

A Predictive Mathematical Model in the Recurrence of Bladder Cancer

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Abstract—The aim of this paper is to evaluate the risk of tumor recurrence after surgical operation (TUR: trans-urethral resection). The prognostic significance of some clinical features in 380 patients with primary superficial bladder carcinoma is studied. By means of survival analysis techniques a mathematical model of risk of tumor recurrence is obtained. © 2005 Elsevier Ltd. All rights reserved.

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1. INTRODUCTION

Transitional bladder cancer represents about 2% of all human tumors. It supposes an important public health problem because it is biologically very aggressive and causes more than 130,000 deaths by year all around the world. Superficial bladder tumors are characterized by *recurrence* (reappearance of a new tumor) in 50–70% of cases. Although most recurrences are still superficial, *progression* to muscle-invasive disease occurs in 10–30% of patients, therefore, when superficial bladder tumor is diagnosed, it is important to identify patients who are at risk of disease recurrence and progression. If it were possible to define exactly which subset of superficial bladder tumors have more risk to recur and to progress, preemptive therapy could be used. Identifying the prognostic factors that determine that risk in each patient remains a subject of extensive research [1,2].

Biotechnological advances have allowed us to use different therapeutic procedures (surgery, radiotherapy, chemotherapy, immunotherapy) successfully, but still, many patients suffer an unfavorable outcome without control of disease.

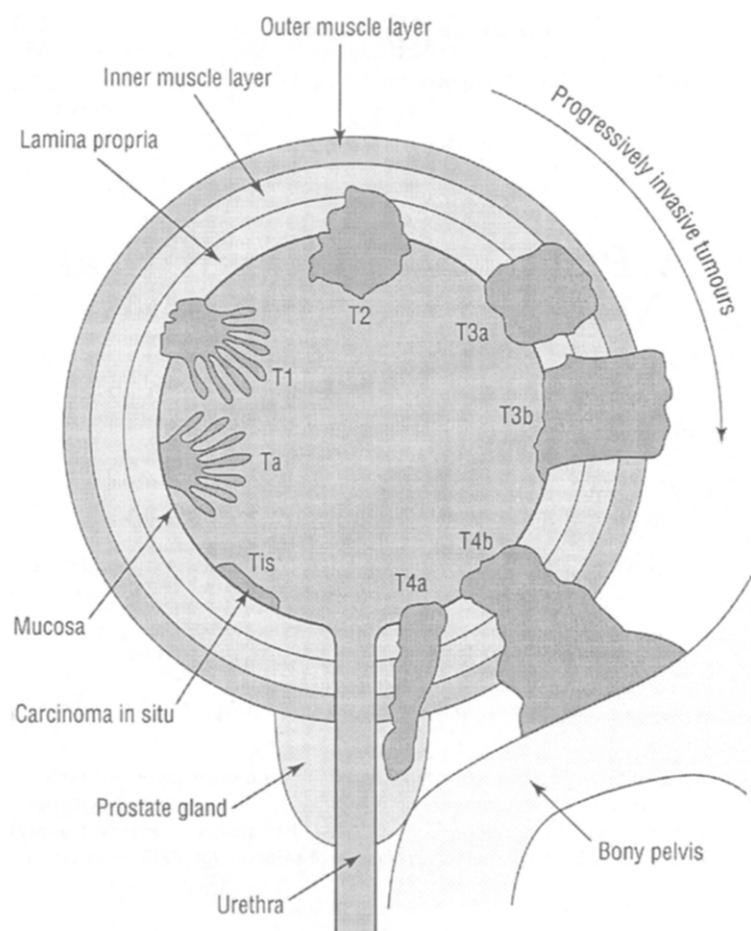


Figure 1. Tumor staging in bladder cancer according to TNM system.

Multiple clinical and pathological variables are important in predicting outcome in patients with transitional bladder cancer, among which pathological stage and grade of differentiation are recognized as the most important [3,4]. Therefore, an ideal prediction model should combine stage and grade, along with any other features shown to be associated with outcome in a multivariate model (histological characteristics, size, number of tumors, etc).

The TNM system (classification of 1997) is generally used to establish the stage of the bladder tumors [5] (see Figure 1).

Tis: tumor is limited to the mucosa and is flat (a carcinoma *in situ*).

Ta: tumor is papillary and it is limited to the mucosa.

T1: tumor penetrates the lamina propria but not the muscle layer.

T2-T4: tumor invades muscle and is staged from T2 to T4 according to the depth of infiltration of muscle tissue or the extent to which the surrounding tissue is affected.

Superficial bladder tumors (Stages Ta and T1) have trend to produce recurrences (generally with similar stage). Tumors that invade the bladder muscle are highly aggressive and have a strong potential metastasise preferentially to regional lymph nodes, lungs, liver, and bone.

The *histologic grade* (or grade of cell differentiation) establishes according to the WHO (World Health Organization) 1999 classification [6],

G1: Urothelial carcinoma grade I (differentiated),

G2: Urothelial carcinoma grade II (intermediate differentiation),

G3: Urothelial carcinoma grade III (poor differentiated).

Well differentiated tumors (G1 grade) have generally low aggressivity while poor differentiated tumors (G3 grade) are highly aggressive (cause many recurrences) [7].

Nowadays, a field of this urological cancer that is being studied deeply, is the capacity that several parameters (clinical, biochemical, cellular, genetic, and molecular) have for establishing the biological behavior of the tumor, and therefore, the outcome of the disease. This group of parameters that characterizes to the tumor could be managed by mathematical analysis in order to obtain models with predictive capacity of the disease outcome about patient survival and probabilities of recurrence of disease. With this model, it is possible to choose the best treatment for each patient.

Prediction models can be used to counsel patients, determine the need for adjuvant therapy, stratify patients in risk groups, and develop appropriate postoperative surveillance programs tailored to risk for cancer progression. The models have to be easy to use.

Many models for clinical prediction (prognosis or diagnosis) are published in the medical literature every year but few such models find their way into clinical practice. The aim is to construct and evaluate a prognostic mathematical model for predicting the outcome of superficial bladder cancer of transitional cells (Stage T-1) that increases the results obtained until now and to establish its efficacy and its capacity to be reproduced by other groups.

