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Advanced Stages and Increased Need for Adjuvant Treatments in Breast Cancer Patients: The Effect of the One-year COVID-19 Pandemic

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Abstract. *Background/Aim: The COVID-19 lockdown includes restrictive measures and temporary health system reorganization. Resources were shifted to COVID-19 patients, screening programs were temporary suspended, and oncological care suffered slow-down. The aim of the study was to evaluate the impact of these measures on breast cancer patients. Patients and Methods: All breast cancer patients referred to our unit from February 21, 2019 to February 21, 2021 were enrolled. Type of treatments and surgery, TNM, tumor diameter, and predictive and prognostic factors were analyzed. Results: Out of 445 patients with a breast cancer diagnosis, 182 (40.9%) were enrolled in the COVID-19 group (from February 21, 2010 to February 21, 2021). These patients were compared with 263 (59.1%) patients pre-COVID-19. Tumor diameters were bigger in the COVID-19 group. Type of surgery and N staging were statistically significantly different. Extreme advanced disease incidence was significantly different between the groups (2.7% COVID-19 group vs. 0 pre-COVID-19 group, p=0.011). Incidence of post-surgical radiation-therapy was higher in the COVID-19 group. Other variables analyzed were comparable without a statistically significant difference. Conclusion: COVID-19 led to increased tumor dimensions, advanced N-staging, and increased need for adjuvant treatments in breast cancer.*

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Since the beginning of 2020, Sars-CoV-2 infection dramatically spread worldwide (1). National lockdown was introduced in many countries as a strategy to flatten the curve of the pandemic (2). These restrictions have changed the daily routine and, especially during the first lockdown, have been associated with a decrease in, or cessation of, most non-COVID-19 health services (3).

Temporary national health system reorganization led to an increased concern about the effect on non-COVID-19 patients requiring time-critical access to health-care services (4-6). Patients with cancer, for which timely diagnosis and timely initiation of treatment are crucial to ensure optimal result, have been strongly affected by these health system flaws (5-7).

Since the beginning of the lockdown, multiple changes have been advised by professional and scientific committees regarding cancer patients management. However, heterogeneity has been observed in the implementation of these recommendations aiming to avoid delays in cancer care (5, 8-10). Despite these exhortations, especially during the first lockdown. oncological diagnostic procedures and care suffered a significant slowdown and screening programs were temporarily suspended (9, 11, 12). Early diagnosis, especially in breast cancer, improves oncological outcomes by providing care at the earliest possible stage and is therefore an important public health strategy in all settings (13). In the last years, breast cancer screening led to an increase in early staging, and together with the evolution of

treatments, have improved cancer outcomes and reduced invasive treatments (14).

Additionally, fear and anxiety play a major role in the course of patient's disease even in normal times (15). During the COVID-19 pandemic, infection related anxiety of patients could impact diagnosis and progression of breast cancer (16). According to this hypothesis, there have been reports of patients who, despite having a breast cancer diagnosis, refused treatments due to anxiety of Sars-CoV2 infection (16).

The aim of our study was to evaluate the increase in incidence of advanced breast cancer stages due to COVID-19 pandemic and its impact on surgical procedures or treatments.

Patients and Methods

Study design. In our retrospective study, we analyzed all patients with a diagnosis of breast cancer referred to our Breast unit from February 21, 2020 to February 21, 2021. These patients were enrolled to our study and considered as the COVID-19 group. These patients were compared with patients referred to our Breast department during the same periods of the previous year (From February 21, 2019 to February 21, 2019), which consisted the Pre-Covid-19 group. Five hundred and twenty-two patients were considered in our study. The study was approved by the local Ethical Committee of the Fondazione Policlinico Tor Vergata (reference 122/21).

Number of patients admitted in the Breast unit were reported and patients without malignancy were excluded from the analysis. For each patient, age, sex, date of diagnosis, tumor subtype, and staging and type of treatments (*e.g.* surgery, neoadjuvant therapy) were recorded. Diagnosis was mainly obtained by core needle biopsy or Vacuum assisted biopsy. In patients without previous diagnosis and in patients with advanced disease, diagnosis was obtained by definitive pathological examination after surgical biopsy.

