Original Article
Middle East Journal of Cancer; January 2023; 14(1): 102-111

Comparison of Disease-Free Survival of Breast-Conserving Surgery and Mastectomy Using Propensity Score as Inverse Probability Treatment Weighting

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Please cite this article as: Ghavami V, Hajebi Khaniki S, Homaei Shandiz F, Akbari Sharak N. Comparison of disease-free survival of breast-conserving surgery and mastectomy using propensity score as inverse probability treatment weighting. Middle East J Cancer. 2023;14(1):102-11. doi: 10.30476/mejc.2022.91347.1623.

Abstract

Background: Survival after breast conserving surgery (BCS) vs. modified radical mastectomy (MRM) is a controversial issue. In this study, we want to compare the disease-free survival (DFS) of women who underwent BCS with those treated by MRM.

Method: In this historical cohort study, a total of 1097 women who were diagnosed with breast cancer between 2001 and 2007 and received modified MRM or BCS were entered into the study and followed up to March 2017. Kaplan-Meier estimator and extended cox model, and Cox proportional hazards model with propensity score weighting were implemented to compare overall survival between two groups.

Results: A total of 283 women with a maximum follow-up of 11.1 years and age 47.17 ± 11.278 were met the inclusion criteria. The results of the extended cox model did not show any difference between the survival of two groups ($P = 0.35$). After implementing the Cox model with propensity score weighting, the inferences remained unchanged ($P = 0.67$).

Conclusion: The patients treated with BCS tend to have the same DFS rate as those who underwent a mastectomy in a randomized controlled trial-like setting using propensity score weighting.

Keywords: Inverse probability of treatment weighting (IPTW), Breast neoplasms, Mastectomy, Modified radical, Segmental mastectomy

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Introduction

Breast cancer is the most commonly diagnosed cancer and the first cause of cancer death among females, so that there were about 2.26 million newly diagnosed female breast cancer cases worldwide in

Received: May 31, 2021; Accepted: June 29, 2022

2020.[1] In addition, breast cancer is the leading cause of cancer-related deaths among Iranian women, with a projected 16967 newly diagnosed cases in 2020.[2] Although previous trials indicated that equivalent survival rates among the patients receiving breast conserving surgery (BCS) and those having a mastectomy,[3-5] a number of studies in the USA and Europe have reported that younger patients are increasingly being treated by mastectomy.[6, 7] One of the specific characteristics of Iranian breast cancer patients is that the age-group 40-49 are the group with most incident cases and is emphasized that they are one decade younger than their western counterparts.[8-10] However, the rate of BCS in Iranian breast cancer is low compared with mastectomy.[11,12] A systematic review study reported that young women with breast cancer have conventionally been more likely to treat with BCS, compared to mastectomy, but concerns regarding recurrence may affect their choice.[13] In recent years, several other countries have compared BCS to mastectomy in breast cancer patients.[4,14-19] However, based on our knowledge, there is not any study comparing BCS and mastectomy in terms of the long-term outcomes for Iranian female patients. In most observational studies comparing the effectiveness of mastectomy versus BCS, no special measures were taken to eliminate the selection bias. For instance, early stage and younger patients are more likely to get BCS than mastectomy, which might bias the assessment of the surgical type impact. For Iranian breast cancer patients, we conducted a retrospective observational research to compare BCS with mastectomy. In order to remove selection bias, we also applied a propensity score (PS) -weighting strategy.

Materials and Methods

This historical cohort study included a total of 1097 women who were diagnosed with definitive breast cancer between 2001 and 2007 and received modified radical mastectomy (MRM) or BCS at Ghaem Hospital or Omid Hospital of Mashhad University of Medical Sciences and followed up to March 2017. Written informed consent was obtained from all patients.

In BCS, a wide local excision was done aiming to remove part of the breast containing cancer. Mastectomies were a category for extensive techniques, and MRM was the most common one in this group. Patients had adjuvant therapies after tumor excision, such as radiation, chemotherapy, and hormone therapy.[20]

We only included patients who received adjuvant radiotherapy and excluded patients whose radiotherapy dose was unknown and in stage IV. Finally, we entered 283 patients in the analysis whose treatments were completed.

