Breast Cancer: Targets and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Is Breast Conserving Surgery Efficacious in Breast Cancer Patients with *BRCA1* or *BRCA2* Germline Mutation?

Selman Emiroglu[1], Enver Özkurt[2], Neslihan Cabıoglu[1], Abdullah Igci[3], Pinar Saip[4], Hulya Yazici[4], Tolga Ozmen[5], Vahit Ozmen[1], Mahmut Muslumanoglu[1], Mustafa Tukenmez[1]

[1]Breast Surgery Unit, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey; [2]Department of Surgery, Ozel Basari Hospital, Istanbul, Turkey; [3]Department of Surgery, American Hospital, Istanbul, Turkey; [4]Department of Medical Oncology, Institute of Oncology, Istanbul University, Istanbul, Turkey; [5]Division of Gastrointestinal and Oncologic Surgery, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

Correspondence: Selman Emiroglu, Breast Surgery Service, Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Fatih, Istanbul, 34390, Turkey, Email selman.emirikci.82@istanbul.edu.tr

Breast Cancer: Targets and Therapy downloaded from https://www.dovepress.com/ on 20-Mar-2023
For personal use only.

Background: The optimal surgical therapy for newly diagnosed breast cancer with germline mutations in susceptibility genes is still uncertain for many physicians. In this study, we aimed to determine the efficacy of breast conserving surgery (BCS) in breast cancer patients with *BRCA1* or *BRCA2* mutation by assessing its outcomes and locoregional recurrence (LR) rates.

Materials and Methods: Seventy-five patients operated with BCS or mastectomy for breast cancer between 2006 and 2017 and had *BRCA1* or *BRCA2* mutation were included in the study. Effects of the performed breast surgery and clinicopathological characteristics on surgical outcomes, LR rates and survival were analyzed with showing the distribution of *BRCA1* and *BRCA2* germline mutations.

Results: The median age of the patients was 42 years (20–77). *BRCA1* mutations were found in 46 (61.3%) patients and *BRCA2* mutations in 29 (38.7%) patients. Compared to *BRCA2* carriers, *BRCA1* carriers were more likely to have higher tumor grade (84.8% vs 44.8%; $p = 0.001$) and non-luminal subtype tumors (67.4% vs 13.8%; $p = 0.001$). A total of 44 (58.7%) patients underwent unilateral mastectomy and 31 (41.3%) patients underwent BCS. At a median follow-up time of 60 (12–240) months, LR was observed in 6 patients equally divided in both BCS and mastectomy groups. LR rates were slightly higher after BCS versus mastectomy (9.7% and 6.8%, respectively). Additionally, there were no statistically significant differences in disease-free survival (DFS) and disease-specific survival (DSS) rates after 10 years in the BCS group versus the mastectomy group ($p = 0.117$ and 0.109, respectively), but in fact, the rates were better in the BCS group.

Conclusion: Our findings indicate that BCS may serve as an efficacious alternative to mastectomy for breast cancer patients with *BRCA1* or *BRCA2* mutation. Additionally, tumor size, lymph node positivity, and TNM stage should be taken into consideration for a better surgical decision-making.

Keywords: *BRCA1* or *BRCA2* germline mutation, breast conserving surgery, surgical decision, locoregional recurrence

Introduction

Breast cancer (BC) is the most prevalent cancer among women worldwide.[1] Approximately, 5–10% of BC cases are hereditary.[2] *BRCA1* (Breast Cancer 1 gene) and *BRCA2* (Breast Cancer 2 gene) are malignancy associated tumor suppressor genes that account for 80% of the highly penetrant inherited BC cases.[3] *BRCA* mutations are associated with hereditary breast and ovarian cancer syndrome. Researchers have reported that *BRCA* mutation carriers have a life-time risk of BC up to 69–72%, and they have a 10 to 30 times higher risk of developing ovarian cancer compared to the normal population.[4]

The integration of genetics tests into the care of cancer patients leads the physicians to use the results of germline mutations in breast cancer susceptibility genes for making a better treatment decision.[5] Several studies identified that

Received: 18 November 2022
Accepted: 8 February 2023
Published: 21 February 2023

© 2023 Emiroglu et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

early-stage BC patients who were treated with BCS at a young age had an increased likelihood of ipsilateral breast tumor recurrence after BCS that followed by radiotherapy (BCT).[6,7] Family history of BC, genetic predisposition for BC (ie *BRCA1* and *BRCA2* mutations) or other risk factors are more likely to be in the young BC patients, confounding the role of age and treatment in the clinical outcomes.[8] As reported in national comprehensive cancer network clinical practice guidelines for breast cancer, version 3.2022, overall survival (OS) outcomes of BCT or mastectomy for young BC patients are similar and some studies showed improved survival and lesser post-surgical complications with BCS.[7]

Choosing the appropriate surgical approach for BC patient with *BRCA* mutation requires consideration of several questions; what is the efficacy of BCS versus mastectomy? Is BCS associated with a higher risk of locoregional recurrence (LR)? What is the risk of contralateral cancer? Is contralateral prophylactic mastectomy beneficial for survival?

