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Modeling the recurrence–progression process in bladder carcinoma

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Abstract

Wei–Lin–Weissfeld (WLW) method is used to analyze different states of the superficial vesical carcinoma distinguishing between recurrences and the possibility of progression. Two approaches are considered in this analysis to represent different aspects of the disease from a clinical point of view: the first one attempts to focus on the effect of the clinico-pathological factors on recurrences by regarding a progression before the recurrence as a censoring event, meanwhile the second one analyzes these same effects on either recurrence or progression, whichever comes first. A predictive model of recurrence or progression based on clinico-pathological factors is presented.

Keywords: Proportional hazards; Recurrent events; Bladder carcinoma; Wei–Lin–Weissfeld method

1. Introduction

Bladder carcinoma is a highly aggressive neoplasm and the second most common malignancy encountered by urologists. It is the fourth most frequent solid tumor among men and the seventh most frequent among women, with more than 350 000 new cases diagnosed annually worldwide [1]. Fortunately, approximately 80% of patients with newly diagnosed bladder carcinoma present *superficial* transitional cell carcinoma (TCC), which can be managed with transurethral resection (*TUR*) [2]. However, more than 50% of the patients will have *recurrences* (reappearance of a superficial tumor) and 10%–30% of the patients will have *progression* to muscle invasive disease [3].

There are many advantages in establishing the risk factors associated with the recurrence and progression of bladder cancer and in creating a model that allows the prediction of the disease process after the TUR. Firstly, this will provide information to the physician about the patient's recurrence–progression process that allows him to program in a more rigorous way the follow-up of the patient. As a consequence, we accomplish a major objective: that of reducing the number of painful check tests on the patients with lower risk. Furthermore, it allows us to reduce the programming-visit, and to prioritize and pay more attention to the cases that need it. In that way, both time and sanitary expenses are minimized.

A number of studies have been performed to identify prognostic factors for the *first recurrence* of *superficial* TCC in the bladder cancer after *TUR* and an initial treatment [4–8]. However very few studies [9] have systematically

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investigated the *multiple recurrences* of this cancer (the main characteristic of *superficial* TCC of the bladder) and its associated factors as well as the *progression*. So we would be interested in the analysis of associated factors of the risk of a *new recurrence* or a *progression* in the multiple events of bladder carcinoma with the aim of creating a predictive model of this disease process. Besides, from a medical point of view a deeper knowledge of the process can help to better understand the disease's course and thus arrive at a better treatment adjust.

For the analysis of *time to the first event* the Cox proportional model has mostly been used [11] with the associated partial likelihood principle [12]. In the last few years several methods have been proposed to analyze recurrent events. Three extensions of the Cox model have become popular: the Andersen and Gill (AG) [13], the Prentice, Williams and Peterson (PWP) [14] and the Wei, Lin and Weissfeld (WLW) [15] (see [16] for a performance of these models and their applications). In [17] a review of methods for recurrent events is shown and the same authors have just published a book on the topic [18].

Several authors have used the WLW method to study processes with a recurring and a terminating event [19–21]. The terminating event could be any event of essential interest which precludes further observation of the process. In our case the recurring event is the reappearance of the TCC tumor and the terminating event is the progression because this leads to a more aggressive treatment, including bladder extirpation. The WLW method has been deeply studied, see [22] for a recent contribution.

The paper is organized as follows: in Section 2 we review the WLW method and two different approaches to analyze the recurrence–progression process are considered. In Section 3 we apply the WLW method to our bladder cancer database to study the predictive factors of recurrence and progression and estimate the risk of both events. We validate the model and finally in Section 4 the most relevant conclusions are presented.

2. The WLW method and the recurrence–progression process

2.1. The WLW method

Let T be the first event time. The *hazard function* expresses the risk or hazard of the event at some time t, and is defined by [10]

$$\lambda(t) = \lim_{h \to 0} \frac{\mathrm{P}(t \le T < t + h \mid T \ge t)}{h}.$$

The hazard function of the proportional hazard model [11] is

$$\lambda(t) = \mathrm{e}^{\beta' Z(t)} \lambda_0(t), \tag{1}$$

where β is a $p \times 1$ vector of unknown regression parameters, $\lambda_0(t)$ is an unspecified baseline hazard function and $Z = (Z_1, \ldots, Z_p)'$ is a $p \times 1$ vector of possibly time-varying covariates. Let C denote the time from the study entry until the end of the study. This is the censoring time. We can determine $X = \min(T, C)$ and $\Delta = I\,(T \le C)$, where $I()$ is the indicator function. So if $\Delta = 1$ the event occurs, and if $\Delta = 0$ we say that the observation is right-censored. Assume that T and C are independent conditional on Z. Let (X_i, Δ_i, Z_i) for each patient $(i = 1, \ldots, n)$. Then the partial likelihood function [12] for β is

$$L(\beta) = \prod_{i=1}^{n} \left\{ \frac{\mathrm{e}^{\beta' Z_i(X_i)}}{\sum_{j=1}^{n} Y_j(X_i) \mathrm{e}^{\beta' Z_j(X_i)}} \right\}^{\Delta_i}, \tag{2}$$

where $Y_j(t) = I(X_j \ge t)$. This function is not strictly a likelihood, but it can be treated as a likelihood for purposes of asymptotic inference [12]. The corresponding score function $\frac{\partial \log L(\beta)}{\partial \beta}$ is

$$U(\beta) = \sum_{i=1}^{n} \Delta_i \left\{ Z_i(X_i) - \frac{\sum_{j=1}^{n} Y_j(t) \mathrm{e}^{\beta' Z_j(t)} Z_j(t)}{\sum_{j=1}^{n} Y_j(t) \mathrm{e}^{\beta' Z_j(t)}} \right\}. \tag{3}$$