Patient's visits after surgery were scheduled as follows:

- Every three months in the first post-surgery year,
- Every six months between the second and fifth year,
- Annually from the fifth year till the end of follow-up.

The database included age at diagnosis, clinical stage of cancer (based on tumor, nodes, and metastases (TNM) system), type of surgery, body mass index (BMI), progesterone receptor (PR), and estrogen receptors (ER) status.

Local recurrence, distant metastasis, or death were the primary outcomes of this study and the period of follow-up was computed from the date of surgery until the date of one of these endpoints. A patient's status is censored, if she did not encounter one of the objectives. This study was related to a research project and received approval by the Ethics Committee of the Mashhad University of Medical Sciences (ethics code: IR.MUMS.REC. 1398.0163).

Statistical analysis

In retrospective studies that use observational data, the assignment of treatment groups to research subjects is not random, so estimation of the treatment effect is along with bias. The presence of confounders between treatment assignment and observed characteristics is a motivation to use PS methods to eliminate the effects of confounding.[21, 22]

Rosenbaum and Rubin defined PS as the conditional probability of treatment assignment

Table 1. Patient and tumor characteristics stratified with surgery

Variable	All patients (n=283) Frequency (%)	BCS (n=29)	MRM (n=254)	*P*-value
Age (years)				
≤ 45	137 (48.4)	15 (51.7)	122 (48.0)	0.710
> 45	146 (51.6)	14 (43.8)	132 (52.0)	
Age	47.17 ± 11.278	45.15 ± 11.36	47.4 ± 11.268	0.310
BMI (kg/m^2)				
≤ 30	190 (67.1)	19 (65.5)	171 (67.3)	0.840
> 30	93 (32.9)	10 (34.5)	83 (32.7)	
Clinical stage				
I, II	160 (56.5)	23 (79.3)	137 (53.9)	0.009
III	123 (43.5)	6 (20.7)	117 (46.1)	
Estrogen receptor				
negative	129 (45.6)	15 (51.7)	139 (54.7)	0.760
positive	154 (54.4)	14 (48.3)	115 (45.3)	
Progesterone receptor				
negative	142 (50.2)	13 (44.8)	128 (50.4)	0.570
positive	141 (49.8)	16 (55.2)	126 (49.6)	

BMI: Body mass index, BCS: Breast-conserving surgery, MRM: Modified radical mastectomy

given the observed covariates.[23] It defines as follows:

$$e\_i=pr(z\_i=1|X\_i)$$

, where z denoting treatment variable and X is a vector of covariates. PS is estimated based on two techniques: logistic regression and generalized boosted models but logistic regression is more common and popular.

There are four different options after estimating PS for controlling confounding factors: propensity score matching (PSM), PS stratification, inverse probability weighting, and covariate adjustment based on PS.[24]

In survival data, the inverse probability of treatment weights (IPTW) based on PS minimizes bias compared with other methods of using PS. IPTW uses the PS as a weight defined as follows:

$$w\_i=Z\_i/e\_i+ ((1-Z\_i))/(1-e\_i)$$

, where e_i is the PS and Z_i is an indicator of assigning treatment (or exposure). In the weighting sample which created syntactic based on these weights, the distribution of covariates is independent of treatment assignment.[24]

This study aims to compare two surgical treatments, BCS and mastectomy. We first conducted a descriptive analysis of demographic and clinical patient's features according to the purpose. Second multivariate cox regression was used to figure out factors which affected the disease-free survival (DFS). Then PS was estimated based on logistic regression and stage and age variables, and IPTW was calculated to eliminate selection bias. Finally, we used an adjusted Kaplan–Meier estimator and weighted log-rank test based on IPTW to compare DFS among the patients receiving BCS and mastectomy. Analysis was performed by R 3.6.3 using survey, survival, and RISCA packages.[26]

Results

Out of 283 patients who met the basic inclusion criteria, 29(10.2) had BCS (89.8), and 254 had MRM. Of those, according to TNM staging, 160 were in the early stage (stage I and II). The mean age in the MRM group was higher than BCS. The mean age for BCS was 45.15 ± 11.36 years compared with 47.4 ± 11.268 years for the MRM group. In the BCS group, 51.7 % were with negative ERs, and 55.2% were with positive PR. In general, 67.1% of patients were not obese, and 3.9% were in the obesity range. BCS and MRM groups were compared using Pearson chi-square tests for categorical variables and a t-test for age. In general, patients who were older and in a higher stage were more likely to undergo MRM compared with BCS (Table 1).

