RESEARCH COMMUNICATION

Survival Analysis of Women with Breast Cancer under Adjuvant Therapy in South India

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Abstract

While there has been much research in identifying risk factors and prognostic factor for breast cancer for breast cancer survival, the research specific to South Indian population is limited: Most of the association studies between breast cancer and risk factor have been widely studied in developed countries. This study attempts to explore the survival experience of breast cancer patients treated under adjuvant and neo-adjuvant therapy. The data were obtained from a Government Cancer Hospital, Tamil Nadu, South India and included 522 women diagnosed and treated with adjuvant and neo-adjuvant therapy between January2000 to December 2008 and follow up to May 2010. The survival experiences under two treatments are presented using Kaplan-Meier survival curves. The important prognostic variables for response to treatment survival were identified using Cox regression with and without time-dependent covariates. Of the 522 cases, 248(47.5%) were of stage2 (A&B), 249(47.7%) were of stage3 (A&B). About 90% received neo-adjuvant therapy. About 94% of the patients had response to treatment. The Cox model showed that apart from the chemotherapy, number of children, child birth status and stage3B and 4 turn out to be significant predictors for response to treatment survival. This is the first study to evaluate adjuvant therapy effects under hospital setup in South India. The results show that response to treatment survival is related poor in advanced stage patients under treatment.

Keywords: Breast cancer - Kaplan-Meier - Cox proportional hazards model - time-dependent Cox model

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Introduction

In cancer studies, the main outcome of interest is the time to occurrence of event like death, relapse etc. Breast cancer is one of the most common and feared cancers in cancer deaths after lung cancer (Ries et al., 2000). Breast cancer survival data are skewed and consist of complications in the pattern of early events and in the end stage. In general, cancer studies measure the length of survival after diagnosis of cancer and treatment (Rajaeefard et al., 2009). It is common for a proportion of individuals to remain alive and response to treatment (Duncan et al., 1976; Haybittle et al., 1959; Todd et al.,1983; Zahl et al., 1997) at the end of the follow-up period, and only a lower limit on their actual time to event is known. This paper presents the survival probabilities of breast cancer patients attending a government cancer hospital in Tamil Nadu, South India.

Materials and Methods

Survival time is the time period to occurrence of an event. In breast cancer studies it may be death, response, relapse or toxicity. The survival times are often censored which makes the problem of modeling and inference difficult. Kaplan-Meier (Kaplan et al.,1958; Kleinbaum 1996; Lee and Wang 2003) extended the concept of life table to analyze the censored data and Cox (Cox 1972) opened the whole field of regression analysis to censored survival data.

Kaplan-Meier method is a nonparametric approach for survival analysis It incorporates information from all of the observations, both censored and uncensored by considering survival to any point in time as a series of steps defined by the observed survival and censored times (Hosmer and Lemeshow, 1999). In the analysis of survival time, we estimate the conditional probabilities of successful steps and then multiply them together to obtain an estimate of the over all survivorship function. These step intervals are defined by a rank ordering of the survival times. Each interval begins at an observed time and ends just before the next ordered time and is indexed by the rank order of the time point defining its beginning. Suppose there are k patients have events in the period of follow-up at distinct times . As events are assumed to occur independently of each other, the probabilities of surviving from one interval to another may be multiplied together to give the cumulative survival probability. The

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probability of being alive at time tj, S(tj), is calculated by

$$S(t_j) = S(t_{j-1})\left(1 - \frac{d_j}{n_j}\right) \qquad (1)$$

where $t_o = 0, S(0) = 1$. The value of S (t) is constant between times of events, and therefore the estimated probability is a step function that changes value only at the time of each event. In case of every individual to experience the event without censoring, this KM method would simply reduce to the ratio of the number of individuals event free at time divided by the number of people who entered the study. The median survival time may not be possible to estimate when the number of event of interest is less than half of the total population.

