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Methodological Article

Modeling Clinical Outcomes in Prostate Cancer: Application and Validation of the Discrete Event Simulation (DES) Approach

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ABSTRACT

Objectives: Treatment landscape in prostate cancer has changed dramatically with the emergence of new medicines in the past few years. The traditional survival partition model (SPM) cannot accurately predict long-term clinical outcomes because it is limited by its ability to capture the key consequences associated with this changing treatment paradigm. The objective of this study was to introduce and validate a discrete-event simulation (DES) model for prostate cancer. **Methods:** A DES model was developed to simulate overall survival (OS) and other clinical outcomes based on patient characteristics, treatment received, and disease progression history. We tested and validated this model with clinical trial data from the abiraterone acetate phase III trial (COU-AA-302). The model was constructed with interim data (55% death) and validated with the final data (96% death). Predicted OS values were also compared with those from the SPM. **Results:** The DES model's predicted time to chemotherapy and OS are highly consistent with the final observed data. The model accurately predicts the OS hazard ratio from the final data cut (predicted: 0.74; 95% confidence interval [CI] 0.64–0.85 and final actual: 0.74; 95% CI 0.6–0.88). The log-rank test to compare the observed and predicted OS curves indicated no statistically significant difference between observed and predicted curves. However, the predictions from the SPM based on interim data deviated significantly from the final data. **Conclusions:** Our study showed that a DES model with properly developed risk equations presents considerable improvements to the more traditional SPM in flexibility and predictive accuracy of long-term outcomes.

Keywords: modeling, discrete event simulation, prostate cancer, treatment sequence.

Prostate cancer is the second most common cancer among men, with nearly 1.1 million new cases reported around the world each year [1]. It is also one of the leading causes of cancer deaths [2]. Although androgen deprivation is the mainstay of advanced prostate cancer treatment, almost all patients progress to castration-resistant prostate cancer (CRPC) and eventually develop metastasis [3]. In the past 5 to 6 years, the introduction of highly effective novel therapies has dramatically changed the treatment landscape for patients with metastatic CRPC (mCRPC). Overall survival (OS) has improved significantly with the availability of new treatments, including sipuleucel-T (2010) [4], cabazitaxel (2011) [5], abiraterone acetate plus prednisone (2011–2013) [6,7], enzalutamide (2012–2014) [8,9], and radium-223 (2013) [10]. The treatment landscape is expected to continue to change for patients with prostate cancer, as a number of new therapies are in clinical development [11] to target earlier stages of prostate cancer, with the goal of delaying or stopping disease progression.

As new treatments are moving to address earlier stages of the disease, clinical trials often cannot fully capture the experiences of individual patients because of limited follow-up durations. Surrogate endpoints (e.g., progression-free survival, metastasis-free survival, biochemical recurrence-free survival) are used in clinical trials to demonstrate the clinical benefit of new treatments. An association between surrogate endpoints and OS needs to be established to quantify the value of new treatments. In addition, both payers and clinicians are interested in defining "optimal" treatment pathways or sequences for patients with prostate cancer. Therefore, a model that can track multiple lines of treatment is warranted.

Although novel treatments in prostate cancer have demonstrated promising clinical benefits, they also typically come with

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increased costs. Payers across the globe often require cost-effectiveness evaluations of new agents to inform their reimbursement decisions. Rarely have oncology economic models been developed to reflect treatment pathways [12]. A survival partition model (SPM) with three health states (e.g., progression-free, postprogression, and death) is the most common solution to evaluate oncology treatments, especially for advanced or metastatic cancers, including mCRPC [13–18]. In a recent review conducted by the U.K. National Institute for Health and Care Excellence (NICE) Decision Support Unit [19], the majority of recent appraisals for oncology treatments used an SPM approach. Although the SPM approach allows for replication of trial results, such as those for progression-free survival (PFS) and OS, with relative ease and is simple to implement, its fundamental structural assumption—that both a surrogate endpoint, such as PFS, and a hard endpoint, such as OS, are independent—is a major limitation. This limitation may cause increased uncertainty when extrapolating survival beyond the trial period if OS data are immature. Additionally, with the changing treatment paradigms that have come with the emergence of new medicines in the past few years, this simple approach is not able to capture all the key events and treatments that could have significant impacts on patient clinical outcomes, medical resource utilization, and costs.