The longest period of follow-up was 11.1 years. If a patient failed to be followed up after being diagnosed within this time, they were censored. The average number of years without an illness was 3.4. Comparison of DFS between BCS and MRM groups were done using the log-rank test

Table 2. Analysis of factors associated with disease free survival using multivariate Cox regression and tests of proportionality hazard

Variable	Multivariate Cox Beta (SE)	HR	95 % CI for HR	*P*-value	*P*-value for proportionality hazard assumption
Clinical stage					
I/II	Reference	-	-		
III	0.42 (0.22)	1.52	(1.09-3.092)	0.05	0.010
Age					
≤ 45	Reference	-	-		
>45	-0.29 (0.22)	0.74	(0.49- 1.14)	0.17	0.920
BMI					
≤ 30 (kg/m^2)	Reference	-	-		
>30 (kg/m^2)	0.09 (0.24)	1.11	(0.69-1.75)	0.67	0.810
ER					
Positive	Reference	-	-		
Negative	-0.03(0.27)	0.96	(0.56-1.65)	0.89	0.840
PR					
Positive	Reference	-	-		
Negative	0.22 (0.27)	1.24	(0.73-2.1)	0.42	0.970
Surgery					
BCS	Reference				
MRM	-0.35(034)	0.71	(0.36-1.39)	0.32	0.440

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; BCS: Breast-conserving surgery; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor

and Kaplan-Meier estimator plot (Figure 1). The result of the log-rank test showed no difference in the survival of the two groups ($P = 0.31$).

Cox regression was implemented to find out covariates related to DFS time, and the proportionality hazard assumption was checked using the test of correlation between Schoenfeld residuals and survival time (Table 2). This