The main objective of this paper is to establish new prognostic factors for bladder cancer and their influence in the behavior of tumor for developing recurrences. Evaluation of survival data is performed by the analysis of data in the form of times from a well-defined *time origin* until the occurrence of some particular event or *end-point*. This end-point may be the death of the patient or an other event such as tumor recurrence. The period of time from the time origin to the end-point is the *survival time*. In our study, the time origin concern to the so-called TUR (trans-urethral resection): a surgical endoscopic technique used to remove the macroscopic tumor from the inner of the bladder. The end-point is the first tumor recurrence.

The main reason why survival data are not amenable to standard statistical procedures, is that survival data are generally not symmetrically distributed, and so it will not be reasonable to assume that the variable *time* has a normal distribution, and although this difficulty could be resolved by transforming the data to achieve this status, for example by taking logarithms, there is a second difficulty: survival times are frequently *censored*. The survival time of an individual is said to be *censored* when the end-point of interest has not been observed for that individual (recurrences times are unknown). This is because the patient has no tumor recurrence at the end of the period of time of study, or the patient is lost for follow-up, for example. Nevertheless, censored survival time from these last patients must not be removed from the analysis since it would represent to lose that information. Some references that provide methods of survival analysis, illustrated with practical examples are [8–11].

The paper is organized as follows. In Section 2, the data on the survival times of 380 patients and their characteristics (explanatory variables) are described. In Section 3, survival data are conveniently summarized through estimates of the *survivor function* and *hazard function*. Methods for estimating these functions from a single sample of survival data are said to be *non-parametric* or *distribution-free*. The survival times are the only used data and the statistical analysis is performed using the *Kaplan-Meier* method. It's estimated the survivor probability until instant t . Further, numerical and graphical summaries of the survival times for individuals in a particular characteristic are presented. In this way, it is obtained a first selection of prognostic factors in the tumor recurrence. In Section 4, a multivariate analysis is performed by using the *Cox proportional hazards* model with stepwise selection of prognostic factors. That model explores the relationship between the survival time of a patient and explanatory variables, and unifies and extends the nonparametric procedures of Section 3. After Cox model has been fitted to the set of survival data, in Section 5, the adequacy of the fitted model is assessed. The using of diagnostic procedures for model checking is essential in the modelling process. In Section 6, the evaluation of results is presented.

Numeric process and graphics have been carried out with statistical package S-PLUS [12], and SPSS.

2. DATA AND SELECTION OF VARIABLES

Study Patients

From 1973 to 2003, 380 patients with primary superficial transitional cell carcinoma of the bladder were initially treated with transurethral resection at *La Fe* University Hospital from Valencia (Spain).

Patients Characteristics

Variables considered for this study were *sex* and *age* (categorized in four groups for non-parametric analysis). Out of the patients, 84.5% were men with a mean age of 63.54 years; tumor *stage* (pTa and pT1) and tumor *grade* (G1, G2, and G3), *number* of tumors (one or more than one) and tumor *size* (< 1 cm, 1–3 cm, or > 3 cm), *treatment* (Thiotepa, Adriamidine, Cisplatin, no treatment, and other treatments), see Table 1.

For all patients times from TUR to first recurrence is considered. 152 cases are censored (40% of patients). There are 228 recurrences in the data (see Figure 2).

Figure 1. Patients characteristics and statistics log-rank and Breslow.

Variable	No. Patients	(%)	Median Days	Log-Rank	Breslow
Stage				0.3884	0.9593
pTa	86	22.6	1102		
pT1	294	77.4	1193		
Grade				0.1711	0.0415
G1	222	58.4	1285		
G2	131	34.5	848		
G3	27	7.1	767		
Sex				0.3844	0.8338
Men	321	84.5	1144		
Women	59	15.5	1427		
Number				0.0176	0.0398
One	313	82.4	2121		
Two or more	67	17.6	808		
Size				0.0167	0.0078
< 1 cm	81	22.1	1211		
1–3 cm	209	55.0	1289		
> 3 cm	87	22.9	606		
Age				0.7412	0.4887
≤ 60 years	139	36.6	1173		
between 61 and 70 years	129	33.9	1285		
between 71 and 80 years	91	23.9	98		
> 80 years	21	5.6	767		
Treatment				0.0336	0.0469
Thiotepa	219	57.6	1.427		
Adriamidine	49	12.9	746		
Cisplatin	39	10.3	1.211		
No treatment	38	10.0	1.629		
Others treatments	35	9.2	813		

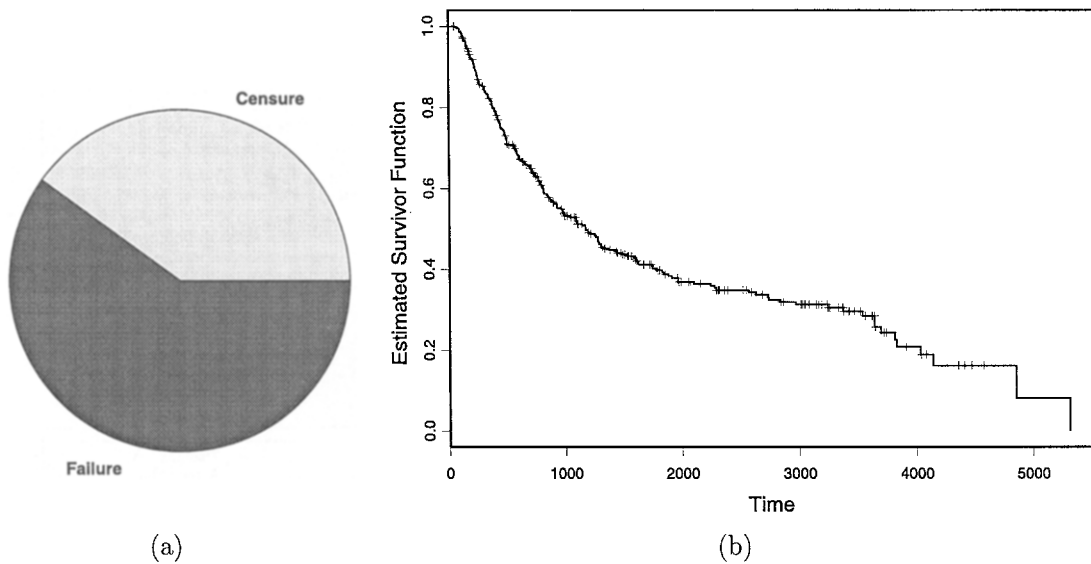


Figure 2. Rate of failure/censure and the *Kaplan-Meier* estimate survival function.

3. NONPARAMETRIC ANALYSIS

Nonparametric analysis is used when no distribution probability is considered for survival times until death or failure (recurrence tumor in our case). *Kaplan-Meier* method is used to estimate the survival function [8, p. 19].

