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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*

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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).

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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.

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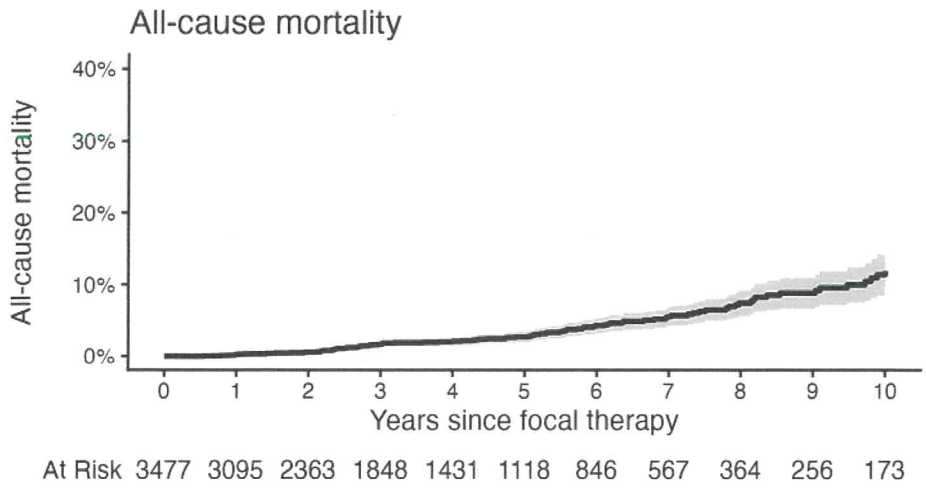

Fig. 1 – Cumulative incidence plot for all-cause mortality. The ten-year cumulative incidence of all-cause mortality was 12% (95%CI 8.8-15%; 101 events).