Prior administration of neoadjuvant chemotherapy, data were collected from clinical notes. Surgery procedure was distinguished between breast conservative surgery, surgical biopsy and breast invasive surgery. Breast conservative surgery included all procedures with partial gland removal but with complete removal of the lesion. Partial removal of the lesions, when a complete resection of the tumor could not be achieved was considered as surgical biopsy. Otherwise, breast invasive surgery comprised complete removal of the glandular tissue. Preoperative image-guided wire localization was reported for breast conservative surgery and the lesions were considered as non-palpable.

Clinical and pathological N stage and axillary surgical procedure were analysed in the study cohort. Patients without clinical or radiological lymph node involvement underwent sentinel lymph node biopsy procedure (SLNB). Otherwise, patients with axillary involvement or SLNB positive underwent axillary lymph node dissection (ALND).

Tumor maximum diameter was collected from pathological examination in case of complete removal of the tumor. Otherwise, in patients treated with upfront neoadjuvant therapy, information regarding tumor diameter was obtained from breast magnetic resonance reports at diagnosis. In both cases, diameter was reported in millimetres. Lymph node involvement was collected from pathological examination in case of axillary surgery. Otherwise, was obtained from imaging or clinically lymph node involvement. Metastasis was evaluated by PET-CT scan. Staging was based on recommendations from AJCC 2018 (edition VIII) of TNM classification. Grading of the neoplasia was determined from pathological examination. Estrogen receptor (ER), progesterone receptor (PR), and Ki67 index were expressed as percentage of positive cells in specimens studied with immunohistochemistry. Over-expression of human epidermal growth factor receptor 2 (HER2+) was identified by immunohistochemistry and confirmed by FISH, and reported as a dichotomous variable (HER+ yes/no).

Statistical analysis. Data were collected into an EXCEL sheet (Microsoft, Washington, DC, USA). Continuous variables, are reported as median and ranges. T test was used to examine the significance of differences between the two groups. Categorical data were recorded as numbers and percentages. Analysis was performed using the Fisher's exact test in case of dichotomous variables or Monte Carlo test for non-dichotomous variables. Variables with assigned p-values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS statistical package version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

From February 21, 2020 to February 21, 2021 a total of two hundred and fourteen (n=214) patients were discussed at our breast cancer multidisciplinary meeting (COVID-19 group) compared to three hundred and eight (n=308) in the same period of the previous year (Pre-COVID-19 group). During the pandemic we observed an absolute reduction of about 30% of discussed cases. Twenty-four cases of the COVID-19 group (11.2%) were follow-up patients and were excluded from the analysis. According to this indication, 31 cases of the Pre-COVID-19 group (10.1%), were excluded as well (p=0.0667). Additionally, patients with malignant suspicious lesions not confirmed by pathological examination were excluded from the study and were 9 (4.2%) and 14 (4.5%) cases, respectively, in the COVID-19 and pre-COVID-19 groups (p=1.000).

Four hundred forty-five patients fulfilled the inclusion criteria: COVID-19 group (n=182) and pre-Covid-19 group (n=263) and were analyzed. Out of these, 2 (1.1%) patients were male in the Covid-19 group *versus* 4 (1.5%) in the pre pandemic group (p=1.000).

Medians of age were 62.6 years (range=32-93 years) in the COVID-10 group and 61.2 years (range=32-90 years) in the Pre-lockdown group; relative p-value was 0.206. During the COVID-19 period, 37 (20.3%) patients underwent invasive breast cancer, 116 (63.7%) conservative breast cancer, and 29 (15.9%) diagnostic biopsies. During the previous year, pre-COVID-19, surgical procedures included: 80 (30.4%) invasive breast cancer surgeries, 108 (59.4%) conservative breast cancer surgeries, and 30 (11.4%) diagnostic biopsies showing a statistically significant difference compared to COVID-19 group p=0.002 (Table I).

