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A Personalised Clinical Dynamic Prediction Model to Characterise Prognosis for Patients with Localised Prostate Cancer: analysis of the CHHiP Phase III Trial

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Title

A Personalised Clinical Dynamic Prediction Model to Characterise Prognosis for Patients with Localised Prostate Cancer: analysis of the CHHiP Phase III Trial

Short running title

Dynamic predictive model for prostate cancer

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Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon reasonable request to the corresponding author.

The Institute of Cancer Research (ICR) Clinical Trials and Statistics Unit (CTSU) supports wider dissemination of information from the research it conducts to increase cooperation between investigators. Trial data are obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and Intellectual Property. Requests are reviewed by the Trial Management Group in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the Trial Management Group and approved by the Independent Data Monitoring and Steering Committee, as required. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymizing identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with Cancer Research UK data sharing guidelines.

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Abstract

Background

The CHHiP trial assessed moderately hypofractionated radiotherapy in localised prostate cancer. We utilised longitudinal prostate-specific antigen (PSA) measurements collected over time to evaluate and characterise patient prognosis.

Methods

We developed a clinical dynamic prediction joint model to predict the risk of biochemical or clinical recurrence. Modelling included repeated PSA values and adjusted for baseline prognostic risk factors of age, tumour characteristics and treatment received. We included 3,071 trial participants for model development using a mixed-effect submodel for the longitudinal PSAs, and a time-to-event hazard submodel for predicting recurrence of prostate cancer. We evaluated how baseline prognostic factor subgroups impacted on the nonlinear PSA levels over time and quantify the association of PSA on time-to-recurrence. We assessed bootstrapped optimism-adjusted predictive performance on calibration and discrimination. Additionally, we performed comparative dynamic predictions on patients with contrasting prognostic factors and investigated PSA thresholds over landmark times to correlate with prognosis.

Results

Patients that developed recurrence had generally higher baseline and overall PSA values during follow-up and had an exponentially rising PSA in the two-years before recurrence. Additionally, most baseline risk factors were significant in the mixed-effect- and relative risk submodels. PSA value- and rate-of-change was predictive of recurrence. Predictive performance of the model was good across different prediction times over an 8-year period, with an overall mean AUC of 0.70, mean

Brier score of 0.10, and mean integrated calibration index of 0.048; these were further improved for predictions after 5 years of accrued longitudinal post-treatment PSA assessments. PSA thresholds less than 0.23ng/mL after 3 years were indicative of a minimal risk of recurrence by 8 years.

Conclusions

We successfully developed a joint statistical model to predict prostate cancer recurrence, evaluating prognostic factors and longitudinal PSA. We showed dynamically updated PSA information can improve prognostication, which can be used to guide follow-up and treatment management options.

Keywords: joint model, prostate cancer prognosis, biochemical and clinical failure, prostate-specific antigen (PSA), intensity modulated radiotherapy (IMRT), hypofractionation.

1 Introduction

Prostate cancer is the second most common cancer in men globally [1]. In the UK, at diagnosis over half of men (56%—61%) present with localised prostate cancer (TNM staging: T1b–T3aN0M0) [2]. Radical treatment with neoadjuvant hormone therapy and intensity-modulated radiotherapy (IMRT) is less invasive and generally better tolerated for long-term quality-of-life than radical prostatectomy [3–5]. Following the publication of three randomised controlled trials, including CHHiP, showed that moderately hypofractionated radiotherapy was non-inferior to conventional (2 Gray/fraction) radiotherapy; hypofractionation is now used as a standard of care in Europe and North America [6–10].

At diagnosis, patients are routinely stratified into the National Comprehensive Cancer Network (NCCN) risk groups, which guide initial treatment management decisions [11]. NCCN risk groups are defined by presenting tumour features at diagnosis, including TNM staging, Gleason score (GS), and prostate-specific antigen (PSA), that are used to predict prognosis [12]. Although these prognostic factors may stratify patient groups, they do not always accurately predict the risk of biochemical or clinical failure of individual patients [13].

