Competing Risk Modelling using Cumulative Incidence Function: Application to Recurrent Bladder Cancer Data

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Abstract—In this study, the effects of some clinical variables on the survival times of patients with bladder cancer were examined. The effects of these variables on sub-distribution of the failure types were determined using the proportional sub-distribution hazards regression model described in Fine and Gray (1999). Published dataset on 294 bladder cancer patients with four clinical outcomes were analyzed using Cumulative Incidence Function approach. The four outcomes included 184 (≈64%) patients that experienced recurrence of bladder cancer after receiving chemotherapy treatments. Two patients died of bladder cancer while 27 patients died of other causes and the remaining 76 patients did not experienced any of these three outcomes, and as a result, were considered censored. Among the covariates considered, only the patients' initial number of tumors and initial size of tumor were incorporated into our analysis due to high proportion of missing observations in others. Results from this work showed that, patients with tumour recurrence have highest risk of dying than those from other causes. Further results showed that, the number of tumor was positively associated with the recurrence of cancer of the bladder($RR = 1.1386,\ p = 0.0005$). However, the size of the tumor did not demonstrate a significant effect on the patients' survival time. It can therefore, be concluded that patients with tumor recurrence have low probability of survival from bladder cancer than patients that experienced other events. Above all, number, but not size of tumor could adversely affect the survival time of bladder cancer patients, especially those with tumor recurrence after bladder cancer treatment.

Keywords—Bladder Cancer, Competing risks, Cumulative Incidence Function, Survival time, Transurethral resection.

1. INTRODUCTION

The urinary bladder is a hollow, balloon-like organ located in the pelvis that collects and stores urine until it is ready to be excreted from the body and bladder cancer is the abnormal growth of tissue in the bladder. The literature has it that urinary bladder cancer is one of the most common cancers worldwide, with the highest incidence in industrialized countries (Zarzouret al., 2008). Bladder cancer is the fourth leading cause of cancer and the ninth leading cause of cancer deaths among American men with approximately 60,000 new cases diagnosed each year (MGBC, 2015). Bladder cancer incidence is lowest in Asia and South America, approximately 70% lower than what is being experienced in the western industrialized countries (Zarzour et al., 2008).

Some of the identified risk factors of bladder cancer occurrence are smoking, occupational exposure, chemotherapeutic drugs, infections, gender, age, race and radiation therapy to the pelvic area (Jacob, 2015) among others. Cigarette smoking is known to be the greatest risk factor for bladder cancer with up to 65% and 25% of cases occurring in men and women respectively (Burch, 1989; Seripa et al., 2001). The above statistics simply showed that bladder cancer occurrence is gender sensitive with men mostly affected than the women. Individuals with occupational exposure to dyes, rubbers, textiles, paints, leathers, and certain chemicals (e.g. polycyclic aromatic hydrocarbons such as benzene and beta-naphthylamine) are at higher risk for developing bladder cancer (Seripa et al., 2001). Cases of bladder cancer are also common among the elderly population with about 50% of cases occurring in people aged 72 or older while the median age of diagnosis is around 65 years (MGBC, 2015).

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The use of certain drugs for the treatment of cancer, particularly cyclophosphamide (Cytoxan), has equally been linked to the development of transitional cell carcinoma of the bladder (Jacob, 2015). Chronic or recurrent urinary tract infections, schistosomiasis, kidney stones, bladder stones, and long-term indwelling bladder catheters have all been linked to squamous cell carcinoma of the bladder (Seripa et al., 2001; Jacob, 2015).

There are four primary types of bladder tumours that can be distinguished on the basis of the appearance (morphology) of the cells under a microscope. The first and the most common one is the Transitional cell carcinoma, which is also known as *urothelial carcinoma* (ACS, 2015). This type of bladder cancer affects the transitional epithelium that lines the wall of the bladder. More than 90% of bladder tumours are classified as transitional cell carcinomas (Seripa et al., 2001).The second one is the Squamous cell carcinoma which represents about 4% of all bladder tumours and is most commonly associated with chronic irritation of the bladder that can be caused by long-term indwelling bladder catheters or by bladder calculi (stones) (Jacob, 2015). Another one is the adenocarcinoma which is an extremely rare form of bladder cancer accounting for less than 1% of all bladder tumours. The last one is the Small cell carcinoma which is also very rare and represents about 1% of all bladder tumours (Jacob, 2015). Generally, it is known that at the time of diagnosis, approximately 75% of bladder tumours are superficial; 20% are invasive; and up to 5% are metastatic in nature (MGBC, 2015).