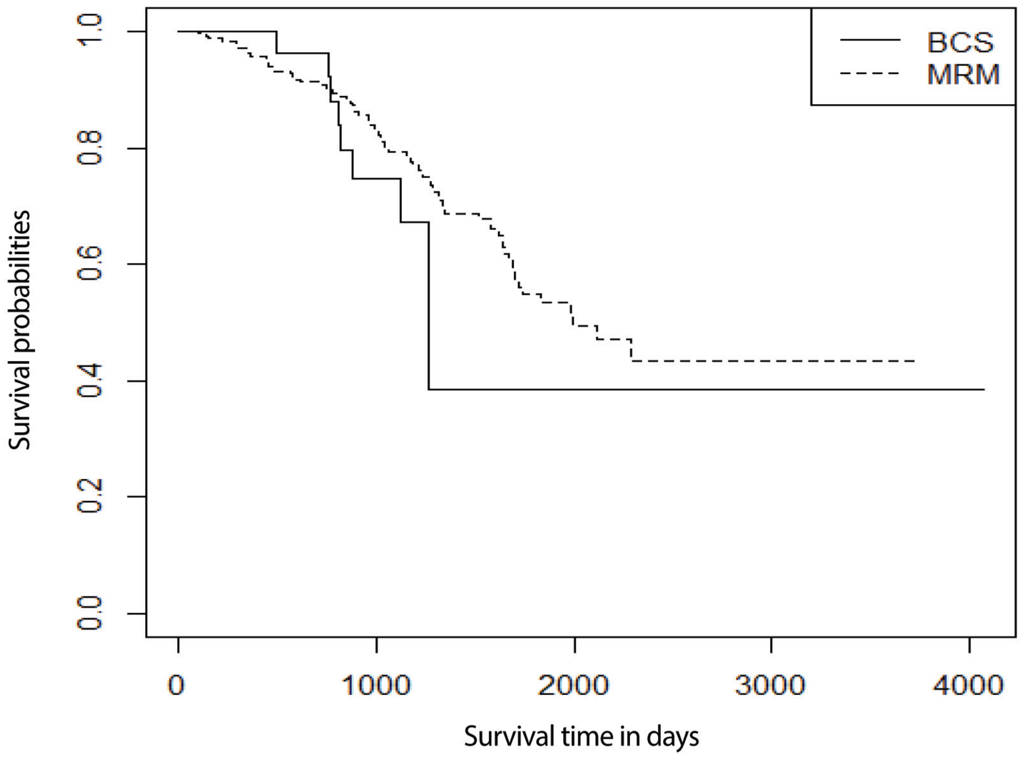

Figure 1. This figure shows the Kaplan-Meier survival estimator plot for the surgery variable.
BCS: Breast-conserving surgery, MRM: Modified radical mastectomy

assumption just was violated for the stage of disease covariate. There are two options available in this situation: an extended Cox model or a stratified Cox model. An extended Cox with Heaviside function was used to calculate a hazard ratio since, unfortunately, stratified Cox does not allow us to evaluate the stratified variable and produce a hazard ratio. To select a logical cut point for Heaviside function, the Kaplan Meier estimator was plotted and evaluated (Figure 2). Two curves were much closer together at earlier times until around 1600 days and after this time they diverged, so a choice for the Heaviside function threshold was 1600 days. In general, this plot showed that patients in the early stages had higher survival compared with patients in the advanced stage.

Association between DFS time and covariates was investigated by implementing the extended Cox regression (Table 3). The results showed no significant association between MRM and BCS (P = 0.35). For the stage of the disease, there were two hazard ratios one for above 1600 days and the other for below 1600 days. The results showed a non-significant hazard ratio (P = 0.43) for the effect of stage of the disease before 1600 days and a highly significant (P = 0.006) hazard ratio when the follow-up time was beyond 1600 days. It means that after 1600 days the hazard of event for the patients in advanced stage (stage III) was 5.02 times of those in an early stage, while this hazard before 1600 days was 1.21 times and was not significant.

As patients with advanced stage and older age preferred to have mastectomy rather than BCS, these two factors were included to the multivariate logistic regression as predictors with BCS as the outcome to estimate PS, followed by IPTW, a PS