PSA is used in routine follow-up to monitor for cancer recurrence and define biochemical failure. After radiotherapy, typically nadir PSA values (the lowest concentration) are observed; the nadir directly defines each patient's biochemical failure threshold [14]. Data collected during routine follow-up, including repeat measures of PSA, may be of additional prognostic value to update the predicted risk of recurrence. Studies have investigated pre-treatment prognostic factors of the risk of biochemical failure in CHHiP [7]. In this work, in addition to (baseline) pre-treatment information, we propose the use of joint modelling methodology [15–18]. We incorporate

PSA values collected over time (the longitudinal process) to obtain updated predictions of the risk of biochemical- or clinical failure (the time-to-event process), as new information becomes available. This could lead to a more personalised approach to follow-up care and management. For instance, if a patient remains recurrence-free for a prolonged period, and the PSA trajectories would classify the patient as having a low recurrence risk, then a possible recommendation could be to reduce the patient's follow-up schedule, resulting in less burden for both patients and clinics. Conversely, if the patient's risk increases, it may enable the clinician to initiate more intensive follow-up or direct alternative therapies as appropriate [19].

The objective of our research is to develop a clinical dynamic prediction joint model utilising longitudinally collected PSAs to then predict the risk of future recurrence in the CHHiP trial. We present dynamic predictions of the developed model on prognosis for two patients contrasting in their baseline prognostic factors, then evaluate the predictions and performance with internal bootstrapped validation. We then deduce PSA thresholds that are indicative of good prognosis, with minimal ی ىЬ risk of recurrence.

2 Methods & Materials

2.1 Study design & procedure

CHHiP is an international, multicentre, randomised, phase III, non-inferiority trial. Men with localised prostate cancer (T1b-T3aN0M0) were randomised (1:1:1) to receive conventional radiotherapy 74Gy in 37 fractions (f) over 7.4 weeks, or one of two hypofractionated radiotherapy schedules: 60Gy/20f in 4 weeks or 57Gy/19f over 3.8 weeks. The protocol mandated hormone therapy in men with NCCN intermediate and high-risk disease, for at least 3 months (maximum 6 months) before start of

radiotherapy and continued until the end of radiotherapy; this was optional for low-risk patients. Bicalutamide monotherapy or luteinising-hormone-releasing-hormone analogue plus possible short-term anti-androgen (LHRHa) were permitted according to patient and physician's choice. PSA values were recorded pre-hormone therapy and pre-radiotherapy; then at weeks 10, 18, and 26 after start of radiation therapy; and then at intervals of 6 months after end of radiotherapy for 5 years; then annually thereafter. The trial was registered (ISRCTN97182923), approved by the London Multicentre Research Ethics Committee (04/MRE02/10) and by the institutional research board of each participating international site. This study was conducted in accordance with principles of good clinical practice; full details of the trial design have been described previously [7].

2.2 Outcomes

Prostate cancer recurrence was defined as the composite of biochemical or clinical failure or death due to prostate cancer. Biochemical failure was defined using the Phoenix definition of a 03! حي ÔÈÅ ÎÁÄÉÒ طى ςÎÇ7Í , [14]. Clinical failure included: recommencement of hormone therapy, local recurrence, lymph node or pelvic recurrence, and distant metastases. Time-to-recurrence was calculated as the time between the patient's closest pre-treatment PSA before hormone therapy (time origin ò سي π , and the first primary endpoint event. The median time between the closest pre-treatment PSA and randomisation was 15 weeks. Patients who were alive and recurrence-free or died due to causes unrelated to prostate cancer were censored at their last known follow-up date, with administrative censoring of longitudinal follow-up taking place at 10 years after time origin.

For this study, only patients who received hormone therapy and had at least one post-treatment PSA were included for model development. Complete-case analysis

was undertaken for the baseline prognostic factors. We based analyses on a data snapshot taken on October 9, 2019.

2.3 Joint modelling statistical methodology

A Bayesian shared-parameter joint modelling framework was used to develop the clinical dynamic prediction joint model (CDPJM). We specify a mixed-effects submodel to model PSA trajectories over time, and a Cox hazard submodel to model the time-to-recurrence endpoint. The shared parameters link the two submodels together, allowing us to quantify how a specific PSA trajectory is associated with risk of prostate cancer recurrence.

In the mixed effect submodel, baseline prognostic factors are included as fixed effects, while random effects are included to capture the individual variability of each patient's presenting PSA (random intercept) and deviation over time (random slopes). Deviations of PSA from the predicted trajectory are assumed to follow normally distributed measurement errors; PSA is log-transformed to conform to the distributional assumptions. Natural (restricted) cubic splines are employed to capture the nonlinear PSA over time. Implementing these splines is advantageous as they allow nonlinear PSAs to be flexibly modelled, without specific parametric assumptions needed, such as exponential-decay-growth, or biphasic parameterisations [20,21]. The splines split the range of the continuous PSA values into sub-intervals.