Table I. *Distribution of types of surgery between the groups with relative p-values, absolute numbers and (percentage).*

	COVID-19 group (n=182)	Pre-COVID-19 group (n=263)	*p*-Value
Breast invasive surgery	37 (20.3%)	80 (30.4%)	**0.002**
Conservative surgery	116 (63.7%)	153 (58.2%)	
Diagnostic biopsy	29 (15.9%)	30 (11.4%)	
SNLB	147 (80.8%)	224 (85.3%)	0.244
SNLB positive	30 (20.4%)	27 (12.1%)	**0.038**
ALND	53 (26.9%)	55 (20.9%)	**0.041**

SNLB: Sentinel lymph node biopsy; ALND: axillary lymph nodes dissection. Bold values indicate statistical significance.

Table II. *TNM distribution between groups with relative p values, absolute numbers and (percentage).*

	COVID-19 group (n=182)	Pre-COVID-19 group (n=263)	*p*-Value
T			0.095
T *in situ*	22 (12.1%)	36 (13.7%)	
T1	78 (42.8%)	157 (59.7%)	
T2	46 (25.3%)	51 (19.3%)	
T3	9 (4.9%)	7 (2.6%)	
T4	9 (4.9%)	4 (1.5%)	
N			**0.006**
N0	96 (52.7%)	133(50.5%)	
N1	26 (14.3%)	41 (15.6%)	
N2	18 (9.9%)	11 (4.2%)	
N3	13 (7.1%)	9 (3.42%)	
M			
M0	168 (92.3%)	245 (94.3%)	0.852
M1	14 (7.7%)	18 (5.7%)	

Bold value indicates statistical significance.

SNLB was performed in 147 (80.8%) patients in the COVID-19 group, where 30 (20.4%) obtained a positive cancer diagnosis at histological examination. In the Pre-COVID-19 group, 224 (85.3%) patients underwent SNLB and positive results were recorded in 27 cases (12.1%). Incidence of lymph node positivity through SNLB showed a statistically significant difference, 30 (20.4%) cases in the COVID-19 group *versus* 27 (12.1%); p=0.038. Conversely, indications for SNLB did not show statistically significant difference, p=0.244 (Table I). During the COVID-19 period, ALND was performed in 53 (26.9%) patients compared to 55 (20.9%) in the Pre-COVID-19 group, showing a statistically significant difference with a p-value of 0.041 (Table I).

At pathological examination of surgical or diagnostic specimens, 151 (82.9%) were determined as ductal carcinoma, 20 (11%) as lobular carcinoma, and 11 (6.1%) were defined as others in the COVID-19 group. In the Pre-COVID-19 group, 215 (81.7%), 30 (11.4%) and 18 (6.8%) were determined as ductal carcinoma, lobular carcinoma, and others, respectively. No statistically significant differences were found (p-value=0.744). Out of these, 21 (11.5%) were determined as *in situ* carcinoma during the COVID-19 period and 43 (16.3%) in the control group, p=0.214.

Median tumor diameters were 21.7 mm (range=1.5-80 mm) in the COVID-19 group and 16.9 mm (range=1-80 mm) in the control group. Diameters of the lesions showed a statistically significant difference between the groups, p=0.003. Despite a higher incidence of T2, T3 and T4 in the pandemic group, T distribution did not show a statistically significant difference, p=0.091 (Table II).

Lymph node involvement showed a statistically significant difference between groups (p=0.006); grading of involvement is presented in Table II. COVID-19 group exhibited higher incidence of N2, 9.9% *vs*. 4.2% in Pre-COVID-19 group showing a statistically significant difference with a p-value of 0.019. Fourteen patients (7.7%) presented metastatic breast cancer disease in the COVID-19 group compared to 22 cases (8.3%) with metastasis in the Pre-COVID-19 group (p=0.861).

During the pandemic period, 6 (3.3%) patients presented extreme advanced breast cancer (Figure 1). Instead, only 1 (0.4%) case was reported during the previous year, showing a statistically significant difference (p=0.019).

Pathological specimen prognostic and predictive factors are described in Table III. All these variables did not show any statistically significant difference and their distribution and relative p-values are summarized in Table III. Out of 29 (15.9%) patients that did not undergo upfront surgery, 18 (9.8%) underwent neoadjuvant therapy in the COVID-19 group. Administration of neoadjuvant therapy was carried out in 2 (1.1%) patients as bridging therapy due to simultaneous Sars-CoV2 infection. In the pre-Covid-19 group, 32 (12.2%) did not undergo upfront surgery and neoadjuvant therapy was administered in 22 (8.36%). Statistically significant differences were found in both: p=0.265 and p=0.615.

