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Effects of a COVID-19 Pandemic on Breast Cancer Management

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic caused some difficulties in the management of breast cancer, so we examined the effect of this challenging condition on the diagnosis and treatment of breast cancer.

Methods: In this study, the 26 month period from March 2019 to April 2021 was divided into two periods according to the start date of the pandemic. The previous 13 months were defined as A, the next 13 months as B, and the first 3 months of both periods were defined as A* and B*. All patients diagnosed with breast cancer were evaluated retrospectively based on hospital records, in terms of some characteristics like histopathological, and molecular subtypes of the tumor, primary systemic treatment (PST) frequency and its model, axillary staging method before PST, and surgical method. The results were evaluated with the chi-square test, and $p>0.05$ was statistically significant.

Results: All patients were female, 356 cases were in the A period, 30.3% of them had PST as neoadjuvant chemotherapy (NAC) and 37% (n=40) had sentinel lymph node biopsy before PST. There were 281 patients in period B, 116 cases received PST (41.2%); NAC and neoadjuvant endocrine therapy (NET) were staged radiologically and cytologically if necessary. When the findings of periods A and B (and A*-B*) were compared, the difference in PST in B compared to period A was statistically significant ($p=0.005$), insignificant for NAC ($p=0.849$), and highly significant for axillary approach and NET ($p=0.000$). In period B, more breast-conserving surgery (BCS) was applied, which may have been due to more initiation of PST. Overall, results in A* and B* were broadly similar to periods A and B.

Conclusion: During the COVID-19 pandemic, some adjustments were made in breast cancer management plans. PST was applied more often, NET became an option to start treatment, the axillary staging was performed based on a non-invasive method and surgically, BCS was performed more frequently.

Keywords: COVID-19 outbreak, breast cancer, primary systemic therapy, neoadjuvant chemotherapy, sentinel lymph node biopsy

INTRODUCTION

The severe acute respiratory syndrome-coronavirus-2 outbreak has created some unexpected challenges in healthcare around the world. There are still disruptions in health services in all countries that still prevail and can be fatal, especially in conditions that affect the immune system, such as cancer. The risk of morbidity and mortality with the transmission of coronavirus disease-2019 (COVID-19) infection is 4.5 times higher than that in the general population (1).

However, early diagnosis and treatment are particularly important for cancer patients and should not be delayed or compromised. For this reason, some changes have been made to the standard care for breast cancer patients to refrain from the risk of infection, and relevant guidelines have been prepared (1-3).

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More than 600 newly diagnosed breast cancer patients apply to the oncology clinic of our hospital every year, more than half of them are treated by the breast surgery department of the surgery clinic, and their treatment is planned by discussing the case in the breast tumor council after preliminary diagnostic procedures are achieved. But when the epidemic started, our hospital was been organized as a COVID-19 center, when the first case was identified in our country namely in March 2020. Accordingly, health services and work plans have changed, elective surgeries have been cut for a short while, and there are still some restrictions. During this period, some changes were made in the treatment planning and application in patients with breast cancer.

In this study, we reviewed the effect of the pandemic on the diagnosis and treatment of breast cancer in our center in terms of the number of patients, the way of starting the treatment, the choice of neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET) for primary systemic treatment (PST), the approach to the axilla, and the surgical technique, by comparing these parameters with those of the previous similar time.

METHODS

According to "March 2020" the Start date of the Pandemic, the 26-month between March 2019 and April 2021 were divided into two periods. The 13-month period before March 2020 was defined as periods 'A' and the 13 months after that as period 'B.'

We also aimed to examine whether the effects of uncertainties and restrictions in the B period, especially in the first months of the pandemic, were different in the first 3 months compared to the whole process. As result, the first 3 months of periods A and B were handled separately as A* and B*.

The study was approved by the Ethics Committee of the Universtiy of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, with the decision dated 07.01.2021-271.

