Original Article

Prognostic Factors Associated with Curing in Patients with Breast Cancer: A Joint Frailty Model

Abstract

Background: Recurrent event data arise frequently in longitudinal medical studies. In many situations, there are a large portion of patients without any recurrences, manifesting the "zero-inflated" nature of the data. Moreover, there often exists a terminal event which may be correlated with the recurrent events. The goal of this study is to extend the application of joint frailty model to identify the prognostic factors associated with curing in patients with breast cancer. **Methods:** As a prospective study, medical records of women who had been attended to Cancer Research Center, Shahid Beheshti University of Medical Sciences from January 1998 to February 2016 were reviewed. Finally, after an initial review of medical records, 711 patients were included in the study and analyzed. A checklist that included items drawn from the demographic background of patients was provided in the study. Two joint frailty models for zero-inflated recurrent events, combining a logistic model for "structural zero" status (Yes/No) and a joint frailty proportional hazards model for recurrent and terminal event times were performed to identify factors associated with BCS. **Results:** The mean age of patients was 38.2 years. The numbers of subjects with 1, 2, 3, and 4 recurrent events were 392, 207, 97, and 15, respectively. The median follow-up time was 6.87 years. There were 137 (19.2%) deaths from cancer during the follow-up. Among the 574 patients who were censored, 418 had no tumor recurrence. Thus, there may exist a large portion of "cured" subjects. We can see that the radiation (OR = 6.02, CI = (3.87, 8.61)) and tumor size interaction with radiation (OR = 1.065, CI = (1.002–1.26)) were significant in the cure model ($P < 0.05$) which means that patients with smaller tumor sizes were more likely to be cured by radiation therapy. **Conclusions:** Our proposed models can help investigators to evaluate which treatment will result in a higher fraction of cured subjects. This is usually an important research question in biomedical studies.

Keywords: *Breast neoplasm, cure model, frailty, survival analysis*

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Introduction

Breast cancer is the most common cancer among women worldwide comprising 16% of all female cancers and it is estimated that 519,000 women died in 2004 because of breast cancer.[1] Although, the incidence of breast cancer in developed countries is more than developing countries, about 50% of all diagnosis of breast cancer[2] and majority (69%) of all breast cancer deaths occur in developing countries.[2] The incidence rate of breast cancer is rising in Iran too. Based on a review of published articles from January 1998 to December 2005, the incidence rate of breast cancer was reported as 22/100,000 in Iran. About 72% of the breast cancers diagnosed included a tumor over 2 cm.[3-5] Most patients present with an advanced stage of the disease are younger than the patients in Western countries.[6]

Breast cancer can be detected at early stages and it has been shown that if breast cancer discovered early, it can often be cured.

In many situations, a substantial portion of subjects has no recurrent events. i.e., we have zero-inflated recurrent event data. Zero-inflated models have been proposed for many types of data, e.g., continuous[7] and count data.[8]

In these models, a portion of the data has an outcome of Y = 0 with a probability P, while the remaining subjects have a specific distribution hence, zero values can come from either the "structural zero" or from ("random zero"). These models can be classified as special cases of finite mixture models of two distributions.[9] It is possible that we observe zero recurrent

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events for some subjects. Clinically, it is an extension of cure models for single event data.[10] For a cured case, a zero means that none of the events of interest occurs, which maps to waiting until infinity. For a noncured case, the event of interest will occur eventually if the follow-up time is long enough. Although given a finite maximum of follow-up, we may not observe its occurrence, i.e. their follow-up is stopped before the occurrence of the first event.[11] For a subject who has no events being observed, we cannot determine whether he is "cured" or "not cured." However, the aforementioned cure models can provide an estimate of the probability of "cure". By doing this, we can identify the treatment that results in a high proportion of "cured" subjects, and make the distinction between these two situations. More recently, Rondeau extended the "cure" model to recurrent events in the frailty model framework.[12]

On the other hand, there is an increasing interest in the joint analysis of recurrent and terminal events, e.g., death, as the recurrent and terminal events are often correlated. Other related work includes Ghosh and Lin (2000), Ye *et al*. (2007), Huang and Liu (2007), Liu and Huang (2008, 2009).[13-17] As many of these articles showed that ignoring the informative terminal events could lead to biased estimates and there may be different impacts of "cure" on recurrent events.[18] Thus, it is important to consider recurrent and terminal events in the "cure" model framework.[19] Accordingly, our purpose in this study was to extend the applications of joint frailty model to identify the prognostic factors associated with curing in patients with breast cancer

