Interpreting Prostate Cancer Predictions

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The goal of this application is to provide outcome predictions for prostate cancer patients. In particular, we are interested in outcomes of death and metastatic clinical failure (CF). Event times are calculated using the time of treatment (surgery or radiation) as time zero.

For a particular patient, we can imagine possible outcome events that can occur. At a particular time $t > 0$, the patient may be in one of the following four outcome states: (1) had a CF and then died, (2) had a CF but still alive, (3) alive without CF, and (4) died without prior CF.In the application, we provide estimates of the proportion of subjects (with given baseline characteristics and a particular treatment assignment) that will be in each of the 4 outcome states at a particular time t. We call these probabilities "state occupancy probabilities." Below, we provide some brief descriptions of the model used to estimate these probabilities.

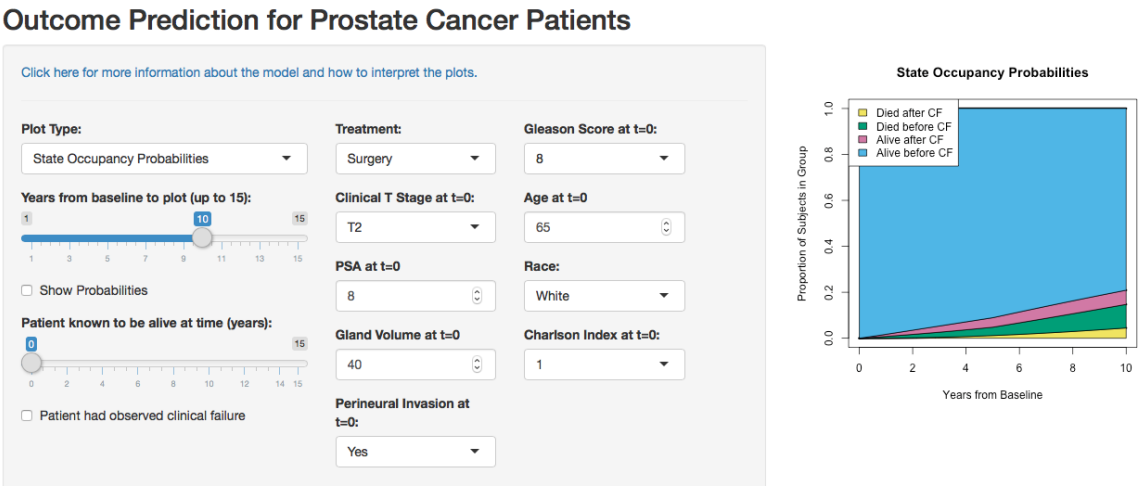
1 Example Prediction

Suppose we had a population of 1000 patients all with the same set of patient characteristics and treatment assignment. The state occupancy plots tell us what proportion of these subject we expect to be in each of the four states at each time t. We can estimate these probabilities across a range of t values to explore how these probabilities change over time. The RShiny application provides estimates of the state occupancy probabilities across specified values of t. The application also provides the overall survival probability across t (which is just the probability of not having died by each time t) and the event-free probability at time t (which is the probability of not having died or had a clinical failure by time t).

In **Figure 1**, we show the predicted state occupancy probabilities supposing that all 1000 patients had the application's default patient characteristics and supposing the patients all received surgery. In this plot, the x-axis represents time post-baseline and the y-axis represents the proportion of the 1000 subjects that are in each of the groups (cumulatively). To obtain the state occupancy probabilities at time t, imagine a vertical line on the plot at time t. The part of the plot in blue represents the proportion of subjects that would be alive without clinical failure at time t. The pink part represents the proportion of subjects that would be alive with a previous clinical failure at time t. The green and yellow sections represent the proportions of subjects that would have died without prior clinical failure and

