Cox Models Survival Analysis Based on Breast Cancer Treatments

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Abstract

Background: The aim of this study is to evaluate the association between different treatments and survival time of breast cancer patients using either standard Cox model or stratified Cox model.

Methods: The study was conducted on 15830 women diagnosed with breast cancer in British Columbia, Canada. They were divided into eight groups according to patients' ages and stage of disease Either Cox's PH model or stratified Cox model was fitted to each group according to the PH assumption and tested using Schoenfeld residuals.

Results: The data show that in the group of patients under age 50 years old and over age 50 with stage I cancer, the highest hazard was related to radiotherapy (HR= 3.15, CI: 1.85-5.35) and chemotherapy (HR= 3, CI: 2.29- 3.93) respectively. For both groups of patients with stage II cancer, the highest risk was related to radiotherapy (HR=3.02, CI: 2.26-4.03) (HR=2.16, CI:1.85-2.52). For both groups of patients with stage III cancer, the highest risk was for surgery (HR=0.49, CI: 0.33-0.73), (HR=0.45, CI: 0.36-0.57). For patients of age 50 years or less with stage IV cancer, none of the treatments were statistically significant. In group of patients over age 50 years old with stage IV cancer, the highest hazard was related to surgery (HR=0.64, CI: 0.53-0.78).

Conclusion: The results of this study show that for patients with stage I and II breast cancer, radiotherapy and chemotherapy had the highest hazard; for patients with stage III and IV breast cancer, the highest hazard was associated with treatment surgery.

Keywords: Cox PH regression; Stratified Cox model; Breast cancer; Treatment

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Introduction

The aim of some medical studies is to identify prognostic factors of patients' survival time based on clinical classification. Many researchers consider survival data analysis to be the application of two conventional statistical methods: parametric if the distribution of survival time is known and semiparametric if the distribution is unknown. The Cox proportional hazard regression model is the most widely used semiparametric survival model in the health sciences [1]. A key reason why the Cox model is widely popular is that it relies on fewer assumptions compared to parametric models [2, 3]. The fundamental assumption in this model is the proportionality of the hazard function. The Proportional Hazards (PH) models assume that the hazard ratio of two people is independent of time. Where PH assumption is not met, it is improper to use standard Cox PH model as it may entail serious bias and loss of power when estimating or making inference about the effect of a given prognostic factor on mortality. A review of survival analysis in cancer journals reveals that only 5% of all studies using the Cox PH model considered the underline assumption [4]. When the proportional assumption is not met, other modifications or other models must be used for analysis of survival data. In this paper, PH assumption was tested by Schoenfeld residuals. Accordingly, either Cox's PH model or stratified Cox model was fitted according to the PH assumption. All models were fitted to population-based data from British Columbia, Canada.

Materials and Methods

Study Design

The data in this study describe 15830 women diagnosed with breast cancer in British Columbia during 1990-1999, and followed to 2010. All women were identified from the population-based BC Cancer Registry.

Patients' treatments included hormone therapy, chemotherapy, surgery, and radiotherapy. These were coded using binary variables equal to one if the subject received the treatment and zero otherwise. A patient can have more than one kind of treatment.

We defined survival time as a period between the diagnosis of disease and death or the end of patient follow-up.

A binary censoring variable was used to indicate whether a patient died of breast cancer.

Statistical Analysis

Cox PH model and stratified Cox model for analyzing breast cancer survival data were considered.

The Cox PH model is usually written in terms of the hazard model formula. This model gives an expression for the hazard at time t for an individual with a given specification of a set of explanatory variables denoted by the X.

The Cox model is specified as:

$H(t, x, b) = h_0(t) \exp(X b)$

With this parameterization the hazard ratio is:

$HR(t, x_1, x_0) = \exp(b(x_1 - x_0))$

The Cox PH model assumes that the hazard ratio for any two specifications of predictors is constant over time, and Schoenfeld residuals can be used to assess the PH assumption .The "Stratified Cox (SC) model" is a modification of the Cox Proportional Hazards (PH) model that allows for control by "stratification" of a predictor that does not satisfy the PH assumption. Predictor that does not satisfy the PH assumption is being adjusted by stratification, whereas the predictor that satisfies the PH assumption is being adjusted by its inclusion in the model. The hazard ratio value for the effect of variables in each stratum can be estimated. Nevertheless, the hazard ratio value for the effect of stratified variable cannot be estimated [5-7].

