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Factors Affecting the Survival of Patients with Breast Cancer Referring to Motamed Cancer Institute, ACECR Tehran Using the Cure Model

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Abstract

Breast cancer is the most common cancer among women. This study aimed to determine the disease-free survival and its prognostic factors among Iranian patients. In this longitudinal study, 559 cases of breast cancer were studied. The subjects were registered in Motamed Cancer Institute, Tehran, Iran, during the period 1997-2007 and were followed up to 2013. The data were analyzed using STATA version 11 software. The results of this study showed that lymph node involvement and tumor size were associated with disease-free survival time. The group with lymph nodes involvement had an odds of survival 55% lower than the other group (P = 0.01). With one unit increase in the tumor size, the odds of survival decreased by 53% (P < 0.001). Level of education, type of surgery, ER, and age was not identified as prognostic factors. The impact of lymph node involvement and tumor size on survival is verifying the importance of early detection of the disease, the need for awareness of women and the implementation of screening programs in this regard.

Key words: Breast cancer, Cure model, Disease-free survival, Lymph nodes, Size of the tumor.

Introduction

Breast cancer is one of the most common cancers causing lots of death among women. The incidence of breast cancer is 22 per 177 thousand in Iranian women and its prevalence is 127 per 177 thousand people globally [1-3]. The growth potential of breast cancer and the patient's resistance to malignancy varies widely among different individuals and different stages of the disease. The doubling time of breast cancer varies from several weeks in tumors with rapid growth to months or years in slow-growing tumors. It should be noted that breast cancer is considered a two-fold disease affecting the breast and the body as a whole. Although early breast tumors and topical control issues are manageable, the possibility of systemic metastases and their lethal consequences should not be ignored as breast cancer may cause metastasis to any member, and bone, lung, or liver involvement is approximately seen in 85% of women with illness. Breast cancer is multi-stage cancer, and after the definitive diagnosis, the clinical stage is introduced and the tumor-lymph node-metastasis (TMN) system is used for this purpose [4,5].

Considering that breast cancer is the deadliest and most common malignancy among women, trying to survive patients after diagnosis and improving their quality of life is very important nowadays. Several factors have been identified as prognostic factors in the survival of breast cancer: tumor malignancy grade, tumor size, the higher number of other lymph nodes, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor (HER2) and

pre-menopausal age, receiving different types of treatments (surgery, radiotherapy, chemotherapy, hormone therapy), socioeconomic status (lower education, low economic status), different fertility status and body mass index [6-8].

However, the most important factor in the prognosis of breast cancer is the stage of the disease in which the disease is diagnosed. For patients who are diagnosed with an early stage of disease, the 5-year survival rate is about 80%, while for patients with advanced disease; this rate is about 50%. Considering that in most cases, the disease is diagnosed in advanced stages, the prognostic factors can be effective in the early diagnosis of this disease [9].

In some diseases, due to high mortality in the advanced stages, if the disease is diagnosed at an early stage, a proportion of people may have a longer survival time or even recovered from it. In survival studies, in the case of long-term survivors, the use of commonly used parametric and semi-parametric models (such as the semi-parametric Cox model and survival parameter models) is not fit, since, in these models, it is assumed that all subjects in the study are expected to experience death or recurrence [10,11]. Cure rate models are used to analyze this type of data.

In cure models, a proportion of individuals in long-term survivors and may be considered as cured [12].

Before using the cure model, two presumptions should be considered: patients with long-term survival and follow-up times. One of the presumptions that should be considered when using cure models is to test the existence of patients with long-term survival in the community. The question is whether a significant percentage of people have long-term survival or not. Of course, in some cases, the existence of cured people is proved using clinical experience and biological evidence. If such evidence or information is not available, statistical tests can be used to check the presence of these patients. By using the parametric test and the likelihood ratio test, the existence of a free fraction is investigated in which a survival model with an arbitrary distribution is considered under the zero hypothesis, and an under alternative hypothesis, the cure survival model is fitted with data.

