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An analysis of the recurrence–progression process in bladder carcinoma by means of joint frailty models

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ABSTRACT

Multiple sequential recurrences are one of the most important characteristics of superficial transitional cell carcinoma of the bladder, more than 50% of the patients will have *recurrences* (reappearance of a new superficial tumor). When in the same subject recurrent events are considered and these observed events are clustered into groups, independence between the clustered survival times cannot be assumed. A natural way to model the dependence of clustered event times is through the introduction of a cluster-specific random effect: the *frailty term*. On the other hand, between 10% and 30% of patients diagnosed with bladder carcinoma will present a muscle invasive *progression*, so the observation process of *recurrences* could be interrupted by a major failure event (*progression*). In this regard, a joint modelling of the two processes could make the study of a joint evolution over time possible, giving unbiased and efficient parameters. We jointly analyze recurrences and progression processes by means of the *joint frailty model*.

1. Introduction

In recent years, there has been a growing interest in studying processes which generate events repeatedly over time such as recurrent infections in AIDS patients [1] and the process recurrence–progression in bladder carcinoma [2] among others. In this regard, several modeling approaches have been proposed to analyze this type of data [3] where the interest centers on the effect of covariates on the failure risk.

The general framework is the survival analysis area. Survival analysis is a set of statistical tools to analyze data related to times from an origin time until the occurrence of some or other event. The period of time from the start point to the event is the survival time, represented by a nonnegative random variable T for each individual. Generally two functions are of central interest: the survival function and the hazard function. The survival function $S(t)$ is the probability that survival time T be greater than t, $S(t) = P(T > t)$, and the hazard function is the instantaneous probability of event at time t per unit time, given survival up to time t. On the other hand, if the event of interest is not observed during the follow-up period the survival time is censored. It is usually required that survival time be independent of the censoring mechanism, that is to say, the follow-up of the individual is interrupted by causes independent of the event. Otherwise, the censoring is named informative.

When the event of interest occurs repeatedly in the same subject, a correlation between the recurrent relapse times may exist due to either *heterogeneity* among individuals or *event dependence*. *Heterogeneity* is produced because some subjects have a higher (or lower) event rate than the other ones, due to unknown or unmeasurable effects such as, for example

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