Methods

Study design and participants

This prospective cohort study was conducted at the Shahid Beheshti Breast Cancer Research Center, using medical records. Eligibility criteria required subjects to be female; the follow-up period was at least 18 years after initial surgery from January 1998 until February 2016. In this follow-up period, we identified 711 recurrent breast cancers and included them in the current study. Length of follow-up was not considered as inclusion criteria. Based on the time protocol of the Cancer Research Center, the patient's information was reviewed and updated. Criteria for entering each patient in the study: All patients with a definite diagnosis of breast cancer who were followed up at Shohada Tajrish Hospital for at least 6 months after surgery. Exit criteria in this study were including incomplete information for each patient that these observations were made due to a defect in medical records and patient pathology reports. Moreover, patients who have been followed up for up to 5 months and variables that overlap with the results of the research were removed. Patients from the time of breast-conserving surgery were considered at risk of recurrence or death.

All procedures performed in the study were in accordance with the ethical standards of the institutional ethics committee approval from the medical science of Tarbiat Modares University. The current study was extracted from a Ph.D. thesis, which was checked and approved by the Ethics Committee of the Tarbiat Modares University of Medical Sciences (IR.TMU.PHNS.REC.1396.91).

Variables assessment

Data on the original breast cancer (diagnosis date, surgery type, tumor stage, the number of involved lymph nodes tumor grade, family history, and treatment) were obtained and confirmed via medical records. Reported breast cancer recurrences or new primary breast cancers diagnosed after study enrollment were adjudicated by breast oncologist. Recurrent cancers were classified as any type of recurrence: local/regional or distant metastasis and patients with no recurrence. Follow-up time was censored at the time of death (if not from breast cancer), at the last documented staff contact date, or at study completion (Feb 1, 2016)

Statistical analysis

To examine modeling recurrent event data, we fitted the frailty proportional hazards model that is specified as

$$\lambda_i\,(t|\nu_i) = \lambda_0(t)\,\exp\,(\beta^T Z_i + \nu_i)$$

Where, β is the regression coefficient, $\lambda_0(u)$ is the baseline hazard function. When there exist a high portion of zero events, there may be patients who have no probability to experience the events, or they are or "cured" denote by A = 1 for "cured," and A = 2 otherwise ("not cured"). Notably, subjects with zero recurrent events could fall in either class. A cure frailty model was proposed by Rondeau.[12]

In part I, a logistic model is used to describe the probability of cure, namely $p_i = P\,(A_i = 1)$:

$$\text{logit}\,(p_i) = \alpha^T Z_i$$

Part II is a frailty proportional hazards model for the recurrent event among those "not cured"

$$\lambda_i\,(t|\nu_i, Ai = 2) = \lambda_0(t)\,\exp(\beta^T Z_i + \nu_i)$$

Also, there exists a terminal event (death duo cancer) correlated with recurrences, for patients who not cured, the hazard for death is:

$$h\,(t|\nu_i, A_i = 2) = h_0(t)\,\exp(\eta^T Z_i + \nu_i)$$

By combining the above equations, we have a joint model of recurrence and survival with a cure fraction. A "cured subject cannot experience any recurrence, nor death due to the disease and death due to other causes will be considered as censoring.

In this article, we present two zero-inflated models for the recurrent event data with a large portion of zero events, both models have three parts: (1) a logistic model for

"cure" which comes from those patients with no probability to experience the relapses; (2) a frailty proportional hazard model for the recurrent events of other subjects who are not cured; and (3) a Cox model for death with shared frailty from the recurrent event model, clinically, on whether there is "cure" for the terminal event (death). The analysis was performed using R software (version 10.3.2), and the estimation has been implemented in Proc NLMIXED of SAS software.

