Personalised medicine for multiple outcomes : methods and application

Rüten-Budde, A.J.

Summary

Statistical analysis aims to find data based answers to important research questions in a variety of research areas. The Field of statistics called survival analysis is where the topics of this thesis find their place. Survival analysis deals with life-time data. In this type of data the time from a specific starting point until an event of interest occurs are recorded. In medical research for example, time from diagnosis of disease until death could be studied. What characterizes life-time data, also called survival data, is that it is generally incomplete. Some individuals in the data might not have experienced the event of interest at the end of the study period or have dropped out of the study before the event has occurred. These data are called *right-censored*. The event time is unknown, it is known however, that the event had not occurred before the last observation time. To handle this particular type of missing data, and other similar types, special methodology is necessary summarized under the term survival analysis.

Survival analysis is used by clinicians to identify risk factors associated with the occurrence of a clinical event of interest. For example in cancer research, clinicians use survival models to investigate if a patient's age, sex, tumor size, and other clinically relevant variables are associated to the risk of death. To describe the evolution of disease complex mathematical models are required. Patients may experience several disease related events in different orders. *Multi-state models* can be applied in such context. Another extension of survival models is to add a random effect, also called *frailty*. Frailty terms are used to model unobserved covariates which might have an effect on the event of interest. In all studies not all relevant patient or disease characteristics can be collected and therefore the survival model is incomplete. Random effects quantify the so called unobserved heterogeneity resulting from an incomplete model.

Survival models may be used to investigate the effect of risk factors on clinical events of interest and to predict survival probabilities. Such predictions inform both patients and clinicians of a patient's prognosis and may help in the shared decision making process. Prediction models are available for a variety of diseases and there is a demand for more and more sophisticated models. Ordinary prediction models are often limited to a single prediction time point. This means that predictions can only be made at a particular time, such as at time of diagnosis of disease. When a patient comes back for a follow-up visit, such models are not able to provide accurate predictions. A patient may experience disease related events over time which are not taken into account by a model that considers only risk factors known at diagnosis or at start of treatment. *Dynamic prediction* models provide updated predictions from different time points during follow-up. They are able to include updated information

as it becomes available. A simple idea to create dynamic prediction models is through the *landmarking* approach. Predictions are made from a chosen landmark time point by using a subset of the data consisting of patients still alive at that time. Multiple landmark times can be chosen to make predictions from different time points during follow-up.

The main objective of this thesis was to develop clinically relevant survival models for patients with high-grade soft tissue sarcoma of the extremities, in particular the development and validation of prediction models for use in clinical practice. The interdisciplinary collaboration between the Mathematical Institute of Leiden University and the Leiden University Medical Center resulted in important contributions to the care of soft tissue sarcoma patients [2, 4, 5].

In Chapter 1 basic concepts of survival analysis are introduced as well as more complex models that are used in this thesis. After a short introduction of general concepts, such as the hazard and survival function, frailty models are discussed which add random effects to a survival model. Later on, the simple one end-point survival model for a single event of interest is extended to multiple end-points by introducing competing risks models. More complicated event structures are described thereafter using multi-state models, in which transitioning states where an individual can move through are allowed. Next, dynamic prediction models are introduced as well as measures of discrimination that assess the predictive accuracy of survival prediction models. Some information about the motivating soft tissue sarcoma data set are given. Finally, the developed prediction tool is discussed. An outline of this thesis ends the chapter.

In Chapter 2 a novel frailty model for multi-center data with two competing events is proposed. In practice not all relevant covariates to explain the variance of event times between subjects can be collected. Random effects, called frailty, quantify the unobserved heterogeneity resulting from an incomplete model. Frailty variables that are shared by individuals who were treated in the same hospital are used to model unobserved heterogeneity on the hospital level; they could be interpreted as the "hospital effect" on the competing events. The patients treated in some hospitals may, corrected for covariates, live longer than those treated in other hospitals. This "hospital effect" may be an interest of study. The novelty of the proposed frailty model lies in the construction of the frailty variables. Two frailty variables, one for each competing event, are constructed from three independent gamma distributed frailty components. Each frailty is the sum of two frailty components, a cause-specific and a shared frailty component. This allows for the two frailties to be correlated. The model is estimated using the expectation-maximization algorithm which additionally provides empirical Bayes estimates for each hospital's frailties.