The data were divided into eight groups according to patients' ages (age≤50, age>50) and stage of disease (I, II, III, IV) [8], and each group was assumed to have different PH assumptions. For each category of patients, Schoenfeld residuals were used to assess the PH assumption. Consequently, either Cox's PH model or stratified Cox model was fitted according to the PH assumption.

Results

Study was performed on 15830 breast cancer patients. Mean age of patients was 59.1± 13.4.

30.4 percent of patients were 50 years old or younger, and 69.6 percent were older than 50. 58.9% of patients were censored in this study, which means they were alive until the end of the follow up; and 41.1% of patients died because of breast cancer or other reasons.

In patients under age 50 years old, 69.2% were censored and 30.8% died. In patients over age 50 years old, 54.4% were censored and 45.6% died. 39.2 % of patients were in stage I cancer, 36.6% of patients were in stage II, 7.1% of patients were in stage III, and 4.8% were in stage IV.

95% of patients received surgery, 72.1% received radiotherapy, 35% received chemotherapy and 51.5% received hormone therapy (Table 1).

Table 1. Number (%) of patients according to age, stage of disease, and type of treatment.

Factor		N	Percent
Age	≤50	4805	30.4%
	>50	11025	69.6%
Stage	I	6206	39.2%
	II	5793	36.6%
	III	1124	7.1%
	IV	764	4.8%
Status	alive	9329	58.9%
	dead	6501	41.1%
Surgery	Yes	15027	95%
	No	798	5%
Radiotherapy	Yes	11410	72.1%
	No	4412	27.9%
Chemotherapy	Yes	5544	35%
	No	10277	65%
Hormone therapy	Yes	8147	51.5%
	No	7670	48.5%

The results of testing proportional hazard assumption are shown in table 2 and a plot of residuals for the variable "stage" is shown in Figure 1. Considering the residual plots and chi-square values related to variables, the only variable "stage" doesn't satisfy proportional hazard assumption.

The results of Stratified Cox model are shown in table 3.

Category of patients with stage I breast cancer

The data show that in the group of patients under age 50 years old with stage I cancer, the effect

Table 2. Test of proportional hazard assumption

variable	rho	X^2	P-value
age	0.0108	0.4074	0.5233
stage	-0.0437	7.119	0.0076
surgery	-0.0093	0.3247	0.5688
radiotherapy	0.0062	0.1295	0.719
chemotherapy	-0.0138	0.6652	0.4147
stage*surgery	-0.0015	0.0086	0.9261

Table 3. Hazard ratio estimated in cox model based on death due to breast cancer by stage and type of treatment

		Age≤ 50			Age>50		
Stage	**Variable**	**N**	**HR**	**95%CI**	**N**	**HR**	**95%CI**
I	**Surgery**	168	0.15*	(0.03, 0.62)	468	0.09*	(0.04, 0.19)
	Radiotherapy	155	3.15*	(1.85, 5.35)	359	1.34*	(1.09, 1.65)
	Chemotherapy	85	2.06*	(1.52, 2.8)	62	3*	(2.29, 3.93)
	Hormone therapy	44	1.51*	(1.06, 2.13)	232	1.91*	(1.59, 2.29)
II	**Surgery**	597	0.13*	(0.06, 0.28)	1066	0.25*	(0.16, 0.39)
	Radiotherapy	554	3.02*	(2.26, 4.03)	889	2.16*	(1.85, 2.52)
	Chemotherapy	554	1.02	(0.76, 1.36)	379	-----	-----
	Hormone therapy	280	-----		853	-----	-----
III	**Surgery**	194	0.49*	(0.33, 0.73)	312	0.45*	(0.36, 0.57)
	Radiotherapy	215	2.15	(0.85, 5.39)	362	1.23	(0.89,1.69)
	Chemotherapy	217	0.17*	(0.06, 0.51)	228	0.88	(0.71, 1.09)
	Hormone therapy	129	-----		320	-----	
IV	**Surgery**	72	0.79	(0.56, 1.1)	198	0.64*	(0.53, 0.78)
	Radiotherapy	125	-----		350	-----	-----
	Chemotherapy	118	0.99	(0.67, 1.46)	173	-----	-----
	Hormone therapy	96	-----		382	-----	-----

