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Our clinical experiences in patients with de novo and secondary metastatic breast cancers

De novo and secondary metastatic breast cancers

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Abstract

Aim: While breast cancer may be de novo, that is, metastatic at the time of diagnosis, a local tumor at initial diagnosis may metastasize to other regions over the course of treatment and follow-up. This study aimed to reveal the clinical, pathological, and survival differences in patients with de novo metastatic and secondary metastatic breast cancer who were followed up and treated in our clinic, and to investigate factors that may have an effect on survival.

Methods: The data of female patients who were diagnosed with metastatic breast cancer, treated, and followed up in our clinic between January 2000 and May 2021 were retrospectively analyzed. Patients were divided into two groups: the de novo metastatic disease group (Group 1) and the secondary metastatic disease group (Group 2). Clinical and pathological data of the groups were analyzed.

Results: Patients with de novo metastatic disease most commonly had bone metastases. But in the secondary metastatic disease group, the most common metastasis type was multiorgan metastases. The rate of triple negativity was significantly lower in Group 1. When the groups were analyzed in terms of survival, the median time was 77 ± 10.89 months in the de novo metastatic group and 66 ± 10.15 months in the secondary metastatic group (P = .05).

Conclusion: Our study demonstrated that de novo metastatic breast cancers had a better prognosis than secondary metastatic breast cancers even though they tend to metastasize early.

Keywords

breast cancer, de novo, metastasis, survival

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Introduction

Breast cancer is the most common type of cancer in women. Around 1.7 million new cases of breast cancer are diagnosed each year, and 520,000 patients die from breast cancer.[1] Moreover, the incidence of breast cancer is rising every year, and it has been predicted that the annual number of cases will reach 3.2 million by 2050.[2]

While breast cancer may be de novo, that is, metastatic at the time of diagnosis, a local tumor at initial diagnosis may metastasize to other regions over the course of treatment and follow-up.[3] Nearly 30% of node-negative patients with local breast cancer at initial diagnosis and 70% of node-positive patients develop distant metastasis during follow-up and treatment.[4]

Thanks to advances in treatment methods and extensive screening programs, mortality rates of breast cancer have decreased by 25–38%.[1] However, it has been observed that screening programs implemented in a similar way for breast cancer have not significantly decreased the incidence of de novo metastatic breast cancer.[5] The prognosis and clinical course of patients with metastatic breast cancer may vary depending on patient and tumor characteristics. Although there are palliative treatment options after the occurrence of distant metastasis, it is believed that the patient loses the chance of curative treatment.[4]

This study aimed to reveal clinical, pathological, and survival differences in patients with de novo metastatic and secondary metastatic breast cancer who were followed up and treated in our clinic, and to investigate factors that may have an effect on survival.

Materials and Methods

This study was approved by the Karamanoğlu Mehmet Bey University Clinical Research Ethics Committee (Date: 31.08.2022, Decision No: 08/03). The data of female patients who were diagnosed with metastatic breast cancer, treated, and followed up in our clinics between January 2000 and May 2021 were retrospectively analyzed. Patients were divided into two groups: the de novo metastatic disease group that included patients with metastatic disease at initial diagnosis (Group 1, n = 113) and the secondary metastatic disease group that included patients who developed distant metastasis during their follow-up after the treatment of the primary tumor (Group 2, n = 178). Male patients, patients with primary tumors other than breast carcinoma, those who died from causes other than breast cancer, and those who could not be regularly followed up for various reasons were not included in the study.

Demographic data, metastasizing organs, surgical and/or medical treatments, clinical and histopathological findings of the tumor, mortality rates, and overall survival of the patients who met the study criteria and were included in the study were evaluated. In terms of these data, the differences between Group 1 and Group 2 and the variables that may have an effect on overall survival were statistically analyzed. For calculating the follow-up times used in the analysis of the intergroup difference in survival, the follow-up period after the diagnosis was taken into account for Group 1, while the follow-up period after the development of metastatic disease was taken into account for Group 2.

Ethical Approval

This study was approved by the Clinical Research Ethics Committee of Karamanoğlu Mehmet Bey University (Date: 31.08.2022, Decision No: 08/03).