First, the analysis is carried out for all 380 patients and subsequently, the same analysis is executed for individuals in a particular group (according to explanatory variables). The way of comparing the survival times in a particular group is to plot the corresponding estimates of the survival functions from different categories for each explanatory variable. Further, it is contrasted the null hypothesis of equality of the corresponding survivor functions. In this case, nonparametric *log-rank* [8, p. 42] and *Wilcoxon* (Breslow) [8, p. 45] tests are used.

Kaplan-Meier estimate is plotted for all 380 patients in Figure 2. The survival function shows a marked slope during the first 2,000 days (five years and a half), while in the remainder period of study the decrease of the slope is less strong.

In fact, the survivor probability (that is, probability of no recurrence tumor) is 75% a year and a half (approx. 556 days); 52.49% at three years (approx. 1088 days), while from five years (approx. 1828 days) to nine years (approx. 3242 days) the survivor probability decreased from 39.29% to 30.55%.

On the other hand, from median estimation, more than half of patients do not have recurrence tumor until 1,173 days (3.3 years) after TUR of tumor.

Table 1 and Figure 3 show the *log-rank* and *Breslow* tests and the survivor functions for individuals in a particular group (for each explanatory variable). *Log-rank* and *Breslow* statistics are significant (at the 5% level) in the equality of survivor functions for the patients characteristics *number*, *size*, and *treatment*; and only *Breslow* statistic is significant for *grade*. This could be due to that *Breslow* statistic gives more weight to the first observations, while *log-rank* statistic gives the same weight to all observations. Therefore, the *Breslow* statistic is less sensitive than the *Log-Rank* in the last observations.

Pair comparisons from three categories show the following results: *grade*, there are significant differences between grades G1 and G2, and between grades G2 and G3. For the variable *size*, there are significant differences for two first levels (< 1 cm and 1–3 cm) versus the third level (> 3 cm). Finally, the variable *treatment* provides evidence of significant differences between Thiotepa and the rest of the treatments.

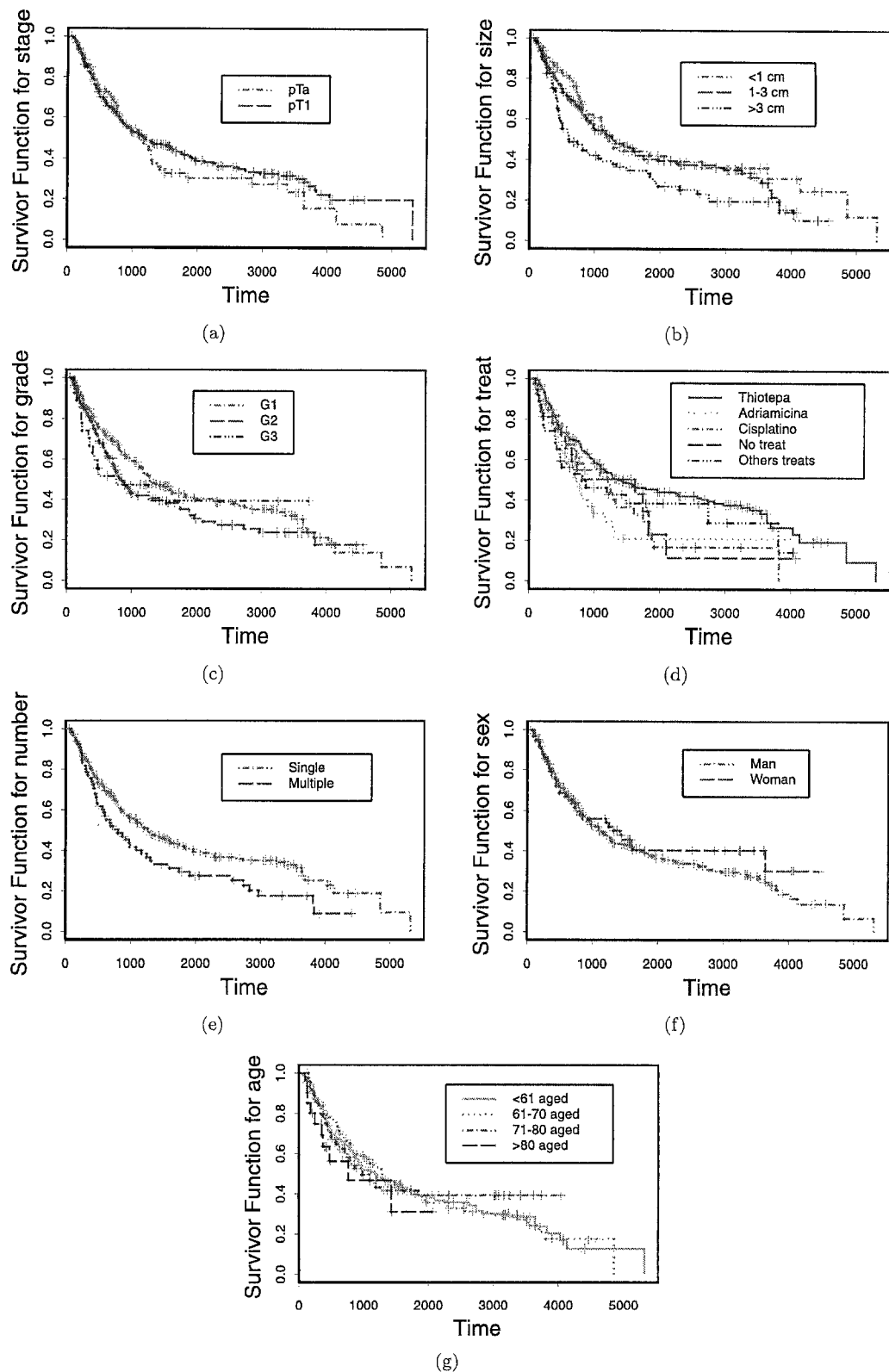


Figure 3. Kaplan-Meier estimate of the survival function.

4. MULTIVARIATE ANALYSIS

The survival experience of the 380 patients depends on several variables, whose values have been recorded for each patient at the time origin. The aim of this section is to determine which of explanatory variables have an impact on the free of disease time of the patients (survival time).

