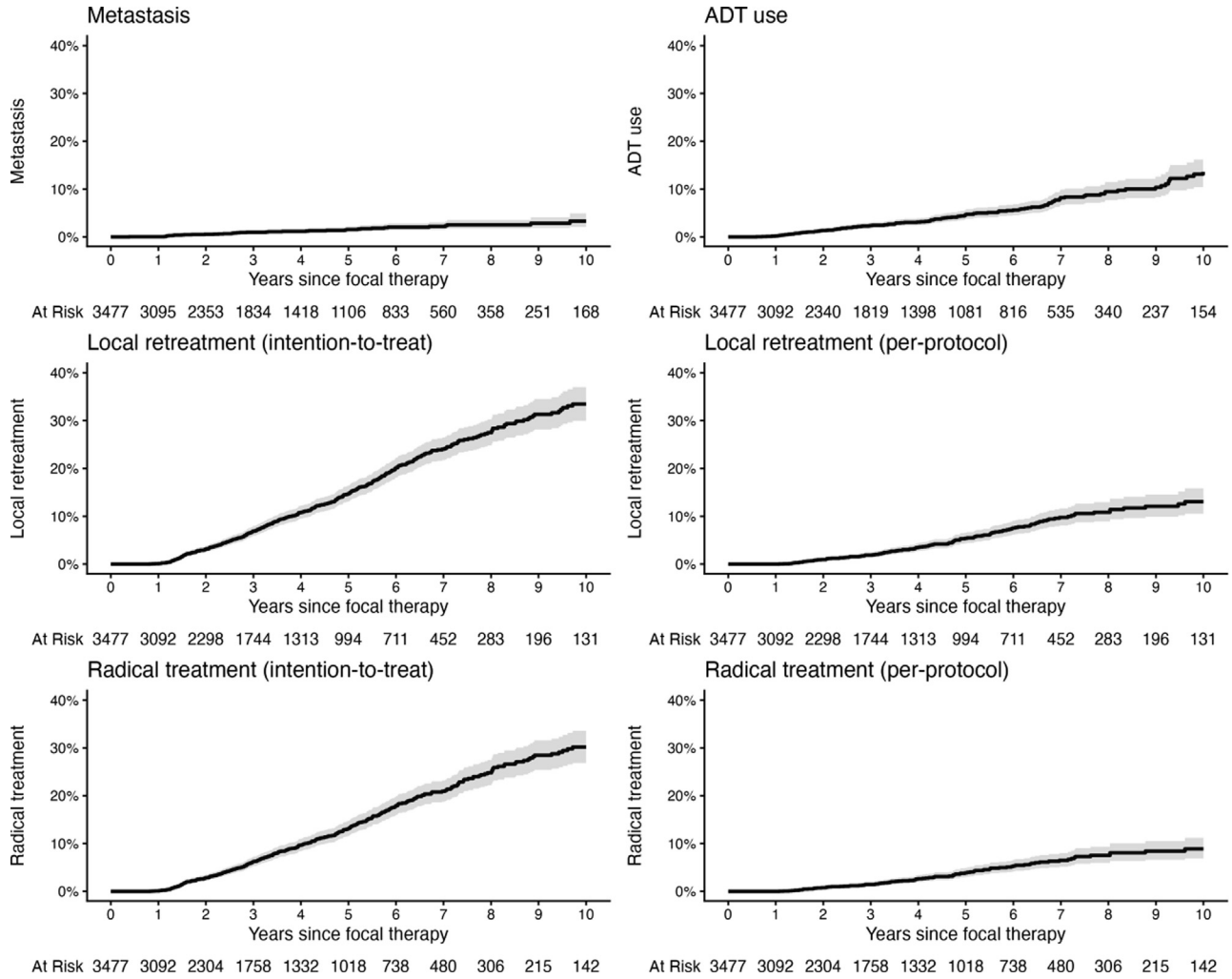

Fig. 2 – Cumulative incidence plots for other secondary outcomes. The ten-year cumulative incidence of each outcome was: metastasis: 3.3% (95%CI 2.1-4.9%; 42 events); ADT use: 14% (95%CI 11-17%; 136 events); local retreatment (intention-to-treat): 33% (95%CI 30-37%; 414 events); radical treatment (intention-to-treat): 30% (95%CI 27-34%; 373 events); local retreatment (per-protocol): 13% (95%CI 11-16%; 139 events); radical treatment (per-protocol): 8.9% (95%CI 6.9-11%; 99 events).

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

(n = 391; Supplementary Fig. 5). An additional 3 and 3 patients who received three focal ablative sessions and whole-gland ablation, respectively, subsequently underwent radical treatment, therefore, 397 patients underwent radical treatment. In intention-to-treat analyses, the 10-yr cumulative incidence of local retreatment was 33% (95% CI = 30–37%; 414 events) and of radical treatment was 30% (95% CI = 27–34%; 373 events). Of the 397 radical treatment cases, 106 satisfied our described indications for radical treatment (Supplementary Fig. 6). In per-protocol analyses, the 10-yr cumulative incidence of local retreatment was 13% (95% CI = 11–16%; 139 events) and of radical treatment was 8.9% (95% CI = 6.9–11%; 99 events).