Statistical Analysis

The analyses in the study were carried out using the SPSS software package version 21.0. The level of error was set at $P < .05$ in all analyses. The normality of data distribution was checked using the Kolmogorov-Smirnov test. Frequency table results were given for categorical variables and descriptive measures for numerical variables (mean ± standard deviation (SD) or median (min–max) in non-parametric cases). Student's t-test or Mann-Whitney U test was used for the comparison of the two groups. The Chi-square analysis was used to test whether categorical variables were related to each other or not. Overall survival and disease-free survival were calculated using the Kaplan-Meier method. The Log-Rank test was used to evaluate whether there was a difference between the groups in terms of survival times. Risk factors that may have an effect on survival were analyzed with Cox's proportional hazards model.

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

Comparative basic demographic and clinical data of the patients included in the study are summarized in Table 1. The analysis of the data of 113 de novo metastatic and 178 secondary metastatic breast cancer patients who met the study criteria showed a mean age of 52.21 ± 13.43 in Group 1 and 48.37 ± 12.94 in Group 2. Tru-cut biopsy was the most commonly used biopsy technique in both groups. This was followed by excisional and fine-needle biopsy techniques, respectively. There was no statistically significant difference between the groups in terms of the biopsy techniques used (P = .75).

The most common histological type was infiltrative ductal carcinoma in 77.9% (n = 88) of the patients in the de novo metastatic disease group and 81.5% (n = 145) of the patients in the other group, followed by infiltrative lobular carcinoma and mixed type (features of both infiltrative ductal and infiltrative lobular carcinoma) in both groups (Figure 1). The groups were statistically similar in terms of histopathological types (P = .57). The histopathological features of the tumors of the groups are summarized in Table 2.

The evaluation for tumor size revealed a median tumor size of 3.5 (range, 1–10) cm in Group 1 and 3.5 (range, 0.8–12) cm in Group 2 (P = .52). T stage of 40 (35.4%) patients and N stage of 53 (46.9%) patients in the de novo metastatic disease group could not be evaluated. In Group 1, the most common T stage was T2 (26.5%), followed by T4 (15.9%), T3 (13.3%), and T1 (8.8%) tumors, while in Group 2, 97 (54.5%) patients had T2 tumors, followed by T3 (28.7%), T1 (8.4%), and T4 (6.2%) tumors. In terms of lymph node involvement, the most common N stage in Group 1 was N3 (17.7%), followed by N1 (16.8%), N2 (10.6%), and N0 (8%), while the most common N stage in Group 2 was N1 (30.3%), followed by N2 (23.6%), N0 (23%), and N3 (19.7%) tumors. The comparison of the groups by sites of metastasis showed a statistically significant difference (P = .002) (Figure 2).

The incidence of lymphovascular and perineural invasion on histopathological examination was similar in both groups (52.3% (n = 34) and 38.9% (n = 65), respectively, P = .06). Seventy-four percent (n = 54) of the patients in Group 1 and 58.2% (n = 89) of the patients in Group 2 had grade 2 tumors (P = .018). The groups were similar in terms of estrogen and Cerb-B2 receptor positivity (P = .057 and P = .44, respectively). In terms of progesterone receptor positivity, the rate of positive patients was significantly

higher in Group 1 (63.9% (*n* = 62) and 46% (*n* = 64), respectively, *P* = .007). While the groups were similar in terms of triple positivity (33% (n = 32) and 23.2% (*n* = 32), respectively, *P* = .09), the rate of triple negativity was significantly lower in Group 1 (4.1% (*n* = 4) and 15.1% (*n* = 21), respectively, *P* = .007).

Surgical and/or medical treatment methods of the patients are summarized in Table 3. Of the patients in Group 1, 45.1% (*n* = 51) did not undergo any surgical intervention, while 49.6% (*n* = 56) underwent modified radical mastectomy. In Group 2, 89.3% (*n* = 159) of the patients underwent modified radical mastectomy and 7.3% (*n* = 13) underwent breast-conserving surgery. In terms of chemotherapy, the groups had a statistically significant difference in the rates of not receiving chemotherapy and receiving palliative, adjuvant, and neoadjuvant chemotherapy (*P* < .001). Furthermore, the rate of hormone therapy was statistically significantly higher in Group 2 (*P* = .04). There was no difference between the groups in terms of Herceptin treatment (*P* = .42). There was a significant difference between the groups in terms of radiotherapy (*P* < .001).