According to the World Health Organization (WHO), specific fruit and vegetables had been found to act as catalyst at reducing the risk of bladder cancer (Brinkman & Zeegers, 2008). Fruits and yellow-orange vegetables, particularly carrots and those containing selenium, are

probably associated with a moderately reduced risk of bladder cancer. Citrus fruits and cruciferous vegetables were also identified as having a possibly protective effect against the tumour (CCC, 2015). However, study by Brinkman & Zeegers (2006) showed little correlation between cancer reduction and high consumption of fruits and vegetables as compared to the statistically significant reduction among men that consumed large amounts of cruciferous vegetables.

One of the objectives for treating patients with bladder cancer might be to remove the tumour or to prevent the tumour recurrence/metastasis or to prevent tumour progression from superficial to muscle-invasive bladder cancer. In any of these cases, the possible effects of some other prognostic factors other than that of the chemotherapy might be significantly important at predicting the survival times of the patients. This study therefore seeks to examine the effects of some of these factors as they affect the treatment of patients with bladder cancer tumours.

2. MATERIALS AND METHODS

2.1 Data Description

The data used in this work were published data which had been previously discussed in the literature (see Andrews et al., 1985 and Wei et al., 1989). The data can be accessed in the R statistical software through the library '**`survival`**'.

The data were on 294 bladder cancer patients with four clinical outcomes that represented the patients' status or outcomes (events)at the end of the study. These outcomes included patients with local bladder cancer tumour recurrence after receiving chemotherapy treatment, patients that died of bladder cancer, patients that died of other causes different from bladder cancer and patients that did not experience any of the above three clinical outcomes, and as a result, were considered censored.

Based on the four categories of clinical outcomes, all the 294 bladder cancer patients in this study therefore included 189 (about 64%) patients that experienced recurrence of bladder cancer, 2 patients that died of bladder cancer disease and the 27 patients that died of other causes while remaining 76 patients were censored. Each patient in this study was administered with one of these chemotherapy treatments – Placebo, Pyridoxine (vitamin B6) and Thiotepa (an antineoplastic drug).Thus, of the entire 294 bladder cancer patients in the study, 128 were administered with placebo, 85 with Pyridoxine and 81 with Thiotepa over all the four clinical outcomes.

About 68% (87), 67% (57) and 56% (45) of the patients that received Placebo, Pyridoxine and Thiotepa respectively had recurrence of bladder cancer tumour while one of the two patients that died of bladder cancer received placebo and the other one were administered with Thiotepa.

Out of the 27 patients that died of other (unknown) causes different from bladder cancer, 10 (37%) patients were given Placebo, 7 (26%) patients received Pyridoxine and the remaining 10 (37%) received Thiotepa. Details of the patients' characteristics in this study are provided in Table 1. In this clinical experiment, no patients experience more than one outcome (event).

Table 1. Summary of the characteristics of 294 bladder cancer patients with respect to the number and types of events (outcomes) as well as the chemotherapy treatment received.

Chemotherapy Treatment	Events (Outcomes)				Total
	Censored	Cases of Tumour Recurrence	Death from Bladder Cancer Disease	Death due to unknown causes (Other Deaths)	
Placebo	30	87	1	10	**128**
pyridoxine(vitamin B6)	21	57	0	7	**85**
Thiotepa	25	45	1	10	**81**
Total	**76**	**189**	**2**	**27**	**294**

Among the metrical covariates in the data were the patients' initial number of tumours and initial size of tumour. These two were incorporated in the analysis while others were ignored due to high proportion of missing observations in them.

There are various ways of modelling competing risks data which include parametric and non-parametric techniques. In this work, the non-parametric approach of cumulative incidence function is adopted for modeling the data. All analyses were performed within the environment of R statistical package (www.r-project.org).

2.2 Model Specification

Competing risks usually arises in studies in which there are more than two ($r > 2$) mutually exclusive events or outcome of interest into which an individual may be classified. In other words, there are r ($r > 2$) mutually exclusive causes of failure and an individual can only experience only one of the causes at the end of the study. When competing risks are present, classical survival analysis techniques (Dalgaard, 2002; Pintilie, 2006; Yahya & Ulm, 2009) may not be appropriate to be adopted for modeling such data.