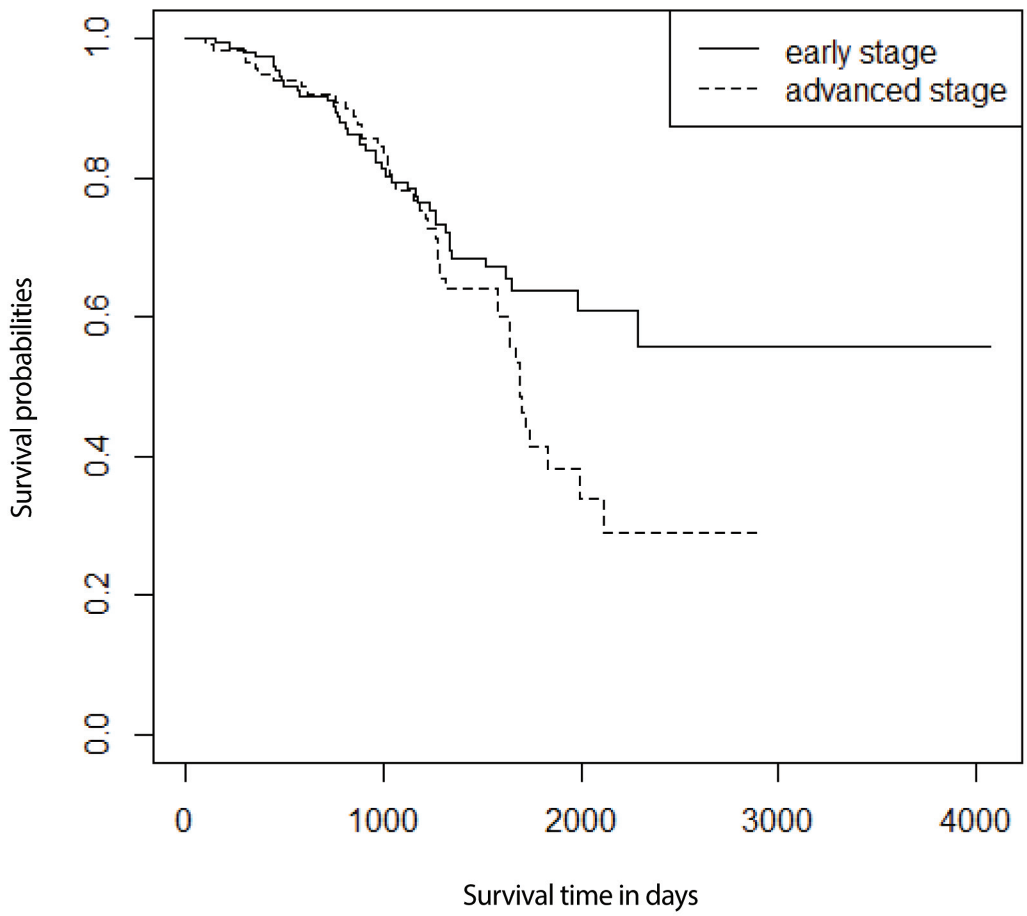

Figure 2. This figure shows the Kaplan-Meier survival estimator plot for the clinical stage variable.

technique computed to account for confounders. We implemented Cox model with IPTW adjustment to evaluate BMI, ER, PR, and surgery type effects on DFS time. None of the covariates were statistically significant in the model (Table 4). According to the results, the patients with MRM had lower hazard to experience failure than women with BCS but this difference was not considered significant (*P*-value= 0.67). An adjusted Kaplan-Meier estimator was plotted and adjusted log-rank test was applied to compare BCS and MRM (Figure 3). The plot showed that women who underwent MRM had a higher risk of failure in the first three years following surgery, but between the third and fifth years after surgery, the survival of the MRM group increased, and after the fifth year, the survival of this group gradually decreased and then stabilized. Despite these modifications, there was no discernible difference between the two groups according to the log-rank test (*P* = 0.86).

Discussion

This study intended to estimate and compare the DFS of the patients diagnosed with breast cancer undergoing either BCS or modified radical mastectomy. To meet the objective of this research, we used a hospital-based breast cancer dataset. Inverse probability of treatment weights based on PS was used to tackle the problem of the effects of confounding variables in this observational study. The influence of the kind of medication used for treatment on DFS together with demographic and clinical factors was examined using two distinct forms of Cox regression with and without the IPTWs. According to the age and tumor stage of the patients, the PS were determined. Using the inverse probability