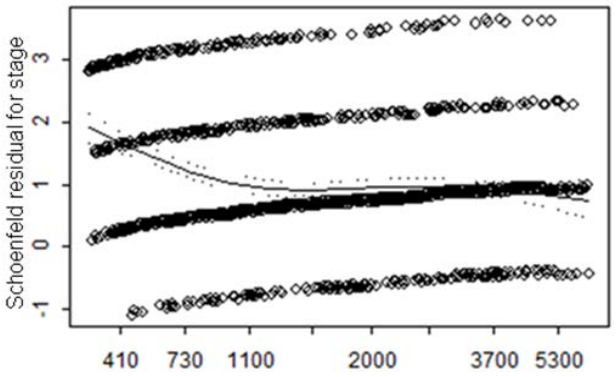

Figure 1. Scaled Schoenfeld residual for ”stage”.

of all four types of treatments were significant; the highest hazard was related to patients who received radiotherapy. In this group, the patients who received radiotherapy had higher hazard than the patients without radiotherapy (HR= 3.15, CI: 1.85- 5.35). In stage I breast cancer, radiotherapy was associated with a decline in the survival rate of patients.

For patients over age 50 years old with stage I cancer, the effects of all four types of treatments were significant. The highest hazard was related to patients who received chemotherapy. In this group, the patients who received chemotherapy had higher hazard than the patients without chemotherapy (HR= 3, CI: 2.29- 3.93). In stage I breast cancer, chemotherapy was associated with the decreased survival rate of patients.

Category of patients with stage II breast cancer

For patients fewer than 50 with stage II cancer, surgery and radiotherapy were meaningful; the highest risk was related to radiotherapy. In this group, the patients who received radiotherapy had higher hazard rather than those without radiotherapy (HR=3.02, CI: 2.26, 4.03).

For patients over 50 with stage II cancer, surgery and radiotherapy were significant. The highest risk was related to radiotherapy. In this

group, the patients who received radiotherapy had higher hazard rather than those without radiotherapy (HR=2.16, CI: 1.85, 2.52). In stage II breast cancer, radiotherapy was associated with a decline in the survival rate of patients.

Category of patients with stage III breast cancer

For patients under 50 with stage III cancer, surgery and chemotherapy were meaningful. The highest risk was related to surgery. In this group, the patients who received surgery had lower hazard rather than those without surgery (HR=0.49, CI: 0.33-0.73).

For patients over 50 with stage III cancer, the variable surgery was significant; the highest risk was related to surgery. In this group, the patients who received surgery had lower hazard rather than those without surgery (HR=0.45, CI: 0.36-0.57).

Both chemotherapy and surgery were associated with increased survival rate of patients with stage III cancer; however, the hazard rate of patients who receive surgery is higher than patients who receive chemotherapy.

Category of patients with stage IV breast cancer

For patients of age 50 years or less with stage IV cancer, none of the treatments were significant.

In the group of patients over age 50 years old with stage IV cancer, variable surgery was significant; the highest hazard was related to surgery. In this group, Patients who received surgery had lower hazard rather than those who did not receive surgery (HR=0.64, CI: 0.53-0.78). For patients with stage IV cancer, surgery was associated with increased survival rate of patients.