This study aimed to determine the efficacy of BCS in BC patients with *BRCA1* or *BRCA2* mutation by assessing its outcomes and LR rates and to provide answers to the questions asked above. Thereby allowing better surgical decision-making.

Materials and Methods

Patient Selection and Ethical Approval

Between 2006 and December 2017, 5750 patients were diagnosed with BC at Istanbul University's Istanbul Faculty of Medicine, General Surgery, Division of Breast Surgery, and *BRCA1* and *BRCA2* genetic tests were performed on 450 patients. In this study, the demographic and clinicopathological data of 75 patients were analyzed. This study has been approved by Istanbul University's Istanbul Faculty of Medicine (2022/1948). All patients were informed about the study's purpose, content, and intervention, and their oral and written consent was obtained.

All patients were *BRCA1* and/or *BRCA2* mutation carriers with small insertion/deletion mutations or rearrangements in *BRCA1* and *BRCA2*. The genetic test results were abstracted from electronic medical records. Genetic tests were performed at the Cancer Genetics Department at Istanbul University's Oncology Institute. *BRCA1* and *BRCA2* genes were screened for mutations in fragments between 197 and 823 bp length for Sanger Sequencing and about 450 bp length for NGS using a Multiplicome BRCA MASTR Dx Kit, which has a CE-IVD certificate in the MiSeq Illumina Platform. Rearrangements in *BRCA1* and *BRCA2* were evaluated by using both the MiSeq NGS platform and multiplex ligation-dependent probe amplification (MLPA) analysis.

Patients Evaluation and Data Collection

Patients were evaluated for demographic characteristics, surgery type, clinicopathological characteristics (surgical margin status, stage, molecular subtype, hormone receptor status, HER2/neu status, etc.), adjuvant and neoadjuvant treatments (chemotherapy, radiotherapy, and hormonal therapy), follow-up time, OS, disease-free survival (DFS) and disease-specific survival (DSS). Patients were followed-up closely, and physical examination findings were recorded at each visit. Dates of death and causes of death were recorded in accordance with the data received from the hospital records and patients' relatives. LR is defined as a recurrence in the ipsilateral breast/chest wall or regional nodal basin, contrary to the distant site, whereas, local recurrence is a recurrence in the breast.

Each case of BC with *BRCA* mutation was re-reviewed by a dedicated breast pathologist at our institution to confirm the histologic diagnosis. Estrogen receptor (ER), progesterone receptor (PR), HER2/neu and Ki-67 positivity were assessed using immunohistochemistry (IHC). The histologic classification was based on WHO criteria and histologic grade in the Nottingham system. ER and PR were considered positive if ≥1% cells showed nuclear staining. Cases were considered HER2/neu- positive when they are IHC-3+ or SISH (Silver in situ hybridization)-amplified. The staging was made according to the American Joint Committee on Cancer (7th edition).[9]

Clear margins were required for BCS; a frozen section diagnosis was performed to judge whether the margins were clear. Patients who underwent BCS and mastectomy and have a large tumor (ie, >5 cm) and/or 4 positive lymph nodes are referred for radiotherapy, whereas patients with 1 to 3 positive lymph nodes may receive radiotherapy if they have other high-risk factors. All patients have been discussed in the multidisciplinary meetings by surgeons, radiologists,

pathologists, genetic counselors, radiation and medical oncologists. Based on the decision in the multidisciplinary meetings, patients may receive neoadjuvant or adjuvant chemotherapy or endocrine therapy depending on tumor clinicopathologic characteristics and clinical stage.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program (version 25.0, IBM Corp., Armonk, NY, USA). Descriptive statistical methods (eg, number, percentage, median) were also used. Kaplan–Meier analysis was used to calculate survival rates. In two-tailed univariate analyses, each parameter was tested using Fisher's exact test or the chi-square test to assess the associations of documented variables between *BRCA1* and *BRCA2* carriers depending on the surgical technique. OS was not analyzed because there were no deaths due to non-cancer causes. The effects of various prognostic factors related to tumors and patient characteristics on DFS and DSS were investigated using the Log rank test. In all statistical analyses, a *p*-value of 0.05 was considered significant.