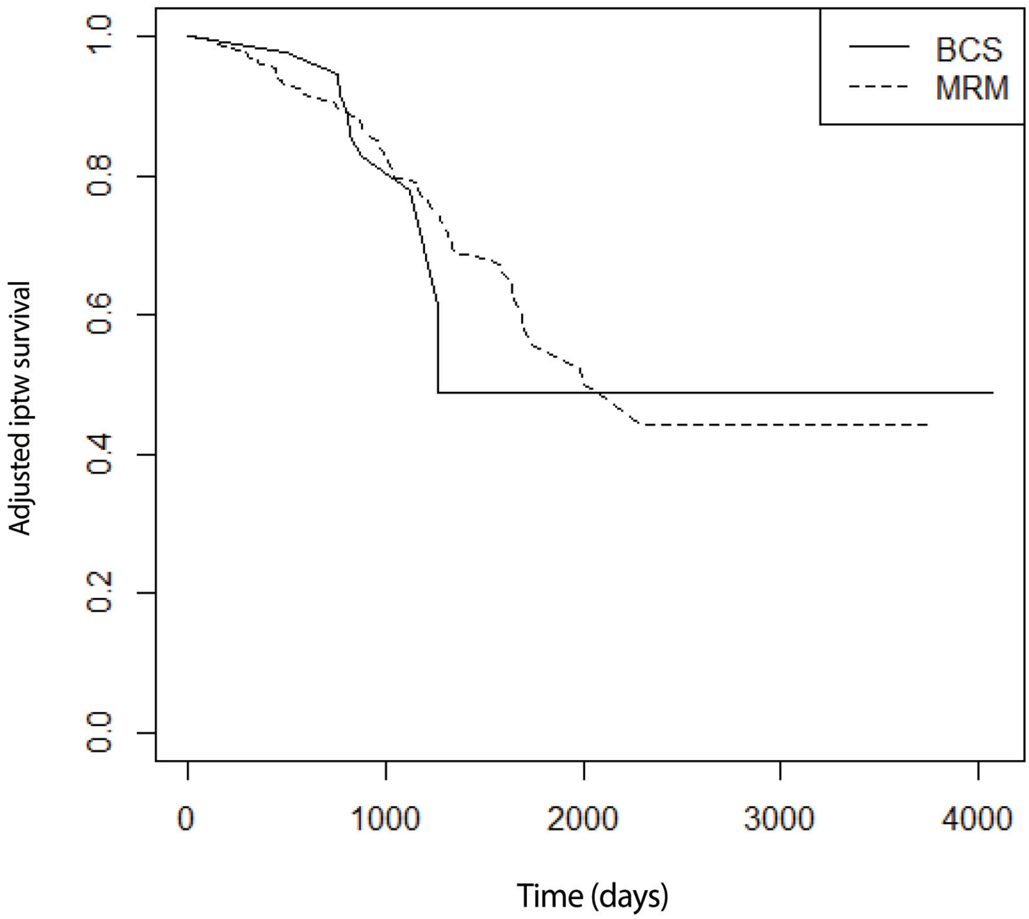

Figure 3. This figure shows the adjusted Kaplan- Meier estimator for the surgery variable.
BCS: Breast-conserving surgery, MRM: Modified radical mastectomy

Table 3. Extended cox with Heaviside function with cut point at 1600 days

Variable	Beta (SE)	HR	*P*-value
BMI			
≤ 30 (kg/m^2)	Reference	-	
>30 (kg/m^2)	0.07 (0.23)	1.08	0.760
ER			
Positive	Reference	-	
Negative	-.02 (0.27)	0.98	0.930
PR			
Positive	Reference	-	
Negative	0.21 (0.27)	1.24	0.370
Operation			
BCS	Reference		
MRM	-0.26 (0.34)	0.76	0.350
Stage*h1	0.19 (0.24)	1.21	0.430
Stage* h2	1.61 (0.58)	5.01	0.006

SE: Standard error; HR: Hazard ratio; BMI: Body mass index; BCS: Breast-conserving surgery; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor; h1, h2 are Heaviside functions define as bellow: $h1(t)=\{1(1, t \leq 1600\ \ 0,\ x \geq 1600)$; $h2(t)=\{1(1, t \geq 1600\ \ 0,\ x < 1600)$

of treatment weighting multiple Cox regression, our study revealed that the DFS rates of BCS and mastectomy patients were not significantly different after a median of 3.5 years.

The main finding of this study is in line with the general consensus that BCS and MRM patients have similar long-term survival rates.[5] The result of the study of Sinnadurai et al.[15] indicated that while BCS was significantly associated with favorable prognostic features, the five-year overall survival was not significantly different for patients who were treated through BCS or mastectomy. They ran the stratified Cox regression based on PS in 20 quantiles to ensure the elimination of confounding effects. However, the Inferences remained unchanged following PS analysis. In the research by Wrubel et al., the patients were matched using a 1 to 1 closest neighbor approach, and the PS were calculated using race, age, tumor location, laterality, histology, grade, and several other tumor-related characteristics. They came to the conclusion that BCT had a better 5-year overall survival rate than mastectomy.[26] The mentioned study modeled I/II stages patients, though we have not excluded the stage III patients from the analysis. The finding of Wang et al. who applied the weighting PS matching to adjust for tumor biology and therapy supports the better outcome of BCS over mastectomy.[27] But, they just examined the stage I patients.

