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BREAST IMAGING

ORIGINAL ARTICLE

Radiological and clinicopathological findings of breast cancer during the COVID-19 pandemic: a comparative study with the pre-pandemic era

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PURPOSE

The diagnosis and surgical treatment delays that occurred during the coronavirus disease-2019-(COVID-19) pandemic may have affected breast cancer presentation. This study aimed to determine whether there was a difference in the clinicopathological characteristics of breast cancers during the pandemic by comparing them with similar cases from the previous year. The study also aimed to determine the radiological findings of breast cancers during the pandemic.

METHODS

A retrospective review was made of patients who underwent surgery for breast cancer between March 11, 2020, and December 11, 2020 (the pandemic group). These patients were compared with similar patients from the previous year (the pre-pandemic group). The postoperative histopathology results of both groups were compared, and the preoperative radiological findings of the pandemic group were defined.

RESULTS

There were 71 patients in the pandemic group and 219 patients in the pre-pandemic group. The tumor size was significantly greater, lymph node involvement was more frequent, and waiting time for surgery was longer in the pandemic group ($P < 0.001$, $P = 0.044$, $P = 0.001$, respectively). There was no significant difference between the groups in respect of *in situ*/invasive tumor distribution, histological type and histological grade of tumor, the presence of lymphovascular/perineural invasion, multifocal/multicentric focus, and Breast Imaging Reporting and Data System Classification ($P > 0.15$). The radiologic findings of breast cancer during the pandemic typically showed characteristics of malignancy.

CONCLUSION

Patients diagnosed with breast cancer during the COVID-19 pandemic had larger tumor sizes, more frequent lymph node involvement and longer waiting time for surgical treatment. Screening programs should be continued as soon as possible by taking necessary precautions.

KEYWORDS

COVID-19, breast cancer, mammography, screening interruption, surgery delay

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Although coronavirus disease-2019 (COVID-19) was first seen in China in the last month of 2019, it quickly spread all over the world due to fast human-to-human transmission. Following the first recorded case in Turkey on March 11, 2020, a re-organization of the healthcare system was implemented that required a series of restrictions, just as in other countries. Within these restrictions was the proviso that while emergency medical interventions would continue, there would be delays in the diagnosis and treatment of oncology cases. The management of breast cancer was affected by these changes, and in accordance with the recommendations of several national and international scientific communities, breast cancer screening programs were temporarily postponed.[1-3]

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These guidelines, which were formed for the diagnosis and treatment of breast cancer during the pandemic, consider the increasing demand for medical resources and aim to balance the risk of delaying treatment against potential exposure to the virus. Breast cancer screening was interrupted in this period, and radiological examinations were restricted to a limited number fof symptomatic diagnostic cases. Due to the screening programs that are widely applied throughout the world, breast cancer can be detected at an earlier stage. In a study conducted in Italy, the incidence of late-stage breast cancer (T2–T4) decreased steadily by 30% in a period of fewer than eight years following the introduction of organized mammography screening.[4] Consequently, breast cancer mortality was shown to decrease by up to 40%.[5]

It has been assumed that because of the temporary cessation of screening programs or the delay in surgical treatment for confirmed cancers due to the pandemic, the clinicopathological characteristics of breast cancer could change. Therefore, the aim of this study was to determine whether there was a difference in the clinicopathological characteristics of breast cancers diagnosed during the pandemic by comparing these with cases in the corresponding period before the pandemic. The study also aimed to determine the radiological characteristics of breast cancers diagnosed during the pandemic.

Methods

This retrospective study was approved by the Institutional Review Board of Ege University (21-3.1T/44). Since the study was retrospective, informed consent by patients and providers was not required.

Patients

A retrospective review was made of patients diagnosed with breast cancer in a 9-month period starting from March 11, 2020, when the first COVID-19 case was recorded in Turkey, to December 11, 2020. During this period, 158 patients were diagnosed with breast cancer. Of these, 87 were excluded from the study, including 56 who received neoadjuvant chemotherapy, 9 with a history of breast cancer surgery, 5 with radiological examinations performed at another center, and 17 with operations performed at another center. Thus, a total of 71 patients who met the criteria and were operated on were included in the study for evaluation as the pandemic group.