Statistical Analysis

All patients diagnosed with breast cancer were analyzed retrospectively using breast cancer board records. The number of patients, whether the patients were metastatic at the time of diagnosis, the histopathological structure, and molecular subtype of the tumor, the selected model as PST and its frequency of use, sentinel lymph node biopsy (SLNB) for axillary staging before PST, and the surgical method were examined. The results were analyzed with the chi-square test, and a p-value of <0.05 was statistically significant.

RESULTS

Our study population consisted of female patients with a mean age of 61 years (22-91) in period A, and 59.5 years (30-88) in period B. When analyzed according to the histopathological structure of the tumor, an equal number of patients with ductal carcinoma *in situ* was in A and B periods the same (n=27), but rates of them were 7.5%-9.6% respectively. In periods A, and B respective number of patients received the diagnosed with lobular carcinoma [n=16 (4.5%) vs. n=24 (8.5%)], and invasive ductal carcinoma [n=313 (88%) vs. n=230 (81.9%)] (Table 1).

We also defined breast cancer patients according to their molecular subtypes. In periods A, and B, respective numbers of patients had luminal A [n=210 (63.8%) vs. n=147 (57.9%)], luminal B [n=20 (7.9%) vs. n=20 (7.9%), HER-2 (+) [n=61 (18.6%) vs. n=55 (21.6%)], triple-negative breast cancer [n=38 (11.6%) vs. n=32 (12.6%)]. The results of the two periods were found to be similar in terms of histopathological structure.

In period A, 15, and in period B, 12 patients had metastatic breast cancer at their first admission with a similar metastatic breast cancer detection rate (4.2%) (Table 2).

In period A, 356 patients had newly diagnosed breast cancer, and 30.3% (n=108) had received all PST all in the form of PST. Before PST, 40 (37%) cases had undergone SLNB.

In period B, the total number of patients decreased by 22% to 281, and 116 (41.3%) patients were started on PST. In the PST group 10 (3.5%) patients received NET, and 106 (37.8%) PCT. SLNB was not applied to any patient in period B before PST. In

Table 1. Histopathologic characteristics of tumors and patients'

Characteristics of tumor and patients	A	B
Age (median)	61	59.5
DCIS	27	27
Lobular	16	24
Ductal	313	230
Total	356	281

DCIS: Ductal carcinoma *in situ*

Table 2. Specific characteristics of the tumors

Molecular subtype of tumor	A	B
Luminal A	210	147
Luminal B	20	20
HER-2 (+)	61	55
Triple-negative	38	32
Total	356	281
M+	**15**	**12**

the comparison of these periods, the rates of receiving PST and NAC was found to be borderline significant (p=0.005), while the intergroup difference was found to be highly significant (p=0.000) in terms of receiving NET and SLNB for axillary staging before PST (Table 3).

The total number of patients in A* was 75, and in B* 79. In periods A* and B *, the same number of patients (n=20) were started on NAC, in period B a slightly higher number of patients (53% vs. 38.3%) received NAC, but without any statistically significant intergroup difference (p=0.0849). In A*, 12 patients underwent SLNB before PST, while SLNB was not performed in B* with a highly significant intergroup difference (p=0.000), (Table 4).

Our patients were also analyzed according to the surgical procedures; mastectomy (Mx) or breast-conserving surgery (BCS) they had undergone in periods A and B. In period A 232 (71%) of the 334 cases were treated with BCS, while Mx was applied to 102 patients for treatment (n=96; 27%) or prophylaxis (n=6; 1.8%) In period B, a total of 228 patients underwent surgery, including BCS (n=181: 79%) and Mx (n=47: 21%). Within the first 3 months, BCS was performed for 57 (24%), and Mx for 20 (21%) patients in A*, while in B* 40 (22%) patients received BCS, and Mx was performed for 13 (27%) patients (Table 5).

Six patients who have diagnosed in period A and completed PST did not want to wait on days when surgical procedures were limited in our hospital and were operated on other centers. In period B, 4 patients died from COVID.