However, some studies which compared the survival of patients who underwent BCS and mastectomy using the national cancer registry data did not use the PS matching methods.[28, 29] Patients in the higher stages of cancer were more prone to receive the mastectomy over BCS, which might justify the superior survival for BCS compared to mastectomy. In addition, a recent study that was conducted as a 6-year national follow-up study in Sweden suggested that patients who underwent BSC followed by radiotherapy would live longer than those who underwent mastectomy followed by radiotherapy, even after controlling for previously unmeasured confounders.[30] To add more, the result of a large cohort study in California resulted that patients who undertook BCS had significantly improved overall survival when compared with women treated with mastectomy. However, the result was not stable in subgroup analysis based on age and hormone receptor status.[31]The contradiction among our results and theirs might be in terms of different methods of adjustment and not using the PS matching techniques.

While clinical confirmation of DFS rate in the patients who underwent BCS or MRM is almost based on randomized controlled trials, it does not apply to community practice where patients are not selectively assigned to treatments that are not in concordance with a controlled, clinical trial environment. Researchers have traditionally used multiple models to account for patient character-

Table 4. Multivariate Cox regression adjusted with IPTW that calculated based on stage and age

Variable	Beta (SE)	HR	95 % CI for HR	*P*-value
BMI				
≤ 30 (kg/m^2)	Reference	-	-	
>30 (kg/m^2)	0.51 (0.23)	1.7	(0.78 - 3.50)	0.18
ER				
Positive	Reference	-	-	
Negative	-0.14 (0.30)	0.67	(0.33 - 1.33)	0.24
PR				
Positive	Reference	-	-	0.83
Negative	-0.07 (0.29)	0.93	(0.47 - 1.81)	
Operation				
BCS	Reference			
MRM	-0.18 (.24)	0.83	(0.36 - 1.92)	0.67

SE: Standard error; HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; BCS: Breast-conserving surgery; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor; IPTW: Inverse probability of treatment weighting

istics' adjustment; however, they are now turning to PSM and IPTW because of the stronger theoretical basis of these methods.[20, 32] In this study, the age and stage of disease were considered as factors affecting the choice of BCS or MRM. Firstly, the two variables were considered important in terms of the surgeon's opinion. However, the relationship between the tumor stage and treatment type was also statistically significant. Based on the result of Martin et al.[33] and Al–Gaithy et al,[34] patients with small tumors were are likely to have BCS, whereas patients who have moderate to large-sized tumors and are aged 60 years or older are likely to have mastectomy which was similar to our result. However, in the study of Al–Gaithy the positive HER2 and triple-negative receptor status were also significantly correlated with mastectomy. Moreover, Koksalmis et al.[35] showed that the most important factors affecting the surgeons' choice were post-operative process-related factors, especially the demand for esthetic appearance and conversely, the least significant criteria were tumor-related factors. According to the result of a nationwide study done by Machuca et al.[36] number of affected lymph nodes, tumor size, and location were determinants of BCT, while the histological type was not significant. In conclusion, the majority of the studies supported our conclusions about the important factors that can influence the treatment decision. However, we were unable to utilize many of the missing data for other factors, such as tumor size, and histology.

One of our limitations in this study was high rate of missing in many variables which forced us to omit those probably important variables out of the study. For instance, there may be some other variables which could be potentially regarded in the IPTW analysis, but we could not apply them. Second, because of its retrospective nature, this study is not adequate to conclusively prove that BCS is not superior to mastectomy.

The strength of our study is that it investigated the DFS of patients after BCS compared to MRM according to individualized patient risk factors. One of the study's weaknesses is that although we were able to adjust for certain confounders, we were unable to account for the potential of unmeasured variables. In the meanwhile, we think there is a minimal risk of bias because unmeasured confounding since we have taken into account the main source of confounding (age and stage of tumor).

Conclusion

Our retrospective cohort study of female patients with breast cancer showed that breast-conserving treatment was not related to improved DFS compared with mastectomy.

Acknowledgments

This study was supported by the Student Research Committee of Mashhad University of Medical Sciences, Mashhad, Iran (Project No. 980163).

Conflict of Interest

None declared.

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