Original Article: Determination of Multiple Recurrences after Breast Surgery using a Random Effect Model

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ABSTRACT

The aim of this study was to determine multiple recurrences after breast surgery using a random effect model. This is a cohort study in which 342 patients were evaluated after breast surgery during the period 2015 to 2020. All information of breast cancer patients was extracted from their files and their recurrence rate was evaluated and predicted based on the fragility model. The risk of multiple local recurrences and metastases increases in people under 40 years of age compared to people over 55 years of age. Also, tumor size (more than 20 mm) has a significant effect on the risk of local recurrence and metastasis in patients. In addition, patients with HER2 + have a higher risk of multiple local recurrences and metastases. The correlation between multiple local recurrences and metastasis in these patients was 0.79 in the combined model. Also, the values of fragility variance for local recurrence and metastasis were 1.1 and 7.39, respectively. The results of this study showed that patients with the same explanatory variables have different risk of metastasis. Also, the relationship between two types of metastatic and local recurrences was high in patients with breast cancer, which is of great importance in the process of diagnosis and treatment of this disease.

Introduction

Breast cancer is the second most common cancer in women after skin cancer. Every year, a large number of people are diagnosed with breast cancer [1]. One of the possible consequences of breast cancer after treatment (surgery) is the return of the disease in two forms of metastasis or local (local) and it has been seen that the primary cause of death in breast cancer is tumor invasion and metastasis [2]. In fact, tumor

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recurrence in the chest area is called local recurrence and recurrence in axillary lymph nodes is called regional recurrence [3]. The difference between this recurrence and metastasis is that it does not occur through the bloodstream and the cells located near the tumor cause this recurrence by regrowth. Despite significant advances in the diagnosis and treatment of breast cancer, mortality as well as breast cancer metastasis in women undergoing surgery and necessary treatments remains a medical problem [4]. Various studies have shown that patients with metastases have shorter lifespans than other patients [5,6]. On the other hand, the return of the disease as a metastasis reduces the quality of life of the patient in terms of physical and psychological dimensions [7]; Therefore, recognizing the factors affecting the occurrence of recurrence and metastasis and also examining the relationship between two types of metastasis and local recurrence in each other in patients with breast cancer is of great importance in the process of diagnosis and treatment of this disease [8].

Therefore, determining the risk factors related to each of these types of recurrences separately, taking into account the correlation between them, is significant for many clinicians. Numerous factors have been studied and identified in various studies on the occurrence of metastasis; however, with the knowledge of these factors alone [9], the occurrence of metastasis can not be predicted; Because some of these factors are attributed to the personality or environmental characteristics of the individual that are specific to the individual and as a correlation factor cause a relationship between the occurrence of various recurrent events for the patient. It is because of these characteristics that despite the similarity of the two individuals in terms of prognostic factors, a patient sooner or later develops a variety of local recurrences and metastases (Figure 1) [10,11].

Multiple recurrences occur frequently in clinical medicine, epidemiology, and other applied research fields [12-15]. Various models have been proposed to fit the recursive event data, which are essentially a generalization of the Cox proportional hazards model. In addition, in studies in which multiple failures occur during follow-up for the individual, there are always individual factors in a way that correlates the timing of events in the same individuals and also the cause of differences between individuals. Standard survival models, like the Cox proportional hazards model, ignore unobserved individual effects and lead to incorrect estimation of model parameters.

In recent studies, the use of a random component is used to express these unknown factors and the correlation between recorded events of an individual. This random component is called fragility [16]. Fragility often indicates a random effect, unrelated correlation, and scatter in survival data. In cases where there is a sharp difference between a subset of patients, the fragility model is used to calculate such heterogeneity in the study population [17]. The use of fragility component in the Cox relative risk model causes regression coefficients to be estimated more accurately and the effect of patients' individual characteristics to be included in the model. In various studies, the fragility model has been used to analyze the data [18]. Various authors also used the fragility model in breast cancer data. Combined models in survival analysis, due to the ability to simultaneously investigate two recurrent events and achieve odd estimates for parameters, can be used to analyze follow-up studies including simultaneous investigation of two survival events. Therefore, according to the issues raised and the increase in the incidence of this disease in Iran, the purpose of this study was to determine the prognostic factors on the survival of breast cancer patients and also to simultaneously evaluate two types of local recurrence and metastasis using the combined fragility model.