The median follow-up time was 27 (range, 4–92) months in the de novo metastatic disease group, while it was 54 (range, 6–240) months in Group 2. The follow-up time of Group 2 was statistically significantly longer (*P* < .001). The comparison of the post-metastasis follow-up times revealed a statistically significantly longer follow-up time in the de novo metastatic disease group (27 (range, 4–92) and 16 (range, 1–108) months, respectively, *P* < .001). During the follow-up period, 23 (20.4%) patients in Group

Table 1. Analysis and Comparison of Demographic and Some Clinical Characteristics of De Novo and Secondary Metastatic Breast Cancer Patients

	De novo group n (%)	Secondary group n (%)	*P*
Age	52.21 ± 13.43	48.37 ± 12.94	.016
Follow up time,mo	27 (4-92)	16 (1-108)	<.001
Comorbidity			
No	69 (61.1)	120 (67.4)	.26
Yes	44 (38.9)	58 (2.6)	
Alcohol			
No	107 (94.7)	171 (96.1)	.57
Yes	6 (5.3)	7 (3.9)	
Smoking			
No	104 (92)	172 (96.6)	.084
Yes	9 (8)	6 (3.4)	
Malignancy in family			
No	86 (76.1)	138 (77.5)	.77
Yes	27 (23.9)	40 (22.5)	
Childbirth			
No	12 (10.6)	22 (12.4)	.65
Yes	101 (89.4)	156 (87.6)	
Tumor side			
Right	54 (47.8)	76 (42.7)	.64
Left	58 (51.3)	101 (56.7)	
Bilateral	1 (0.9)	1 (0.6)	
Tumor localization			
Upper outer	52 (46)	97 (54.5)	.64
Lower outer	21 (18.6)	24 (13.5)	
Upper inner	12 (10.6)	22 (12.4)9	
Lower inner	7 (6.2)	10 (5.6)	
Central	9 (8)	12 (6.7)	
Multi centric	12 (10.6)	13 (7.3)	
Metastasis Site			
Bone	44 (38.9)	37 (20.8)	.002
Liver	8 (7.1)	11 (6.2)	
Lung	10 (8.8)	17 (9.6)	
Multi organ	34 (30.1)	94 (52.8)	
Others	17 (15)	19 (10.7)	
Mortality			
No	90 (79.6)	134 (75.3)	.38
Yes	23 (20.4)	44 (24.7)	

Table 2. Analysis and Comparison of Histopathological Characteristics of De Novo and Secondary Metastatic Breast Cancer Patients

	De novo group n (%)	Secondary group n (%)	*P*
Tumor size, cm	3.5 (1-10)	3.5 (0.8-12)	.52
Histological grading			
Grade [1]	0 (0)	10 (6.5)	.018
Grade [2]	54 (74)	89 (58.2)	
Grade [3]	19 (26)	54 (35.3)	
Type of biopsy			
Excisional	41 (36.3)	57 (32)	.75
Tru-cut	60 (53.1)	100 (56.2)	
Fine needle	12 (10.6)	21 (11.8)	
Histological Type			
IDC	88 (77.9)	145 (81.5)	.57
ILC	9 (8)	8 (4.5)	
Mix(IDC+ILC)	3 (2.7)	7 (3.9)	
Others	13 (11.5)	18 (10.1)	
Estrogen receptor			
Negative	30 (30.9)	60 (43.2)	.057
Positive	67 (69.1)	79 (56.8)	
Progesterone receptor			
Negative	35 (36.1)	75 (54)	.007
Positive	62 (63.9)	46 (46)	
Cerb-B2			
Negative	35 (36.1)	57 (41)	.44
Positive	62 (63.9)	82 (59)	
Triple positive			
No	65 (67)	106 (76.8)	.09
Yes	32 (33)	32 (23.2)	
Triple negative			
No	93 (95.9)	118 (84.9)	.007
Yes	4 (4.1)	21 (15.1)	
Lymphovascular-perineural invasion			
No	31 (47.7)	102 (61.1)	.64
Yes	34 (52.3)	65 (38.9)	

IDC, Infiltrative Ductal Carcinoma; ILC, Infiltrative Lobular Carcinoma.