In the Cox hazard submodel it is assumed that the risk of recurrence depends on the trajectory of the longitudinal PSA biomarker. Thus, the trajectory parametrised via the mixed-effect submodel, considering the entire longitudinal history up to a time point t for each patient, is imputed into the Cox parameterisation as a linear

predictor, with a specified association structure where the features of the longitudinal PSA biomarker outcome are included. Typical associations structures are the value or the rate-of-change of PSA, or a linear combination of the two. I.e., this combinatory association structure of the PSA trajectory (at time ò) could be associated with the hazard of recurrence at that same point in time.

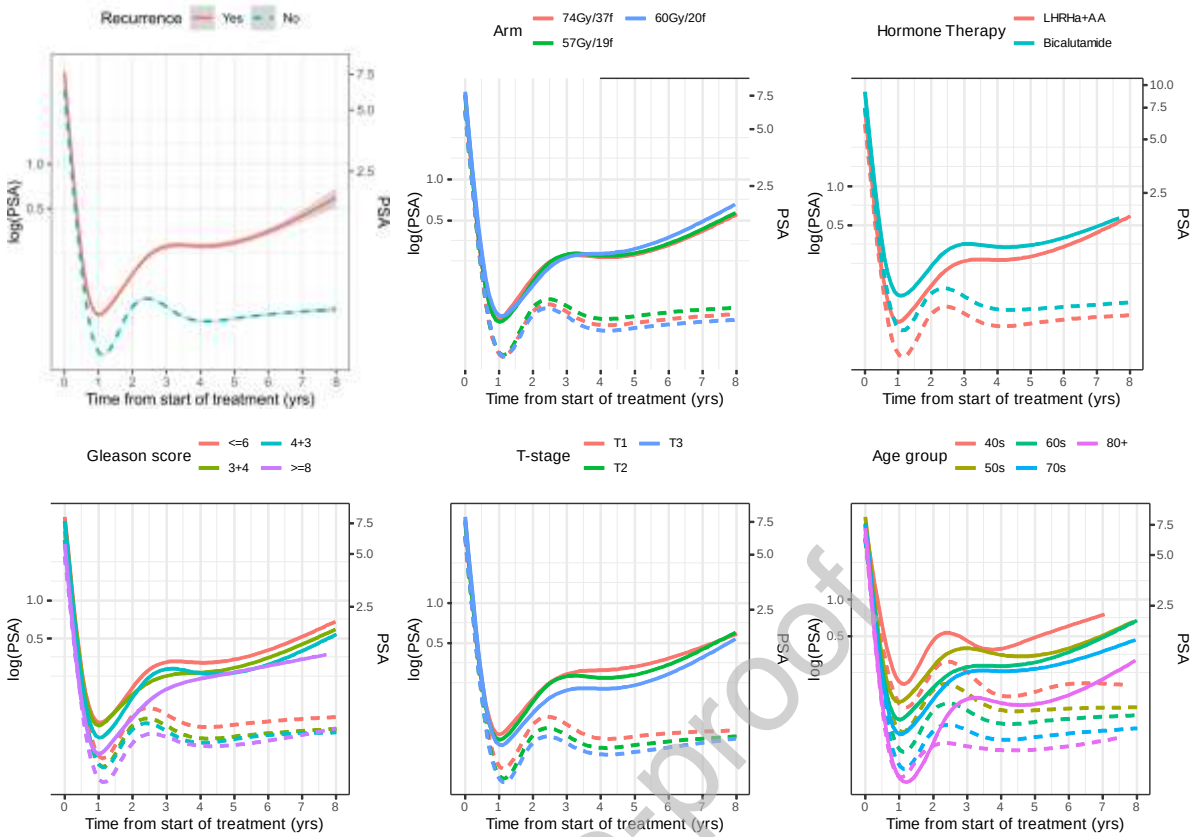
Models were developed using R software (v4.1.0). The individual submodels were fitted by maximum likelihood estimation using the *survival* (v3.2-11) and *nlme* (v3.1-152) R packages; the fully specified joint model was estimated with Bayesian Markov chain Monte Carlo sample algorithm, using *JMbayes2* (v0.1-64–0.2-3) [22–24]. Computation was performed on a CentOS 8 Linux high-performance computer and Windows 10 Intel Core i9-8950HK CPU. Further details can be found in the *supplementary materials*.

