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Impact of COVID-19 Pandemic on Surgical Breast Cancer Patients Undergoing Neoadjuvant Therapy: A Multicentric Study

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Abstract. *Background/Aim: Due to the SARS-CoV-2 pandemic, many scientific committees proposed neoadjuvant therapy (NACT) bridging treatment as a novel strategy and indication. The aim of the study was to evaluate the impact of COVID-19 pandemic on breast cancer patients undergoing NACT. Patients and Methods: All breast cancer patients referred to two Breast Units during COVID-19-pandemic were enrolled. Results: Out of 814 patients, 43(5.3%) were enrolled in the COVID-19-group and compared with 94 (7.9%) similar Pre-COVID-19 patients. We observed a reduction in the number of patients undergoing NACT, p=0.0019. No difference was reported in terms of clinical presentation, indications, and tumor response. In contrast, a higher number of vascular adverse events was reported (6.9% vs. 0% p=0.029). Immediate breast cancer reconstructions following invasive surgery suffered a significant slowdown (5.9% vs. 47.7%, p=0.019). Conclusion: COVID-19 caused a reduction in the number of patients undergoing NACT, with no changes in terms of indications, clinical presentation, and tumor response. Furthermore, there was an increased incidence of vascular events.*

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Neoadjuvant therapy (NACT) was introduced in the 1970s, aiming to downstage inoperable locally advanced breast cancer and turn it operable (1). Subsequently, NACT indications were extended to early breast cancer, aiming to permit more conservative breast surgeries (2). Nowadays, NACT is widely used, with the indications and aims changing frequently (3). NACT, a systemic treatment, might be somewhat more likely to eradicate micro-metastatic disease and improve overall survival than might a therapy delayed until after breast surgery (4, 5). Moreover, it permits to test tumor response to drug therapy *in-vivo*, which could be used as adjuvant treatment (5).

Since the beginning of the past year (2020), SARS-CoV-2 has dramatically spread worldwide and an epidemiological emergency was declared (6). Several restrictions and preventive measures were introduced as a strategy to flatten the epidemiological curve of the pandemic (7). All these measures have disturbed daily life and impacted public health; especially in non-COVID-19 related disease (8).

During the pandemic, clinicians caring for oncological patients must balance efforts and resources to adequately treat their patients while minimizing their access to the hospital in order to reduce the risk of exposure to coronavirus (9). Accordingly, many recommendations are issued by scientific committees and researchers for the management of breast cancer disease during the COVID-19 emergency (9, 10). All these proposals are driven by the common aim to preserve breast cancer treatments and avoid delays (11-13). Patients with a SARS-CoV-2 infection and a concomitant breast cancer diagnosis were strongly recommended to treat COVID-19 disease first, utilizing bridging therapy in order to avoid cancer progression (13, 14). In this perspective, a novel indication for NACT was emphasized and proposed as a strategy.

The aim of this study was to evaluate the impact of COVID-19 pandemic on the numbers, indications, and short-term outcome of breast cancer NACT.

Patients and Methods

Study design. In this retrospective study, we evaluated all patients with breast cancer diagnosis referred to Tor Vergata Breast (Tor Vergata Hospital, Rome, Italy) and to Modena Breast Units (Hospital of Modena, Modena, Italy) from March 1, 2019 to March 1, 2021.

One thousand nine hundred and eighty-four (n=1984) patients were considered in our study. This multicentric retrospective study was approved by the local Ethical Committee of the Fondazione Policlinico Tor Vergata (reference 122/21).

We analyzed all patients with breast cancer diagnosis, admitted to Tor Vergata Breast Unit and to at Modena Breast Unit undergoing neoadjuvant therapy from March 1, 2020 to March 1, 2021. These patients were designated as COVID-19 group and were compared with patients referred to both Breast departments during the same periods of the previous year (From March 1, 2019 to March 1, 2019), designated as Pre-Covid-19 group.

For each patient, ages, sex, type of tumor, date of diagnosis and tumor staging were reported.