3.4. Landmark analysis

A total of 426 patients had at least 7 yr of follow-up without experiencing any primary or secondary endpoint prior. Median follow-up for those alive at last follow-up was 8.9 yr (IQR = 7.7–10.8). There were no prostate cancer-specific deaths. The 10- and 12-yr cumulative incidences, respectively, of all-cause mortality were 5.9% (95% CI = 2.8–8.9%; 15 events) and 15% (95% CI = 8.4–22%; 24 events); of metastasis were both 0.45% (95% CI = 0.042–2.3%; 1 events); of ADT use was 7.3% (95% CI = 4.3–12%; 16 events) and 13% (95% CI = 8–19%; 22 events); of local retreatment in the intention-to-treat analysis was 14% (95% CI = 10–18%; 39 events) and 18% (95% CI = 13–24%; 44 events); of radical treatment in the intention-to-treat analysis was 13% (95% CI = 8.9–17%; 36 events) and 18% (95% CI = 13–24%; 42 events); of local retreatment in the per-protocol analysis was 4.2% (95% CI = 2.1–7.3%; 11 events) and 5.0% (95% CI = 2.6–8.6%; 12 events); and of radical treatment in the per-protocol analysis was 2.9% (95% CI = 1.3–5.5%; 8 events) and 4.9% (95% CI = 2.2–9.3%; 10 events; Fig. 3).

3.5. Subgroup analyses

Analyses stratified by ablative modality are shown in Figure 4, Supplementary Figure 7 and Supplementary Tables 2–3. For focal HIFU and cryotherapy, respectively, 10-yr cancer-specific mortality was 0.15% and 0%; all-cause mortality was 12% and 6.5%; metastasis was 3.3% and 2.8%; ADT use was 13% and 21%; local retreatment in intention-to-treat analysis was 34% and 35%; radical treatment in intention-to-treat analysis was 30% and 34%; local retreatment in per-protocol analysis was 13% and 16%; and radical treatment in per-protocol analysis was 8.5% and 13%.

Analyses stratified by EAU risk group are shown in Figure 5, Supplementary Figure 8 and Supplementary Table 4. For patients with unfavourable-intermediate-risk and high-risk disease, respectively, 10-yr cancer-specific mortality was 0.37% and 0.19%; all-cause mortality was 14% and 13%; metastasis development was 4.2% and 4.7%; ADT use was 15% and 15%; local retreatment in intention-to-treat analysis was 48% and 33%; radical treatment in intention-to-treat analysis was 46% and 28%; local retreatment in per-protocol analysis was 19% and 16%; and radical treatment in per-protocol analysis was 16% and 9.5%.

4. Discussion

4.1. Interpretation of results

Our data provide the best available evidence supporting focal HIFU and cryotherapy as treatment options for non-metastatic prostate cancer. In this multicentre cohort with high representation of unfavourable-intermediate- and high-risk cases (48%), there was very low mortality due to prostate cancer (0.13%) and metastases (3.3%) by 10 yr post-treatment. We also conducted a landmark analysis focusing on outcomes for patients conditional on remaining event-free up to 7 yr post-treatment, demonstrating no late increases in cancer-specific deaths or metastases between 10 and 12 yr after treatment, suggesting focal therapy outcomes remain durable into late follow-up.

The strengths of this study include its large multicentre prospective cohort, long-term follow-up, diverse case mix including a large proportion of unfavourable-intermediate and high-risk disease, and use of two ablative modalities. This is the largest reported cohort of patients treated with focal HIFU and cryotherapy with long-term follow-up.

Only one other focal therapy study has reported 10-yr outcomes, a small French cohort of 121 patients with predominantly (65%) low-risk cancer undergoing focal cryotherapy [18]. Ten-yr cancer-specific mortality and metastases were 0 and 6.1%, respectively. Our data are also comparable to 10-yr results reported after radical treatments in the ProtecT trial (cancer-specific mortality: 0.6–1.0%; metastases: approximately 3–4%) and recent population-based and multicentre cohort studies (cancer-specific mortality: 0–12%; metastases: 4–20%) [3,19–25].

Studies have shown the need for salvage therapies after radical treatment is not insignificant. Population-based studies have reported that 11–14% of patients require salvage radiotherapy postradical prostatectomy over medium- to long-term follow-up [26–28]. ADT use for biochemical recurrence postradiotherapy has been reported at 13–15% [28–30]. Ten-yr estimates for local retreatment and ADT use in our focal therapy cohort were 33% and 14%, respectively. Furthermore, of patients who required radical treatment, we estimated only a small proportion had an imperative indication for radical treatment; many patients with recurrence after the initial focal ablative session could have been suitable for a further ablative session, and we have shown previously that this further ablative treatment confers only a minimal detriment to genitourinary function [16]. Although some patients who required a second focal ablative session may still require further local treatment, there is increasingly substantial evidence that radical treatment postfocal therapy is feasible and confers good oncological and acceptable functional outcomes in the short to medium term [31–35]. Notably, the morbidity and functional outcomes of postablation radical prostatectomy are comparable to those of primary radical prostatectomy and certainly appear favourable over salvage radical prostatectomy postradiotherapy [36–39].

