ORIGINAL ARTICLE

Prediction of Breast Cancer Metastasis Via Decision Tree Modeling

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Abstract

Background: Nowadays, breast cancer (BC) metastasis is a nightmare for women and one of the main challenges among researchers worldwide. Unlike traditional statistical methods that are not able to handle and take into account the complexity of effects and existence of interactions among predictor variables, the decision trees can overcome these problems. This study aimed to predict and identify the main prognostic factors of BC metastasis status (binary response) using decision tree modeling.

Methods: This retrospective cohort study was conducted on 375 patients with BC who had registered with the Comprehensive Cancer Control Center from 1998 to 2013. Some demographic features related to the conditions of the Person's disease and the type of treatment received were recorded. We applied a tree-based approach using the Gini index as the homogeneity criterion to explore the factors affecting metastasis occurrence in BC patients.

Results: The mean (SD) age of BC patients with and without metastasis was 55.7 (12.4) and 43.1 (7.2) years, respectively ($P<0.001$). The rate of metastasis was 33.3%. The five most important risk factors for metastasis of tumor proposed by tree diagram were age at diagnosis, grade of tumor, type of surgery, number of deliveries, and axillary surgery. The prediction accuracy of the proposed model was 84.3%, and its sensitivity and specificity were 66.4% and 93.2%, respectively.

Conclusion: Age at diagnosis was the most important factor for predicting breast cancer metastasis, so that breast cancer patients aged over 54 were at high risk of metastasis.

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Keywords: Breast neoplasms, Neoplasm metastasis, Decision trees, Machine learning, Risk factors

Introduction

According to the World Health Organization (WHO) report, cancer is the second major reason of death globally, and the incidence of breast cancer (BC) has had an annual increase in women all over the world, especially among Iranian women in recent decades.[1, 2] BC is one of the five most common cancers in Iran.[2] Therefore, diagnosis of BC in early stages can increase the probability of success of treatment. It is a logical and smart approach to use new methods to predict the occurrence of cancers that are not as aggressive and costly as possible. Metastasis is a well-known phenomenon in most prevalent cancers. Among BC patients, the main cause of death is metastases at distant sites.[3] The rate of metastases in BC has increased in recent years, probably due to early detection by specialized medical methods. Although advances in medical sciences ensure a bright future to treat various types of cancers, the effectiveness of diagnostic tests depends heavily on their precision and diagnosis in the early stages. Thus, prevention is always a priority in the health system of any country

because, in addition to reducing treatment costs, it helps to avoid as much as possible aggressive methods such as chemotherapy and adjuvant therapy. Moreover, identification and detection of metastasis have great importance from the clinical perspective.[4] Traditional statistical methods perform poorly in situations such as lack of normality assumption, variable selection, and evaluation of interactions as the number of predictive variables increase.[5] Thus, the old conventional methods used to analyze data usually are not able to explain both the complex relationships of the risk factors with the outcome and risk factors with each other. Nowadays, the important role of statistical methods and their undeniable position is not unknown to anyone. Despite many efforts of researchers in different disciplines for studying primary causes and treatment of BC, it seems that early prediction is of great importance, using advanced statistical methods in clinical studies. The decision tree which is known as one of the non-parametric models is a powerful algorithm, especially for classification. This data mining method divides subjects based on predetermined criteria using multiple risk factors into groups that are similar in terms of outcome occurrence. More recently, the application of decision trees in medical science has been growing.[5] Decision trees using predefined splitting criteria and based on the status of risk factors divide individuals into homogeneous subgroups (classes) according to the occurrence of the outcome.[6-8] The popularity of classification and regression trees (CART or C&RT) among researchers is due to their main characteristics and advantages such as flexibility in using different response scales; also, easy interpretation due to visual representation, especially for clinicians, leads to the creation of a user-friendly method.[9, 10] In the present research, the status of metastasis of patients with BC was evaluated after a 5-year survival period. Our main purpose in this study was to apply the decision tree method to identify important prognostic factors and prediction of metastasis as a (binary) response variable in patients with BC.