Usually, pre-neoadjuvant diagnosis was obtained from a core needle biopsy or a Vacuum assisted biopsy. Tumor staging and lesions' maximum diameter (reported in millimetres) were collected from breast magnetic resonance reports at diagnosis. Pre-neoadjuvant treatments and lymph nodes staging were collected from magnetic resonance imaging or positron emission tomography-computed tomography (PET-CT) scan. Metastasis was evaluated by PET-CT scan. SUV max of the primary tumor and of the lymph nodes were reported and analyzed. Breast cancer staging based on recommendations from AJCC 2018 (edition VIII) of TNM classification was reported (13). Data from biopsy specimens were included in this study. Tumor grading was reported from pathological examination. Prognostic and predictive factors for breast cancer [estrogen receptor (ER), progesterone receptor (PR), and Ki67 index] were collected and expressed as percentages of positive cells in specimens studied through immunohistochemistry. Over-expression of *Her2* gene (HER2+) and a relative score were determined by immunohistochemistry and confirmed by FISH.

Administration of neoadjuvant chemotherapy or hormonotherapy, adverse events, type and duration of treatment data were collected from clinical notes, reported and analyzed between the groups.

Clinical response was defined by the primary tumor response after neoadjuvant treatments and evaluated by magnetic resonance (radiological response) and by surgical pathological examination (pathological response). Clinical response was reported and categorized as follows: complete response, complete radiographic resolution of tumor; partial response, 50% or greater reduction of tumor; stable disease, stable or no more than 25% increase or decrease in primary tumor size; progressive disease, more than 25% increase in tumor size.

Surgical procedure following neoadjuvant treatments was reported and distinguished between conservative surgery and invasive surgery. Conservative surgery included all surgical procedures with a partial gland removal while invasive surgery included all procedures with a complete removal of the glandular breast tissue.

The axillary surgical procedure was analysed. Patients without clinical or radiological lymph nodes involvement at pre neoadjuvant treatment underwent sentinel lymph node biopsy procedure. Otherwise, patients with previous malignant axillary involvement or sentinel lymph node positivity at frozen section examination underwent axillary lymph node dissection. Adjuvant radiotherapy, chemo and hormone therapy were reported and analyzed between the groups.

Statistical analysis. Data were collected into the EXCEL database (Microsoft, Washington, DC, USA). Continuous variables were reported with median and ranges. *t*-test was used to determine whether there were significant differences between the two groups. Categorical data were recorded in 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 March 1, 2020 to March 1, 2021, eight hundred and fourteen (n=814) patients were discussed at the breast cancer multidisciplinary meetings (COVID-19 group) at Tor Vergata Breast and to at Modena Breast Units. This group was compared to the one thousand and one hundred seventy patients (n=1170) discussed in the same period of the previous year (Pre-COVID-19 group). During the pandemic, we observed an absolute reduction of roughly 30% of discussed cases.

Out of eight hundred and fourteen cases, in the COVID-19 group, forty-three (n=43) patients were to undergo breast cancer neoadjuvant therapy and fulfilled the inclusion criteria (5.3%). During the previous year, 94 cases (7.9%) underwent neoadjuvant treatment, showing a statistically significant difference, $p=0.019$. Out of these patients, no case of neoadjuvant treatment was reported in male patients during the COVID-19 period *versus* 1 case (1%) in the Pre-COVID-

Table I. *Pre neoadjuvant tumor staging and prognostic and predictive factors.*

	COVID-19 Group (n=43)	Pre-COVID-19 Group (n=94)	*p*-Value
T			0.670
T1	7 (16.2%)	22 (40.23%)	
T2	24 (55.8%)	40 (42.5%)	
T3	7 (16.2%)	9 (20.9%)	
T4	2(4.6%)	3 (3%)	
N			0.137
N0	22 (51.1%)	29 (30.1%)	
N1	16 (37.2%)	34 (36.1%)	
N2	1 (23.3%)	9 (9.5%)	
N3	0	2 (2.1%)	
Grading			0.830
G1	0	0	
G2	12 (27.9%)	22 (24.4%)	
G3	28 (65.11%)	44 (46.6%)	
ER (%)	45.9±46.1	38.7±44.1	0.369
PR (%)	23.8±33.1	18.6±31.6	0.147
Ki67 Index (%)	43.3±21.0	41.9±22.1	0.554
HER2			0.861
Score 0	9 (20.9%)	21 (22.3%)	
Score 1	11 (25.6%)	18 (19.1%)	
Score 2	10 (23.2%)	22 (24.4%)	
Score 3	13 (30.23%)	21 (22.3%)	