Methods

Data collection: This study was a survival study in which all patients with breast cancer referred to Imam Reza Hospital during 2015 to 2020, were considered as a statistical population and patients with a definite diagnosis of breast cancer were studied as a historical group and were studied. The required data were extracted using the patients' medical records and their

latest status in terms of disease recurrence was recorded by telephone follow-up in this center. Inclusion criteria of each person in the study include all patients with a definite diagnosis of breast cancer who have been in Imam Reza Hospital in Tabriz for at least 6 months after their surgery; Exclusion criteria included incomplete information for each patient and patients who had undergone surgery for a maximum of five months. The final sample size was 342 patients. The variables studied in this study include age, time of diagnosis, family history of breast cancer, tumor size, extent of lymph node involvement after surgery, metastasis, type of surgery, tumor grade, estrogen receptor, progesterone receptor, chemotherapy, Stage of the disease (the staging system is called TNM staging). The main basis of this staging is 3 important factors which are: T means tumor size, N means involvement or non-involvement of regional lymph nodes and M presence or absence of distant metastasis and receptor for human epidermal growth factor HER2 + (HER2). Positive means that cancer cells have high amounts of this protein, which is a receptor for human epidermal growth factor and causes cancer cells to grow faster and the tumor to spread to other parts of the body to occur faster.

In this historical cohort study, we tried to include all patients who had a definite pathological diagnosis and whose information could be used. It should be noted that live patients who did not experience local recurrence and metastasis at the end of the study and patients who did not have information about their survival status after a certain period of time were not considered. Data were analyzed using a random effect model or a fragility model.

Ethical considerations: This study was approved by the ethics committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.151).

Results

In this cohort study, 342 patients with breast cancer were studied as a sample. Univariate and multivariate analysis were performed for these patients. Univariate and multivariate analysis were performed for these patients. The age of the patients was between 22 and 84 years with a mean of 84 and a standard deviation of 11 and a mean of 47 years. The median follow-up time of patients was 113 months. Out of 342 patients studied, 87 patients (4.25%) had recurrence and for the remaining 225 patients (74.6%) the desired progression did not occur. The median disease-free survival time was 57.30 months with a minimum of 6 months and a maximum of 187 months. The frequency distribution of other independent variables studied in this study is presented in Table 1.

Table 1. Frequency distribution of characteristics of breast cancer patients with breast cancer referred to the hospital

Variable		N(%)
Family history	NO	233 (68.1%)
	Grade I	52 (15.2%)
	Grade II	57 (16.7%)
Tumor size	<2	72 (21.1%)
	2-5	211 (61.7%)
	>5	59 (17.3%)
Disease stage	I	44 (12.9%)
	II	168 (49.1%)
	III	121 (35.4%)
	IV	9 (2.6%)
Chemotherapy	Yes	330 (96.5%)
	No	12 (3.5%)

According to the results obtained from Table 2, using Kaplanmeier's estimate, the median time to disease-free survival (the time until the first recurrence after surgery is called disease-free

survival time) was estimated to be 30.75 for breast cancer patients. Survival rates of 1, 3 and 5 years without disease for patients were 96%, 79% and 68%, respectively.

Table 2. 1, 3 and 5 year disease-free survival rate of patients with breast cancer referred to the hospital

Follow-up time (Year)	Probability of survival
1	96%
3	79%
5	68%

Table 3 shows the distribution of the number of local recurrences and metastases among patients. According to the obtained odds ratio, it can be said that the chance of patients to experience recurrence of metastasis is about 6 times more than local recurrence.