Table 3. First line of treatment and staging of axille before treatment

First line of treatment and approach to axilla	A	B	p
PST	108	116	0.005
NAC	108	106	0.005
NET	0	10	0.000
SLNB	40	0	0.000
Total	356	281	-

PST: Primary systemic therapy, NAC: Neoadjuvant chemotherapy, NET: Neoadjuvant endocrine therapy, SLNB: Sentinel lymph node biopsy

Table 4. Comparison PST and SLNB between in A* and B* period

	A*	B*	p
PST	20	20	0.849
SLNB	12	0	0.000

PST: Primary systemic therapy, SLNB: Sentinel lymph node biopsy

Table 5. The surgical method used in both period and A*and B*

Surgical method	A* (%)	A	B* (%)	B
BCS	57 (24.5)	232	40 (22)	181
Mx	20 (21)	96	13 (27)	47
Prophylactic Mx	3 (3.75)	6	0 (0)	0
Total	80	334	53	228

BCS: Breast-conserving surgery, Mx: Mastectomy

DISCUSSION

The COVID pandemic has caused some problems in the field of health apart from itself. It directly affected health services, patients, and healthcare workers. Knowing that it is necessary to avoid risks while planning the treatment of our patients, we tried overcoming them with the least morbidity, especially for patients with breast cancer. Our hospital has been organized as a COVID-19 center since March 2020, when the first case was identified in our country, and elective surgeries were interrupted for a while and continued partially for a certain period.

The risk of morbidity and mortality with the transmission of COVID-19 infection in cancer patients is 4.5 times higher than that in the general population (1). For this reason, some changes have been made in the standard care that avoids the risk of infection for breast cancer patients in the world and in our country, and guidelines have been prepared to that end (1,2).

According to the current staging method of breast cancer, treatment should be started according to the molecular subtype. The first step of treatment option is general surgery or PST, according to criteria such as hormone receptor status, tumor size, axillary involvement, nuclear grade of the tumor, Ki-67 proliferation index, which is evaluated individually in each patient. Triple-negative and cERB 2 (+) cases are the most common patients in whom PST is started because these patients respond well or even completely to treatment. Luminal A-B tumors respond less to PST, but less surgery in these conditions necessitated some changes in treatment planning (1-3).

In our country, a study was initiated to provide a consensus on what can be done in order not to disrupt breast cancer treatment in the first days of the pandemic (3). In this study, where we also participated in, 46 statements related to 28 different case scenarios were voted electronically by a panel consisting of 51 surgeons and medical oncologists with the necessary skills and experience in breast cancer management, using the Delphi method. While 37 of them reached a consensus in the first round as acceptance or rejection, nine of them were put to vote as the required decision threshold could not be reached in the second

round. At the end of two rounds, a statement was approved as a proposal for each of the 14 case scenarios.

For patients with node-negative, small-sized triple-negative, HER-2-positive, and luminal A-like tumors, the consensus was that neoadjuvant systemic therapy should be administered until conditions improve for surgical treatment. Panelists also agreed to expand systemic therapy for patients with clinically and completely responsive HER-2-positive and luminal B-like tumors after application of neoadjuvant systemic therapy (3).

While evaluating our patients, we considered the current conditions, the Turkish consensus report, and the other guidelines; we postponed reconstructive surgery, benign breast surgeries, those with low-grade malignancy, and only operated on cancers that should not be delayed. The breast cancer council did not take a break from its work at our hospital, it continued online for the first 3 months, then in accordance with the pandemic measures and with the participation of as few specialists as possible from all departments.

We had to use the resources of the operating room very sparingly, during the 2nd and 3rd waves, (December 2020 and April 2021), the operating room was converted into an intensive care unit (4). Based on these challenging conditions, and up-to-date information, we reduced the number of invasive procedures.