Results

Patients and Tumors General Characteristics

The median age of the patients was 42 years (20–77 y). There was no statistically significant difference in the age distribution of the patients based on *BRCA1* or *BRCA2* mutation ($p = 0.443$). Most patients had invasive ductal carcinoma (73.3%), tumor stage II and III (78.7%) and grade III tumors (69.3%). Moreover, 26.7% of patients had multicentric tumors and 45.3% had LVI. Axillary positivity was present in 49.3% of the patients. *BRCA1* patients group had a significantly higher rate of grade III tumors (84.8% vs 44.8%; p=0.001) (Table 1).

Table 1 Demographics and Clinicopathologic Characteristics of BRCA1 and BRCA2 Mutation Carriers

Variables	Category	Total (n:75)	BRCA1(+) (n:46)	BRCA2(+) (n:29)	p-value
		n(%)	n(%)	n(%)	
Median Age (Min.-Max) year	**Total**	42(20–77)	43(25–77)	41(20–58)	0.443
Age	≤40	32(42.7)	18(29.1)	14(48.3)	0.589
	>40	43(57.3)	28(60.9)	15(51.7)	
Age	≤50	57(76)	33(71.7)	24(82.8)	0.406
	>50	18(24)	13(28.3)	5(17.2)	
Family history of breast cancer	First-Degree	14(18.7)	8(17.4)	6(20.7)	0.474
	Second- or Third-Degree	26(34.7)	14(30.4)	12(41.4)	
	Negative	35(46.7)	24(52.2)	11(37.9)	
Family history of other cancer	GIT	16(21.3)	6(13)	10(34.5)	**0.041***
	Other	8(10.7)	7(15.2)	1(3.4)	
	Negative	51(68)	33(71.7)	18(62.1)	
Tumor type	IDC	55(73.3)	36(78.3)	19(65.5)	0.344
	Other	20(26.7)	10(21.7)	10(34.5)	

(*Continued*)

Table 1 (Continued).

Variables	Category	Total (n:75)	BRCA1(+) (n:46)	BRCA2(+) (n:29)	p-value
		n(%)	n(%)	n(%)	
pT Stage	I	16(21.3)	9(19.6)	7(24.1)	0.856
	II–III	59(78.7)	37(80.4)	22(75.9)	
N Stage	N-	38(50.7)	24(52.2)	14(48.3)	0.927
	N+	37(49.3)	22(47.8)	15(51.7)	
Grade	I–II	23(30.7)	7(15.2)	16(55.2)	**0.001***
	III	52(69.3)	39(84.8)	13(44.8)	
Multicentricity	Single	55(73.3)	36(78.3)	19(65.5)	0.344
	Multiple	20(26.7)	10(21.7)	10(34.5)	
LVI	Yes	34(45.3)	20(43.5)	14(48.3)	0.866
	No	41(54.7)	26(56.5)	15(51.7)	
In-situ component	Yes	48(64)	30(65.2)	18(62.1)	0.976
	No	27(36)	16(34.8)	11(37.9)	
Surgical approach	BCS	31(41.3)	20(43.5)	11(37.9)	0.815
	Mastectomy	44(58.7)	26(56.5)	18(62.1)	
Contralateral prophylactic mastectomy (n:44)	Yes	12(27.3)	6(23.1)	6(33.3)	0.684
	No	32(72.7)	20(76.9)	12(66.7)	
Prophylactic TAH-BSO	Yes	14(18.7)	9(19.6)	5(17.2)	0.999
	No	61(81.3)	37(80.4)	24(82.8)	
Molecular subtype	Luminal A-B/ HER2(-)	31(41.3)	10(21.7)	21(72.4)	**<0.001***
	Luminal B/ HER2(+)	9(12)	5(10.9)	4(13.8)	
	Non luminal B/ HER2 (+)	17(22.7)	16(34.8)	1(3.4)	
	Triple negative	18(24)	15(32.6)	3(10.3)	
Molecular subtype	Luminal	40(53.3)	15(32.6)	25(86.2)	**<0.001***
	Non luminal	35(46.7)	31(67.4)	4(13.8)	

Note: *p<0.05; Chi-Square Tests (Pearson Chi-Square. Continuity Correction. Fisher's Exact Test), in bold.
Abbreviations: pT, pathologic tumor; N, node; GIT, gastrointestinal tract; IDC, invasive ductal carcinoma; BCS, breast conserving surgery; LVI, lymphovascular invasion; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Thirty-five (46.7%) patients had no family history of BC, 14 (18.7%) patients had a first-degree family history and 26 (34.7%) patients had second- or third-degree family history. *BRCA2* carriers were more likely to have a family history of gastrointestinal tract (GIT) cancer ($p = 0.041$) (Table 1).

Hormone Receptor Status

According to the molecular subtype classification, 41.3% of the tumors were luminal A-B, 12% were luminal-HER2 positive, 22.7% were non-luminal HER2 positive and 24% were triple negative. *BRCA2* mutation carriers were more

likely than *BRCA1* mutation carriers to have hormone receptor positivity and luminal molecular subtypes (86.2% vs 32.6%, respectively; $p<0.001$) (Table 1).