1 and 44 (24.7%) in Group 2 died. Although the mortality rate was lower in Group 1, there was no statistically significant difference in mortality rates between the groups (*P* = .38).

Overall survival and disease-free survival were calculated using the Kaplan-Meier method. Figure 3 illustrates the overall survival charts for both groups. In the secondary metastatic disease group, the rate of five-year disease-free survival was 89 ± 2.4% months and the disease-free survival of 75% was 48 ± 8.13 months. In this group, the rate of five-year overall survival was 90.5 ± 2.3% and the overall survival of 75% was 72 ± 8.49 months. The overall survival analysis performed by considering the post-metastasis follow-up time of the second group and the follow-up time of the first group showed a median time of 77 ± 10.89 months in the de novo metastatic disease group and 66 ± 10.15 months in the secondary metastatic disease group. The survival rate of 75% was attained at 62 ± 16.12 months in Group 1 and 37 ± 5.14 months in Group 2. Whether there was a difference between the groups in terms of overall survival was evaluated with the Log-Rank test, which showed a statistical difference between the two groups (longer overall survival in Group 1) (*P* = .05).

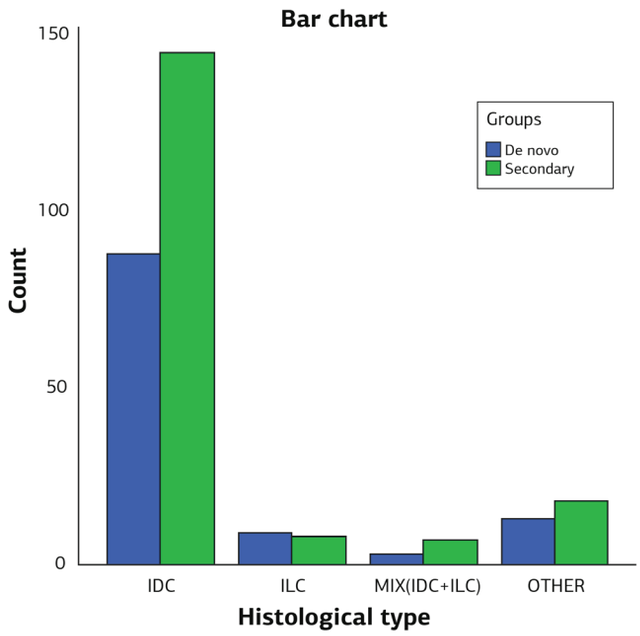


Figure 1. *Bar Chart Showing the Histological Types of the Tumors in Both Groups (P = .57)*

Table 3. Analysis and Comparison of Treatment Options of De Novo and Secondary Metastatic Breast Cancer Patients

	De novo group n (%)	Secondary group n (%)	*P*
Surgery			
MRM	56 (49.6)	159 (89.3)	<.001
BCS	4 (3.5)	13 (7.3)	
SM	2 (1.8)	0 (0)	
Not applied	51 (45.1)	6 (3.4)	
Chemotherapy			
No	4 (3.5)	8 (4.5)	<.001
Palliative	53 (46.9)	1 (0.6)	
Adjuvant	19 (16.8)	143 (80.3)	
Neoadjuvant	37 (32.7)	26 (14.6)	
Radiotherapy			
No	54 (47.8)	62 (34.8)	<.001
Palliative	36 (31.9)	23 12.91)	
Yes	23 (20.4)	93 (52.2)	
Hormonal therapy			
No	58 (51.3)	70 (39.3)	.04
Yes	55 (48.7)	108 (60.7)	
Herceptin			
No	79 (69.9)	132 (74.2)	.42
Yes	34 (30.1)	46 (25.8)	

MRM, Modified Radical Mastectomy; BCS, Breast-Conserving Surgery; SM, Simple Mastectomy.