The focus is modelling the *recurrence hazard* (*risk of recurrence*) at time t . The *recurrence hazard* is obtained from the *hazard function* $h(t)$ (see [8, p. 11]) and its related with the survival function as follows,

$$S(t) = \exp(-H(t)), \quad (1)$$

where

$$H(t) = \int_0^t h(u) du. \quad (2)$$

The function $H(t)$ is called the *cumulative hazard*.

The *hazard function* is obtained from the basic model for survival data: *proportional hazard model* [8, Ch. 3; 10, Ch. 3].

Let us suppose that the *recurrence hazard* at time t depends on the values of p explanatory variables $X_1, X_2, \dots, X_p$. Let us denote that $x_{1i}, x_{2i}, \dots, x_{pi}$ be the values of these variables at time t for the i^{th} individual. Then, the *Cox regression model* is given by

$$h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}) h_0(t), \quad (3)$$

where $h_0(t)$ is called *baseline hazard function*, β_i are coefficients to be determined and $\beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi}$ is called the *risk score* or *linear predictor*. Note that hazard function for the i^{th} individual is proportional to the function $h_0(t)$ (hazard function of the reference individual). Further, the hazard ratio between different individuals is constant and independent of the time,

$$\frac{h_i(t)}{h_j(t)} = \frac{\exp(\beta' x_i)}{\exp(\beta' x_j)}, \quad (4)$$

where $\beta = (\beta_1, \beta_2, \dots, \beta_p)$ is the coefficient vector of explanatory variables and β' is the transpose of β .

The maximum likelihood estimates of the β -parameters in the proportional hazards model can be found by maximizing this log-likelihood function by using the *Newton-Rapshon* procedure,

$$\log L(\beta) = \sum_{i=1}^n \delta_i \left\{ \beta' x_i - \log \sum_{l \in R(t_i)} \exp(\beta' x_l) \right\}, \quad (5)$$

where $L(\beta)$ is the likelihood function in the Cox regression model [8, p. 68] and $R(t_i)$ called *risk set*, is the set of individuals who are at the risk of tumor recurrence at time t_i .

On the other hand, the objective of this modelling procedure is to determine which combination of explanatory variables affects the form of the hazard function. In this process, we use the statistic $-2\log\hat{L}$. The process consists of introducing and removing variables while it's verified if the value of variation of $-2\log\hat{L}$ results significant. This strategy of selection is suggested in [8, p. 83], since automatic routines may provide a wrong model.

Indicator or *dummies* variables are generated for the analysis. From *treatment* (five categories) four *dummies* are defined: Adriamicine, Cisplatine, no treatment and others treatments. From *grade* (three categories) two *dummies*: G2 and G3. From *size* (three categories) two *dummies*: 1–3 cm and > 3 cm. *Sex*, *number*, and *stage* are dichotomic variables. The *age* is continuous. In this way the individual of reference is a man with a median age 63.54 years, with only one tumor, of pTa stage, G1 grade, with a size minor than 1 cm and with Thiotepa treatment after TUR.

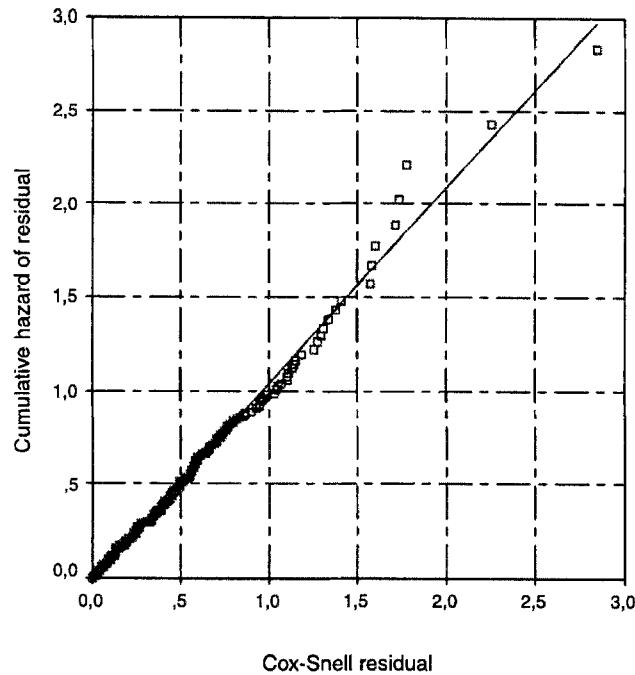
Parameters estimates in the Cox regression model are presented in Table 2.

5. VALIDATION AND DIAGNOSTIC

The aim of this section is to determinate if the model has been fitted rightly to set of survival data. In a first step, the model-checking procedure of the survival analysis is based on *residuals*: *Cox-Snell*, *Martingale*, and *deviance*. In a second step, it is determined whether any particular observation has an undue impact on the model. In a third step, it is tested the assumption of proportional hazards.

Table 2. Cox regression model. Parameters estimates.

Parameter	$\hat{\beta}$	$\text{Exp}(\hat{\beta})$	$\text{se}(\hat{\beta})$	z	p -value	lower.95	upper.95
pT1	-0.343	0.709	0.171	-2.01	0.0450	0.508	0.992
1-3 cm	0.243	1.276	0.185	1.31	0.1900	0.887	1.834
> 3 cm	0.687	1.988	0.216	3.18	0.0015	1.301	3.036
G2	0.301	1.352	0.152	1.98	0.0470	1.004	1.821
G3	0.420	1.523	0.305	1.38	0.1700	0.838	2.767
Adriamicine	0.570	1.769	0.205	2.79	0.0054	1.184	2.643
Cisplatine	0.235	1.265	0.221	1.06	0.2900	0.820	1.951
No treatment	0.463	1.588	0.250	1.85	0.0640	0.973	2.592
Others treatments	0.277	1.319	0.253	1.10	0.2700	0.804	2.166

Figure 4. Cumulative hazard plot of the *Cox-Snell* residuals.