Surgical Treatment Strategy in Patients

As it shown in Figure 1, 31 patients had BCS (41.3%) and 44 (58.7%) patients underwent unilateral mastectomy. Of the *BRCA1* mutation carriers, 43.5% had BCS and 56.5% had unilateral mastectomy, whereas 37.9% of *BRCA2* mutation carriers had BCS and 62.1% had unilateral mastectomy ($p=0.977$). Contralateral prophylactic mastectomy was performed in 27.3% (12/44) of the patients who underwent mastectomy, 6 patients had *BRCA1* mutation and 6 patients had *BRCA2* mutation ($p=0.684$). Bilateral salpingo-oophorectomy (BSO) ± total abdominal hysterectomy (TAH) was performed in 18.7% (14/75) of all patients, 9 patients had *BRCA1* mutation and 5 patients had *BRCA2* mutation ($p=0.999$) (Table 1).

Patient's Follow-Up, OS and Recurrences

At a median follow-up period of 60 (12–240) months. The overall mortality rate was 9.3% (n = 7) and all the seven patients died from cancer causes. LR was observed in 6 patients, 2 had *BRCA1* mutation and 4 had *BRCA2* mutation. Three LRs were observed in each BCS and mastectomy groups. Five patients were under the age of 50 years, and one was over. In addition, 5 patients had grade III tumors. None of the 6 patients underwent prophylactic TAH-BSO. Four patients received adjuvant chemotherapy, while 2 received neoadjuvant chemotherapy. In both *BRCA1* and *BRCA2* mutation carriers, there were no statistically significant differences in loco-regional, distant, or contralateral recurrence with respect to several clinicopathological features ($p>0.05$) (Table 2).

The 6 LR that were observed were as follows: 3 local recurrences (only in the breast), 1 thoracic (pectoral muscle) recurrence and 2 axillary recurrences. In the BCS group, LR was detected in 2 triple negative patients. Systemic metastasis was observed in one patient with a triple negative molecular subtype. Of the 3 LRs seen in the BCS group, 2 were detected within the first 10 years and one was detected after 10 years. Although the surgical margins of 3 patients were negative with local recurrence after BCS, the closest surgical margin in one patient was less than 1 mm and one patient was multicentric (Table 3). Moreover, in the 6 cases with LRs in, there was no significant difference between BCS and mastectomy in terms of recurrence site, LR interval, systemic metastasis rate or systemic metastasis interval.

Patient's DFS and DSS

However, LR rates were slightly higher in *BRCA1* and *BRCA2* mutation carriers who underwent BCS than in those who underwent mastectomy (9.7% and 6.8%, respectively). Moreover, 10-year DFS and DSS rates between the BCS and mastectomy groups were closer and the rates were slightly better in the BCS group. In univariate analysis, patients with tumor grade I or II and luminal subtypes had improved DSS rates ($p = 0.030$ and 0.044, respectively), whereas patients

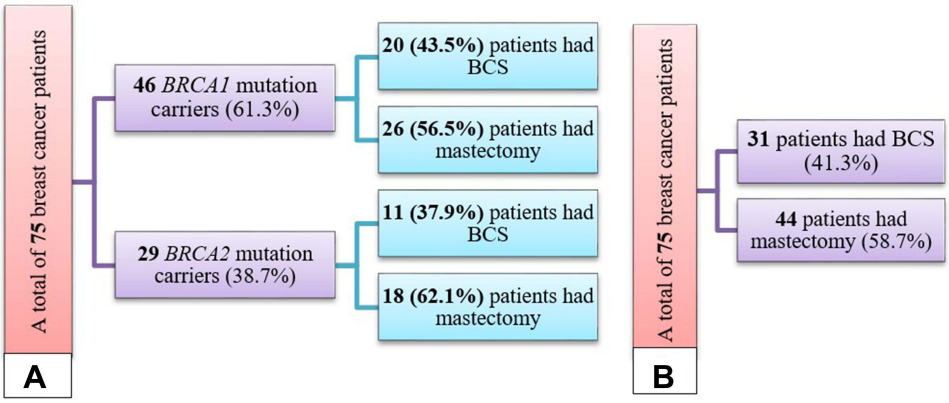


Figure 1 (**A**) All patients' distribution according to *BRCA1* or *BRCA2* mutation carrying and surgical treatment strategy. (**B**) All patients' distribution according to the surgical treatment strategy.