Our cohort included only a small proportion of low-risk cases (4.3%), whereas 23% and 25% of cases were unfavourable-intermediate- and high-risk, respectively.

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

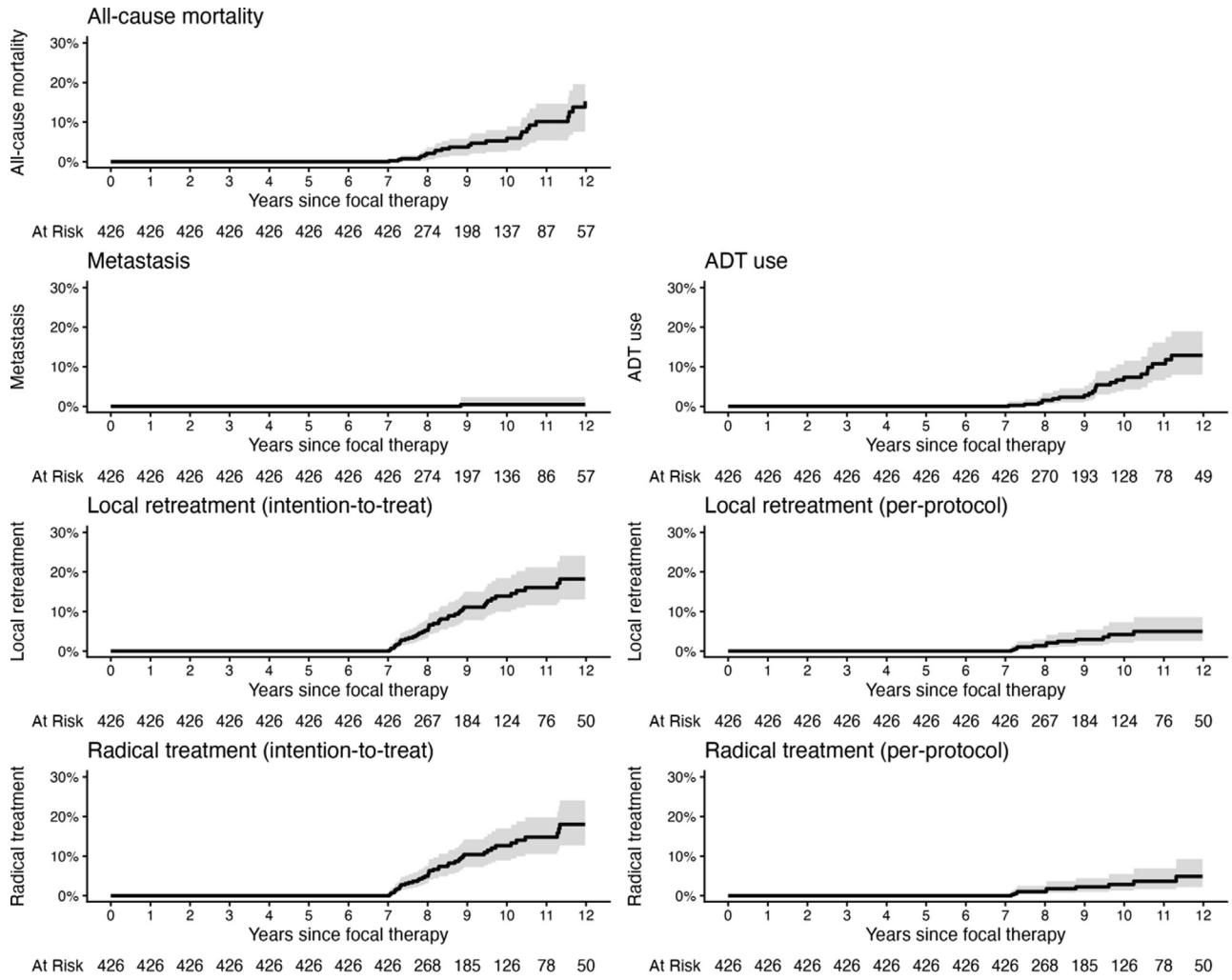

Fig. 3 – Cumulative incidence plots for outcomes in landmark analysis focusing on patients who had at least seven years follow-up and who remained local retreatment-, ADT-, and metastasis-free up to that landmark (*n* = 426). There were no prostate cancer-specific deaths. The ten- and 12-year cumulative incidences, respectively, of other outcomes were: all-cause mortality: 5.9% (95%CI 2.8-8.9%; 15 events) and 15% (95%CI 8.4-22%; 24 events); metastasis: both 0.45% (95%CI 0.042-2.3%; 1 events); ADT use: 7.3% (95%CI 4.3-12%; 16 events) and 13% (95%CI 8-19%; 22 events); local retreatment (intention-to-treat): 14% (95%CI 10-18%; 39 events) and 18% (95%CI 13-24%; 44 events); radical treatment (intention-to-treat): 13% (95%CI 8.9-17%; 36 events) and 18% (95%CI 13-24%; 42 events); local retreatment (per-protocol): 4.2% (95%CI 2.1-7.3%; 11 events) and 5.0% (95%CI 2.6-8.6%; 12 events); radical treatment (per-protocol): 2.9% (95% CI 1.3-5.5%; 8 events) and 4.9% (95%CI 2.2-9.3%; 10 events).