5.1. Residuals

5.1.1. Cox-Snell residuals

The *Cox-Snell* residuals for the i^{th} individual is given by

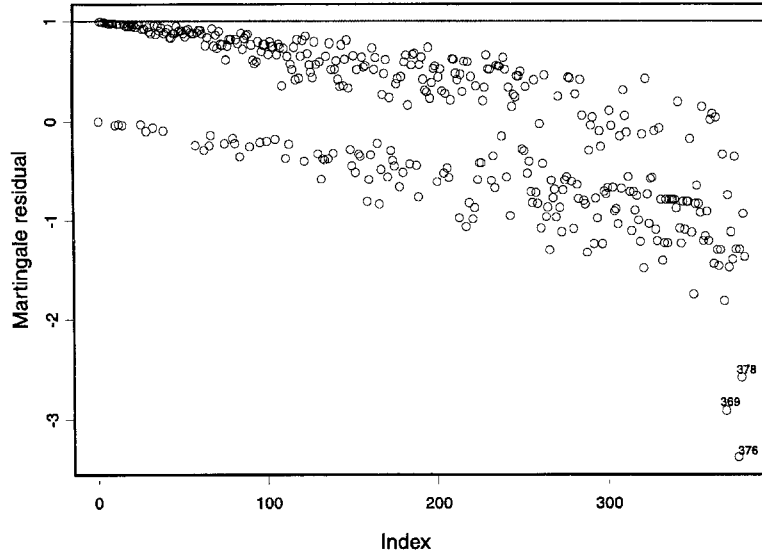
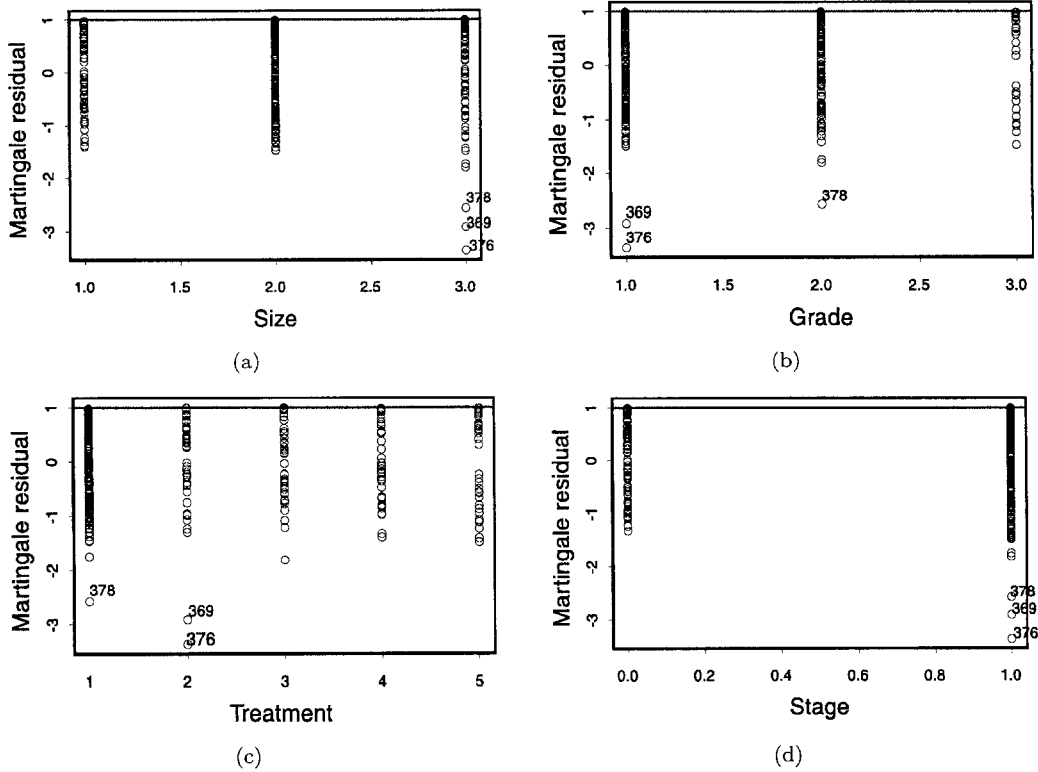
$$r_{C_i} = \exp(\hat{\beta}'x_i) \hat{H}_0(t_i) = \hat{H}_i(t_i) = -\log(\hat{S}_i(t_i)). \quad (6)$$

If T is the random variable associated with the survival time of an individual and $S(t)$ is the corresponding survival function, then

$$Y = -\log(S(t_i)) \sim \text{Ex}(\lambda = 1). \quad (7)$$

As r_{C_i} has an exponential distribution, a graphic of pairs of points $(r_{C_i}, \hat{H}(r_{C_i}))$ fitted to a line with origin in $(0,0)$ and with slope one, will show that the survivor model is satisfactory, [8, p. 122].

Indeed, Figure 4 shows that the cumulative hazard of residuals is fitted to a line with origin in $(0,0)$ and with slope one. So, the model is rightly fitted.

Figure 5. Index plot *Martingale* residuals.Figure 6. *Martingale* residuals against the variables.

5.1.2. Martingale residuals

The *Martingale* residual for the i^{th} is given by the expression,

$$r_{M_i} = \delta_i - r_{C_i}, \quad (8)$$

where δ_i takes the value 0 if the observation is censored and the value 1 if it is a failure. *Martingale* residuals may be interpreted as the difference between the observed and the expected number of failures in the time interval $(0, t_i)$.

To this effect, a plot of these residuals will highlight those individuals with a bigger difference, and, consequently, their survive times wouldn't been well fitted by the model (*outliers*).

In Figure 5, very negative values belong to individuals with a long survival time (longer than expected), and residuals near the unity indicates that individuals have an unexpected short survival time. Consequently, patients 369, 376, and 378 have a time free of disease longer than predicted.

It would be useful to plot these residuals against survival time or explanatory variables since that may indicate whether any particular time or any explanatory variable value are not well fitted by the model.

In fact, Figure 6 shows that outstanding values are those corresponding to patients 369, 376, and 378. In particular, patients 369 and 376 have the greatest value of residual and moreover belong to groups with the same features in size (> 3 cm), grade (G1), treatment (Adriamicine), and stage (pT1).

5.1.3. Deviance Residuals

The *deviance* residual for the i^{th} individual is defined by

$$r_{D_i} = \text{sgn}(r_{M_i}) [-2 \{r_{M_i} + \delta_i \log(\delta_i - r_{M_i})\}]^{1/2}, \quad (9)$$

where $\text{sgn}(\cdot)$ is the sign function, which takes the value $+1$ if its argument is positive and the value -1 if it is negative.

This kind of residuals are a transformation of *Martingale* residuals and generate values that are symmetric around zero when the fitted model is appropriate. They are also useful to detect *outliers*.

In both plots of Figure 7, the cluster of points is rather compact, distributed around zero, and we do not find any points with an absolute value of residual unusually large, or too far from the others. Although in a less remarkable way that in *Martingale* residuals plots, patients 369, 376, and 378 have the most negative residual value. Deviance residuals also detect those patients whose survival time is shorter than expected from the model. This is the case of patients 2, 3, 4, and 5.