The Cox model (Cox, 1972; Cox and Oakes,1984) is the most commonly used approach for analyzing survival time data in medical research. The regression model, which describes the relationship between the occurrence of event and covariates in the survival-analysis. Let denote the value of a vector of covariates for individual at time . Then the PH model is given by

$$h(t, X) = h_0(t)\exp\left[\sum_{i=1}^{p} X_i\beta_i\right] \qquad (2)$$

The model may also be generalized to allow for effects that vary over time, and therefore no longer proportional assumption. The time-dependent Cox model is expressed as

$$h(t, X(t)) = h_0(t)\exp\left[\sum_{i=1}^{p_1} X_i\beta_i + \sum_{j=1}^{p_2} X_j(t)\delta_j\right] \quad (3)$$

This work considers information from 522 Breast cancer patients' data diagnosed between January 2000 and December 2008 at the Government Cancer Hospital, Tamil Nadu, South India and follow-up period up to May 2010. The event of interest is response to treatment under treatments. The stages of the disease are classified based on the 5 point scale (Stage 2A, 2B, 3A, 3B, 4) (Engel et al., 2003; Michaelson et al., 2002).

Results

The response to treatment population for neo-adjuvant

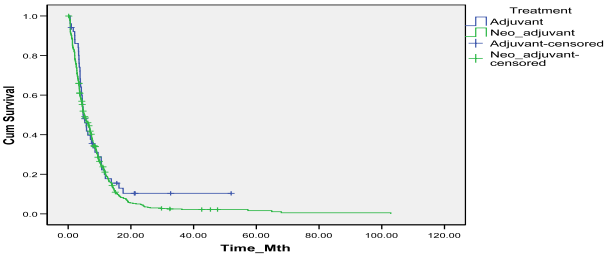

Figure 1. Kaplan-Meier Survival Estimates for Neo-adjuvant and Adjuvant Groups

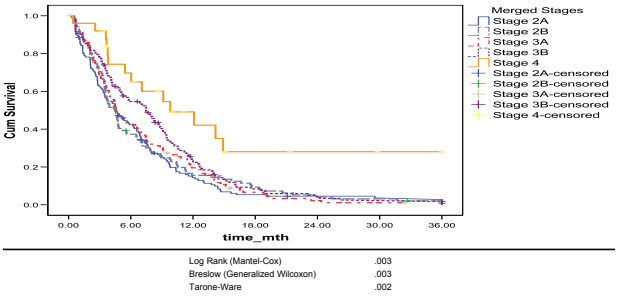

Figure 2. Kaplan-Meier Survival Estimates for Breast Cancer Stages over Time

among different stages varies from 55% to 98% and that of adjuvant among different stages varies from 67% to 90%. As expected the early stages usually give higher response than later stages. However the difference between Neo-adjuvant and Adjuvant was no significant difference among stages (see Figure 1). Hence for further analysis we combined two therapies of treatment.

Regarding overall survivorship function median response falls in the interval 3-6 months and median response time is 166.4 days. Table.III presents the survival of the patients according to the stages of the disease. From the table we note that there is considerable variation in the median response times. The Kaplan-Meier survival estimates between stages of breast cancer over a period of time are given in Figure 2. The log rank test gives significant differences between curves. The stage 4 patients response is significantly lower than other stages ($p < 0.003$).

The Cox model with and without time to adjust all

Table 1. Life-Table Estimates Between Stages with Median Response Times (MRT)