This contrasts with most existing focal therapy data, in which patients with high-risk disease are usually excluded from treatment protocols [5]. Although we did not formally compare estimates between EAU risk groups, the absolute differences between groups at 10 yr were generally marginal. For example, the 10-yr cumulative incidence of metastases was 2.1% for favourable-intermediate-risk versus 4.2% and 4.7% for unfavourable-intermediate-risk and high-risk disease, respectively. Although current EAU and American Urological Association guidelines support focal therapy for intermediate-risk disease only, our analyses demonstrate focal therapy to have efficacy in high-risk disease too [17,40].

4.2. Limitations

Registry data are inherently subject to biases from missing data, both for specific datapoints and right-censored data.

Clinical practice regarding patient selection, treatment delivery, and follow-up likely differed between institutions and evolved over time; heterogeneity may have influenced outcomes. In particular, the application of further local treatments and ADT was not standardised. While we explored potential indications, ultimately, the reasons for these choices were not recorded. Whether ADT was combined with other systemic agents was also not recorded.

We did not explore post-treatment PSA kinetics, though there is no accepted definition of biochemical failure after focal therapy. A planned future analysis of these registries will validate existing definitions.

Lastly, although HIFU and cryotherapy are the most commonly used modalities, we have not included data on other modalities in current use, such as irreversible electroporation.

4.3. Future research

Further research into focal therapy for high-risk disease is warranted. Trials randomising between focal and radical treatment for intermediate-risk disease have struggled to