Table 3. Distribution of number of local recurrences and metastases

Number of metastases			Number of local recurrences	Odds ratio
Total	>1	0		
225	98	127	0	6.5
117	105	12	>1	
342	203	139	Total	

In this part of the study, a fragility model combined with the basic hazard functions approximated by the maximum likelihood estimate method was used to estimate the parameters. Considering the risk ratio and confidence interval obtained from the model fitted in Table 3, it can be said that the risk of local recurrence and metastasis is higher for patients with tumor grade greater than 1. Also, the risk of multiple local recurrences and metastases increases in people under 40 years of age compared to people over 55 years of age. Also, tumor size (more than 20 mm) has a significant effect on the risk of local recurrence and metastasis in patients. In addition, patients with HER2 + have a higher risk of multiple local recurrences and metastases. The correlation between multiple local recurrences and metastasis in these patients was 0.79 in the combined model. Also, the values of fragility variance for local recurrence and metastasis were 1.1 and 7.39, respectively (Table 4).

Table 4. Results of combined fragility modeling for multiple recurrent recurrent events and metastasis in breast cancer patients

Variable			The proposed model	
			HR	CI95%
Local recurrence	Reference group age (older than 55 years)	<40	2.91	1.77-4.80
		40-55	1.33	0.95-1.90
	Reference group tumor grade (grade I)	I	2.80	1.60-5.11
		II	4.84	1.35-3.22
	Reference group tumor size (less than 20 mm)	>20mm	1.66	1.20-2.30
	HER2 + reference group (not available)	Have	1.90	1.19-2.90
Metastasis	Reference group age (older than 55 years)	<40	1.55	0.31-4.21
		40-55	0.81	0.48-1.31
	Reference group tumor grade (grade I)	I	1.66	1.18-2.09
		II	4.55	2.18-9.82
	Reference group tumor size (less than 20 mm)	>20mm	5.93	5.88-13.82
	HER2 + reference group (not available)	Have	2.20	1.18-4.82

Discussion

In the present study, which was designed to simultaneously investigate multiple local recurrences and breast cancer metastases. A total of 342 women were examined at Imam Reza Hospital in Tabriz. One of the challenges in this study was to investigate the correlation between time to local recurrence and metastasis, so that first of all the number of recurrences and recurrence time varies from patient to patient and the recurrence of each patient is not independent. Depends on the history of relapses, and patients may have a higher risk of death after relapse. Third, in the data set, 58% of patients with local recurrence experienced metastatic recurrence, while 49% of patients with local recurrence had metastatic recurrence [15]. As a result, it can be said that there is a strong correlation between time to local recurrence and metastasis. Therefore, estimating the correlation between multiple recurrences is very important and this correlation should be included in the data analysis. In the present study, in order to simultaneously consider two recursive events and obtain more accurate results, the combined brittleness model for multiple recurrent events and the maximum likelihood method were used to estimate the risk functions [16]. The proposed model has the ability to show the correlation between the two types of recurrences. This method can also cover the connections between recurring events and the final event. This method is better and more efficient than using two separate models. According to the results obtained from the fitted model, it can be said that the risk of local recurrence is related to the risk of metastasis recurrence. P = 0.79. The age distribution of women with breast cancer in the country shows that the age of diagnosis in Iran is lower than in Western Europe and North America and women are more likely to get the disease, which is confirmed by studies conducted in this field in the country. The median disease-free survival time in this study was 64 months and the five-year disease-free survival rate for patients was 68%, which is consistent with the results of similar studies [17-20]. HER2 positivity of patients was a prognostic factor for the occurrence of metastasis in the fragility model, which has been shown in some studies as a prognostic factor in the occurrence of metastasis. The degree of tumor malignancy was recognized as a significant factor in the prognosis of metastasis and local recurrence of patients, which is consistent with studies in this field. Various studies have shown that patients with first-degree malignancy had a higher survival than patients with second- and third-degree malignancies [21-24].

Limitations

One of the limitations of the present study is the assumption of common stochastic effects under which the dependent final event model divides the fragility into a multiple recurring event model. While it is easy to implement this model of shared random effects, it does provide a relatively strong premise about the relationship between heterogeneity between individuals.

Conclusion

The results of this study showed that patients with the same explanatory variables have different risk of metastasis. Also, the relationship between two types of metastatic and local recurrences was high in patients with breast cancer, which is of great importance in the process of diagnosis and treatment of this disease.

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