In Chapter 3 the effect of interval censoring is studied on the predicted accuracy of a binary disease marker. The motivation comes from cancer care. After surgery a patient is regularly screened for local recurrence and distant metastasis. Once a recurrence is diagnosed, however, it is only known that it occurred between the last negative and the first positive screening. Additionally, if a patient dies after a negative recurrence screening, then it is unknown whether he developed a recurrence between

the last screening and death. The predictive value of this time-dependent recurrence variable can be summarized by time-specific Area Under the receiver operating characteristics Curve (AUC) measures. The effect that ignoring the interval-censored nature of the observation time has on the time-specific AUC in both incident/dynamic and cumulative/dynamic definition is studied through simulations. AUC estimates derived from different methods for fitting two types of models are compared: the Cox model with time-dependent covariate, which ignores interval-censoring and the illness-death model for interval-censored data.

Chapter 4 is the first in a series of publications based on the growing soft tissue sarcoma data set. A data set of 687 patients with high-grade soft tissue sarcoma of the extremities treated surgically was collected from 4 international tertiary centers. The effect of risk factors on local recurrence and distant metastasis/death was studied using a 3-state multi-state model. Multi-state models describe the evolution of the disease close to reality and allow detailed insights into the effect of risk factors on disease progression. After surgery a patient starts in the starting state "alive without evidence of disease", he can then move to the local recurrence state and subsequently to the distant metastasis/death state or move to distant metastasis/death directly. For each of the three transitions the effect of risk factors was studied allowing for the effects to differ between transitions. Of particular interest was the effect of surgical margin. Surgical margin describes the amount of healthy tissue surrounding the tumor that is dissected during tumor removal surgery. The association with survival and local recurrence was of great interest for clinicians as it impacts the functional outcome after surgery.

Chapter 5 is the continuation of the soft tissue sarcoma project, with a data set of 766 patients collected from 5 international tertiary centers. The motivation came from the need of clinicians for an easy to use prediction tool for patients with soft tissue sarcoma. Two prediction models one for survival and one for the probability of local recurrence were developed using Cox and Fine and Gray's methodology. The survival model is a simple one end-point model, the model for local recurrence however, needs to consider the competing risk of death. The models predict the probability of surviving 3, 5, and 10 years as well as the probability of developing a local recurrence within 3, 5, and 10 years from time of surgery respectively. The advantage of using Fine and Gray's model for competing risks to model covariate effects on the probability of developing local recurrence is that estimated regression coefficients are more intuitive to interpret for clinicians compared to the cause-specific hazards model. The prediction models were implemented in the PERSARC mobile application to be used by clinicians to improve patient care [4, 5]. An internal validation considering calibration plots and the C-index demonstrated good calibration and discrimination of the prediction models.

In Chapter 6 a dynamic prediction model based on the growing soft tissue sarcoma data set was developed. Data of 2232 soft tissue sarcoma patients was collected from a total of 14 international tertiary centers. The aim was to develop a prediction tool able to make updated survival predictions for patients during follow-up. After surgery a patient has scheduled follow-up visits to monitor him and to screen for

adverse events. Events like local recurrence and distant metastasis affect the future prognosis. Also the fact that a patient survived a length of time after surgery may give an insight into the future prognosis. This requires dynamic predictions for a patient to be updated over time. For this purpose a landmark supermodel was used to predict the probability of surviving an additional 5-years from different prediction time points during follow-up. Local recurrence and distant metastasis, are used to update predictions over time and covariates were investigated for time-varying effects. The model was internally validated.

In Chapter 7 the previously developed dynamic prediction model for soft tissue sarcoma patients is updated and externally validated. The updated model is based on 3826 patients collected from 17 international tertiary centers and a randomized controlled trial. Data for external validation consisted of 1111 patients from a single tertiary center. The updated dynamic prediction model now includes grade as additional covariate in the model. This important covariate was initially omitted because the previously collected data contained mainly grade III patients. During this research, the data set has been significantly augmented and now includes a large cohort of grade II patients. A successful external validation showed that the model was able to adequately predict the probability of surviving an additional 5-years from different prediction time points during follow-up. The model is implemented in the updated PERSARC mobile application [4, 5].

In Chapter 8 a multi-state model was developed for 982 Ewing sarcoma patients that were treated surgically according to the EURO-E.W.I.N.G99 protocol. The starting time of analysis is the time of surgery, from which a patient can move to different states corresponding to disease progression. Adverse events considered in the multi-state model were local recurrence, distant metastasis of the lungs, distant metastasis at other locations, and death. The effect of risk factors was studied on the transitions between disease states and the effect was allowed to differ between transitions. A particular interest lay in the effects of surgical margins, histological response, and radiotherapy treatment.