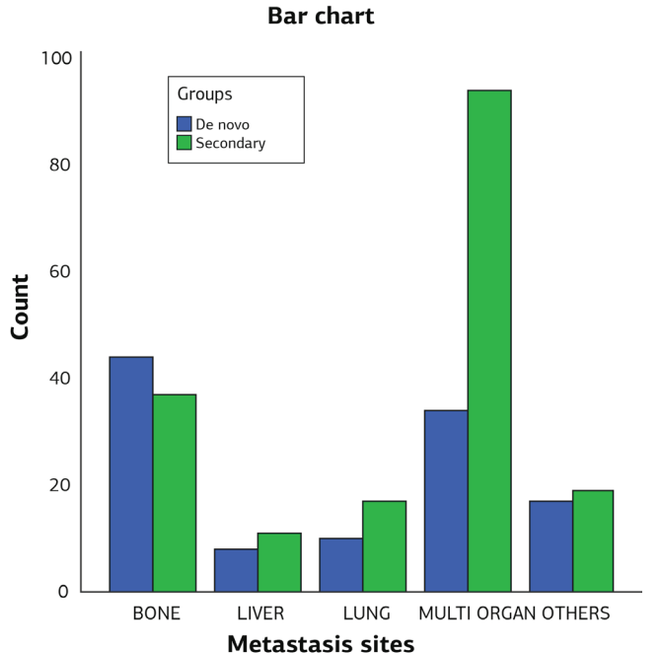


Figure 2. *Bar Chart Showing the Metastasis Sites in Both Groups (P = .002)*

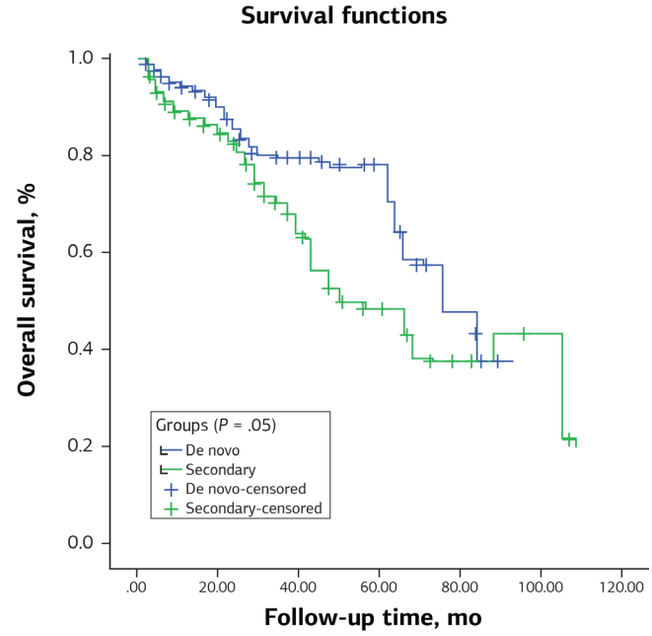


Figure 3. *Kaplan-Meier Curves of Overall Survival in the De Novo (N = 113) and the Secondary Metastatic Group (N = 178)*

Risk factors that may affect survival were analyzed with Cox's proportional hazards model. Accordingly, being in Group 1 or Group 2 did not have a statistically significant effect on overall survival (P = .054). Of other variables for which a Cox regression analysis was carried out with a single variable, factors such as age, presence of any comorbid disease, laterality, quadrant of involvement, multicentric involvement, histological type of the tumor, T stage and N stage of the tumor, histological grade, estrogen receptor positivity, progesterone receptor positivity, Cerb-B2 positivity, and having received chemotherapy, Herceptin treatment, and radiotherapy or not were found to have no effect on mortality (P > .05). Not receiving hormonal therapy (HR = 2.13, 95% CI = 1.29–3.52, P = .003) was found to be associated with increased mortality.

Discussion

Despite the more frequent use of screening methods, the incidence of de novo metastatic breast cancer is increasing day by day.[6] In spite of this increase in incidence, studies on both de novo and secondary metastatic breast cancer have shown significant improvements in the survival of patients in both groups over time thanks to new therapeutic agents and advancements in care.[7]

Some studies have shown more frequent hormone receptor positivity, a higher rate of nodal involvement, and better survival outcomes in de novo metastatic breast cancers than in secondary metastatic breast cancer.[1,8] The results of our study also showed a statistically significantly higher rate of progesterone receptor positivity in the de novo metastatic disease group (P = .007). Although the groups were similar in terms of estrogen receptor positivity and Cerb-B2 positivity (P = .057 and P = .44, respectively).