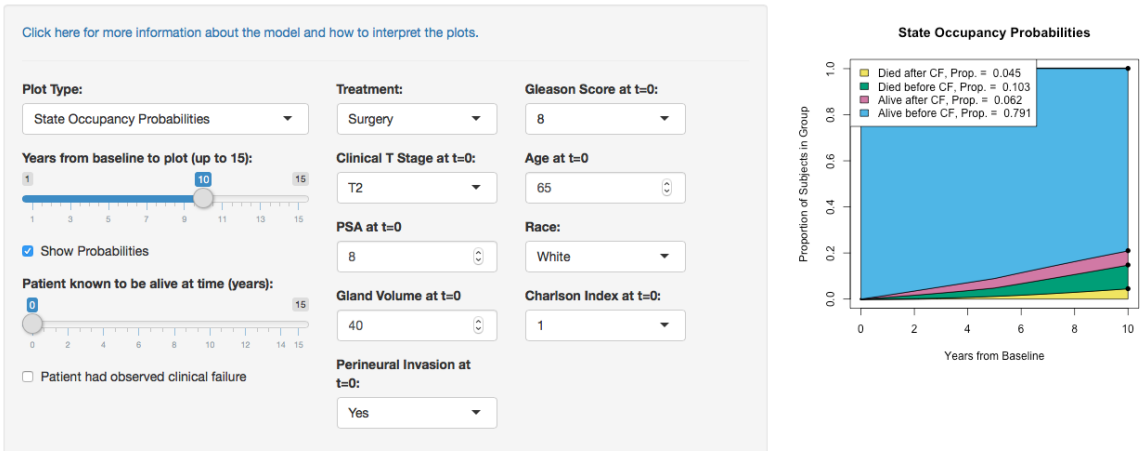
after prior clinical failure at time t respectively.

Figure 1: State Occupancy Probabilities for Default Characteristics under Surgery



Suppose we are interested in the state occupancy probabilities at $t = 10$ years from baseline. We can obtain the exact predicted probabilities by selecting "Show Probabilities." This will give us the plot in **Figure 2** below.

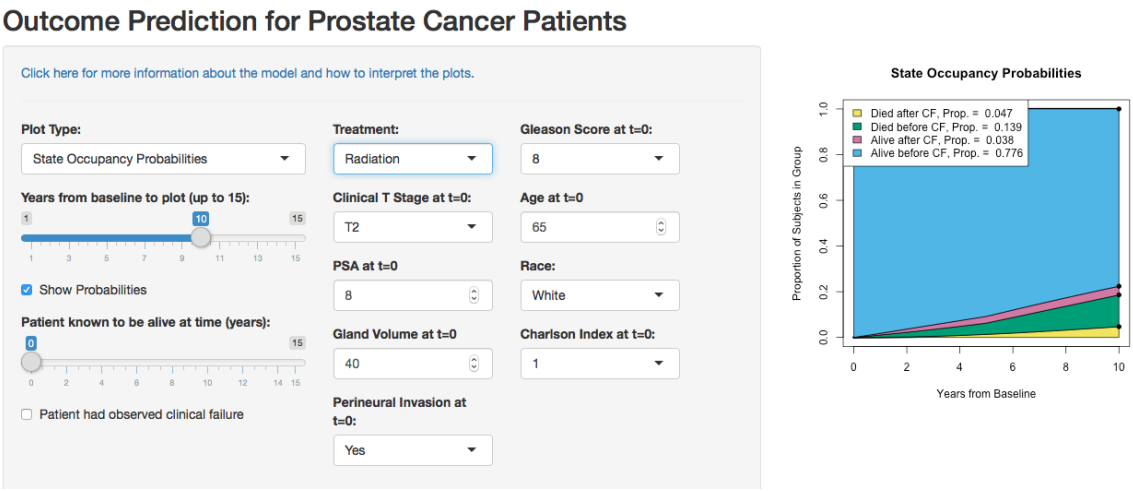
Figure 2: State Occupancy Probabilities for Default Characteristics under Surgery



According to the predictions in **Figures 1 and 2**, roughly 45 (4.5%) of the 1000 subjects would have died after prior clinical failure by 10 years, 103 (10.3%) would have died without prior clinical failure, 62 (6.2%) would be alive with prior clinical failure, and 791 (79.1%) would be alive without prior clinical failure (note these numbers add to 1001 due to rounding).

Suppose we want to compare these probabilities to the probabilities under radiation therapy. We can select "radiation" from the treatment dropdown menu, and we get **Figure 3** below.