Then, using the likelihood ratio test, which has a 1-degree freedom distribution of chi-square, the existence of cured individuals is investigated. After obtaining sufficient evidence about the presence of long-term survivors, it should be investigated whether the presence of cured subjects in the study is not due to a lack of follow up. For this purpose, Mahler and Zhou draw a table under the independent conditions and the parallelism of the time of censorship and the uniform distribution or exponentiation of the time of censoring by simulation [11]. In some cases, with the use of clinical experience and bio-evidence, the existence of a cured fraction in the data is confirmed. Because of the random pattern of censored data, one cannot easily identify cured people from censored data [11], and one can only estimate the probability of being cured in a particular society through maximum likelihood methods [11,13].

Determining the factors affecting the survival of cancer patients is one of the ways to help develop healthcare and cancer programs. The most common criteria for treating cancer patients is the disease-free survival time. The disease-free survival time is defined as the time from the onset of the disease to the return of illness or death [14].

This study aimed to determine the factors affecting the survival of patients with breast cancer. In this study, the cure model was used to determine the factors affecting the survival of breast cancer patients due to long-term survival in individuals. What distinguishes this study from previous studies is the use of 50 cut-off points for cancer diagnosis age, which has been obtained using the change point models [15].

Materials and Methods

In this survival study, 559 patients with breast cancer were studied. They were referred to the Center for Diseases of Motamed Cancer Institute in Tehran from 1997 to 2007. In 2013, these patients were followed. The beginning of the study was based on pathological diagnosis of breast cancer and their status (the first recurrence/no recurrence of breast cancer) was

recorded through telephone inquiry. Because of no information above of a specific point of time for some subjects with no recurrence of breast cancer status, there was right censoring in the data. According to the follow-up results, the duration of disease-free survival (the time from the breast cancer diagnosis until the first recurrence) was calculated. Demographic and clinical variables included in this study were education (lower than a diploma, diploma, and higher), lymph node, tumor size, type of surgery (Bare and MRM), positive and negative estrogen receptor, and age of diagnosis. In this study, a cut-off point of 50 was used for the age variable [15].

To investigate the factors affecting the survival of patients with breast cancer, the Mixture cure rate model, and STATA version 11 software were used.

Cure rate model: Two categories of cure models were presented including mixture cure rate model and non-mixture cure rate model. In the mixture cure rate model, people are divided into two groups; those who are cured and those who are prone to the event, or, in particular, susceptible or uncured individuals. If p is the proportion of curing, the survival function for the cure rate model is expressed as follows:

$$S(t) = p + (1-p)\, S_U(t)$$

In which S_U (t) is a survival function for non-cured individuals. For its modeling exponential distributions, gamma, log-normal, Weibull can be used [11, 12]. In this model, $S(0) = p + (1-p)\, S_U(0) = p + (1-p) = 1$; $t = 0$, that is, all individuals are alive at zero time and when $t=\infty$ then $S(\infty)=p+(1-p)S_U(\infty)=p+(1-p)\times 0=p$, which means that a proportion of individuals (p) remains cured. The cured rate (p) may be dependent on auxiliary variables [12]. To model the cure rate using the auxiliary variables, we can use the logistic relevance function or the log-log relevance function. The main goal in mixture cure rate models is to estimate the ratio of cured individuals, estimating the survival function for prone individuals and the factors affecting these two [10,11].

Results and Discussion

In this longitudinal study, the mean age of the patients at the time of diagnosis was 46.31 ± 17.16 years (Table 1). The age range at the time of diagnosis was 24-83 years. The mean and median follow-up time of patients was 81.43 ± 55.72 and 68.36 months and the follow-up period was 17-6 years. In total, 179 (32%) deaths occurred and the rest were considered as right censors. 289 (50.9%) patients had lower diplomas and the rest had a diploma and higher education. The majority of patients (63.2%) had lymph node involvement. In most patients, 470 (83%) performed MRM and the rest BCS (breast preservation). 321 (57%) of individuals were positive estrogen receptors and the rest were negative estrogen receptors. Description of study variables is reported in Table 1.