Plotting *deviance* residuals against *risk score*, we may detect those individuals with risk of failure below the mean value (*risk score* very negative), and those above it (high *risk score*). Patient with highest *risk score* (number 109) is very near of 0, suggesting that this observation is well fitted by model. And, again, patients with greatest deviance residuals handily separate from the remaining observations.

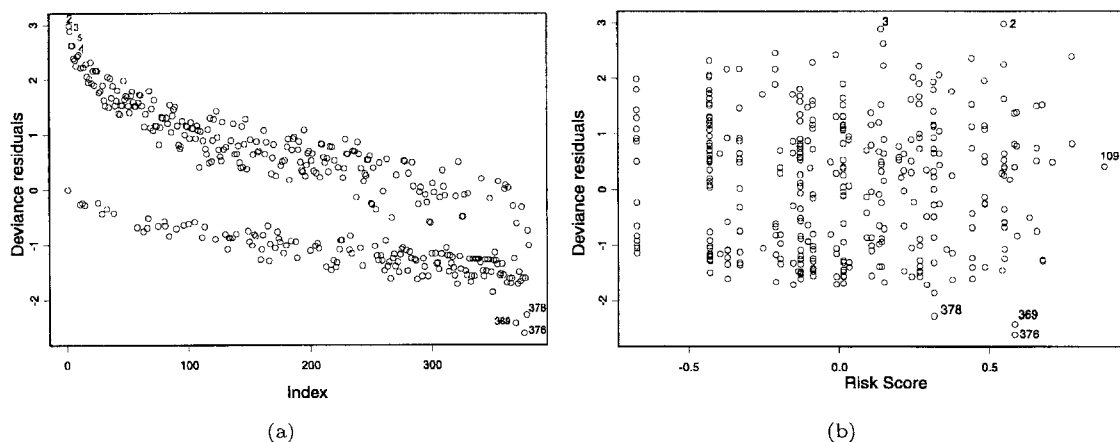


Figure 7. Index plot *deviance* residuals and *deviance* residuals against the values of the risk score.

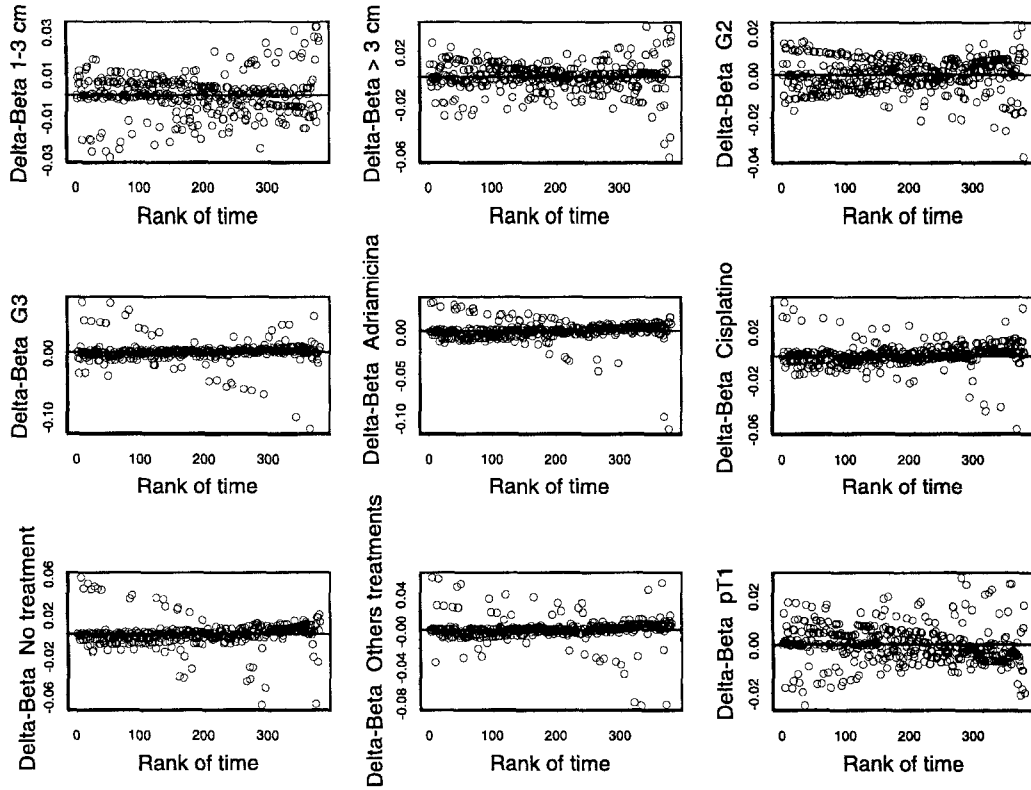


Figure 8. *Delta-Beta* for the variables against rank order of survival time.

5.2. Identification of Influential Observations

This section is addressed to determine whether any particular observation has an undue impact on model based inferences. We consider two kinds of influence.

5.2.1. Influence of observations on an parameter estimate

If the i^{th} observation has an untoward effect on the j^{th} parameter estimate, $\hat{\beta}_j$, it would be reflected in the difference $\hat{\beta}_j - \hat{\beta}_{j(i)}$, where $\hat{\beta}_{j(i)}$ denotes the j^{th} parameter estimate when the i^{th} observation is removed from the data base. The following approximation is available [13],

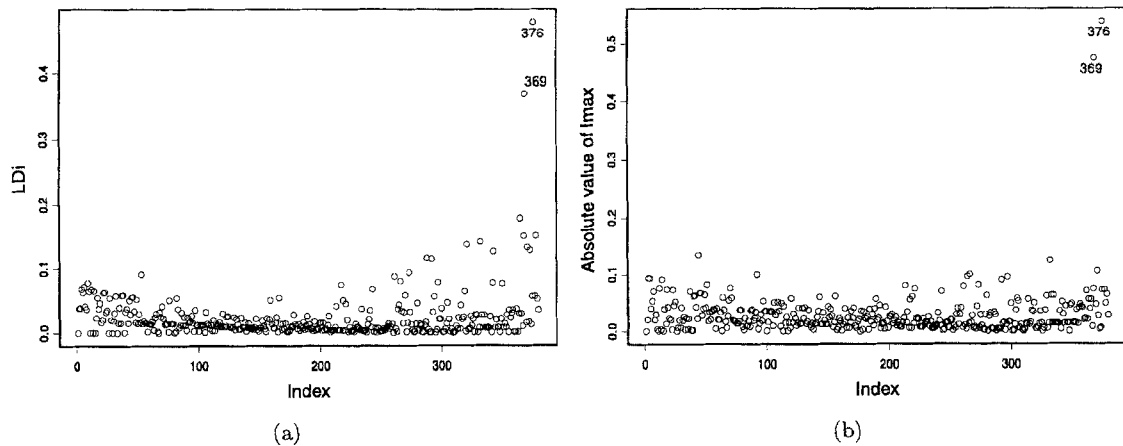
$$\Delta_i \hat{\beta}_j \approx \hat{\beta}_j - \hat{\beta}_{j(i)}, \quad (10)$$