In the period when the working hours in the operating room were very restricted, PST was brought to the agenda in the Tı-T2 HER-2 negative luminal A and B patients, for whom we did not routinely prefer. As well as NET became an option in treatment, it was chosen as the PST before surgery; NET came to the fore with only extremely limited indications previously ie. for only those who could not receive NAC or had no chance for surgery. Before and during period A, SLNB for axillary staging was being applied before PST, although with gradually decreasing frequency. The SLNB procedure before PST was not applied anymore in period B because of its decreasing use and overwhelming information indicating that the surgical procedure increased morbidity, and that radiological evaluation and then, if necessary, biopsy yielded comparable results (2,3).

In this way, the number of intraoperative frozen examinations decreased. The reduction of frozen procedures to be studied in fresh material with a high risk of contamination and working with cytological samples fixed with 70% alcohol also reduced the risk exposed by pathology department workers.

With the pandemic, interruptions, and disruptions were seen in cancer screening programs worldwide, and the number of newly diagnosed breast cancer patients decreased compared to the period A. Corsi et al. (1) reported an approximately 32% decrease in the rates of newly diagnosed breast cancers in their breast cancer clinics "a non-COVID center" compared to the same period as the previous year (93 vs. 63).

In another study conducted in France, a decrease of 43.5% was reported during the pandemic (5). In our study, a 22% decrease was noted between periods A and B. The first 2 months were conducted in the studies conducted in Italy and France. The pandemic started earlier in Italy and France and led to serious disruptions in health services. Our country was relatively more prepared against a pandemic. In these two studies, authors reported that elective surgery was not performed in the first month, while in our hospital, cancer surgery continued, albeit to a limited extent.

Curigliano et al. (6) listed suggestions on how breast cancer treatment should be performed in this process. Accordingly, there are 4 categories in health services; emergency, high, medium, and low priority; breast cancer is in the high and medium-risk group. The authors emphasize that cancer patients should be treated in clean hospitals or departments with meticulously careful use of resources. In our hospital, a vertical structuring plan was applied during the COVID process, and the departments allocated to COVID patients in our hospital, which consists of five blocks, and the entrance and exit of other departments and the work schedules of the employees were arranged separately (4).

Similar recommendations were made to surgeons in the guide written by Curigliano et al. (6) and in the Turkish consensus report (3). These recommendations concern basic patients whose NAC was completed, and emphasize performing emergency-priority surgeries, but postponing surgeries to be performed for benign conditions, esthetic indications, oncoplastic procedures larger than level 1, and reconstruction plans. We followed these rules. While prophylactic Mx and reconstruction were performed in 6 patients in period A, none of the patients included in this study in period B underwent these surgeries.

The study by Rocco et al. (7), it was aimed to evaluate how breast surgeons adapt their surgical activities due to the rapid spread of COVID-19 around the world. A panel of 12 breast surgeons from the most affected areas of the world held a virtual meeting on April 7, 2020, and a web-based questionnaire was designed to assess changes in surgical practices to be carried out by breast surgeons from various countries. The virtual meeting showed that different countries and regions are experiencing different stages of the pandemic. Surgery was given priority to patients with aggressive disease who were not candidates for PST, patients with the progressive disease under neoadjuvant systemic therapy, and those who completed neoadjuvant therapy.

Although 100 breast surgeons who participated in this survey favored traditional standards for treating potentially fatal diseases such as breast cancer, it was concluded that as the situation worsened, alternative strategies should be adopted. In a consensus study conducted in our country, it was observed that surgeons participating from different centers were not willing to postpone surgery in the first round of voting (3).

Physicians dealing with breast cancer in China, the origin of the COVID-19 pandemic, emphasized that the timing of the surgery should be decided according to factors such as the severity of the pandemic and the allocation of medical resources in their study, where they sought an answer to the question of how to manage the treatment in this period. For this purpose, by presenting a short algorithm, surgical candidates who received the diagnosed with T1N0 tumors were allocated for surgery, and patients with breast cancers at T2 and N1 and above stages were allocated as PST candidates (8).