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

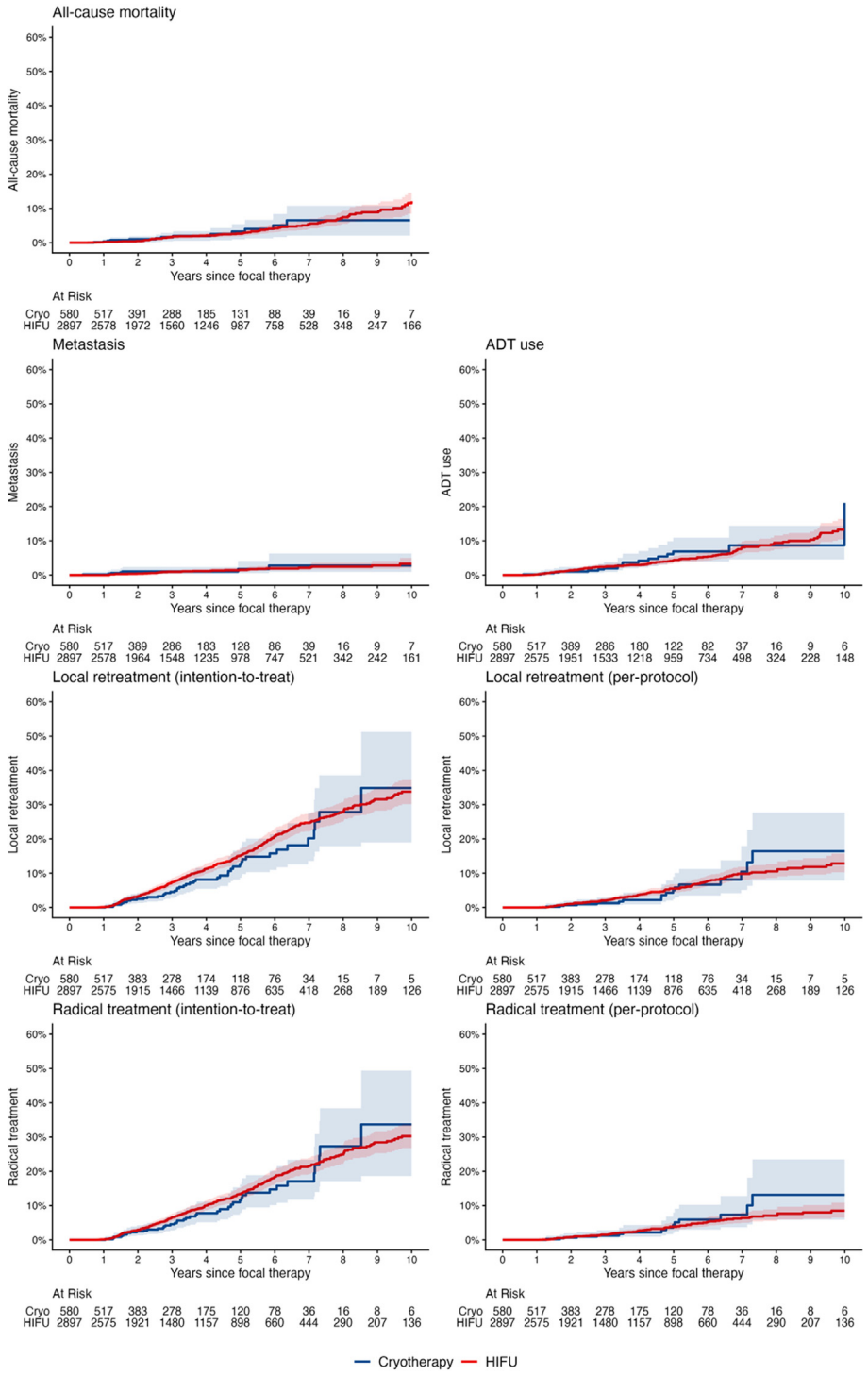

Fig. 4 – Cumulative incidence plots for outcomes in subgroup analysis based on whether patients underwent HIFU or Cryotherapy. The cumulative incidence plot for cancer-specific mortality is shown in Fig. S7 and ten-year cumulative incidence estimates are reported in Table S3.

recruit or prevent between-arm contamination due to insufficient patient and clinician equipoise [41–43]. A trial focusing on high-risk disease may recruit more successfully and would further shape the role of focal therapy. For example, for *de novo* hormone-sensitive metastatic disease, we recently completed recruitment for the multicentre IP2-ATLANTA randomised-controlled trial comparing standard care, radical treatment, and ablation (NCT03763253) [44]. Nonetheless, while we have published observational comparisons between focal and radical treatment using propensity-score methodology, there are ongoing randomised-controlled trials that should be supported, such as PART (ISRCTN17249875) [6,7].

Second, patient selection for focal therapy can vary considerably between institutions and countries. Risk factors affecting treatment failure should be investigated; refined eligibility criteria or an accurate risk calculator would be valuable for patient selection and counselling by better