where $\Delta_i \hat{\beta}_j$ (called a Delta-Beta) is the j^{th} component of vector $r'_{S_i} \text{var}(\hat{\beta})$, where $\text{var}(\hat{\beta})$ is the variance-covariance matrix of the vector of parameter estimate in the fitted model, and r_{S_i} is the vector of the *score* residuals, [8, p. 133].

Therefore, observations that have an influence on $\hat{\beta}_j$ will be such that the values of $\Delta_i \hat{\beta}_j$ are larger in absolute value than in other observations. This can be perceived graphically, as it is shown in Figure 8. In all the plots, we notice compact clouds around zero. It must be emphasize that in plots corresponding to treatment Adriamicine and grade G3, the $\Delta_i \hat{\beta}_j$ reach the highest value. These observations more influential belong to patients with longer survival time. For the sake of testing these approximations, the exact value of $\hat{\beta}_j - \hat{\beta}_{j(i)}$ has been calculated. The $\Delta_i \hat{\beta}_j$ underestimates the exact value and it is always lower than standard error. In particular, Adriamicine's plot highlights patients 369 and 376.

5.2.2. Influence of observations on the set of parameter estimates

The exclusion of a given observation may not have a great influence on the estimation of any particular parameter. However, it may affect the whole set of parameter estimates and,

Figure 9. Index plot of LD_i and $l_{\max}$.

consequently, estimations based on the fitted model could change. There are several statistics for assessing this influence, we will use two. The first one consists in examining the amount by which the statistic $-2 \log \hat{L}$ changes when each observation in twin is left out. This is given by the expression,

$$2 \left\{ \log L(\hat{\beta}) - \log L(\hat{\beta}_{(i)}) \right\},$$

where $L(\hat{\beta})$ is the value of L when the model is fitted to all observations, and $L(\hat{\beta}_{(i)})$ when the model is fitted after omitting the i^{th} . In [14], it is shown that an approximation can be computed from $LD_i = r'_{S_i} \text{var}(\hat{\beta}) r_{S_i}$ (LD means *likelihood displacement*). An *index plot* of this quantities provides an informative visual summary of the values of the diagnostic.

Another diagnostic is based on the matrix $B = \Theta' \text{var}(\hat{\beta}) \Theta$, where Θ' is the matrix formed from the vectors r_{S_i} . Let $l_{\max}$ be the eigenvector associated with the longest eigenvalue of the matrix B , standardized to have unit length. The absolute value of the i^{th} element of $l_{\max}$ is a measure of the influence of the i^{th} observation [8, p. 137].

From Figure 9, we see that both diagnosis highlight the same patients. They are, again, 369 and 376. Note that the addition of the squares of elements of $l_{\max}$ must be one. Since the additions squares of elements corresponding to patients 376 and 369 is 0.519, these observations represent 50% of the influence of elements from $l_{\max}$.

5.3. Testing Proportional Hazards

We know that hazards are said to be proportional if ratios of hazards are independent of time. If there are one or more explanatory variables in the model whose coefficients vary with time, or if there are explanatory variables that are time-dependent, the proportional hazards assumption will be violated. So, it is required a method to detect this possibility: if there is some form of time dependency in particular variables.

The tests and graphical diagnostics for proportional hazards are based on the *scaled Schoenfeld residuals*, $r_{P_{ji}}^*$ [8, p. 117], and are useful in evaluating the assumption of proportional hazards after fitting a Cox regression model.

Grambsch and Therneau [10] show that the expected value of the i^{th} *scaled Schoenfeld residual* is given by $E(r_{P_{ji}}^*) \approx \hat{\beta}_j(t_i) - \hat{\beta}_j$, and so a plot of the values of $r_{P_{ji}}^* + \hat{\beta}_j$ against the death times should give information about the form of the time-dependent coefficient of X_j , $\beta_j(t)$.

The interpretation of these graphs is greatly facilitated by smoothing shown on each graph by a solid line. An horizontal line in each graph of the Figure 10 indicates no suggestion of nonproportional hazards and that the coefficients of these variables are constant.

This graphical diagnostic is supplemented by a test for each variable, along with a global test for the model as a whole. In Table 3, it is showed the mentioned global test and the tests for each variable.