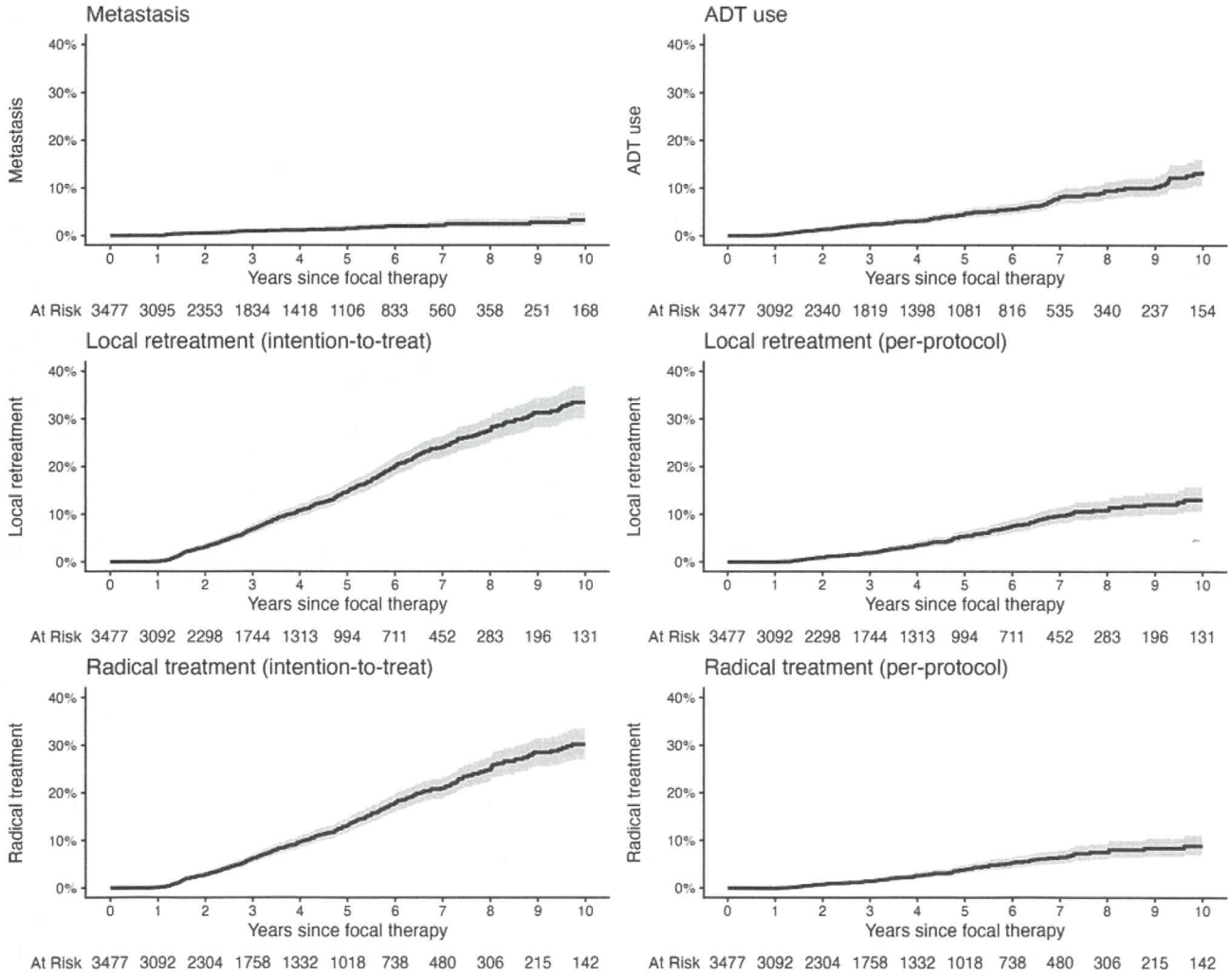

Fig. 2 – Cumulative incidence plots for other secondary outcomes. The ten-year cumulative incidence of each outcome was: metastasis: 3.3% (95%CI 2.1-4.9%; 42 events); ADT use: 14% (95%CI 11-17%; 136 events); local retreatment (intention-to-treat): 33% (95%CI 30-37%; 414 events); radical treatment (intention-to-treat):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

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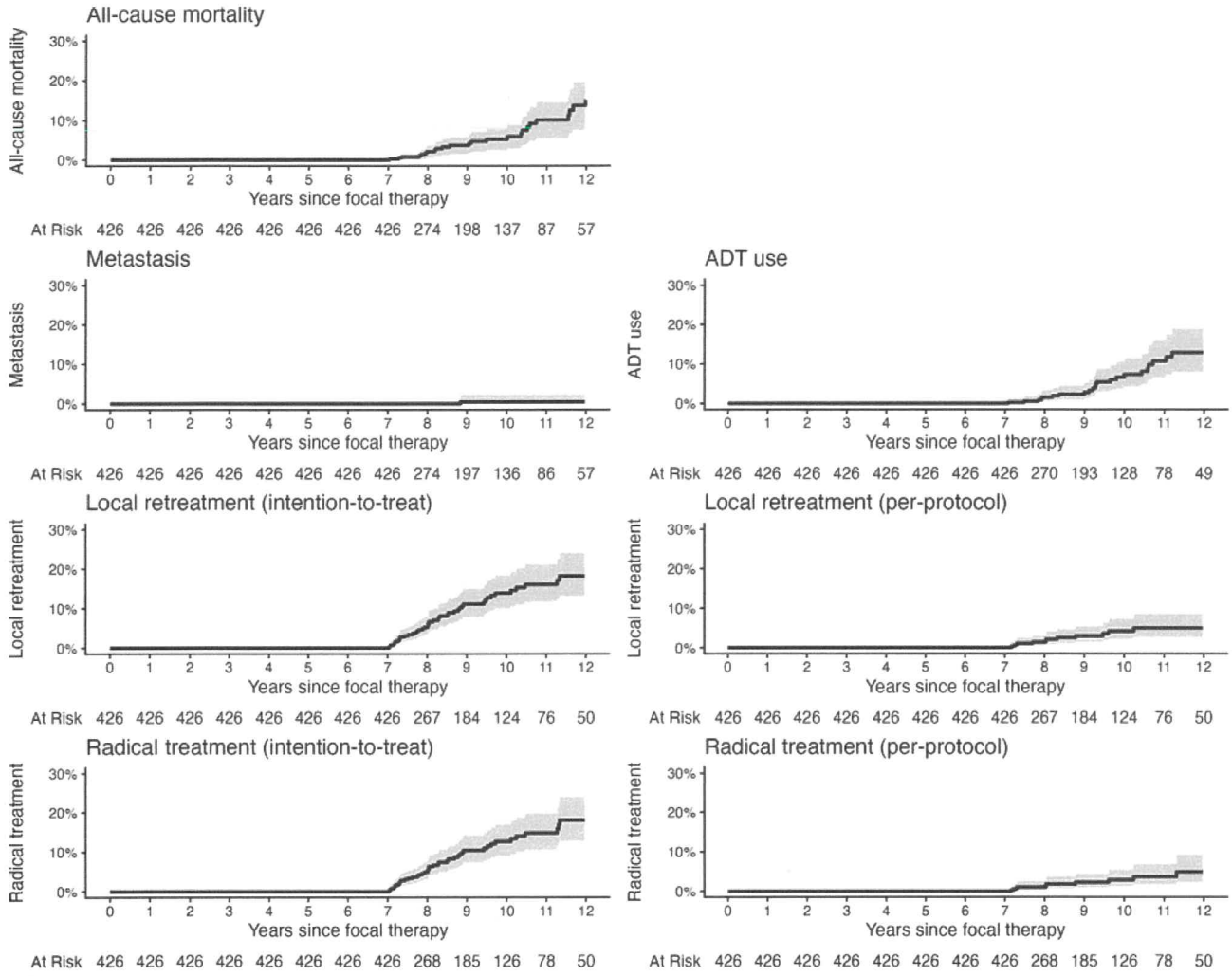