These patients were compared with patients who underwent surgery for breast cancer in the corresponding period of the previous year (March 11, 2019–December 11, 2019). The same exclusion criteria were applied to these patients. In the pre-pandemic period, a total of 352 patients were diagnosed with breast cancer, of which 219 were operated on and were included in the study as the pre-pandemic group. The remaining patients were excluded, as 83 received neoadjuvant chemotherapy, 23 had a history of breast cancer surgery, 8 had radiological examinations performed at another center, and 19 had operations performed at another center.

Main points

- The diagnosis and surgical treatment delays due to the coronavirus disease-2019 (COVID-19) pandemic have affected breast cancer presentation.
- Tumor size was larger and lymph node involvement was more frequent in breast cancers diagnosed during the COVID-19 pandemic than in the pre-pandemic era.
- Patients diagnosed during the pandemic period may have had to wait longer for surgical treatment.

Variables

The imaging findings of the patients with breast cancer in the pandemic group were determined by their preoperative radiological examinations [mammography, ultrasonography (US), and breast magnetic resonance imaging (MRI)]. The evaluation of the findings was made in accordance with the Breast Imaging Reporting and Data System (BI-RADS), version 5.

The postoperative histopathology results of the patients in both groups were reviewed. The largest tumor diameter was accepted as the histological size of the tumor and reported in millimeters. In the presence of more than one focus, the largest focal size was accepted as the tumor size. The presence or absence of metastatic axillary lymph nodes was also recorded for each patient, and, if present, the number of lymph nodes involved was recorded. Pathological T and N staging was based on the recommendations of the AJCC (2018) (edition VIII) for classification.[6] The status of the tumor was also recorded as in situ or invasive.

The histological type of the tumor was categorized into three groups: invasive ductal carcinoma, invasive lobular carcinoma, and others (medullary, apocrine, etc.). Tumor grading was evaluated according to the modified Scarff–Bloom–Richardson grading system. The histological grades of the tumor were classified into two groups: low grade and high grade. Grade 1 tumors were accepted as low grade, and grade 2 and 3 tumors were accepted as high grade. Lymphovascular invasion (LVI), perineural invasion (PNI), and multifocal/multicentric focus were also evaluated and categorized as present or absent. Waiting time for surgery was calculated as the number of days between the date of the first radiological examination of the breast cancer and the date of surgery. The BI-RADS classification of the tumor was also evaluated and categorized as BI-RADS 4 and 5.

The two groups (pre-pandemic and pandemic) were compared in terms of age, histological size of the tumor, axillary lymph nodes status, number of metastatic lymph nodes, T and N stages, *in situ*/invasive tumor distribution, histological type of the tumor, histological grade of the tumor, presence of LVI and PNI, presence of multifocal/multicentric focus, waiting time for surgery, and BI-RADS classification of the tumor.

Statistical analysis

Data analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) software, version 22.0. Data distributions were evaluated with the Shapiro–Wilk test for normality. All variables without normal distribution were reported as median, min–max values, and interquartile ranges (Q1–Q3, 25^{th}–75^{th} percentile values). The categorical variables were reported as numbers and percentages. The Mann–Whitney U test was used to compare age distribution, histological size of the tumor, number of metastatic lymph nodes, and waiting time for surgery between the groups. The frequency distributions of axillary lymph node status, histological type, presence of LVI and PNI, presence of multifocal/multicentric focus, and BI-RADS classification of the tumor in the two groups were examined using a Pearson chi-squared analysis. The frequency distributions of histological grade, T/N stages, and in situ/invasive tumors in the two groups were examined using Fisher's exact test. Variables with assigned values of $P < 0.05$ were considered statistically significant.

Results

Comparisons were made between the pandemic group of 71 patients, who underwent breast cancer surgery between March

11, 2020, and December 11, 2020, and the pre-pandemic group of 219 patients, who underwent breast cancer surgery in the corresponding period of 2019. The median age of the patients was 56 years (Q1–Q3, 46.5–65 years; range: 27–83 years) in the pre-pandemic group and 60 years (Q1–Q3, 46–68.5 years; range: 31–88 years) in the pandemic group. There was no significant difference in the age distribution of the two groups (P = 0.22).