Table 2 Comparison of the Locoregional, Distant and Contralateral Recurrence and Several Clinicopathological Features in *BRCA1* and *BRCA2* Positive Breast Cancer Patients

Variables	Category	All	Loco-Regional Recurrence		Distant Recurrence		Contralateral Recurrence	
		n	n(%)	*p*-value	n(%)	*p*-value	n(%)	*p*-value
Age	≤50	57	5(8.8)	0.999	8(14)	0.719	6(10.5)	0.326
	>50	18	1(5.6)		3(16.7)		0(0)	
Family history of BC	First-Degree	14	3(21.4)	0.117	1(7.1)	0.665	2(14.3)	0.606
	Second- or Third-Degree	26	1(3.8)		4(15.4)		2(7.7)	
	Negative	35	2(5.7)		6(17.1)		2(5.7)	
***BRCA* genetic mutation**	*BRCA1*	46	2(4.3)	0.198	7(15.2)	0.999	4(8.7)	0.999
	BRCA2	29	4(13.8)		4(13.8)		2(6.9)	
Tumor type	IDC	55	4(7.3)	0.654	9(16.4)	0.717	4(7.3)	0.654
	Other	20	2(10)		2(10)		2(10)	
pT Stage	I	16	1(6.3)	0.999	2(12.5)	0.999	0(0)	0.331
	II–III	59	5(8.5)		9(15.3)		6(10.2)	
N Stage	N-	38	2(5.3)	0.430	5(13.2)	0.754	4(10.5)	0.674
	N+	37	4(10.8)		6(16.2)		2(5.4)	
Grade	I–II	23	1(4.3)	0.660	1(4.3)	0.156	2(8.7)	0.999
	III	52	5(9.6)		10(19.2)		4(7.7)	
Multicentricity	Single	55	3(5.5)	0.333	6(10.9)	0.150	4(7.3)	0.654
	Multiple	20	3(15)		5(25)		2(10)	
LVI	Presence	34	3(8.8)	0.999	4(11.8)	0.745	1(2.9)	0.212
	Absence	41	3(7.3)		7(17.1)		5(12.2)	
In-situ component	Presence	48	4(8.3)	0.999	6(12.5)	0.511	5(10.4)	0.410
	Absence	27	2(7.4)		5(18.5)		1(3.7)	
Molecular subtype	Luminal	40	3(7.5)	0.999	4(10)	0.328	4(10)	0.679
	Non luminal	35	3(8.6)		7(20)		2(5.7)	
Surgical approach	BCS	31	3(9.7)	0.687	2(6.5)	0.110	3(9.7)	0.687
	Mastectomy	44	3(6.8)		9(20.5)		3(6.8)	
Contralateral prophylactic mastectomy (n=44)	Positive	12	0(0)	0.551	2(16.7)	0.999	0(0)	0.551
	Negative	32	3(9.4)		7(21.9)		3(9.4)	
Prophylactic TAH-BSO	Positive	14	0(0.0)	0.586	1(7.1)	0.678	1(7.1)	0.999
	Negative	61	6(9.8)		10(16.4)		5(8.2)	

(*Continued*)

Table 2 (Continued).

Variables	Category	All	Loco-Regional Recurrence		Distant Recurrence		Contralateral Recurrence	
		n	n(%)	*p*-value	n(%)	*p*-value	n(%)	*p*-value
Chemotherapy	No	5	0(0)	0.788	0(0)	0.336	1(20)	0.545
	Neoadjuvant	22	2(9.1)		5(22.7)		2(9.1)	
	Adjuvant	48	4(8.3)		6(12.5)		3(6.3)	
Radiotherapy	No	10	0(0)	0.999	3(30)	0.158	0(0)	0.999
	Yes	65	6(9.2)		8(12.3)		6(9.2)	

Note: p<0.05; Chi-Square Test (Pearson Chi-Square. Continuity Correction Fisher's Exact Test).
Abbreviations: pT, pathologic tumor; N, node; IDC, invasive ductal carcinoma; BCS, breast conserving surgery; LVI, lymphovascular invasion; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

with unicentric tumors had high DFS rates (p = 0.045). Additionally, contralateral prophylactic mastectomy did not improve DFS or DSS compared to BCS (p>0.05) (Table 4).

Discussion

In this study, we showed that the prognostic impact of BCS and mastectomy in first primary BC on DFS and DSS was similar within both *BRCA1* and *BRCA2* mutation carriers. Moreover, there was no difference in terms of recurrence site, LR interval, systemic metastasis rate or systemic metastasis interval. Our study is the first to evaluate the effect of BCS and mastectomy directly both in *BRCA1* and *BRCA2* mutation carriers in the Turkish population.