There are four events (outcomes) of interest in this study with r being defined as follows:

$$r = \begin{cases} 1, \ if a \ bladder \ cancer \ patient \ experiences \ tumour \ local \ recurrence \\ 2, \ if a \ bladder \ cancer \ patient \ died \ of \ the \ disease \\ 3, \ if a \ bladder \ cancer \ patient \ died \ of \ other \ cause(s) \\ 4, \ if \ the \ patient \ was \ censored (i.e. did \ not \ experience \ any \ of \ the \ outcomes) \end{cases} \quad (1)$$

The empirical estimate of the cumulative incidence function (CIF) for cause r is given by (Fine, and Gray, 1999; Aalen, 1978):

$$\hat{F}_r(t) = \frac{Number \ of \ observations \ with \ T \leq t \ and \ C = r}{n} \quad (2)$$

where n is the total number of observations. Thus, the CIF can be calculated as the sum, over all of the probabilities, of observing event r at time $t_j$while the individual is still at risk. That is to say that, the individual did not experience any event prior to t_j. If we define the probability of remaining event-free prior to t_j as $\hat{S}_{j-1}$, itthen follows that the joint probability of being event-free immediately prior to t_j and experiencing an event of type r at t_j can be computed by (Lin, 1997)

$$\hat{F}_r(t) = \sum_{\forall \, j, t_j \leq t} \hat{h}_{rj} \hat{S}_{j-1} \quad (3)$$

where h_{rj} is the cause-specific hazard for event r at time t_j. Intuitively,given that an individual has not experienced an event of any typeup to t_{j-1}, the probability of an event of type r in the interval $t_j - \delta$ to $t_j$can be estimated as $\frac{d_{rj}}{n_j}$ where d_{rj} is the number of event r at t_j. It then follows that

$$\hat{F}_r(t) = \sum_{\forall \, j, t_j \leq t} \frac{d_{rj}}{n_j} \hat{S}_{j-1} \quad (4)$$

Thus, the CIF estimator for an event of type r depends not only on the number of individuals who have experienced this type of event, but also on the number of individuals who have not experienced any other type of event. The CIF represents the probability that an individual will experience an event of type $r$at time t_j (Pintilie, 2006; Scrucca et al., 2007).

2.2.1 Model-Based Estimation of the CIF

The predicted CIF can be calculated for a certain value of the covariates using the equation

$$F(t) = 1 - \exp\big(-H(t)\big) \quad (5)$$

where $H(t)$ is the cumulative hazards of sub-distribution regression model which can be estimated using a Breslow-type estimator (Gray, 1988; Fine & Gray, 1999) of the form;

$$\hat{\mathrm{H}}\big(t; x_0, \hat{\beta}\big) = \sum_{t_j \leq t} \left\{ \frac{\exp(x_0 \hat{\beta})}{\sum_{r \in R_j} w_{rj} \exp(x_r \hat{\beta})} \right\} \quad (6)$$

The outer sum is over all time points for which an event of interest was observed.

3. Results and Discussion

Results from the CIF model fitted to the bladder cancer data are presented in this section. The Fig 1 represents the probability of observing these events at various time points (in months). The curve showed that, bladder cancer patients have highest risk of experiencing local tumour recurrence than experiencing deaths either from bladder cancer disease or from any other causes different from bladder cancer tumour. Further results indicated that, as the month of experiencing the disease increases the probability of observing the clinical outcome of interest increases. For example, the probabilities (converted to %) that a bladder cancer patient experiences local tumour recurrence by 10, 20, 30 and 40 months after receiving chemotherapy treatments were 52%, 63%, 68% and 72% respectively.

A fairly detailed result is provided by Fig 2 where the estimated CIF were plotted separately for the three clinical outcomes (excluding the censored) based on the chemotherapy treatments received by the patients.

It can be observed from the CIF graphs in Fig 2 that the incidence of local tumour recurrence in bladder cancer patients that had been previously treated for the disease is higher among those that received Pyridoxine treatments than those that were treated with Placebo or Thiotepa over the patients' survival times. However, if consideration is on the risk of dying from bladder cancer alone, it can be found that the incidence of dying is higher among the patients that were treated with Thiotepa than those treated with other chemotherapies. Similarly, the incidence of death due to other disease is also higher among the patients that were treated with Thiotepa than those treated with some other chemotherapy treatments.