Table 1. Description of the study variables

Variable	N (%)
Educational level	
Lower than diploma	289 (51)
Diploma and higher	279 (49)
Lymph node	
Yes	359 (63)
No	209 (37)
Surgery	
Bare	98 (17)
MRM	470 (83)
Estrogen receptors	
Positive	321 (57)
Negative	247 (43)
Diagnosis age	
Lower than 50 years	370 (66)
Higher than 50 years	189 (34)

First, a Kaplan-Meier diagram was drawn (Figure 1). As shown in the chart, after about 17 years, the graph has flattened and did not reach zero; also, about 40% of people had long-term survival. To use the cure rate model, the adequacy of follow-up time and the presence of cured patients were investigated. The follow-up time of 6-17 years simply indicates that follow-up time is sufficient. For examining the existence of cured

people, the likelihood ratio of the exponential model (zero hypotheses) and exponential cure rate model (the opposite hypothesis) were used. Since the statistic of the likelihood ratio (with a chi-square distribution of 1 degree of freedom) was 7 and higher than 4, the presence of cured subjects was confirmed.

The results of the fitting of the cure rate model to the data showed that only the variables of the lymph node and tumor size were effective on the disease-free survival time (Table 2). In the group with lymph nodes, the chance of recovery was reduced by 55% compared to the group with no lymph nodes (P = 0.01). Also, by increasing one unit to the size of the tumor, the chance of recovery decreases by 53% (P <0.001). Educational variables, type of surgery, estrogen, and age did not affect the disease-free survival time.

Figure 1. KM curve for survival time of breast cancer data

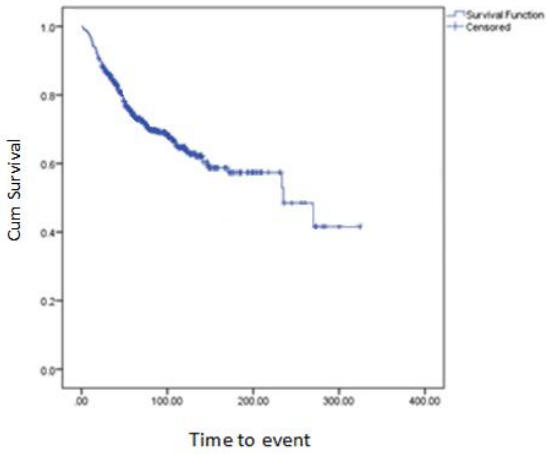

Table 2. Results of fitting the cure rate model to breast cancer data from Motamed cancer institute in Tehran

Variable	b	Exp (b)	CI (b) 95%	P
Educational level				
Diploma and higher	0.01	1.01	(-0.55 ، 0.57)	0.97
Lower than diploma	-	-	-	-
Lymph node				
Yes	-0.08	0.45	(-0.36 ، -0.24)	0.01*
No	-	-	-	-
Tumor size	-0.75	0.47	(-1.16 ، -0.35)	< 0.001*
Surgery				
MRM	0.17	1.19	(-0.41 ، 0.75)	0.31
Bare	-	-	-	-
Estrogen receptor				
Positive	0.16	1.17	(-0.37 ، 0.69)	0.55
Negative	-	-	-	-
Diagnosis age				
Higher than 50 years	-0.02	0.98	(-0.40 ، 0.01)	0.21
Lower than 50 years	-	-	-	-

*Significance level is 95%

In the present study, the factors affecting the survival of breast cancer patients who were referred to the Breast Cancer Research Clinic of Motamed Cancer Institute, ACECR Tehran between 1997 and 2007, were examined using the cure rate model. Based on the findings of the present study, the mean age of the participants in the study was 46.31 ± 17.16, which was consistent with the findings of other studies in the country that reported a mean age of breast cancer patients between 45 and 50 years of age. The age distribution of women with breast cancer in the country indicated that the age of the diagnosis is lower than Western Europe and North American countries, and women are infected sooner [16,17]; the mean age of diagnosis and surgery in other studies, In Iran, was between 46 and 48 years old [18-21]. The mean age of patients in Carleau et al., in Texas, was 56.7 years, Yang et al., in China, Anianova in Nigeria, Sarah et al. were equal and less than 45 years [22-25]. Other studies have also suggested that the incidence of

breast cancer in Iranian women is lower than the mean age of the world. These findings emphasized the need for early diagnosis of breast cancer as one of the most important approaches to control the disease in Iran.