Our results agree with American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology guidelines as they recommended that newly diagnosed BC patients with *BRCA1* or *BRCA2* mutations may be considered for BCT, with local control of the index cancer similar to that of mutation non-carriers.[10] Moreover, the surgical approach for high-risk BC patients should consider many factors, including the patient's age, tumor biology, breast size, genetic risk, oncological history, family history, comorbidities, life expectancy, and the ability to undergo appropriate follow-up.[11] In another study done by Huang et al, they showed that BCT may be a safe surgical option for Chinese female BC patients with *BRCA1* and/or *BRCA2* mutation with taking in consideration tumor size, stage, the number of positive lymph nodes.[5] Furthermore, a study by Magnoni et al reported that, during multi-disciplinary discussion, in addition to taking recent international guidelines and the patient's preferences into account, surgical treatment should be personalized based on BC clinicopathological and genetic features.[12] Taken together, BCS may serve as an effective rational surgical choice in *BRCA1* or *BRCA2* mutation carriers as well as tumor size, lymph node positivity, TNM stage, should be taken into consideration during the surgical decision-making.

Numerous retrospective studies have focused on local control after BCS in *BRCA1* and/or *BRCA2* mutation carriers.[13–15] In these studies, with a limited follow-up period, BCS did not increase the risk of local recurrence in mutation carriers compared with non-carriers. Other studies with longer follow-up periods reported that local recurrence was increased in mutation carriers by approximately 10% at 10 years and 15% at 15 years.[16,17] Co et al compared the inferior survival outcomes and local recurrence rates of BCS and mastectomy in *BRCA* mutation carriers across 18 studies. They concluded that BCS should be recommended for patients with breast cancer with *BRCA* mutations.[18] In meta-analysis study, Wang et al[19] found that BCS was associated with a significantly higher risk of local recurrence than mastectomy, but no significant effect of BCS on OS, DFS, DSS, or metastasis-free survival was observed. These results agree with ours as BCS may serve as a safe alternative to mastectomy for *BRCA* mutation carriers BC patients. In addition, mastectomy will be recommended for larger more advanced tumors.

Table 3 Characteristics of Cases with Loco-Regional Recurrence in *BRCA1* and *BRCA2* Mutation Carriers

	Mutation	Tumor	Tumor/Node Stages	Margin	Age(y)	Family History	Histology	Luminal Features	Recurrence Time (Months)	NACT	Surgery	Recurrence Site
Case 1	BRCA2	Multicentric	T1N1	Negative	50	Positive	IDC+ILC	ER(+)/PR (+)/Her2(-)	130	Negative	BCS	Breast
Case 2	BRCA2	Unicentric	T2N0	Negative	44	Positive	IDC	TN	58	Positive	BCS	Breast
Case 3	BRCA1	Unifocal	T2N0	<1mm	41	Positive	IDC	TN	48	Negative	BCS	Breast
Case 4	BRCA2	Multicentric	T2N1	-	52	Negative	IDC	ER(-)/PR(-)/ Her2(+)	15	Positive	Mastectomy	Thorax wall
Case 5	BRCA2	Unifocal	T2N1	-	48	Positive	IDC	ER(+)/PR (+)/Her2(-)	12	Negative	Mastectomy	Axilla
Case 6	BRCA2	Multicentric	T2N2	-	47	Positive	ILC	ER(+)/PR (+)/Her2(-)	67	Negative	Mastectomy	Axilla

Abbreviations: T, tumor; N, node; TN, triple negative; NACT, neoadjuvant chemotherapy; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BCS, breast conserving surgery.

Table 4 Possible Factors Affecting Disease-Free and Disease-Specific Survival (Univariate Analysis)

Variables	Category	10-Year DFS (%)	*p*-value	10-Year DSS (%)	*p*-value
		74.5		***85.4***	
Age(year)	≤50	71.1	0.588	85.4	0.995
	>50	81		86.7	
Family history of BC	Positive	70.1	0.576	79.3	0.231
	Negative	78.6		92.4	
BRCA genetic mutation	*BRCA1*	77.1	0.296	81.8	0.285
	BRCA2	68.1		92.9	
Tumor type	IDC	74.7	0.877	81.2	0.125
	Others	70.2		100	
pT Stage	I	84.4	0.839	88.9	0.642
	II–III	71.6		84	
N Stage	N-	77	0.273	85.9	0.154
	N+	71.9		80.7	
Grade	I–II	79.4	0.173	93.8	**0.030***
	III	70.9		76.3	
In-situ component	Present	77.3	0.654	85.4	0.744
	Absent	68.6		85.5	
LVI	Present	60.3	0.622	82.2	0.487
	Absent	69.7		88.1	
Multicentricity	Single	79.6	**0.045***	91.6	0.064
	Multiple	60.6		69.7	
Surgical approach	BCS	85.1	0.117	92.3	0.109
	Mastectomy	66.5		80.4	
Contralateral prophylactic mastectomy	Positive	81.5	0.756	90	0.946
	Negative	64.6		79.6	
Prophylactic TAH-BSO	Positive	92.9	0.371	91.7	0.775
	Negative	72.2		85.6	
Molecular subtype	Luminal	79.6	0.606	95	**0.044***
	Non luminal	68.7		75.9	

Note: *p<0.05, Log rank Test, in bold.