Results

Table 1 gives demographic, medical, and treatment characteristics of a total of 711 patients receiving surgery to remove tumors as the study sample. Patient's diagnosis age in this study was between 22 to 84 years with mean and standard deviation 47.84, 11.75, respectively. The most prevalence of stage tumors and grade were 49.1% and 55.8% in patients with stage tumor and grade II, respectively. Among all of the study samples, 68.1% have no family history. Patients may also receive adjuvant treatments such as chemotherapy and/or radiotherapy. Regarding treatment, 64% of women underwent a BSC (the remainder underwent a mastectomy radiation therapy), 96% received adjuvant chemotherapy. To find out the effect of these adjuvant treatments on tumor recurrences, two types of recurrences were recorded: 138 local recurrences, 413 distant recurrences, and 332 (49%) patients had no recurrence, demonstrating the zero-inflated nature of the data. The median follow-up time was 5.96 years. The numbers of patients with 1, 2, 3, and 4 recurrences were 183, 118, 39, and 5, respectively.

Table 1: Frequency distribution of characteristics in patients with breast cancer

Variable	Modalities	*n* (%)
Family history	No	383 (68.1)
	First degree	122 (15.2)
	Second-degree	137 (16.7)
Surgery	BCS	419 (64)
	MRM	223 (36)
Stage	I	114 (12.9)
	II	328 (49.1)
	III	221 (35.4)
	IIII	13 (2.6)
Grade	I	97 (10.8)
	II	321 (55.8)
	III	214 (33.3)
Chemotherapy	Yes	610 (96.5)
	No	89 (3.5)
The number of involved lymph nodes	0	313 (33.1)
	1-3	227 (37.1)
	3-10	135 (21.9)
	>10	68 (7.9)
Hormone therapy	Without hormone therapy	40 (2.9)
	Tamoxifen	397 (83.6)
	Letrozole	131 (7.9)
	Other hormonal treatments	84 (5.6)

There were 273 (39%) deaths from cancer. Among the 407 patients who were censored, 308 had no tumor recurrence, illustrating a large portion of "cured" subjects in the dataset, who had no recurrences and did not die from cancer. Then this joint model was applied. Covariates, such as chemotherapy (Yes/No), radiotherapy (Yes/No), age at baseline, and the maximum tumor size at baseline were included in all three models. We also considered interactions between adjuvant treatments (chemotherapy or radiation) in these models. As a result, only radiation and tumor size interaction was significant in the logistic cure model (2). We included this interaction term in all three sub-models. The estimation results are shown in Table 2.

The interaction of radiation and tumor size was significant in the cure model (P = 0.005). Radiation therapy was obtained as a more effective treatment for patients with smaller tumor sizes; we calculated the radiation effect on the ORs of "cure" for different tumor sizes.

The ORs of radiation effect were 3.73, 1.96, and 0.62 at 5, 10, and 20 cm, respectively, i.e. when the tumor size was large, the radiation decrease the cure probability, However, the chemotherapy did not have a significant effect on the cure (P = 0.13). For not cured patients, the interaction of radiation and tumor size was not significant. And only the main effect of tumor size was significant on tumor recurrences and death. Patients with larger tumors were more likely to have disease recurrences HR = exp (0.048) = 1.049, P = 0.008), as well as higher mortality rates (HR = exp (0.059) =1.061, P = 0.006). We also fit a joint model without cure fraction for tumor recurrences and death, Table 2. However, the interaction between tumor size and radiation was significant on both recurrent and death in this reduced model. But the sign of these effects were different from those in another model. As aresult, not cured patients would not benefit from radiation therapy. Hence, after identifying patients to be cured more likely by radiation by applying a cure model, we would not use radiation therapy to those not likely to be cured.

The estimate of frailty variance in the model with a cure fraction was smaller than that in the reduced model. This suggests that the logistic cure model alone effectively captured the heterogeneity. As a result, there was much less variation in recurrent events for those no cured patients.

Discussion

In this paper, we presented two joint frailty models for zero-inflated recurrent and survival. Our proposed models can help investigators to evaluate which treatment will result in a higher fraction of cured subjects. This is usually an important research question in biomedical studies. The "cure" component in the proposed models also helps explain a large portion of heterogeneity among study subjects.