In addition to publications reporting similar characteristics for both patient groups in terms of prognosis independent of disease-free survival, there are also some reports suggesting better prognosis for patients with de novo metastatic disease who receive systemic chemotherapy.[9,10] Some hypotheses have been proposed regarding the better prognosis for those with de novo metastasis. One of these is that the removal of the primary tumor diagnosed in the early stage with surgery, which is performed as a step of treatment, will cause the disease to become more aggressive in case of a possible metastasis compared to those with de novo metastases.[7] Contrary to these studies, there are also publications reporting a positive effect of local surgical treatments of the primary tumor on the survival of patients with de novo stage 4 tumors.[11,12] Another hypothesis regarding the survival difference between the groups is that drug resistance may have developed due to previous chemotherapeutic treatment in patients with recurrent disease and the treatment response may therefore be worse than in those with de novo metastasis.[7]

Tumor histology has a very important role in guiding treatment and prognosis in advanced breast cancers. A study by Seltzer et al. showed a higher rate of hormone receptor and C-erb B2 positivity in patients with de novo metastatic disease compared to those with secondary metastatic disease.[1] In this way, the chance of hormonal therapy and targeted therapy, and consequently survival time of patients can be increased. In patients with secondary metastatic disease, the tumor histologically tends to be triple-negative for hormone receptors.[13] In our study, the rate of triple negativity was significantly higher in Group 2 (P = .007). This leads to a more aggressive course of the tumor and a shorter survival time.

There are also other proposed hypotheses regarding the better prognosis of patients with de novo metastatic tumors compared to those with secondary metastases. One of these is that mutations of PTEN, a tumor suppressor gene, in patients with de novo metastatic disease do not adversely affect the prognosis of the disease, while mutations of tumors in the secondary metastatic group may affect the prognosis very adversely.[14] Furthermore, depending on the histological characteristics of the tumor, patients with de novo metastatic disease may have a more suppressed immune response, more active steroid biosynthesis, and a higher chance of hormone therapy compared to those with secondary metastases, and these tumors may be more sensitive to drugs targeting the cytoskeleton such as taxanes, which are commonly used in advanced breast cancers.[10,15]

Some prognostic factors have been identified in patients with metastatic breast cancer. A study reported that age at diagnosis, site of metastasis, and hormone receptor status were independent prognostic factors for survival after the development of the first metastatic recurrence.[16] The same study stated that these prognostic factors also apply to de novo metastatic disease.[16] In addition to these, another relevant study found that factors such as an early age during metastasis, Caucasian race, hormone receptor positivity, absence of lymphovascular invasion, low-grade tumors, and absence of internal organ metastasis were prognostic factors that positively affect survival.[7] The same study reported that disease-free survival was also an important prognostic determinant in patients with secondary metastatic disease.[7] In our study, many parameters that may have an effect on mortality were analyzed, and only not receiving hormone therapy was associated with increased mortality (HR = 2.13, 95% CI = 1.29–3.52, P = .003).

Despite the frequent use of screening methods, the absence of a decline in the incidence of de novo metastatic breast cancer has been attributed to several reasons. One of these is that the tumor may metastasize at imaging intervals since it has the potential to grow very rapidly and metastasize at an early stage. Another reason is the insufficiently effective use of screening methods in societies with underdeveloped socioeconomic and educational levels.[5,17]

Limitations

Our study has some inevitable limitations. These include an insufficient level of evidence because of the retrospective design of the study, collection of the data from patient records and operative notes, and the lack of objective examination findings.

Conclusion

In conclusion, our study demonstrated that de novo metastatic breast cancers had a better prognosis than secondary metastatic breast cancers even though they histologically tend to metastasize early. All these results give rise to the question: "Is de novo metastatic breast cancer a different clinical manifestation?". Studies aimed at answering this question may lead to the emergence of new treatment strategies, thus improving the prognosis of metastatic breast cancers.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was waived by the ethics committee due to the retrospective nature of the study.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

None.

Abbreviations

BCS: Breast-conserving surgery
CI: Confidence interval
HR: Hazard ratio
IDC: Infiltrative ductal carcinoma
ILC: Infiltrative lobular carcinoma
MRM: Modified radical mastectomy
SD: Standard deviation
SM: Simple mastectomy
SPSS: Statistical package for the social sciences

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