Therefore, primary prevention is advised by changing lifestyles, avoiding risk factors, and providing extensive information and education, especially through mass media such as radio, television, and newspapers, to raise awareness among young women about breast cancer screening; Secondary prevention including early detection of cancer or pre-cancerous lesions by efficient and effective screening methods, e.x. mammography as the most effective method, for diagnosing breast cancer, can play an important role in reducing the incidence and mortality of breast cancer. These findings emphasize the education of women from an early age about the symptoms of breast cancer and emphasize periodic examinations [24,26-30].

The mean disease-free survival time was 68.36 months in this study. In the study of Khodabakhshi et al., the five-year free-disease survival rate was 72% for patients [31]. In the study of Akbari et al., a five-year survival rate of 77.3% was reported [20]. In this study, the 5-year survival rate was 70%. Also, there was no significant relationship between the age of diagnosis and patient survival in this study. In some other studies, there was no significant relationship between age and survival of patients.

However, in some studies, it has been shown that the patient's higher age is inversely related to survival [34,35]. This, of course, contradicts most studies in other countries [36], while, this trend has been observed in some Iranian studies [20, 36-38]. In the study of Mokhtari Hesari et al. and also in the study of Haghighat et al., the age was not significant [39,40].

This contradiction may be due to the different frequency distribution of Iran age groups compared to other countries. However, this requires a more detailed methodological study.

In the present study, there was no relationship between positive estrogen receptors and survival rate. In Horita et al. and Wolberg et al. studies, there was no significant correlation between positive estrogen receptors and survival rates [41, 42], while this relationship was significant in the study of Khodabakhsi et al. [31]. The contradiction between different studies can mainly be related to the choice of different therapeutic approaches based on the disease stages, patient age, patient preference, physician opinion, and facilities of the center. Also, the existence of multiple confusions can make it difficult to assess the impact of this factor [20,36].

In the present study, tumor size and lymph node involvement in the cure model were significant and had a reversed relationship with the cured patient. In other studies, these variables have been introduced as a prognosis of survival. For example, in the study of Haghighat et al., there was a significant relationship between tumor size and lymph node involvement with the survival of patients [40]. However, in Lackowska et al., a relationship between tumor size and lymph node involvement with survival was reported which reduced survival [43].

This issue emphasizes the importance of using specialized local therapies such as radiotherapy in patients with lymph nodes involvement and indicates the importance of screening for breast cancer and its early diagnosis in stages where the disease has not yet spread to the glands. Health policy-making based on screening and early diagnosis of the disease and providing appropriate facilities for diagnosis and treatment is one of the most effective measures to raise awareness and timely control of the disease and improve the survival of these patients. In the present study, no relationship was found between education level and survival. However, there was a direct relationship between survival rate and education level in the study of Haghighit et al. as people with higher levels of education had more knowledge about methods of prevention and recognition of breast cancer [40]. This difference may be due to the use of different methods to fit the cure model into data. In this study, there was no significant relationship with the type of surgery. This finding has been in line with other studies; Haghighat et al., Kuro et al., as well as Fredmal et al. [40,44,45].

The early diagnosis and the pre-metastatic diagnosis of disease significantly reduced

mortality and morbidity. The use of cure rate models and evaluation of predicting variables on cure rates provide important information to physicians and authorities in this field. In recent years, cure models have found a special place in medical studies, especially in the survival of cancer patients. Researchers can use these models to examine the survival of patients regarding various illnesses. One of the strengths of this study was to use the cure model to investigate the factors affecting the survival of breast cancer patients and use a cut-off point of 50 for the age variable. The age variable was one of the limitations of the present study due to the lack of proper recording of information and variables in patients' records. Other limitations were the small sample size and ancient data.

This study showed that the most important factors influencing the survival of this type of cancer are the involvement of lymph nodes and tumor size. The survival rate is one of the important indicators that, with estimates of disease prognosis, help health policy-makers and physicians to provide a suitable diagnosis and treatment of the disease, and these findings indicate the importance of early diagnosis of the disease. Early diagnosis of the tumors can lead to more survival. Therefore, women's breast cancer awareness of signs and symptoms, screening, and education can help women in this regard.

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Footnotes

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