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

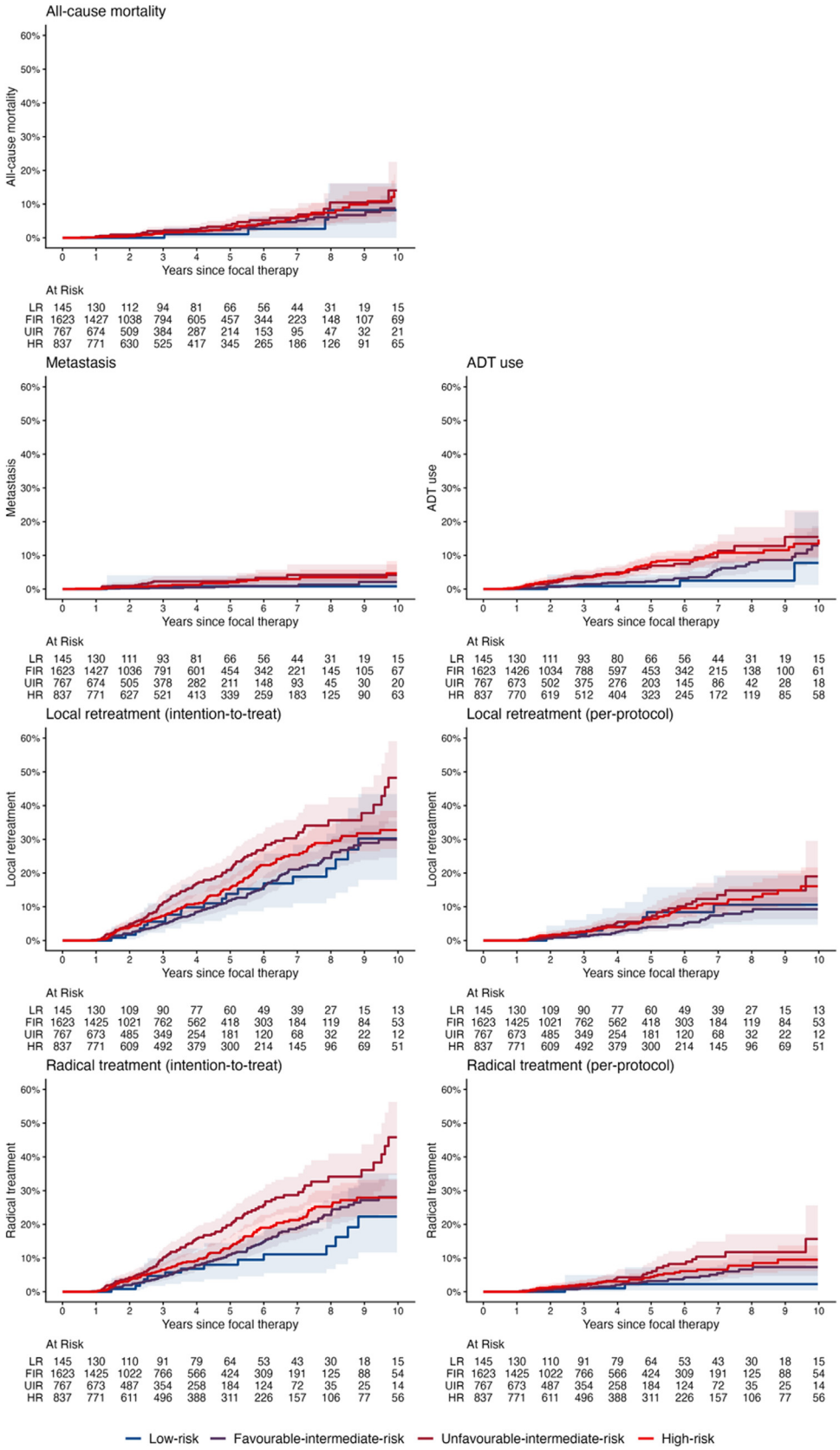

Fig. 5 – Cumulative incidence plots for outcomes in subgroup analysis of EAU 2025 risk groups. The cumulative incidence plot for cancer-specific mortality is shown in Fig. S8 and ten-year cumulative incidence estimates are reported in Table S4. Abbreviations: FIR, favourable-intermediate-risk; HR, high-risk; LR, low-risk, UIR, unfavourable-intermediate-risk.

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

identifying patients for whom focal therapy would or would not be suitable. The need for such a tool has been emphasised by our patient representatives to improve decision-making, particularly in situations where a patient is also eligible for radical treatments. Alongside variables such as PSA and Grade Group, the use of genomic classifiers could be useful in stratifying patients.

Lastly, further data on the detection and management of recurrent disease after focal therapy are needed. To improve detection of recurrent disease, validation of biochemical failure definitions is needed, alongside validation of MRI scoring systems such as TARGET [45–48]. Consensus on how patients should be selected and counselled for salvage radical treatment versus further ablation is required; qualitative research involving patients and clinicians will be helpful for understanding the decision-making process regarding further local treatments. Longer-term oncological and functional outcomes after individual local retreatment modalities should also be established and compared. Such an analysis will require careful adjustment for confounders and time between treatments; a multivariable multistate model, though complex, may prove most useful.

5. Conclusion

Focal therapy using up to two sessions of focal HIFU or cryotherapy could be considered as a first-line treatment for well-selected cases of nonmetastatic prostate cancer alongside radical treatment. Future research priorities should include the development of a dedicated prognostic risk calculator, further prospective assessment of focal therapy for high-risk disease, and improvements in the detection and management of locally recurrent disease.

Author contributions: Alexander Light 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: Light, Ahmed, Shah.
Acquisition of data: Light, Gopalakrishnan, Mayor, Cullen, Boaz, Norris, Morris, Arya, Tanaka, Doherty, Dudderidge, Emara, Emberton, Grey, Hindley, Laniado, McCraken, Moore, Nigam, Noureldin, Orczyk, Rakauskas, Simmons, Virdi, Withington, Zakikhani, Ahmed, Shah.
Analysis and interpretation of data: Light, Peters, Ahmed, Shah.
Drafting of the manuscript: Light.
Critical revision of the manuscript for important intellectual content: Light, Peters, Gopalakrishnan, Mayor, Cullen, Boaz, Norris, Morris, Arya, Tanaka, Doherty, Dudderidge, Emara, Emberton, Grey, Hindley, Laniado, McCraken, Moore, Nigam, Noureldin, Orczyk, Rakauskas, Simmons, Virdi, Withington, Zakikhani, Ahmed, Shah.
Statistical analysis: Light, Peters.
Obtaining funding: Ahmed.
Administrative, technical, or material support: Light.
Supervision: Peters, Ahmed, Shah.
Other: None.

Financial disclosures: Alexander Light certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (for example employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Alexander Light receives research funding from the UK National Institute for Heath and Care Research (NIHR) doctoral fellowship (award no. NIHR304727) and The Urology Foundation. Manit Arya is a mentor in cryotherapy for Boston Scientific. Mark Emberton receives research support from the University College London Hospitals NHS Foundation Trust/University College London NIHR Biomedical Research Centre (BRC); and acts as a paid advisor/-trainer to Sonablate Corp., Angiodynamics Inc, NINA Medical Inc, Albermarle Biosciences Ltd, and Early Health Limited. Richard Hindley receives payments from Sonablate for HIFU teaching and training. Hashim U. Ahmed receives core funding from the UK NIHR Imperial BRC and Imperial NIHR/Cancer Research UK Experimental Cancer Medicine Centre (ECMC); receives research funding from the Wellcome Trust, UK Medical Research Council, Cancer Research UK, Prostate Cancer UK, UK NIHR, and Imperial Health Charity for trials in prostate cancer; is a paid proctor for HIFU (Sonablate Corp), cryotherapy (Boston Scientific), and Rezūm (Boston Scientific); is a paid scientific advisory board member for Francis Medical; has given lectures for Boston Scientific, Ipsen, and Janssen; has received funding to attend scientific conferences from Janssen; and has previously been on the medical advisory board for Janssen but not currently. Taimur T. Shah receives infrastructure support from the NIHR Imperial BRC and Imperial College ECMC; receives research funding from The Urology Foundation, Prostate Cancer UK (PCUK), and Janssen; receives consultation fees from Janssen and Varian; and has received funding to attend scientific conferences from Janssen and Sonablate Corp.