Adjuvant chemotherapy was administered in 50 patients (27.5%) in the COVID-19 group and in 59 patients (22.4%) in the Pre-COVID-19 group, with no statistically significant difference (p=0.262). After surgery, during the pandemic period, 67 (36.8%) patients received hormone therapy and 74 (26.2%) in the control group; p=0.061. Differently, during the pandemic, a higher number of patients received topical radiation therapy 89 (48.9%) *versus* 91 (32.2%) and the relative p-value was 0.003.

Figure 1. *Patients with extremely advanced breast cancer in the COVID-19 group. A) Female 52 years old. B) Female 58 years old. C) Female 49 years old. D) Male 58 years old. E) Female 64 years old. F) Female 68 years old.*

Discussion

Breast cancer is the most frequent oncological disease in women and represents the leading cause of cancer-related death in women worldwide (17). Despite the high incidence, latest statistics reported an improvement in term of prognosis due to empowerment of cancer treatments and higher incidence of early diagnosis, thanks to screening (18). The ability to diagnose breast cancer in earlier stages due to screening, is a fundamental factor responsible for reducing recurrence risk and increasing survival rate (19).

Since the beginning of the COVID-19 lockdown, screening programs were temporary suspended or experienced a significant slowdown (3). Additionally, a decrease in, or cessation of, most non-COVID-19 health services resulted in delays in diagnosis and treatment for breast cancer patients (11). Multiple changes have been advised by professional and scientific societies for breast cancer patient management with recommendations aiming to avoid delays in cancer care (8-10). Despite these exhortations, in our opinion, oncological diagnostic procedures and care suffered a significant slowdown during the last year. In our analysis, the absolute number of discussed cases decreased by approximately 30%. Similar reduction has been reported in the literature for non-COVID-19 patients referred to health care (4, 5, 20-24).

In the Covid-19 group, we observed a reduction in breast invasive procedures and a correlated increase in conservative breast cancer surgery. This surgical choice could be related

Table III. *Prognostic and predictive factors between groups.*

	COVID-19 group (n=182)	Pre-COVID-19 group (n=263	*p*-Value
Diameters	21.7 mm [1.5-80]	16.9 mm [1-80]	**0.003**
ER	77% [0-100]	73% [0-100]	0.305
PR	44% [0-100]	42% [0-100]	0.352
Ki67	19% [5-80]	17% [3-75]	0.902
Grading			0.071
G1	21 (11.5%)	54 (20.5%)	
G2	78 (42.8%)	127 (48.3%)	
G3	67 (36.8%)	77 (29.2%)	
HER2 (positive)	72 (39.6%)	112 (42.6%)	0.493

Diameters, ER, PR and Ki67 are shown as medians and [ranges]; grading and HER2 are presented as absolute numbers and (percentages). Bold value indicates statistical significance.

to changes in the management of breast cancer patients advised by professional and scientific societies (8-9). In fact, during the pandemic, many authors suggested to postpone reconstructive surgery (10). This exhortation and strategy aimed to prioritize oncological surgery and reduce the time of surgical procedures due to the lack of health care resources for non-COVID-19 patients (25, 26). Advantages of conservative breast surgery include a better cosmetic outcome, sexuality may be less affected, and patients do not need to undergo breast reconstruction (27). Furthermore, the length of hospital stay is usually shorter and more hospital beds and resources are available (3-6). The disadvantage of choosing breast conserving surgery is the need for radiotherapy after surgery (27, 28). Otherwise, mastectomy, usually associated with a reconstructive procedure and one-stage immediate reconstruction, should have been the chosen strategy during the pandemic for patients not suitable for conservative breast cancer surgery (29, 30). This strategy usually required longer hospital stay and operation time and could be a disadvantage during a pandemic (6). In our opinion, all these measures, the fear of patients and health care workers, and the choice not to avoid a delay in cancer treatment, led to an increased preference for conservative breast cancer surgery (6-31).