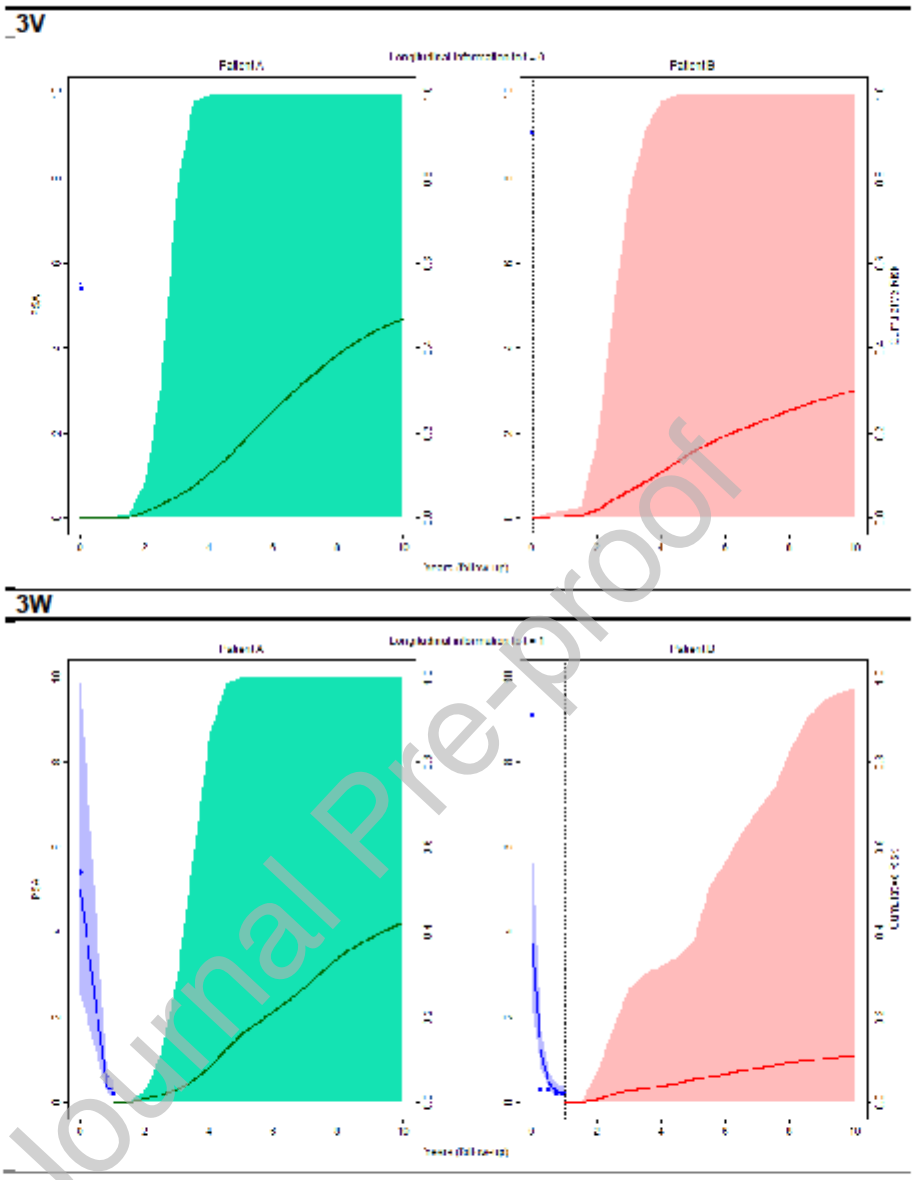
2.4 Dynamic predictions

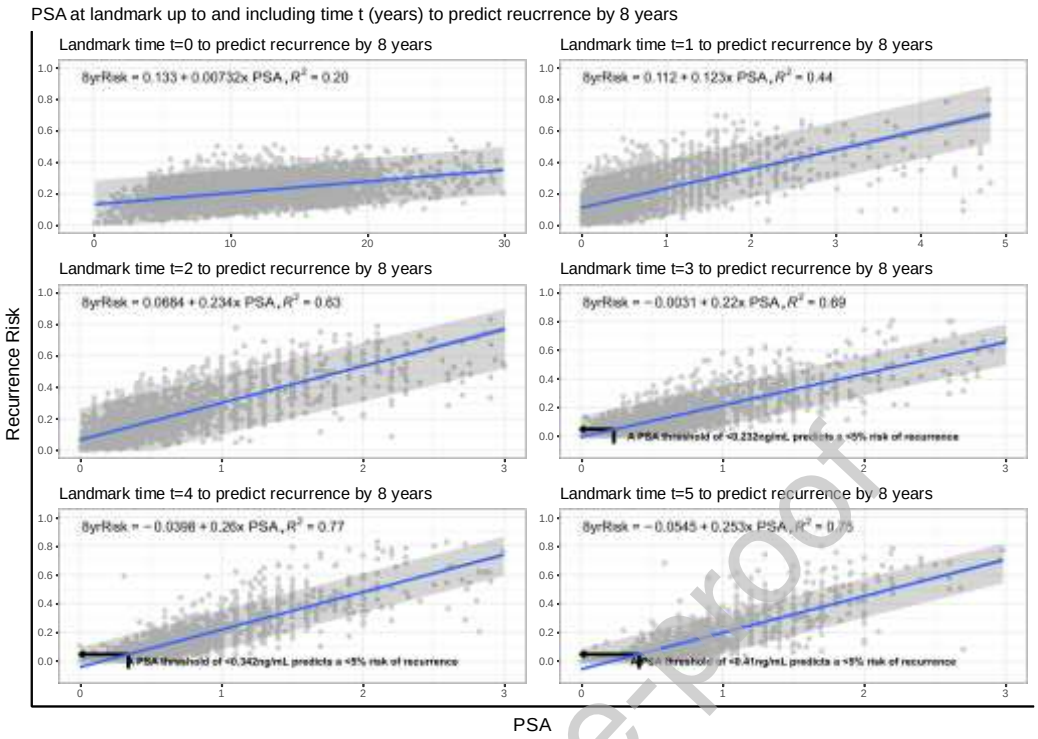
For each individual patient, we considered their longitudinal PSA biomarker values up to the landmark time point ò, where we assumed they are recurrence-free. We wish to make predictions about their prognosis, within some clinically relevant prediction window in the future ò‘ó ∩ ó حي ò, say two-, five-, or ten years from present landmark time ò. The joint model estimates the probability of recurrence within time ó, given the information available up to time ò. These predictions are dynamic, as they can be updated as new follow-up and PSA information becomes available for that patient (that is, by increasing the landmark time ò) [17].

2.5 Assessing predictive performance and risk thresholds

Predictive performance of the joint model was evaluated at varying landmark times, by assessing its discrimination via time-dependent area under the curve (AUC) and







Tables

Table 1 - Baseline characteristics, follow-up time (N=3071) considered in model development. LHRHa – Luteinizing-Hormone-Releasing-Hormone analogue + possible anti-androgen.

Baseline Factors	**N = 3071[1]** **[1] n (%); Median (IQR)**
Allocated fractionation group	
74Gy/37f	1017 (33%)
57Gy/19f	1025 (33%)
60Gy/20f	1029 (34%)
Gleason score	
جى ٪	1022 (33%)
٨ طى ٧	1354 (44%)
٧ طى ٨	598 (19%)
جي '	97 (3%)