***Funding/Support and role of the sponsor*:** The HEAT registry is supported by an unrestricted grant from Sonablate. The funder played no direct role in the study.

***Acknowledgements*:** We would like to thank our patient representatives, Stuart Glen, Ray Monk, and Robin Porter, for their valuable contributions in shaping the interpretation and dissemination of our findings.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2026.05.007.

References

[1] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[2] Hopstaken JS, Bomers JGR, Sedelaar MJP, Valerio M, Fütterer JJ, Rovers MM. An updated systematic review on focal therapy in localized prostate cancer: what has changed over the past 5 years? Eur Urol 2022;81:5–33.
[3] Hamdy FC, Donovan JL, Lane JA, et al. Fifteen-year outcomes after monitoring, surgery, or radiotherapy for prostate cancer. N Engl J Med 2023;388:1547–58.
[4] Reddy D, Eldred-Evans D, Winkler M, Shah T, Ahmed H. MP73-03 the proportion of patients eligible for focal therapy of non-metastatic prostate cancer in The Modern MRI-directed diagnostic pathway. J Urol 2023;209(Suppl 4).
[5] Ślusarczyk A, Gurwin A, Barnaś A, et al. Outcomes of focal therapy for localized prostate cancer: a systematic review and meta-analysis of prospective studies. Eur Urol Oncol 2025;8:1653–72.
[6] 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 2021;24:567–74.
[7] van Son MJ, van 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;24:1120–8.
[8] 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;74:422–9.
[9] 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;76:98–105.
[10] Reddy D, Peters M, Shah TT, et al. Cancer control outcomes following focal therapy using high-intensity focused ultrasound in 1379 men with nonmetastatic prostate cancer: a multi-institute 15-year experience. Eur Urol 2022;81:407–13.
[11] Dickinson L, Ahmed HU, Kirkham AP, et al. A multi-centre prospective development study evaluating focal therapy using high intensity focused ultrasound for localised prostate cancer: the INDEX study. Contemp Clin Trials 2013;36:68–80.
[12] van den Bos W, Muller BG, Ahmed H, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. Eur Urol 2014;65:1078–83.
[13] Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes—a report from a consensus meeting. Eur Urol 2015;67:771–7.
[14] 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.
[15] Warlick CA, Spilseth BD, Dixon CM. Transurethral water vapor ablation: potential for a novel prostate cancer management strategy. Res Rep Urol 2025:17–25.
[16] 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;125:853–60.
[17] Prostate Cancer - Uroweb uroweb.org/guidelines/prostate-cancer. Accessed 21/01/2026.
[18] Marra G, Soeterik T, Oreggia D, et al. Long-term outcomes of focal cryotherapy for low- to intermediate-risk prostate cancer: results and matched pair analysis with active surveillance. Eur Urol Focus 2022;8:701–9.
[19] Peacock M, Quirt J, Morris WJ, et al. Population-based 10-year event-free survival after radical prostatectomy for patients with prostate cancer in British Columbia. Can Urol Assoc J 2015;9:409–13.
[20] Aas K, Berge V, Myklebust TÅ, Fosså SD. Comparative survival outcomes of high-risk prostate cancer treated with radical prostatectomy or definitive radiotherapy regimens. Eur Urol Open Sci 2021;26:55–63.
[21] Suárez JF, Zamora V, Garin O, et al. Mortality and biochemical recurrence after surgery, brachytherapy, or external radiotherapy for localized prostate cancer: a 10-year follow-up cohort study. Sci Rep 2022;12:12589.
[22] Herr DJ, Elliott DA, Duchesne G, et al. Outcomes after definitive radiation therapy for localized prostate cancer in a national health care delivery system. Cancer 2023;129:3326–33.
[23] Falagario UG, Knipper S, Pellegrino F, et al. Prostate cancer-specific and all-cause mortality after robot-assisted radical prostatectomy: 20 years' report from the European Association of Urology robotic urology section Scientific Working Group. Eur Urol Oncol 2024;7:705–12.
[24] Herlemann A, Cowan JE, Washington SL, et al. Long-term prostate cancer–specific mortality after prostatectomy, brachytherapy, external beam radiation therapy, hormonal therapy, or monitoring for localized prostate cancer. Eur Urol 2024;85:565–73.
[25] Stensland KD, Caram MEV, Herr DJ, et al. National long-term survival estimates after radical prostatectomy for prostate cancer. Urology 2024;184:135–41.
[26] Huelster HL, Laviana AA, Joyce DD, et al. Radiotherapy after radical prostatectomy: effect of timing of postprostatectomy radiation on functional outcomes. Urol Oncol: Semin Orig Investig 2020;38:930.e23–e32.
[27] Draulans C, Van Damme N, Isebaert S, et al. Variation in adjuvant and early salvage radiotherapy after robot-assisted radical prostatectomy for prostate cancer: a population-based cohort study. Acta Oncol 2020;59:904–10.