Fig. 3 – Cumulative incidence plots for outcomes in landmark analysis focusing on patients who had at least seven years follow-up and who remained local retreatment-, ADT-, and metastasis-free up to that landmark (n = 426). There were no prostate cancer-specific deaths. The ten- and 12-year cumulative 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

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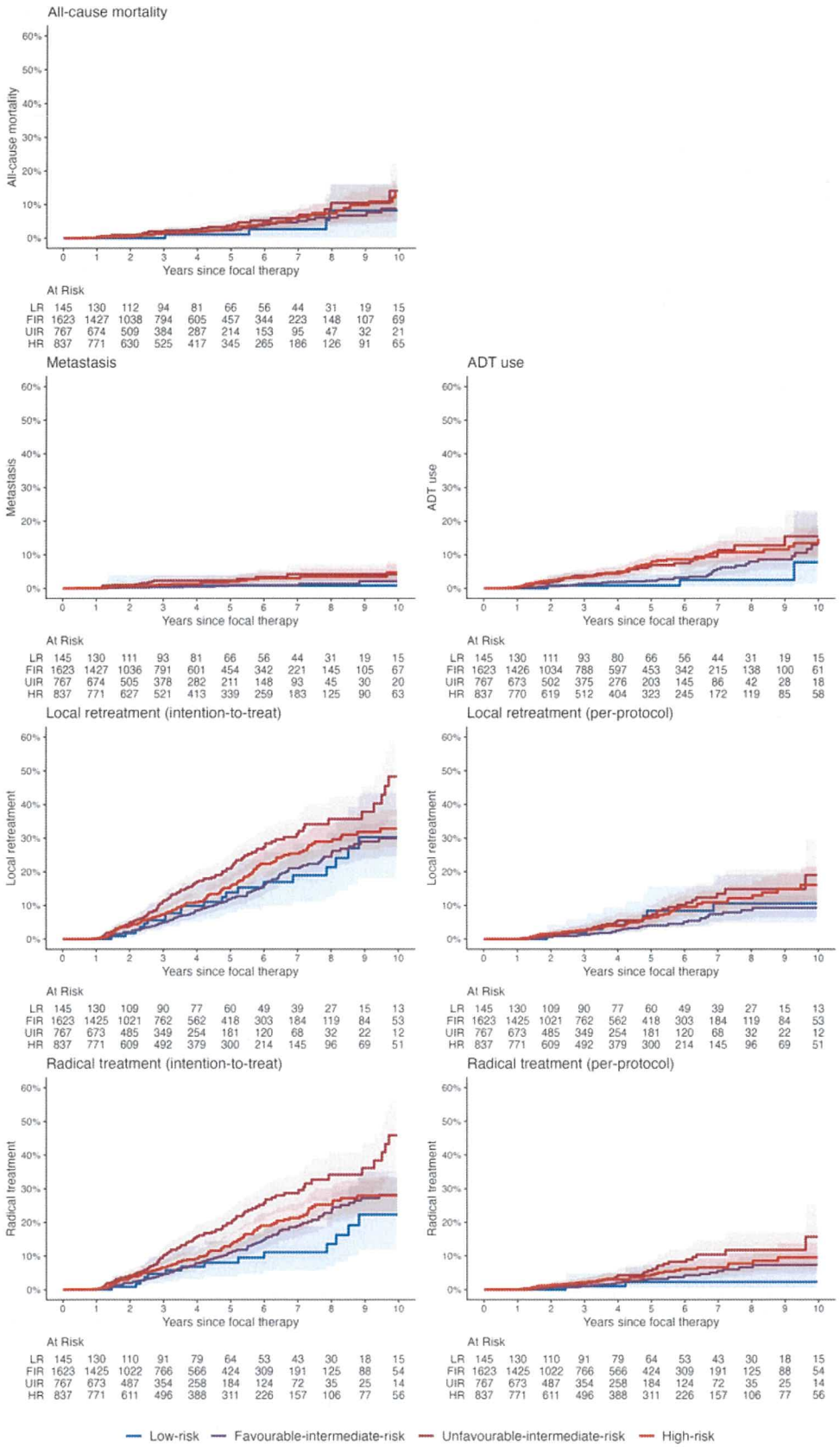

Fig. 5 – Cumulative incidence plots for outcomes in subgroup analysis of EAU 2025 risk groups. The cumulative incidence plot for cancer-specific mortality is shown in Fig. S8 and ten-year cumulative incidence estimates are reported in Table S4. Abbreviations: FIR, favourable-intermediate-risk; HR, high-risk;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

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