Imaging characteristics of patients in the pandemic group

The interpretation of the radiological examinations of the 71 patients in the pandemic group yielded that mammography tests were present for 69 patients and absent for 2 (aged 32 and 33 years). US examinations were conducted in 56 cases and breast MRI examinations in 34 cases. Breast cancer was detected with mammography and US in 56 patients, with mammography alone in 13 patients, and with US alone in 2 patients. When the mammography, US, and breast MRI results were evaluated according to the BI-RADS classification, 23 patients (23/71, 32.4%) were evaluated as BI-RADS 4, and 48 patients (48/71, 67.6%) were evaluated as BI-RADS 5.

In the interpretation of the mammography characteristics, the presentation in 46 cases was as a mass, in 9 cases as structural distortion, and in 8 cases as asymmetrical density; in 1 case, there was no abnormal finding on mammography. When the presence of microcalcification was examined, pathological microcalcification was the sole finding observed on mammography in 5 cases was, while other findings accompanied microcalcifications in 30 cases.

When the US images of the masses were evaluated, the most common morphology was seen to be an irregular shape, in non-parallel orientation, without a circumscribed margin, in a hypo/heterogenous echo pattern, and providing posterior acoustic shadowing. The findings of the 34 cases evaluated by MRI were a mass in 24 cases and non-mass enhancement in 9. In 1 case, there was diffuse brightness in the skin and parenchyma, suggestive of inflammatory-type breast cancer. The characteristics of all 3 imaging modalities (mammography, US, and MRI) of the patients are shown in detail in Table 1.

Clinical and histopathological characteristics

The largest tumor diameters in the pre-pandemic group were between 3 and 100 mm, with a median value of 20 mm (Q1–Q3, 15–27 mm), while in the pandemic group they were between 9 and 78 mm, with a median value of 30 mm (Q1–Q3, 19.5–47

Table 1. Mammography, ultrasonography, and magnetic resonance imaging characteristics of breast cancer in the pandemic group

Findings		n (%)
Mammography	Mass	47 (68.1%)
	Architectural distortion	8 (11.6%)
	Focal asymmetry	8 (11.6%)
	Calcification only	5 (7.3%)
	No findings	1 (1.4%)
Mammography shape	Round/oval	6 (12.8%)
	Irregular	41 (87.2%)
Mammography margin	Circumscribed	1 (2.1%)
	Obscured	4 (8.5%)
	Micro-lobulated	5 (10.7%)
	Indistinct	14 (29.8%)
	Spiculated	23 (48.9%)
Mammography density	High density	34 (72.3%)
	Equal density	13 (27.7%)
US	Mass	53
	Calcification only	2
	Diffuse edema	1
US shape	Round/oval	7 (13.2%)
	Irregular	46 (86.8%)
US margin	Circumscribed	1 (1.9%)
	Not circumscribed	52 (98.1%)
US echo pattern	Hypoechoic	53 (100%)
US orientation	Parallel	10 (18.9%)
	Not parallel	43 (81.1%)
US posterior features	No posterior features	28 (52.8%)
	Enhancement	2 (3.8%)
	Shadowing	23 (43.4%)
MRI	Mass	24 (70.6%)
	NME	9 (26.5%)
	Skin thickening, edema, diffuse non-mass-like enhancement	1 (2.9%)
Mass shape	Round/oval	0
	Irregular	24 (100%)
Mass margin	Circumscribed	0
	Not circumscribed	24 (100%)
Internal enhancement characteristics	Heterogeneous	18 (75%)
	Rim enhancement	6 (25%)
NME distribution	Linear	1 (11.1%)
	Segmental	6 (66.7%)
	Multiple regions	1 (11.1%)
	Diffuse	1 11.1%)
NME internal enhancement patterns	Heterogeneous	5 (55.6%)
	Clumped	4 (44.4%)

n, number of patients; US, ultrasonography; MRI, magnetic resonance imaging; NME, non-mass enhancement.