The state transition approach (i.e., Markov or semi-Markov) is an alternative approach used by some oncology models [19]. This approach incorporates explicit links between clinical endpoints and adds flexibilities to the model for sensitivity analysis. However, the memoryless property of the cohort Markov model requires simplifying assumptions that are often not supported by the clinical data in oncology, whereas implementation of time-dependent transition probabilities makes programming and utilization of the model complex, especially when multiple health states or treatment sequences are considered. Cases in point are a NICE submission using a Markov model to track three lines of therapy among patients with chronic lymphocytic leukemia that defined 39 health states [20] and a recent study attempting to compare survival partition and state transition approaches that was not able to show which approach is more advantageous [21].

The discrete-event simulation (DES) approach, which captures a patient's experiences in terms of events and involves less restrictive assumptions, may provide a better framework for modeling treatment sequences in prostate cancer compared with the SPM approach. The ability of the DES approach to track changes in patient characteristics, health status, treatment history, and treatment switches over the course of the disease could improve modeling accuracy and efficiency. These characteristics also make the DES model superior to the state transition model, as the DES type does not require the creation of multiple health states to track patients when disease progression depends on prior history.

The objective of this study was to introduce and validate a DES modeling framework for prostate cancer. The model uses predictive equations to simulate the experience of a patient with metastatic prostate cancer with regard to a sequence of treatments and to predict OS and other clinical outcomes on the basis of patient characteristics, treatment history, and disease progression at different stages of treatment. This study also compared extrapolations of survival from the DES and SPM approaches, discussing the strengths and the limitations of applying DES in prostate cancer.

Methods

Data Source

Data from the pivotal phase III trial (COU-AA-302) on abiraterone acetate was used to illustrate the application of the DES approach in prostate cancer, in particular mCRPC. The COU-AA-302 clinical trial evaluated the benefit of abiraterone acetate (1000 mg daily) in combination with prednisone (10 mg daily) (referred to as "AAP") compared with prednisone alone for asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC [8,22]. These treatments were administered after failure of androgen deprivation therapy in patients for whom chemotherapy was not yet clinically indicated.

Two analyses of the COU-AA-302 data are available: (1) interim data, at which point 55% of the 733 prespecified all-cause death events had occurred, with a median follow-up of 27.1 months (referred to as the 55% data cut); and (2) final COU-AA-302 trial data, with a median follow-up of 49.2 months and 96% of prespecified deaths observed (the 96% data cut), as was presented by Ryan et al. [22]. For the purpose of this study, the 55% data cut was used to inform the model design and data inputs, and the 96% (final) data cut was used to validate the extrapolation of the survivals from the model,

DES Model

Model structure

A DES model was developed in Microsoft Excel to simulate the progression and treatment of mCRPC. The treatment pathway structure of the model is shown in Figure 1. Events included in the model are treatment discontinuation, start of new treatment, and death. The model must assign the time for treatment start and discontinuation to each patient at each line of treatment. Three lines of treatments are simulated: (1) pre-chemotherapy treatment (first-line), (2) chemotherapy (second-line), and (3) third-line treatment. A patient enters the model with asymptomatic or mildly symptomatic mCRPC and starts a non-chemotherapy treatment. Once the patient discontinues first-line active treatment, he will either move directly to the next treatment or stay off treatment for some time and then move to the next treatment. The patient is at risk of death at all times.

The design of the treatment pathway model structure is based on treatment guidelines in effect at the time the trial was conducted [23], plus the treatment pathways observed in the COU-AA-302 trial, and validated with clinical experts. The treatment pathways captured in the model represent pathways followed by 93% of the AAP patients and 91% of prednisone-alone patients in the COU-AA-302 trial. Among trial pathways not represented in the model's prednisone-alone arm, 7.7% of

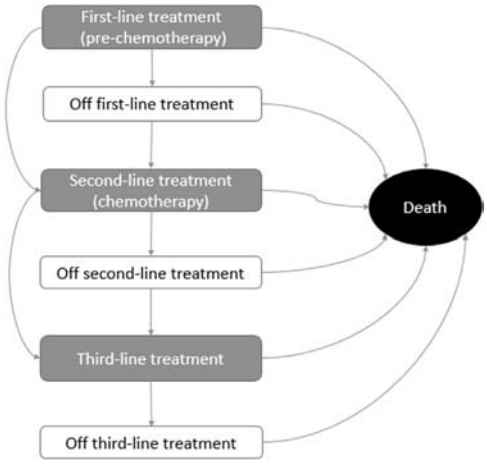

Fig. 1 – Treatment pathway model structure in mCRPC. mCRPC, metastatic castration-resistant prostate cancer.