Table 2: Joint frailty models for zero-inflated recurrent events along with death

Parameter	Proposed model			95% CI	No cure fraction			95% CI
	Est	HR/OR*	SE		Est	HR*/OR	SE	
Cure logistic model								
Intercept	-0.645	-	0.483					
Tumor size Ref (<20)	0.017	1.017*	0.029	0.47,1.92				
Radiation Ref (No radiation)	1.796	6.02*	0.75	3.87,8.61				
Chemo Ref (No Chemo)	-0.353	0.702*	0.304	0.18,2.17				
Age at diagnosis	-0.061	0.941*	0.063	0.79,2.53				
Size * Radiation	-0.216	0.805*	0.042	0.38,094				
Recurrent events								
Tumor size[1] Ref (<20)	0.048	0.65	0.017	0.23,0.87	0.061	1.062	0.017	0.21,1.87
Radiation Ref (No radiation)	0.083	1.086	0.381	0.83,2.06	-1.49	0.22	0.162	0.06,0.41
Chemo Ref (No Chemo)	-0.169	0.917	0.147	0.26,2.47	0.054	1.055	0.193	0.54,1.83
Age at diagnosis	-0.017	0.983	0.096	0.34,2.91	0.012	1.012	0.029	0.71,1.68
Size * Radiation	-0.008	0.992	0.063	0.24,1.83	0.049	1.05	0.033	1.002,1.09
θ *P*=0.001	0.751	-	0.183	-	2.941		0.384	-
Cancer death								
Tumor size Ref (<20)	0.082	1.85	0.016	1.03,2.13	0.041	1.041	0.095	0.48,2.14
Radiation Ref (No radiation)	0.079-	0.924	0.328	0.68,2.73	-1.307	0.27	0.477	0.03,0.64
Chemo Ref (No Chemo)	-0.093	0.911	0.169	0.39,2.95	0.139	1.14	0.211	0.86,1.93
Age at diagnosis	-0.071	0.931	0.068	0.34,1.08	0.194	1.21	0.061	069,2.14
Size * Radiation	-0.006	0.944	0.028	0.53,0.99	0.141	1.15	0.035	1.01,1.83

Est is the parameter estimates; SE is the standard error of the parameter estimate. OR was reported for cure logistic model/HR was reported for Cox model. [1]tumor size <20

Accordingly, this model can provide more precise analysis and offer in-depth insight. For example, we detected a large fraction of cured subjects in this data set. In the breast cancer study, chemotherapy had no significant effect while radiation therapy could lead to a higher probability of cure for small tumor size, the proposed model should be applied when there exist a large fraction of zero recurrent events. Furthermore, we present an estimation method which can be conveniently implemented in SAS Proc NLMIXED. This model can be extended in different directions.[20] Firstly, we can use other frailty distribution, e.g., Gamma.

Secondly, we can model multiple types of recurrent events separately, e.g., local and distant recurrences with two correlated zero-inflated frailty models. Lastly, there may exist nonlinear or time-varying covariate effects in the recurrent or terminal event models, nonparametric methods can be used to capture these effects.

One key advantage of this proposed approach is that different covariate effects can be assessed by the two parts of recurrence hazard functions or death hazard function, these covariates can be time-dependent or independent. In addition, they also provide information on whether one or both types of recurrences can be used as substitute endpoints for overall survival.[21,22] We noticed that locoregional relapses and death are related events. We did the same joint analysis with distant metastasis and death and we conclude that these two events are also associated. We may conclude that if we omit to consider the distant metastasis events Convergence of the model could be hard to obtain in data with few events. However, convergence could be reached when the number of parameters to estimate decrease.[23-26] This study gives estimates of incidence and mortality rates in epidemiology, which are meaningful for clinicians. In analyses of the natural history of cancer, there is great interest in a dynamic prediction of death, that is, in the computation of the predictive distribution of death at a certain moment of time, given the history of events (local or distant relapses) and covariates until that moment.[27] As the strength of this study, the results obtained from the proposed model in this study are highly valued due to controlling the zero events by handling them, unlike other survival models that considered them as a censor. These predictions and a measure of their accuracy are in progress, they may provide valuable insight for future research. Notably, some limitations of this study should be considered. First, these results should be considered with caution, given the small number of recurrent events. It may be as a limitation for this study. Incomplete information of some of these patients was another limitation of our study.

Conclusions

In conclusion, in this sample of breast cancer women, this model can be extended in several directions. Firstly, we can model multiple types of recurrent events separately, e.g., local and distant recurrences in this study, with two correlated zero-inflated frailty models. Secondly, there may exist nonlinear or time-varying covariate effects in the recurrent or terminal event models, nonparametric methods can be used to capture these effects. In the other hand,

our findings provide a deep insight into challenging the clinician to evaluate which treatment will result in a higher fraction of cured subjects. This is usually an important research question in biomedical studies.

Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflicts of interest

There are no conflicts of interest.

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