mm). The median tumor size was significantly greater in the pandemic group ($P < 0.001$) (Table 2). Lymph node involvement was present in 32% of the pre-pandemic group patients and 45.1% of those in the pandemic group. A statistically significantly higher rate of patients in the pandemic group had lymph node involvement ($P = 0.044$). The mean number of lymph nodes involved was 3.9 in the pandemic group and 2.9 in the pre-pandemic group. The median number of lymph nodes involved was 2 in both groups (Q1–Q3, 1–4; range: 1–14 for the pre-pandemic group and Q1–Q3, 1–3.25; range: 1–32 for the pandemic group), with no statistically significant difference ($P = 0.87$). The comparison of the two groups in respect of T and N stages yielded a statistically significant difference between groups in respect of the T stage of the tumor ($P = 0.002$). In the subsequent paired comparisons, T3 stage tumors were seen at a statistically significantly higher rate than Tis, T1, and T2 in the pandemic group ($P = 0.001$, $P < 0.001$, $P = 0.002$, respectively). The N stage distribution between the groups did not show a statistically significant difference ($P = 0.11$) (Table 3). While the pre-pandemic group had a surgery waiting time ranging between 11 and 104 days, with a median value of 44 days (Q1–Q3, 32–60.5 days), the waiting time for surgery was between 12 and 210 days, with a median value of 56 days (Q1–Q3, 36.5–80.5 days), in the pandemic group. The time from the first radiological examination to surgery was statistically significantly longer in the pandemic group ($P = 0.001$).

There were no significant differences between the groups in respect of *in situ*/invasive tumor distribution ($P = 0.22$), histological type of tumor ($P = 0.50$), histological grade of tumor ($P = 0.17$), the presence of LVI ($P = 0.38$) and PNI ($P = 0.97$), the presence of multifocal/multicentric focus ($P = 0.78$), and BI-RADS classification of the tumor ($P = 0.88$) (Table 2).

Discussion

The results of this study showed that the mammography, US, and MRI findings of breast cancer during the pandemic typically showed characteristics of malignancy. On mammography, breast cancers most often presented as a mass of irregular shape, with a spiculated margin, and with high density. When the US images of the masses were evaluated, the most common presentation was seen to be a typical malignant presentation of an irregular shape, in non-parallel orientation, not circumscribed, in a hypo/heterogenous echo pattern, and providing posterior acoustic shadowing. On MRI, the most common presentation was a mass of irregular shape, with a non-circumscribed margin and heterogenous enhancement.

This study hypothesized that because of the delays in breast cancer screening and surgical treatments due to the pandemic, there could be several changes in the clinicopathological characteristics of breast cancers determined in this period. The results of the study showed that tumors determined during the pandemic were larger compared with those in the pre-pandemic period (20 vs. 30 mm). When T staging distribution was evaluated, with the high incidence of T3, it can be said that the tumors determined during the pandemic were at a more advanced stage. In contrast, in a study by Vanni et al.[7] that examined the effects on breast cancer presentation of the delays in the diagnosis and treatment experienced during the COVID-19 pandemic, no significant difference was determined between lockdown and pre-lockdown groups in respect of tumor size. The authors attributed this to the brief time between the suspension of breast cancer screening and the study and stated that larger sized and more clinically evident tumors may be observed in the following months. Vanni et al.'s[7] study included patients in a 2.5-month period from the onset of the pandemic, whereas in the current study, this period was 9 months. Therefore, it can be considered that the longer duration of our study affected the determination of a larger tumor size in the pandemic group. When the doubling time of breast cancer is considered, a certain period of time is needed for the emergence of the results of delayed diagnosis and treatment.[8] Despite the pandemic waves that have been experienced throughout the world and the decrease in case numbers from time to time, breast cancer screening programs have not completely returned to normal pre-pandemic levels. The entire world has experienced more than one peak