Discussion

Olivotto's study showed that chemotherapy causes 10 percent increase in the overall survival rate of women younger than age 50; likewise, it causes at least 4 percent increase in the overall survival of women older than age 50 [9]. Result of our analysis showed that chemotherapy was associated with an increase in the hazard of patients older than age 50 with stage I cancer. Harirchi and his colleagues (2004) showed that patients, who receive radiotherapy, chemotherapy and hormone therapy, have more chance of dying and consequently poorer survival rate [10]. Our finding showed that radiotherapy was associated with increased risk of patients in age group 50 and younger with stage I cancer; likewise, radiotherapy was associated with an increase in the risk for all patients with stage II cancer; In addition, chemotherapy was associated with increased risk of patients age 50 and younger with stage I disease. The results of other studies agree with our findings, in that they associate the lower survival rate with higher stage of disease [11, 12]. Kouro (2008) and Zogung (2006) showed that radiotherapy increases the overall survival rate of patients with stage III cancer [13, 14]; however, in our study the radiotherapy was not significant for group of patients with stage III. Other studies show that chemotherapy and hormone therapy increase the survival rate of patients with early stage of disease [15]. Likewise, in our study the chemotherapy was associated with increased risk of patients older than age 50 with stage I cancer. Anna's study (2009) showed that chemotherapy increases the overall survival rate of patients with stage IV cancer [16]; however, in our study the chemotherapy was not significant for category of patients with stage IV cancer. Franchi (1980) showed that radiotherapy has no effect on overall survival rate of patients with stage III cancer [17]; similarly, in our study the effect of radiotherapy was not significant for patients with stage III cancer.

Surgery is the most effective treatment for patients with early stage of breast cancer. The more reduction of hazard attributed to surgery compared to other treatments can be associated with its old widespread use in treating cancer. Surgical removal of tumor is faster and more efficient in comparison with other types of treatments. In advanced stages of cancer, surgery can be helpful in local control of tumor and reduction of tumor size [11].

Our findings showed that patients with stage I and II cancer who received surgery had higher survival than those who did not receive surgery. Moreover, the patients with stage I and II cancer who received radiotherapy and chemotherapy had lower survival rather than those without these treatments.

For Patients with stage III breast cancer, chemotherapy or other treatments may be applied in order to shrink the tumor and facilitate surgery. Chemotherapy, hormone therapy, or combination of both may be given after surgery in order to reduce the risk of recurrence of cancer. Therefore, different treatment options including each of four types of treatments or combination of them may be considered for patients with stage III breast cancer,

depending on their specific situation. For patients with stage III cancer in our study, the highest increase in the survival rate was related to patients receiving chemotherapy. Hazard ratio of patients who received surgery was more than patients who received chemotherapy. For patients with stage IV disease, the cancer has spread to other organs of the body. In stage IV breast cancer, the main treatment plan will be made up of Systemic therapy including chemotherapy, hormone therapy or combination of both. For patients with stage IV cancer in our study, only variable surgery was significant which was associated with an increase in the survival rate of patients.

In summary, the results of this study showed that for patients with stage I and II breast cancer, radiotherapy and chemotherapy had the highest hazard; In addition, for patients with stage III and IV breast cancer, the highest hazard was associated with treatment surgery.

We caution readers that it is incorrect to conclude causal relationships from our data. Certain breast cancer treatments were associated with improved survival, but treatments were given to a patient based on the severity of their disease, co-morbid conditions, personal preferences and other factors. Only a clinical trial, in which treatment has been randomized, can be used to determine whether treatment has a causal effect on patient survival. Our analysis demonstrates a significant association between treatment and longer survival, and that association might be due to causality.

Abbreviations

The following abbreviations are used in this paper.

PH: Proportional hazards; BC: British Columbia; BCOU: Breast Cancer Outcomes Unit; MSFHR: Michael Smith Foundation For Health Research.

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Conflict of Interest

The authors declare that they have no competing interests.

Authors' Contribution

Alireza Abadi and Hamid Alavi-Majd conceived of the study, and participated in its design and statistical analysis. Parvin Yavari conceived of the study, and participated in its design, coordination, revised the manuscript. Monireh Dehghani-Arani, Erfan Ghasemi and Farzaneh Amanpour performed the statistical analysis and drafted the manuscript. CB participated in coordination and in its design and revision of the manuscript.

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