Time Interval (mths)	Stage 2A n = 147 S(t)	95% CI	Stage 2B n = 101 S(t)	95% CI	Stage 3A n = 107 S(t)	95% CI	Stage 3B n = 142 S(t)	95% CI	Stage 4 n = 25 S(t)	95% CI
0-3	0.62	(0.54, 0.69)	0.70	(0.60, 0.78)	0.69	(0.59, 0.77)	0.78	(0.70, 0.84)	0.92	(0.72, 0.98)
3-6	0.42	(0.34, 0.50)	0.37	(0.28, 0.47)	0.43	(0.34, 0.53)	0.55	(0.46, 0.62)	0.71	(0.48, 0.85)
6-9	0.24	(0.18, 0.32)	0.25	(0.17, 0.34)	0.30	(0.22, 0.39)	0.40	(0.32, 0.48)	0.61	(0.37, 0.77)
9-12	0.14	(0.09, 0.20)	0.15	(0.09, 0.23)	0.20	(0.13, 0.28)	0.22	(0.16, 0.30)	0.48	(0.26, 0.68)
12-15	0.06	(0.03, 0.11)	0.13	(0.08, 0.21)	0.11	(0.06, 0.18)	0.13	(0.08, 0.20)	0.28	(0.09, 0.50)
15-18	0.05	(0.02, 0.10)	0.09	(0.05, 0.16)	0.07	(0.03, 0.13)	0.08	(0.04, 0.14)	0.28	(0.09, 0.50)
18-21	0.04	(0.01, 0.09)	0.06	(0.03, 0.12)	0.03	(0.01, 0.08)	0.06	(0.03, 0.11)	0.28	(0.09, 0.50)
21-24	0.04	(0.01, 0.09)	0.04	(0.01, 0.09)	0.02	(0.00, 0.07)	0.04	(0.02, 0.09)	0.28	(0.09, 0.50)
24-27	0.04	(0.01, 0.09)	0.03	(0.01, 0.08)	0.01	(0.00, 0.05)	0.03	(0.01, 0.07)	0.00	-
27-30	0.03	(0.01, 0.07)	0.03	(0.01, 0.08)	0.01	(0.00, 0.05)	0.03	(0.01, 0.07)	0.28	(0.09, 0.50)
>30	0.01	(0.01, 0.05)	0.01	(0.00, 0.05)	0.01	(0.00, 0.05)	0.01	(0.00, 0.04)	0.28	(0.09, 0.50)
MRT(days)	145.71		146.12		157.04		209.20		348.21	

Table 2. Cox PH and Time-dependent Cox Models for Breast Cancer Data

Covariates	HR	SE	(95% C.I)
Cox PH			
Stage 2B	0.975	0.134	0.749-1.269
Stage 3A	0.965	0.133	0.743-1.253
Stage 3B	0.749	0.127	0.583-0.961
Stage 4	0.400	0.286	0.229-0.701
Abortion	1.172	0.115	0.936-1.467
No of Children	0.937	0.029	0.884-0.992
Chemotherapy	2.151	0.272	1.262-3.664
Radiotherapy	1.162	0.096	0.963-1.403
H/O Cancer	1.102	0.227	0.706-1.719
Childbirth status	1.436	0.153	1.064-1.938
Menopause status	0.918	0.120	0.725-1.162
Age	1.006	0006	0.995-1.018
Cox time-dependent Covariate analysis			
Stages	0.892	0.033	0.830-0.959
Abortion	1.174	0.134	0.938-1.468
No of Children	0.944	0.027	0.893-0.999
Chemotherapy	2.095	0.572	1.227-3.578
Radiotherapy	1.179	0.114	0.976-1.424
H/O Cancer	1.035	0.233	0.665-1.610
Childbirth status	1.412	0.217	1.045-1.908
Menopause status	0.985	0.105	0.800-1.212
Time-dependent variable			
Age	0.9999	0.0001	0.999-1.0000

covariates to identify the significant variables which influence the response are presented in Table 2.

Discussion

When there is a need to analyze medical setup data especially related to response to treatment of cancer patients through treatment over a period of time, the Kaplan Meier and life table are used to describe directly the survival experience of study subjects and usually estimate their survivor function between groups over a period of time. In comparing covariates in terms of survival techniques, it is necessary to adjust for patient-related factors that could potentially affect the survival time of patients. Cox proportional hazards model makes a way for adjusting covariates which are to carry out the analysis using survival data to interpret comprehensively.

Acknowledgements

The authors declare that there is no conflict of interest with this work.

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