Methods

Cancer Registry

In this paper, we used the data from 375 patients with BC which were gathered in a registry-based retrospective cohort study in Tehran in 2016; the study was approved by the research council of Hamadan University of Medical Sciences. These patients had been diagnosed pathologically and followed up for 16 years; they were recorded by a comprehensive cancer control center affiliated with Shahid Beheshti University of Medical Sciences. Also, it should be noted that the data collection tool was a checklist and was extracted from medical records. More detail about study design, checklist and data were presented elsewhere.[11]

The metastasis status (1=yes, 0=No metastasis) of patients with BC of any type was considered as a binary response variable. It should be noted that this definition of metastatic status is related to 5-year survival, which means that patients are followed up for 5 years after they were diagnosed with or started treatment for a disease, and finally their metastatic status is recorded. Also, in order to identify important prognostic factors of metastasis of patients, age, marital status, education, family history of BC, smoking, history of abortion, number of abortions, use of oral contraceptive pills (OCP), hormone therapy, type of hormone, type of BC, stage of BC, recurrence of the tumor, surgical procedure (breast-conserving surgery (BCS) and modified radical mastectomy (MRM)), axillary surgery and the expression of hormone receptors (estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)) were the independent variables in the analysis. This project was approved by the Ethics Committee of Hamedan University of Medical Sciences (Approval ID: IR.UMSHA.REC.1397.377).

Statistical Methods

Descriptive statistics are reported as mean (SD) or frequency (%) for quantitative and qualitative variables, respectively. Univariate analysis was performed using chi-square test and independent T-test if the appropriate and simultaneous effect of the factors was assessed, using decision tree modeling. All the univariate statistical analyses were performed in SPSS 18.0 software and decision tree modeling was carried out, using rpart package in R 3.3.4 software. Finally, a tree diagram was drawn, and the possibility of prediction of response for new subjects was provided. A $P<0.05$ was considered statistically significant.

Results

Mean age of BC patients with metastasis was 55.7 (12.4), which was significantly higher than that in patients without metastasis 43.1)7.2(, ($P<0.001$). Also, a significant difference was observed between the two groups in terms of the number of deliveries ($P<0.001$), number of abortions ($P=0.04$), and duration of breast feeding ($P=0.003$). Moreover, there was no association between metastasis and marital status, family history of BC, smoking and history of abortion (Table 1).

Although almost 10% of patients in both groups did not undergo any surgery, patients with metastasis were more likely to undergo MRM surgery than the others (62.4% versus 31.2%, $P<0.001$). In addition, there was a significant association between BC metastasis and the grade of tumor, recurrence, auxiliary surgery, and estrogen and progesterone receptor (Table 2).

Table 1: Comparison of demographic characteristics between metastasis and non-metastasis patients

Variable	Sub group	With metastasis	Without metastasis	P-value
Age[1]	<40	12 (9.6)	75 (30.0)	<0.001
	40-59	63 (50.4)	175 (70.0)	
	60	50 (40.0)	0 (0)	
Marital status[1]	Single	8 (6.4)	23 (9.2)	0.43
	Married	116 (92.8)	222 (88.8)	
	Divorced/Widowed	1 (0.8)	5 (2.0)	
Family history of breast cancer (BC)[1]	First relatives	12 (9.6)	32 (12.2)	0.52
	Other relatives	14 (11.2)	33 (13.2)	
	No	99 (79.2)	185 (74.0)	
Education[1]	Primary	33 (26.4)	13 (5.2)	<0.001
	High school	59 (47.2)	133 (53.2)	
	Academic	33 (26.4)	104 (41.6)	
Smoking[1]	No	109 (87.2)	219 (87.6)	0.91
	Yes	16 (12.8)	31 (12.4)	
History of abortion[1]	No	81 (64.8)	182 (72.8)	0.11
	Yes	44 (35.2)	68 (27.2)	
Number of deliveries[2]		2.78 (2.06)	1.58 (1.30)	<0.001
Number of abortions[2]		0.66 (1.00)	0.46 (0.82)	0.04
Duration of Breast feeding[2]		37.95 (41.03)	25.84 (25.59)	0.003

[1]Chi-square test; [2]Independent T-test

Table 2: The results of univariate analysis for comparison between the two groups