Table 2. Demographic and clinicopathological characteristics of the groups

Characteristics	Groups		
	Pre-pandemic n	Pandemic n	*P*
Age (years), median (Q1–Q3)	56 (46.5–65)	60 (46–68.5)	0.22
Tumor size (mm), median (Q1–Q3)	20 (15–27)	30 (19.5–47)	**<0.001**
Axillary lymph nodes status			
Negative	149 (68%)	39 (54.9%)	**0.044**
Positive	70 (32%)	32 (45.1%)	
Number of metastatic lymph nodes, median (Q1–Q3)	2 (1–4)	2 (1–3.25)	0.87
Invasive/*in situ* tumor distribution			
In situ	23 (10.5%)	4 (5.6%)	0.22
Invasive	196 (89.5%)	67 (94.4%)	
Histological type			
IDC	132 (67.3%)	40 (59.7%)	0.50
ILC	29 (14.8%)	13 (19.4%)	
Others	35 (17.9%)	14 (20.9%)	
Histological grade			
Low	23 (11.7%)	4 (6%)	0.17
High	173 (88.3%)	63 (94%)	
LVI			
Yes	80 (36.5%)	30 (42.3%)	0.38
No	139 (63.5%)	41 (57.7%)	
PNI			
Yes	25 (11.4%)	8 (11.3%)	0.97
No	194 (88.6%)	63 (88.7%)	
Multifocal/multicentric focus			
Yes	55 (25.1%)	19 (26.8%)	0.78
No	164 (74.9%)	52 (73.2%)	
Waiting time for surgery (days), median (Q1–Q3)	44 (32–60.5)	56 (36.5–80.5)	**0.001**
BI-RADS			
BI-RADS 4	69 (31.5%)	23 (32.4%)	0.88
BI-RADS 5	150 (68.5%)	48 (67.6%)	

Bold values indicate statistical significance. n, number of patients; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PNI, perineural invasion; BI-RADS, Breast Imaging Reporting and Data System.

Table 3. T and N stage distribution between the groups

	Groups		
	Pre-pandemic n (%)	Pandemic n (%)	*P*
T			**0.002**
Tis	23 (10.5%)	4 (5.6%)	
T1	97 (44.3%)	23 (32.4%)	
T2	89 (40.6%)	30 (42.3%)	
T3	8 (3.7%)	12 (16.9%)	
T4	2 (0.9%)	2 (2.8%)	
N			0.11
N0	150 (68.5%)	39 (54.9%)	
N1	50 (22.8%)	24 (33.8%)	
N2	15 (6.9%)	5 (7.1%)	
N3	4 (1.8%)	3 (4.2%)	

Bold values indicate statistical significance. n, number of patients; T, tumor; Tis, carcinoma *in situ*, N, lymph nodes.

in COVID-19 case numbers. Therefore, the current study is of value in showing changes in breast cancer presentation over a longer period.

When the involvement of malignant axillary lymph nodes was evaluated, there was reported to be significantly more malignant lymph node involvement in the lockdown group in Vanni et al.'s[7] study. A significantly high N2 incidence in the lockdown group was also determined when N stage distribution was examined. Another study by Toss et al.[9] reported that a 2-month pause in mammography screening during the pandemic caused an 11.2% increase in the incidence of node-positive breast cancer when compared with the corresponding period of the previous year. Similarly, in the current study, axillary lymph node involvement was significantly more frequent in the pandemic group (45.1% vs. 32%). However, no difference was determined between the groups in respect of N stages.