19 group, p=1.000. Medians of age were 53.7±11.2 years in the COVID-19 group and 53.6±12 years in the Pre-COVID-19 group, and the relative p value was 0.644. Only one patient (2.1%) received neoadjuvant hormone therapy as bridging therapy due to concomitant SARS-CoV2 infection during the pandemic periods *versus* no case in the control group (p=0.313).

In the COVID-19 group, 69 (73.4%), 12 (12.7%) and 1 (1%) case were determined as ductal carcinoma, lobular carcinoma and others, respectively. In the control group, respective incidences were 36 (83.7%), 7 (16.2%) and no case of other type of tumor. No statistically significant differences were found and the p value was 0.872.

Median tumor diameters at magnetic resonance were 34.31±18.2 mm in the COVID-19 group and 30.29±14.8 mm in the control group. Diameters of the lesions did not show a statistically significant difference between the groups, p=0.09. Despite larger dimension in the pandemic group, T distribution did not show a statistically significant difference, p=0.670. T staging is summarized in Table I.

Differently, primary lesions showed a statistically significant difference in term of SUV max at PET-CT scan with higher value during the pandemic 11.92±7.9 *vs.* 7.6±3.8, p=0.005. Lymph node maximum diameters at magnetic resonance were 13.61±8.72 mm in the COVID-19 group *versus* 14.31±10.30 mm in the pre-COVID-19 population and the relative p-Value was 0.383. Pre-NACT lymph nodes involvement did not show a statistically significant difference, p=0.137. N staging is summarized in Table I. Pre-NACT tumor grading did not show any statistically significant difference, its distribution and relative p are presented in Table I with other breast cancer prognostic and predictive factors.

Table II. *Neoadjuvant chemotherapy adverse events leading to treatment suspension.*

	COVID-19 Group (n=43)	Pre-COVID-19 Group (n=94)	*p*-Value
Myeloid toxicity*	2 (4.6%)	2 (2.1%)	0.589
Liver toxicity*	0	1 (1.1%)	1.000
Allergic reaction*	1 (2.3%)	2 (2.1%)	1.000
Vascular adverse event	3 (6.9%)	0	**0.029**

*Severe toxicity or reaction. Significant p-Values are shown in bold.

No difference was reported between the groups in s of NACT therapeutic schedule p=0.991. Due to adverse events, 6 patients (13.9%) were suspended from NACT within three months. During the same period of the previous year, 5 patients (5.3%) reported NACT adverse events and chemotherapy was suspended, p=0.099. NACT adverse events leading to therapy suspension are presented in Table II with relative p-Values. During the pandemic, 3 cases (6.9%) of vascular disease leading to NACT suspension were reported. One case was pulmonary embolism, one deep vein thrombosis and one transient ischemic attack, and relative NSCT schedules were combined with monoclonal antibody in the first two cases and paclitaxel in the third. Patients with pulmonary embolism and deep vein thrombosis were associated with a previous SARS-CoV2 infection. No cases of vascular disease were reported in the pre-COVID-19 group, showing a statistically significant difference between groups, p=0.029.

Both radiological and pathological tumor responses did not show any statistically significant difference between the two periods as shown in Table III, with respective p-Values of 0.854 and 0.820.