Variable	Sub group	With metastasis	Without metastasis	P-value
Using oral contraceptive pills (OCP)[1]	No	97 (77.6)	201 (80.4)	0.53
	Yes	28 (22.4)	49 (19.6)	
Hormone therapy[1]	No	38 (30.4)	77 (30.8)	0.94
	Yes	87 (69.6)	173 (69.2)	
Type of hormone therapy[1]	Nothing	38 (30.4)	77 (30.8)	0.005
	Tamoxifen	70 (56.0)	162 (64.8)	
	other	17 (13.6)	11 (4.4)	
Grade[1]	1	6 (4.8)	28 (11.2)	<0.001
	2	50 (40.0)	142 (56.8)	
	3	69 (55.2)	80 (32.0)	
Recurrence	No	125 (100)	217 (86.8)	<0.001
	Yes	0 (0)	33 (13.2)	
Type of surgery[1]	Nothing	12 (9.6)	25 (10.0)	<0.001
	Breast-conserving surgery (BCS)	35 (28.0)	147 (58.8)	
	Modified radical mastectomy (MRM)	78 (62.4)	78 (31.2)	
Auxiliary surgery[1]	No	89 (71.2)	136 (54.4)	0.002
	Yes	36 (28.8)	114 (45.6)	
Estrogen receptor*[1]	Negative	42 (41.2)	57 (25.7)	0.005
	Positive	60 (58.8)	165 (74.3)	
Progesterone receptor*[1]	Negative	48 (47.5)	69 (31.4)	0.005
	Positive	53 (52.5)	151 (68.6)	
Human epidermal growth factor receptor 2 (HER 2)[1]	Negative	89 (71.2)	205 (82.0)	0.02
	Positive	36 (28.8)	45 (18.0)	

*Due to missing information, sample size was less than 375; [1]Chi-square test; [2]Independent T-test

Classification (decision) tree for metastasis prediction is displayed in Figure 1. In this Figure, 3 out of 7 terminal nodes indicated metastasis and age, grade, type of surgery, axillary surgery, and number of deliveries were the most important predictors in the occurrence of metastatic BC. Prediction accuracy of the proposed model was 84.3%, and its sensitivity and specificity were 66.4% and 93.2%, respectively.

Discussion

Nowadays, more than ever, special attention has been paid to common cancers in the early stages of diagnosis, so they should be the priority of the systems and public health organs. Also, it needs many activities and a global mobilization at the local, national, and international levels among all countries worldwide through planning and applying appropriate policies to decrease the huge

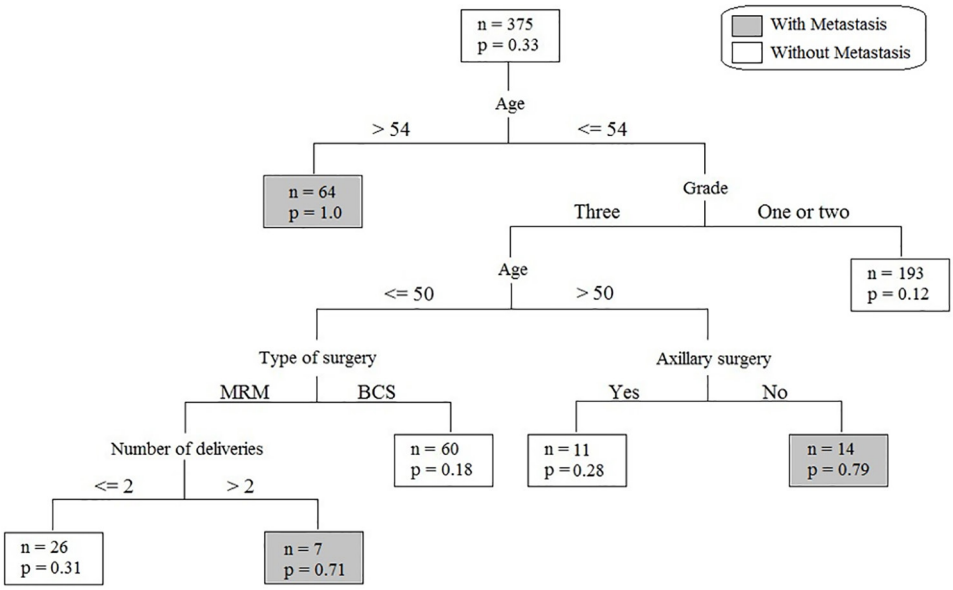

Figure 1: Classification tree for metastasis prediction; n and pare the sample size and probability of having metastases, respectively

losses and costs caused by all cancers. BC is the most common cancer in women worldwide; the leading cause of death in BC is not the primary tumor but the distant organs' metastasis.[12] In this study, the significant reasons for choosing the decision tree model among the types of models have been the simplicity of interpretation of results in the decision tree for clinicians and also lack of restrictive assumptions that exist in most of the statistical models.[5]