Sheng et al. (9), on the other hand, have stated that cancer treatment has changed during the COVID-19 pandemic, and doctors must carefully weigh the risks and benefits of administering immunosuppressive therapy during the pandemic. They have emphasized that tumor biology should guide breast cancer treatment planning, and genomic tumor profiling should be used more often with a resultant increase in the use of PST. Our practice and data also support this view.

NET, which was not preferred previously as a primary treatment, found supporters in this period. According to a survey by Park et al. (10), conducted with 114 physicians from 29 states in the USA, including 42 (37%) medical oncologists, 14 (12%) radiation oncologists, and 58 (51%) surgeons, most of these participants were "rarely" using NET for ER. + Breast cancer before the COVID-19 pandemic. In this process, 54% of them recommended using NET until surgery, while 46% suggested that they could delay the surgery for 2 months without NET. The preferred NET regimen was tamoxifen for premenopausal and an aromatase inhibitor for postmenopausal women. In this study, it was also argued that NET also reduces the rates of axillary surgery and that axillary surgery may not be required after the NET, which changes the clinical scenario of a patient with micrometastasis in the sentinel lymph node as the duration of drug administration is prolonged (10).

In a study presented at the 2020 San Antonio Breast Cancer Virtual Symposium, it was reported that rates of interest in and acceptance of NET by both physicians and patients during the pandemic period increased compared to the previous period, and NETwas started in 36 patients in this small series of 45 patients to act as a bridge until surgery (11). In the series we presented, we found that while NET was not performed as PST in any patient in period A, NET was administered to 10 patients (8.6%) in period B. Although we do not have a prediction about the effect of NET on axillary surgery, this issue is worth examining in a larger series.

The use of radiotherapy as a PST option during the pandemic period has been discussed both in our country and in the world, but any different application specific to this period has not been made.

As for the effect on the COVID-19 pandemic in the choice of technique in patients who can undergo surgery, a surgical technique can be chosen in a way that does not prolong the duration of surgery and hospitalization at times and places where surgery can be performed. In a study in which the results of 64 breast centers in England were compiled, it was reported that 62% of 957 patients who underwent surgery during this period underwent BCS and 37% had a Mx (2).

To summarize, in this study 108 (30.33%) patients received PST in period A and 116 (41.3%) patients in period B. Despite a 22% decrease in the total number of cases between periods A and B, the increase in the rate of PST was found to be significant. Before PST, SLNB was performed in period A, albeit in decreasing numbers, it was not performed in period B.

While NET was planned as the only treatment option for patients who could not receive anesthesia in period A, it was applied as the first treatment choice in period B and to save time until surgery.

Study Limitations

In our opinion, the weakness of this study was that it could not be determined whether there was a delay in the initial diagnosis. Our hospital is not a screening center, only registered women and women who apply themselves are included in the screening group for breast cancer. Other studies conducted during the epidemic will be useful to learn the effects in terms of early diagnosis.

CONCLUSION

During the ongoing COVID-19 pandemic, the breast cancer council of our hospital is still carrying on and makes its decisions, as always, with the "tailoring management" in addition to considering the working schedules of the clinics. Breast surgery for benign conditions, prophylactic and reconstructive surgery were not performed. Prominent differences were observed between periods A and B about PST, where is planned more

frequently when surgery is limited, including NET as PST, probably due to this, BCS was applied more.

The approach to the axilla has changed significantly. In patients with breast cancer, the axillary staging is currently performed only by radiological and cytological examinations in our clinic.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, with the decision dated 07.01.2021-271.

Informed Consent: Obtained from all patients and available in their files.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., A.M.P., B.D.Y., P.Ö.Y., M.M.A., A.A., Concept: S.G., B.D.Y., Design: S.G., B.D.Y., Data Collection or Processing: S.G., A.M.P., P.Ö.Y., A.A., Analysis or Interpretation: S.G., A.M.P., P.Ö.Y., M.M.A., A.A., Literature Search: S.G., A.M.P., Writing: S.G., A.M.P.

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