Abbreviations: LRFS, loco-regional free survival; DFS, disease-free survival; DSS, disease-specific survival; pT, pathologic tumor; N, node; IDC, invasive ductal carcinoma; BCS, breast conserving surgery; LVI, lymphovascular invasion; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Davey et al[20] compared the safety of BCS and mastectomy in patients with BC with *BRCA* mutations in 23 studies. DFS and DSS after 5-years, 10-years or 15-years were equivalent in the BCS and mastectomy groups. Bernstein-Molho et al[21] studied 255 BC patients with *BRCA1* and *BRCA2* mutations over a median of 57.7 months. There was no

significant difference in the OS. Patients who underwent BCS had higher rates of ipsilateral breast tumor recurrence than those who underwent mastectomy with post-mastectomy radiotherapy. Furthermore, Nilsson et al[22] reported that patients who underwent BCS have a higher risk of local recurrence. However, no significant differences in OS, BC death, or distant recurrence were observed between BCS and mastectomy in *BRCA* mutation carriers. In addition, van den Broek et al[23] reported that *BRCA* mutation carriers who underwent BCS had a similar OS compared to those who underwent mastectomy.

According to our findings, contralateral prophylactic mastectomy did not improve DFS or DSS compared to BCS. In a recent study by Makhnoon et al, they found that no evidence of contralateral prophylactic mastectomy-mediated improvement in OS among women with pathogenic variants in *BRCA1* and *BRCA2* and the improvement in OS could be explained by the decrease of contralateral breast cancer risk and cancer mortality.[24] This result also supported the findings of Fayanju et al.[25] Also, Makhnoon et al observed a racial/ethnic difference in the 20-year OS in BC patients who underwent contralateral prophylactic mastectomy.[24] In a study by Metcalfe et al, they demonstrated that women with *BRCA* mutations and treated for stage I or II BC with bilateral mastectomy are less likely to die due to BC than women who are treated with unilateral mastectomy.[26]

All patients in this study were diagnosed with BC and underwent BCS or mastectomy along with other appropriate treatment protocols. At the same time, *BRCA1* and *BRCA2* mutation tests were requested. *BRCA* test results were not available and unnecessary at this stage for the choice of surgical management. This situation is favorable to these patients because patients are more likely to consider mastectomy if they know they have a mutation.

Conclusions

Our findings indicate that BCS may serve as an efficacious rational surgical choice, alternative to mastectomy for BC patients with *BRCA1* or *BRCA2* mutation. Tumor size, lymph node positivity, and TNM stage should be taken into consideration for a better surgical decision-making.

Data Sharing Statement

The data sets of the current study are available from the corresponding author on reasonable request.

Acknowledgments

We would like to express our special appreciation and thank to Ph.D. Candidate Asmaa Mahmoud Abuaisha for her help in data analysis and interpretation and writing this manuscript. Also, we would like to thank M.Sc. Atilla Bozdogan for his meticulous statistical analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors have no conflicts of interest to declare for this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
2. Robson ME, Chappuis PO, Satagopan J, et al. A combined analysis of outcome following breast cancer: differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast Cancer Res*. 2004;6(1):R8–R17. doi:10.1186/bcr658

3. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science*. 1990;250(4988):1684–1689. doi:10.1126/science.2270482
4. Schwartz GF, Veronesi U, Clough KB, et al. Consensus conference on breast conservation. *J Am Coll Surg*. 2006;203(2):198–207. doi:10.1016/j.jamcollsurg.2006.04.009
5. Huang X, Cai XY, Liu JQ, et al. Breast-conserving therapy is safe both within BRCA1/2 mutation carriers and noncarriers with breast cancer in the Chinese population. *Gland Surg*. 2020;9(3):775–787. doi:10.21037/gs-20-531
6. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: risk factors and impact on distant metastases. *Cancer*. 2006;106(1):35–41. doi:10.1002/cncr.21551
7. Gradishar WJ, Moran MS, Abraham J, et al. Breast cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20(6):691–722. doi:10.6004/jnccn.2022.0030
8. Golshan M, Miron A, Nixon AJ, et al. The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy. *Am J Surg*. 2006;192(1):58–62. doi:10.1016/j.amjsurg.2005.12.005
9. Krammer J, Pinker-Domenig K, Robson ME, et al. Breast cancer detection and tumor characteristics in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat*. 2017;163(3):565–571. doi:10.1007/s10549-017-4198-4
10. Tung NM, Boughey JC, Pierce LJ, et al. Management of hereditary breast cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol*. 2020;38(18):2080–2106. doi:10.1200/JCO.20.00299
11. Corso G, Magnoni F. Hereditary breast cancer: translation into clinical practice of recent American Society of Clinical Oncology, American Society of Radiation Oncology, and Society of Surgical Oncology recommendations. *Eur J Cancer Prev*. 2021;30(4):311–314. doi:10.1097/CEJ.0000000000000624
12. Magnoni F, Sacchini V, Veronesi P, et al. Surgical management of inherited breast cancer: role of breast-conserving surgery. *Cancers*. 2022;14(13):3245. doi:10.3390/cancers14133245
13. Pierce LJ, Strawderman M, Narod SA, et al. Effect of radiotherapy after breast-conserving treatment in women with breast cancer and germline BRCA1/2 mutations. *J Clin Oncol*. 2000;18(19):3360–3369. doi:10.1200/JCO.2000.18.19.3360
14. Seynaeve C, Verhoog LC, van de Bosch LM, et al. Ipsilateral breast tumour recurrence in hereditary breast cancer following breast-conserving therapy. *Eur J Cancer*. 2004;40(8):1150–1158. doi:10.1016/j.ejca.2004.01.017
15. Verhoog LC, Brekelmans CT, Seynaeve C, et al. Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1. *Lancet*. 1998;351(9099):316–321. doi:10.1016/s0140-6736(97)07065-7
16. Fowble B. Ipsilateral breast tumor recurrence following breast-conserving surgery for early-stage invasive cancer. *Acta Oncol*. 1999;38(Suppl 13):9–17. doi:10.1080/028418699432716
17. Kreike B, Hart AA, van de Velde T, et al. Continuing risk of ipsilateral breast relapse after breast-conserving therapy at long-term follow-up. *Int J Radiat Oncol Biol Phys*. 2008;71(4):1014–1021. doi:10.1016/j.ijrobp.2007.11.029
18. Co M, Liu T, Leung J, et al. Breast conserving surgery for BRCA mutation carriers-a systematic review. *Clin Breast Cancer*. 2020;20(3):e244–e250. doi:10.1016/j.clbc.2019.07.014
19. Wang C, Lin Y, Zhu H, et al. Breast-conserving therapy for breast cancer with BRCA mutations: a meta-analysis. *Breast Cancer*. 2022;29(2):314–323. doi:10.1007/s12282-021-01312-2
20. Davey MG, Davey CM, Ryan ÉJ, Lowery AJ, Kerin MJ. Combined breast conservation therapy versus mastectomy for BRCA mutation carriers - A systematic review and meta-analysis. *Breast*. 2021;56:26–34. doi:10.1016/j.breast.2021.02.001
21. Bernstein-Molho R, Laitman Y, Galper S, et al. Locoregional treatments and ipsilateral breast cancer recurrence rates in BRCA1/2 mutation carriers. *Int J Radiat Oncol Biol Phys*. 2021;109(5):1332–1340. doi:10.1016/j.ijrobp.2020.11.058
22. Nilsson MP, Hartman L, Kristoffersson U, et al. High risk of in-breast tumor recurrence after BRCA1/2-associated breast cancer. *Breast Cancer Res Treat*. 2014;147(3):571–578. doi:10.1007/s10549-014-3115-3
23. van den Broek AJ, Schmidt MK, van 't Veer LJ, et al. Prognostic impact of breast-conserving therapy versus mastectomy of BRCA1/2 mutation carriers compared with noncarriers in a consecutive series of young breast cancer patients. *Ann Surg*. 2019;270(2):364–372. doi:10.1097/SLA.0000000000002804
24. Makhnoon S, Gutierrez Barrera AM, Bassett R, Afrough A, Bedrosian I, Arun BK. Contralateral prophylactic mastectomy among women with pathogenic variants in BRCA1/2: overall survival, racial, and ethnic differences. *Breast J*. 2022;2022:1447545. doi:10.1155/2022/1447545
25. Fayanju OM, Stoll CR, Fowler S, Colditz GA, Margenthaler JA. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. *Ann Surg*. 2014;260(6):1000–1010. doi:10.1097/SLA.0000000000000769
26. Metcalfe K, Gershman S, Ghadirian P, et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. *BMJ*. 2014;348:g226. doi:10.1136/bmj.g226

Breast Cancer: Targets and Therapy Dovepress

Publish your work in this journal

Breast Cancer - Targets and Therapy is an international, peer-reviewed open access journal focusing on breast cancer research, identification of therapeutic targets and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/breast-cancer—targets-and-therapy-journal