According to our findings, out of all factors, the age (at diagnosis), grade of BC (1, 2, or 3), type of surgery (BCS or MRM), number of deliveries, and axillary surgery were identified as the most important factors. Based on these risk factors, we constructed a more accurate, simple algorithm based on a decision tree to determine which patients are likely to develop metastasis. The findings are somewhat similar and confirm the results of previous studies. For example, in a study,[13] the auxiliary lymph node increased the risk of distant organ metastasis. Also, in some cases implicitly pointed to the effect of age on cancer metastasis. Although in many studies, age was a significant predictor, such that there was a prominent and inverse relationship between the increase in age at diagnosis and a decrease in the risk of distant metastasis to the bones.[14] Based on our findings, age with a cut-off point of 54 was the main predictor of BC metastasis, so that patients aged over 54 were at high risk of metastasis; this is reasonable because an increase in the age leads to an increased risk of metastasis. For example, according to the American Cancer Society, about 1 out of 8 invasive BCs develop in women younger than 45 and about 2 out of 3 invasive BCs are found in women aged 55 or older. In fact, these findings are consistent with those of the study by Watkins that highlighted advancing age is the most common risk factor for BC.[15] This is because the longer we live, the more the opportunities for genetic damage (mutations) in the body; actually, our bodies are less capable of repairing genetic damage. Moreover, earlier studies confirm that women over the age of 50 have a high risk of BC;[15] the overview of previous researches has shown that age is an effective factor in BC metastasis.[16, 17] Furthermore, the second most predictive factor in this study was the grade of the disease. Also, the results of a study indicated that the disease grade is an important factor in the development of BC metastasis.[18]

The overall results of this study are as follows: among people over 50 years old, if the grade of cancer is 3, the probability of metastasis increases. Based on the decision tree algorithm in Figure 1, age has played twice in the making and partitioning of the decision tree; this indicates the importance of age covariate in predicting metastasis. Similarly, the elderly patients with no history of axillary lymph node surgery had a high risk of metastasis in their cancers. In women under the age of 50 years, the type of surgery and number of deliveries had a key role in predicting BC metastasis.

As seen in Figure 1, the chance of metastasis was greater among patients who did not have maxillary surgery. In this regard, many studies have been performed to predict axillary lymph node metastasis in BC patients, which shows the importance of this factor.[19-22] Since lymph nodes have an important role in the body, especially in BC, cancer cells enter the lymph vessels and start growing in the lymph nodes. When cancer cells spread in the axillary nodes (i.e., lymph nodes under the arm), the chance of transitioning of the cells through the lymphatic system increases and metastasises to other parts of the body. On the other hand, surgery might be the only effective tool for removing the lymph nodes to find where the cancer

has spread. Therefore, it is expected that patients who have not undergone surgery will be subject to growth and proliferation outside the control of cancer cells.[23] Also, another significant factor in our study was the type of surgery including MRM and BCS, so that grade III, middle-aged patients who had undergone BCS were less likely to develop metastasis. In a study conducted in Iran, along with a description of features and situations used, it has been found, except in the early stage of BC, that surgeons prefer MRM compared to BCS.[24] Various studies have compared the effectiveness of these two surgical methods.[25-27]

In the present study, the number of deliveries was also recognized as a predictor of metastasis of BC patients. It was shown that the higher number of deliveries (or pregnancies) increased the risk of metastasis. Some studies have found a correlation between the number of deliveries and the onset of breast cancer age.[28]

Also, some studies highlight that diagnosis of BC during pregnancy or in the first postpartum year (PABC) has risks: 1) As women's childbearing is delayed, the chance of PABC increases, and 2) BC in the pregnancy period is usually detected as a palpable mass, leading to surgery as the first treatment modality and MRM being the best choice of operable disease because radiation therapy and chemotherapy increase the risk of fetal malformations.[29, 30] These results imply that our study, using a tree-based model, has been capable of clarifying and identifying important risk factors of BC metastasis.

There are several advantages and strengths in our study. First, using the tree-based model as a powerful method over other classical regression models enabled us to explore and detect an important and complex unknown relationship between the response variable (i.e., binary metastasis status) and covariates, so that effective risk factors were identified. The second strength of the study was the nature and importance of BC data, so that in recent years, extensive studies have been conducted in this area; for this reason, it can be the most important motivation for us. On the other hand, one of the limitations of this study was the fact that the sites and type of metastasis of patients were not recorded though the common sites of metastasis of BC which are the bone, brain, liver, and lung. Therefore, it is possible to identify and detect predictive factors for each type of metastasis separately.

Conclusion

It can be said that increased age leads to an increased risk of BC metastasis. Also, axillary surgeries on BC patients help to decrease the chance of metastasis.

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