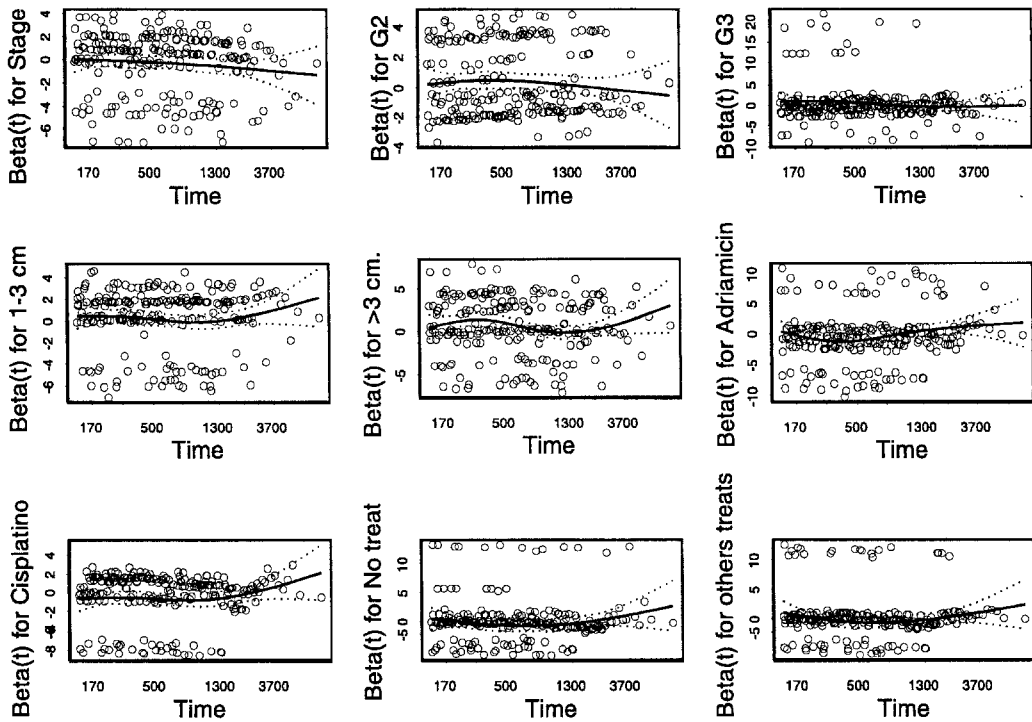


Figure 10. Plots of scaled Schoenfeld residuals against time for each variable.

Table 3. Test for the proportional hazards.

Variable	rho	chisq
pTa	-0.104	2.543
G2	-0.055	0.734
G3	-0.117	3.034
1 - 3 cm	-0.003	0.002
> 3 cm	-0.077	1.369
Adriamicine	0.138	4.334
Cisplatin	0.063	0.919
No treatment	0.022	0.107
Others treatments	-0.002	0.001
GLOBAL		14.474

Here, ρ is the Pearson product-moment correlation between the *scaled Schoenfeld residuals* and time for each variable. The column *chisq* gives the tests statistics for each variable and the last row GLOBAL gives the global test for a χ^2 of 9 degree of freedom. There is some weak evidence for nonproportionality shown in the large GLOBAL test statistic. So, it is examined the assumption of nonproportionality for the variables grade, particularly in G3, and treatment, particularly in Adriamicine.

To test the overall effects of grade and treatment on proportionality, a two- and a four-degree of freedom tests for all two and four coefficients are constructed. The p -values for testing whether $\beta_j(t) = \beta_j$ for grade and treatment are 0.187 and 0.25, respectively. So, it's rejected the assumption of nonproportionality and it isn't considered the addition of any time-dependent variable in the model.

However, another tests, such as *log cumulative hazard plot* made us consider the possibility of time-dependent in some variable. In that case, a subsequent task would be to include a time-dependent variable into Cox model, or to stratify the initial model according to the variable that violates the assumption of proportional hazard.

6. CONCLUSIONS

The Cox model allows us to compare easily risks among the different groups in which patients have been divided according to variables. The reference individual is a man with stage pTa, grade G1, size < 1 cm, treated with Thiotepea after TUR. Main comparisons are summarized in Table 2.

Stage. Patients with tumor pT1 have a risk of recurrence 29%,

$$\frac{h(t; \text{stage} = pT1)}{h(t; \text{stage} = pTa)} = \exp(-0.343) = 0.710,$$

lower than patients with tumor pTa.

Grade. Patients with tumor G2 have a risk of recurrence 27.5% higher than patients with tumor G1, while risk in case of tumor G3 increases 98.6% respect to reference individual.

Size. Individuals with tumor between 1 and 3 cm have a risk 35.2% bigger than patients with tumor < 1 cm, while those with size > 3 cm increase risk a 52.3% with respect to the same group.

Treatment. The treatment with less risk of recurrence is Thiotepea. However, patients treated with Thiotepea represent 57.6% of our data base. So, we may consider that this result isn't enough reliable.

Along the study it has been observed that patients 369 and 376 have high values of *Martingale* and *deviance* residuals, and they are also the most influential on the estimation of the whole set of parameters. Both observations belong to the same groups: stage pT1, grade G1, size > 3 cm and treated with Adriamicine. The two last characteristics correspond to the highest risk of recurrence according with the set model, and, however, they are among the patients with longest time of disease. This fact could justify their behavior in this study.

REFERENCES

1. A. Jaemal, T. Murray, A. Samuels, A. Ghafoor, E. Ward and M. Thun, Cancer statistics 2002, *CA Cancer J. Clin.* **53**, 5–26, (2003).
2. R.J. Black, R. Sankila, J. Ferlay and D.M. Parkin, Estimates of cancer incidence in Europe for 1995, *Eur. J. Cancer* **38**, 99–166, (2002).
3. K. Zieger, H. Wolf, P.R. Olsen and K. Hojgaard, Long-term survival of patients with bladder tumours: The significance of risk factors, *Br. J. Urol.* **82**, 667–672, (1998).
4. K.H. Kurth, L. Denis, C. Bouffoux, R. Sylvester, F.M. Debruyne, M. Pavone-Macaluso and W. Oosterlinck, Factors affecting recurrence and progression in superficial bladder tumors, *Eur. J. Cancer* **31A**, 1840–1846, (1995).
5. UICC International Union Against Cancer, *TNM Classification of Malignant Tumours*, Fourth Edition, (Edited by P. Hermanek and L.H. Sobin), pp. 135–137, Springer-Verlag, Berlin, (1998).
6. World Health Organization, Histological typing of urinary bladder tumours, In *International Classification of Tumours, Volume 10*, Second Edition, Geneva, (1999).
7. F. Millan, G. Chechile, J. Salvador, J. Palou and J. Vicente, Multivariate analysis of the prognosis factors of primary superficial bladder cancer, *J. Urol.* **163**, 73–78, (2000).
8. D. Collett, *Modelling Survival Data in Medical Research*, Second Edition, Chapman and Hall/CRC, Boca Raton, FL, (2003).
9. J.D. Kalbfleisch and R.L. Prentice, *The Statistical Analysis of Failure Time Data*, Second Edition, Wiley-Interscience, Hoboken, NJ, (2002).
10. T.M. Therneau and P.M. Grambsch, *Modeling Survival Data. Extending the Cox Model*, Springer, New York, (2000).
11. D. Oakes, Biometrika centenary: Survival analysis, *Biometrika* **88** (1), 99–142, (2001).
12. W.N. Venables and B.D. Ripley, *Modern Applied Statistics with S*, Fourth Edition, Springer, (2002).
13. K.C. Cain and N.T. Lange, Approximate case influence for the proportional hazards regression model with censored data, *Biometrics* **40**, 493–499, (1984).
14. A.N. Pettitt and I. Bin Daud, Case-weighted measures of influence for proportional hazards regression, *Applied Statistics* **38**, 51–67, (1989).