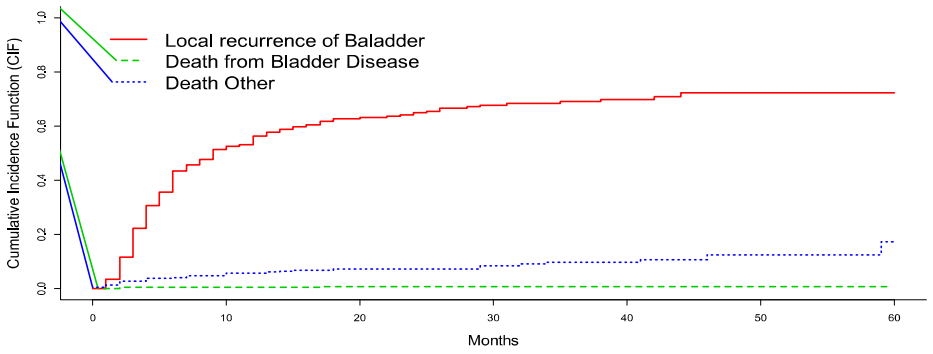


Fig. 1: Graph showing the plots of the estimated CIF on the bladder cancer patients over the three event types (patients' clinical outcomes) excluding the censored observations against the patients' survival times (in months).

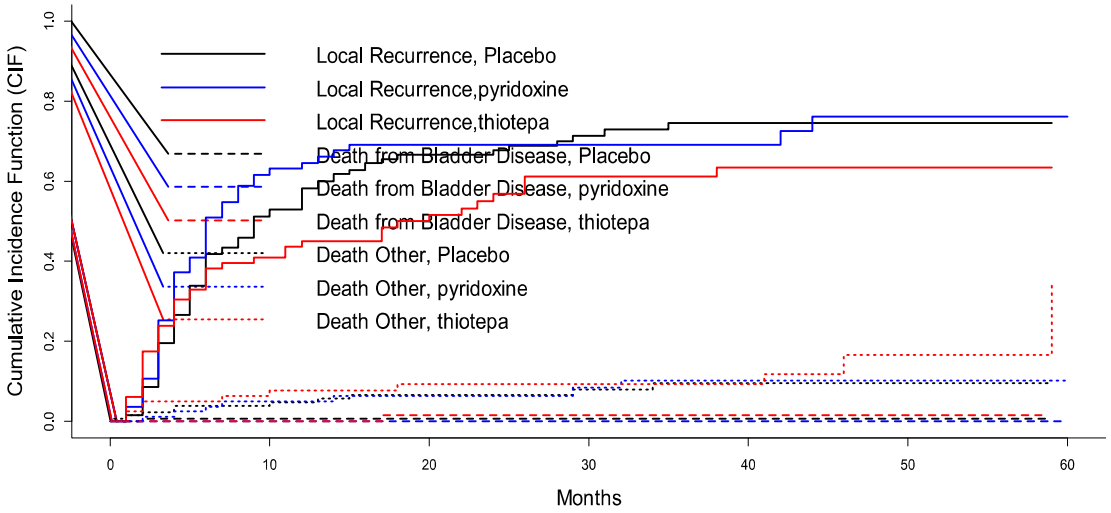


Fig. 2: Graph showing the separate plots of the estimated CIF on the bladder cancer patients over the three event types (patients' clinical outcomes) excluding the censored observations based on the chemotherapy treatment received by the patients against the patients' survival times (in months).

Furthermore, the impacts of the two covariates (number of tumours and size of tumours) on local tumour recurrence in bladder cancer patients after they have been treated were determined. This was achieved by fitting the cumulative hazards of sub-distribution regression model on the data using equations (5) and (6). Results from the model were presented in Table 2.

It can be observed from the results in Table 2 that that the number of tumours positively influenced the local tumour recurrence (RR = 1.1386, p = 0.0005) in bladder cancer patients with about 14% increase in relative risk of having local tumour recurrence. However, the size of tumour did not show any significant influence on patients' local tumour recurrence over time (RR = 1.0280, p = 0.540).