However, we did not observe a significative increase in T distribution as an effect of COVID-19, but we report a significative increase in tumor dimension. Moreover, we report a grater incidence of T2, T3 T4 during the COVID-19 era. In a previous study, we did not report an increase in dimension (11). The discrepancy between these two different results could be explained by the short timeframe between the screening suspension and our previous analysis (11). Usually, the time between diagnosis assessment and surgery is longer than 1 month; and nowadays at 1 year from the beginning of the pandemic we can evidence the impact of screening suspension and cancer delay in the treatment of breast cancer.

Malignant lymph node involvement appeared to be more frequent in the COVID-19 group. We report a significantly greater incidence of positive sentinel lymph nodes during the COVID-19 outbreak. In concordance with this result, incidence of ALND was significantly higher during the pandemic era. N staging distribution seemed to be more advanced in the lockdown group with significant difference between the analyzed groups. The higher incidence of lymph node involvement is in agreement with our previous analysis (11). Lymph node involvement (N staging) is a prognostic factor of breast cancer (32-34). Fortunately, this advanced N staging was not followed by a significative increase in the need of adjuvant chemotherapy despite the higher percentage of treatments in the COVID-19 group. Indication for adjuvant treatment is also related to other factors such as breast cancer prognostic and predictive factors (35-37). Instead, the rate of adjuvant radiotherapy was significantly higher in patients undergoing surgery during the pandemic. This result can only be partially explained by the greater number of conservative breast cancer surgeries (35). Indeed, during the COVID-19 pandemic, approximately 15% more patients underwent adjuvant radiation therapy, while the increase in conservative breast cancer surgery was only 5%. Therefore, the increased use of adjuvant radiotherapy, in the COVID-19 group, could be associated with lymph node advanced stages (38).

The incidence of patients with metastatic breast cancer disease was similar during the two analyzed periods. Metastatic disease is the worst prognostic factor of breast cancer (35-39). The timing and distribution of metastases in breast cancer patients vary considerably and is correlated with tumor factors. In approximately 5% of women with breast cancer, at the time of diagnosis, presented metastases. In other women, metastases become apparent years or even decades after the initial diagnosis (40). Fortunately, the there was a short timeframe of screening suspension and delay in treatment to evidence a different result regarding metastatic disease. Instead, we report an increased number of highly advanced breast cancer (Figure 1). One of these patients presented dysmorphia and one attributed the ulcerated lesions to psoriasis (41). Probably both COVID-19 anxiety and psychiatric disorders have influenced this result (15-16). However, due to the small sample of events in the groups, we do not consider the possibility that these cases are attributable to the delayed treatments due to COVID-19.

Administration of neoadjuvant therapy during the COVID-19 pandemic did not show a statistically significant difference compared to the previous year. The reasons of this finding are that the indications for neoadjuvant therapy are strongly correlated to other features such as breast cancer prognostic and predictive factors rather than tumor size (35-36). According to scientific committees' recommendations, neoadjuvant hormone therapy was used as bridging therapy due to simultaneous Sars-CoV2 infection (42).

Conclusion

The effect of breast cancer screening suspension and oncological treatment delay during the COVID-19 pandemic led to an increased tumor dimension, advanced N staging, and increased need for adjuvant treatments. This was the worst outcome in the short-term follow-up in this study. Hopefully, there will be no further effects, especially in relation to survival or recurrence rate in the long-term follow-up.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Gianluca Vanni, and Marco Pellicciaro: conceptualization, methodology, formal, analysis, review. Marco Pellicciaro: Writing original draft. Gianluca Vanni and Marco Pellicciaro: review and editing. Marco Materazzo and Domiziana Pedini: statistical analysis. Gianluca Vanni, Marco Pellicciaro, Marco Materazzo, Domiziana Pedini, Ilaria Portarena, Chiara Buonomo, Tommaso Perretta, Stefano Rizza, Chiara Adriana Pistolese and Oreste Claudio Buonomo: data curation. Oreste Claudio Buonomo: Supervision. All the Authors reviewed and approved the article.

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