Figure 3: State Occupancy Probabilities for Default Characteristics under Radiation

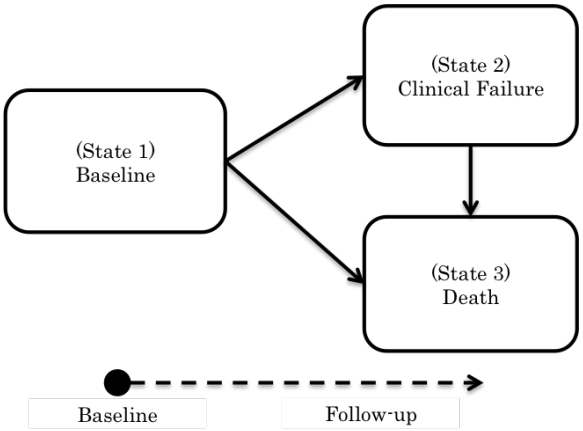


According to the predictions in **Figure 3**, roughly 47 (4.7%) of the 1000 subjects would have died after prior clinical failure by 10 years, 139 (13.9%) would have died without prior clinical failure, 38 (3.8%) would be alive with prior clinical failure, and 776 (77.6%) would be alive without prior clinical failure. This suggests that a slightly greater proportion of subjects would have died under radiation (18.6%) compared to under surgery (14.8%).

2 The Model

We model the outcome data using a multistate illness-death model with two outcome events: clinical failure and death. **Figure 4** provides a graphical representation of the model. Arrows represent possible transitions that a subject could experience. For each arrow, we describe the rate of movement between the two states using a Cox proportional hazards regression model.

Figure 4: Illness-Death Model Diagram



We use Weibull baseline hazards to model the transitions between states 1 and 2 and between states 2 and 3. We use a piecewise constant baseline hazard for the transition between states 1 and 3. Clinical failure time is included as a predictor in the model for the transition between states 2 and 3, and we use the time of clinical failure and the baseline for the model between states 2 and 3.

3 The Fit

We fit the above multistate illness-death model to a dataset of 4544 prostate cancer patients. Details about this model fit can be found in a manuscript titled "Comparison of Surgery and Radiation Therapy Outcomes in Prostate Cancer using Multistate Models." After publication, we will update this document to include additional information about the model fit. The model fit includes the following predictors: Gleason score (5-6, 7=3+4, 7=4+3, 8, 9-10), PSA, T Stage (1/2/3), perineural invasion (yes/no), Charlson Index (0/1/2/3+), age, race (white/african american/other), gland volume, treatment (surgery/radiation), and treatment year (1996-2000/2001-2006/2007-2013). In the application, we present the predictions for the most recent treatment group (2007-2013).

4 State Occupancy Probabilities

After we fit the model, we can use the model estimates to predict outcomes for future patients. For example, we may want to estimate the probability that an individual has died and/or has experienced a clinical failure by various times after baseline using the patient's baseline informations. These probabilities are depicted in the RShiny app.

State occupancy probabilities represent the expected fraction of patients (with specified characteristics) who will be in the each of the four possible states at any follow-up time t. Using the multistate illness-death model, we can derive equations for estimating the state occupancy probabilities for a given set of patient characteristics and treatment assignment. These equations will depend on the parameter estimates from the multistate model.

Here, we present the equations used to estimate the state occupancy probabilities given baseline characteristics and a treatment assignment. We can also estimate these probabilities incorporating additional follow-up post-baseline. Let $\lambda_{jk}(t)$ and $\Lambda_{jk}(t) = \int_0^t \lambda_{jk}(u)du$ denote the hazard and cumulative hazard of transitioning between states j and k at time t. At time t, the state occupancy probabilities are given by

$$P(\text{ dead before time } t \text{ with prior CF } |X) = \int_0^t \left[1 - e^{-\Lambda_{23}(t-u|u)}\right] \lambda_{12}(u) e^{-\Lambda_{13}(u)-\Lambda_{12}(u)}\, du$$

$$P(\text{ alive at time } t \text{ with prior CF } |X) = \int_0^t e^{-\Lambda_{23}(t-u|u)} \lambda_{12}(u) e^{-\Lambda_{13}(u)-\Lambda_{12}(u)}\, du$$

$$P(\text{ alive at time } t \text{ with no history of CF } |X) = e^{-\Lambda_{13}(t)-\Lambda_{12}(t)}$$

$$P(\text{ dead before time } t \text{ with no history of CF } |X) = \int_0^t \lambda_{13}(u) e^{-\Lambda_{12}(u)-\Lambda_{13}(u)}\, du$$

Using the probabilities above, we have that:

$$\begin{aligned} P(\text{ dead before time } t\ |X) =& P(\text{ dead before time } t \text{ with prior CF } |X) \\ &+ P(\text{ dead before time } t \text{ with no history of CF } |X) \end{aligned}$$