[28] Falagario UG, Abbadi A, Remmers S, et al. Biochemical recurrence and risk of mortality following radiotherapy or radical prostatectomy. JAMA Netw Open 2023;6:e2332900.
[29] 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. Eur Urol 2015;67:1009–16.
[30] Fu AZ, Tsai H-T, Haque R, et al. Use of androgen deprivation therapy as salvage treatment after primary therapy for clinically localized prostate cancer. World J Urol 2016;34:1611–9.
[31] Marconi L, Stonier T, Tourinho-Barbosa R, et al. Robot-assisted radical prostatectomy after focal therapy: oncological, functional outcomes and predictors of recurrence. Eur Urol 2019;76:27–30.
[32] Cathcart P, Ribeiro L, Moore C, et al. Outcomes of the RAFT trial: robotic surgery after focal therapy. BJU Int 2021;128:504–10.
[33] Nathan A, Ng A, Mitra A, et al. Comparative effectiveness analyses of salvage prostatectomy and salvage radiotherapy outcomes following focal or whole-gland ablative therapy (high-intensity focused ultrasound, cryotherapy or electroporation) for localised prostate cancer. Clin Oncol 2022;34:e69–78.
[34] Marra G, Marquis A, Yanagisawa T, Shariat SF, Touijer K, Gontero P. Salvage radical prostatectomy for recurrent prostate cancer after primary nonsurgical treatment: an updated systematic review. Eur Urol Focus 2023;9:251–7.
[35] Takemura LS, Costa PHP, Claros OR, et al. Salvage local treatment for recurrent prostate cancer after focal therapy: a systematic review and meta-analysis. Urol Oncol: Semin Orig Investig 2024;42:449.e1–e11.
[36] Onol FF, Bhat S, Moschovas M, et al. Comparison of outcomes of salvage robot-assisted laparoscopic prostatectomy for post-primary radiation vs focal therapy. BJU Int 2020;125:103–11.
[37] Ghoreifi A, Ramacciotti LS, Kaneko M, et al. The outcomes of salvage robotic radical prostatectomy following radiation versus focal therapy: does the primary treatment modality matter? BJUI Compass 2025;6:e70019.
[38] Falkenbach F, Hagemann J, Ambrosini F, et al. Patient-reported outcome measures and decision regret after salvage radical prostatectomy for recurrent prostate cancer following radiotherapy or focal therapy. Cancers 2025;17:396.
[39] Light A, Peters M, Arya M, et al. Salvage focal therapy vs radical prostatectomy for localized Radiorecurrent prostate cancer. JAMA Oncol 2026;12:364.
[40] Eastham JA, Auffenberg GB, Barocas DA, et al. Clinically localized prostate cancer: AUA/ASTRO guideline, Part I: introduction, risk assessment, staging, and risk-based management. J Urol 2022;208:10–8.
[41] Hamdy FC, Elliott D, le Conte S, et al. Partial ablation versus radical prostatectomy in intermediate-risk prostate cancer: the PART feasibility RCT. Health Technol Assess 2018;22:1–96.
[42] Reddy D, Dudderidge T, McCracken S, et al. LBA03-07 imperial PROSTATE-4 comparative healthcare research outcomes of novel surgery in prostate cancer (IP4-CHRONOS): early feasibility, safety and functional outcomes from a pilot RCT. J Urol 2023;209(Suppl 4).
[43] Baco E, Noor D, Galtung KF, Rud E. PD. 19–01 final, three-year oncological results of a randomized clinical trial FARP comparing focal ablation and radical prostatectomy in patients with unilateral clinically significant prostate cancer. J Urol 2025;213.
[44] Connor MJ, Shah TT, Sukumar J, et al. Combination cytoreductive surgery, radiotherapy, or ablation for de novo metastatic prostate cancer: the IP2-ATLANTA internal pilot, Phase 2, randomised controlled trial. Eur Urol Oncol 2026;9:276–85.
[45] Huber PM, Afzal N, Arya M, et al. Prostate specific antigen Criteria to Diagnose Failure of Cancer Control following Focal Therapy of nonmetastatic Prostate Cancer Using High Intensity Focused ultrasound. J Urol 2020;203:734–42.
[46] Stabile A, Orczyk C, Giganti F, et al. The role of percentage of prostate-specific antigen reduction after focal therapy using high-intensity focused ultrasound for primary localised prostate cancer. Results from a large multi-institutional series. Eur Urol 2020;78:155–60.

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007

[47] Light A, Mayor N, Cullen E, et al. The transatlantic recommendations for prostate gland evaluation with magnetic resonance imaging after focal therapy (TARGET): a systematic review and international consensus recommendations. Eur Urol 2024;85:466–82.

[48] Giganti F, Dickinson L, Orczyk C, et al. Prostate imaging after focal ablation (PI-FAB): a proposal for a scoring system for multiparametric MRI of the prostate after focal therapy. Eur Urol Oncol 2023;6:629–34.

Please cite this article as: A. Light, M. Peters, A. Gopalakrishnan et al., Oncological Outcomes Following Focal HIFU and Cryotherapy for Treatment of Nonmetastatic Prostate Cancer in the United Kingdom: An Updated Analysis of 3477 Patients from the Prospective HEAT and ICE Registries, Eur Urol (2026), https://doi.org/10.1016/j.eururo.2026.05.007