Clinical T-stage	
T1	1088 (35%)
T2	1713 (56%)
T3	270 (9%)
Hormone Therapy	
LHRHa	2668 (87%)
150mg Bicalutamide	403 (13%)
Age (years)	69.1 (64.5, 73.2)
Baseline/presenting PSA (ng/mL)	10.3 (7.3, 14.6)

Table 2 – optimism-corrected model metrics from landmark times t=0—7 predicting at a horizon time of eight years. Discrimination – AUC (area under the curve); calibration – ICI (integrated calibration index); overall predictive performance – (Brier score). Mean, [95% bootstrapped CIs] refers to the bootstrapped replications. The ICI & Brier are loss functions (where lower is better), with higher AUC measures indicating better discrimination. Ns are patients remaining at risk at development.

		Optimism-corrected metrics		
Landmark t_{years} for prediction interval [t, 8]	**N still at risk**	**AUC**	**ICI**	**Brier**
٤ سي ◂ ***(baseline)***	3071	0.525 [0.500—0.553]	0.056 [0.043—0.068]	0.16 [0.154—0.166]
٥ سي ◂	3039	0.58 [0.556—0.6]	0.06 [0.045—0.072]	0.153 [0.147—0.16]
٦ سي ◂	2947	0.612 [0.583—0.644]	0.083 [0.069—0.098]	0.153 [0.145—0.16]
٧ سي ◂	2823	0.651 [0.632—0.677]	0.061 [0.049—0.069]	0.123 [0.113—0.132]
٨ سي ◂	2705	0.748 [0.728—0.767]	0.045 [0.036—0.052]	0.097 [0.089—0.106]
٩ سي ◂	2528	0.797 [0.767—0.821]	0.038 [0.031—0.048]	0.068 [0.062—0.075]
١٠ سي ◂	2357	0.838 [0.807—0.868]	0.024 [0.019—0.029]	0.047 [0.039—0.054]
١١ سي ◂	2176	0.806 [0.756—0.873]	0.016 [0.013—0.019]	0.027 [0.022—0.033]