Both tumor size and lymph node involvement are used in breast cancer staging and are prognostic factors.[10] In the current study, both findings (tumor size and lymph node involvement) indicated that more advanced-stage tumors were determined during the pandemic compared with the pre-pandemic period. Similarly, Yılmaz et al.[11] determined early-stage breast cancers at the rate of 52.9% during the pandemic, compared with 81.2% in the pre-pandemic period, and advanced-stage cancers at 47.1% and 18.8%, respectively. Factors due to the pandemic, including the interruption of breast cancer screening programs during the COVID-19 period, the practice of limiting hospital admissions to symptomatic patients, and the hesitation of symptomatic patients to visit any health institution, may have affected this result. Another factor affecting this result was thought to be the delays experienced in the treatment of patients diagnosed with breast cancer. In a study on pregnant patients with breast cancer, it was reported that delays in treatment of 1, 3, and 6 months increased the risk of axillary lymph node involvement by 0.9%, 2.6%, and 5.1%, respectively.[12] In another study, Smith et al.[13] showed that the treatment delay time has a significant effect on the 5-year survival rate after a breast cancer diagnosis. In that study, women with a delay in treatment of >6 weeks were seen to have shorter survival times than those who underwent surgery in a shorter period after diagnosis (<2 weeks), with 5-year survival rates of 80% and 90%, respectively. In the current study, the waiting time for surgery was significantly longer in the pandemic group than in the pre-pandemic group (44 vs. 56 days). During the COVID-19 pandemic, many non-urgent operations were postponed in an effort to protect hospital resources and limit the spread of the virus. It has been estimated that in the first 12-week peak of the pandemic, approximately 38% of cancer operations were canceled worldwide.[14] Therefore, in the current study, the longer waiting time for surgery in the pandemic group is an expected result. However, the definitions of "waiting time for surgery" in the literature show some differences. In some studies, it is defined as the number of days between the date of histological diagnosis of cancer (not the radiological diagnosis) and the date of surgery.[15,16] In the current study, it was calculated as the total number of days between the first radiological examination (mammography, US, or MRI) that reported suspected breast cancer (BI-RADS 4/5) and the date of surgery.

The problems experienced in the management of breast cancer during the COVID-19 pandemic were not only delays to operations but were also experienced at several stages, such as the performance of biopsies and evaluations of histopathological results. As it was thought to be more correct to take all these steps into consideration, the date of the first radiological examination that reported suspected malignancy was taken as the basis for the current study.

In Turkey and throughout the world, there was a significant drop in the number of cancer cases during the COVID-19 pandemic. In a study conducted in the USA, the mean weekly number of newly identified patients with breast cancer during the pandemic was determined to have fallen by 51.8% compared with the pre-pandemic period (2208 to 1064 patients).[17] Another study in Italy reported a drop of 26% in the number of patients newly diagnosed with breast cancer during the pandemic compared with the previous year.[18] In the current study, the total number of breast cancer cases diagnosed in our hospital during the COVID-19 pandemic showed a decrease of 55.1% (352 to 158 patients) compared with the corresponding period of the previous year, and the number of patients with breast cancer underwent surgery fell by 67.5% (219 to 71 patients). However, this decrease does not reflect a decrease in the actual number of patients with breast cancer. The main reasons for this decrease in the incidence of breast cancers appear to be the suspension of screening programs and the re-allocation of healthcare system resources for COVID-19. In addition, the fact that a lower number of patients in the pandemic period had a larger tumor size and more frequent lymph node metastasis suggests that patients either delayed presenting at the hospital or experienced delays in receiving treatment.

There were some limitations of this study, primarily because it was retrospective in design and conducted in a single center, so the sample size was relatively small. However, it is an important study, as it is one of the few to have examined the effects of the COVID-19 pandemic on breast cancer presentation. Moreover, it can be considered more sensitive than abovementioned research (Vanni) since it shows the changes in patients with breast cancer over the longer period of 9 months from the onset of the pandemic.

In conclusion, the results of this study demonstrate that breast cancers during the pandemic showed typical malignant radiological findings. This study also demonstrates that the tumor size was larger and lymph node involvement was more frequent in breast cancers diagnosed during the COVID-19 pandemic. Furthermore, patients diagnosed during this period could have to wait longer for surgical treatment. Despite the significant decrease in mortality rates and the increase in survival as consequences of the widespread implementation of breast cancer screening programs and developments in treatments, the suspension of screening programs and delays in treatments because of COVID-19 have had a negative impact on breast cancer management. The effects of these delays on long-time breast cancer outcomes (disease-free survival and overall survival) would require longer follow-ups. As screening programs are a key element of the early diagnosis of breast cancer, and it is not known when the pandemic will end, it can be recommended that screening programs should be continued without interruption, with all the necessary precautions taken to prevent the spread of infection.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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