Table 2: Results of the cumulative hazards of sub-distribution regression model for testing the covariates effects on local tumour recurrence in bladder cancer patients.

Covariates	Coefficients (β)	Relative Risk (RR)	Standard Error (β)	Statistic	p-value
Number of tumours	0.1298	1.1386	0.0375	3.462	0.0005
Size of tumours	0.0276	1.0280	0.0450	0.615	0.5400

Without loss of generality, the impacts of number of tumours and size of tumours on other competing outcomes were suspended due to sparsity of observations as evident from the summary of patients' characteristics provided in Table 1.

The effects of number of tumours on the local tumour recurrence in bladder cancer patients was again made apparent by the plots of the CIF at some selected number of tumours as shown by the various graphs in Fig 3. Here, the estimated CIFs of patients that experienced local tumour recurrence but with 3, 4, 5 and 8 number of tumours with their corresponding tumour sizes 4, 3, 2

and 5 were plotted against their survival times. Results from various graphs in Fig 3 showed that the estimated CIF for local tumour recurrence in bladder cancer patients increases as the number of tumour in the patients increases over all the patients' survival times.

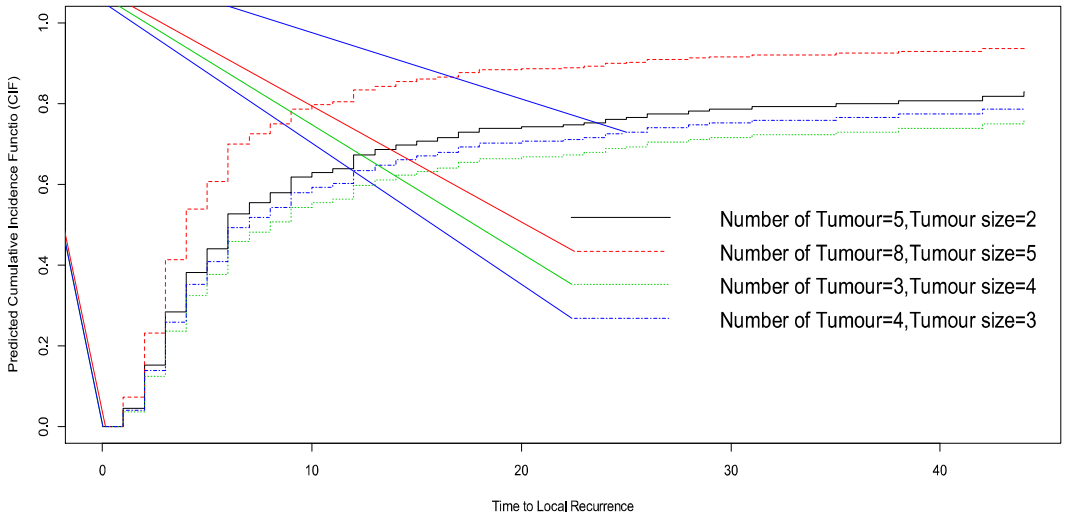


Fig 3: The graphs of the estimated CIFs for bladder cancer patients with local tumour recurrence with 3, 4, 5 and 8 number of tumours.

4. Conclusion

A non-parametric statistical method of analysis of survival data with more than one outcome (i.e. competing risks) was considered in this study. The cumulative incidence functions and sub-distribution hazard model has been employed to model the effects of some prognostic variables on the clinical outcomes of patients with bladder cancer tumours. Findings from this work indicated that bladder cancer patients have high probability of experiencing local recurrence after receiving chemotherapy treatments. Also, bladder cancer patients with local tumour recurrence have low probability of survival from bladder cancer than patients with other clinical outcomes.

Above all, the number of tumours in bladder cancer patients influences the patients' local tumour recurrence of bladder disease. However, the study affirmed the non-significant effect of the initial size of tumour in bladder cancer patients on their local tumour recurrence. It can therefore be concluded that, in the management of patients with bladder cancer tumours, the number, but not size of tumours could be a quick biomarker for local tumour recurrence in the patients. Finally, the summary statistics of the data, within the scope covered in this study, indicated that chemotherapy treatments of bladder cancer patients might later result into local tumour recurrence in the patients. Hence, more effective clinical methods for treating bladder cancer tumour might be desirable.

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