Seventeen patients (39.5%) underwent an invasive breast surgery during the pandemic and 26 (60.5%) received a breast conservative surgery. In the control group, pre-COVID-19, 44 (47.3%) cases undergone an invasive surgery and 49 cases (52.7%) received a conservative procedure. This surgical strategy did not show any statistically significant difference, p=0.460. Conversely, strategy of reconstruction showed a statistically significant difference between the two groups, p=0.019. During the pandemic, only 1 patient (5.9%) received an immediate breast reconstruction following mastectomy *versus* 21 (47.7%) during the previous

Table III. *Neoadjuvant chemotherapy pathological and radiological response.*

	COVID-19 Group (n=43)	Pre-COVID-19 Group (n=94)	*p*-Value
Radiological response			0.854
Complete	13 (30.2%)	22 (23.4%)	
Partial	22 (51.2%)	48 (51.1%)	
Stable disease	4 (9.3%)	8 (8.5%)	
Disease progression	0	2 (2.1%)	
Pathological response			0.820
Complete	16 (37.2%)	28 (29.8%)	
Partial	21 (48.8%)	39 (41.1%)	
Stable disease	4 (9.3%)	11 (11.7%)	
Disease progression	0	2 (2.1%)	

Table IV. *Pathological tumor staging and prognostic and predictive factors.*

	COVID-19 Group (n=43)	Pre-COVID-19 Group (n=94)	*p*-Value
pT			0.549
pT0	15 (34.9%)	19 (20.2%)	
pT1	19 (44.2%)	46 (48.9%)	
pT2	5 (11.6%)	6 (6.4%)	
pT3	1 (2.3%)	3 (3.3%)	
pT4	0	1 (1.1%)	
pN			0.126
pN0	35 (81.3%)	52 (55.3%)	
pN1	4 (9.3%)	18 (19.1%)	
pN2	2 (4.6%)	6 (6.3%)	
pN3	2 (4.6%)	5 (5.3%)	
Grading			0.109
G1	4 (9.3%)	4 (4.3%)	
G2	13 (30.2%)	14 (14.9%)	
G3	7 (16.2%)	24 (25.5%)	
ER (%)	60.4±46.1	46.5±44.9	0.949
PR (%)	13.2±21.7	15.6±28.9	0.247
Ki67 Index (%)	23.0±21.0	24.3±23.7	0.738
HER2			0.766
Positive	8 (18.6%)	15 (16.0%)	
Negative	15 (34.9%)	33 (35.1%)	

year. In both groups, no patients received breast autologous reconstruction.

Surgical axillary procedure did not show a different trend between the two periods, p=0.054: 29 (67.4%) underwent sentinel lymph node biopsy, 1 (2.3%) axillary lymph nodes dissection due to sentinel node positivity, and 11 (25.5%) up front axillary lymph nodes dissection during the pandemic *versus*, 39 (41.9%), 30 (32.1%), and 10 (10.1%) in the control group, respectively.

Pathological staging and prognostic and predictive factors did not show any statistically significant differences and medians and relative p-Values are presented in Table IV.

Following the surgical procedure, 16 patients (37.2%) received adjuvant chemotherapy and 24 (55.8%) adjuvant hormone therapy in the pandemic group. In the pre-COVID-19 group, 37 patients (39.3%) underwent adjuvant chemotherapy and 36 (38.2%) adjuvant hormone therapy. Both these comparisons did not show any statistically significant differences with p values of 0.478 and 0.085, respectively. Indication for adjuvant radiation therapy did not show a statistically significant difference between the two periods, p=0.096.

Discussion

Since the early 1970s, when introduced for breast cancer management, indications for NACT have been broadened and changed (1). First, the treatment was reserved for downstaging inoperable locally advanced breast cancer, to achieve a partial response and an operable condition (1). Subsequently, indication was extended to allow a conservative breast surgery and avoid invasive surgeries (1, 2). Nowadays, NACT aims and indications are further broadened, and its application is widely used, even in early breast cancer (3). In early breast cancer, NACT allows a complete or partial response with high frequencies, permitting the option of a conservative breast surgery (4). Despite allowing more conservative treatments, NACT could be associated with higher frequency of local recurrence if compared with the same chemotherapy used as adjuvant treatment, but reduces distant recurrence and breast cancer mortality (4-15). Indeed, NACT might be somewhat more potent in eradicating a micro-metastatic disease and improving overall survival than adjuvant therapy (4, 5). Moreover, as reported in many studies, the ability to test tumor response to treatment schedule *in vivo* holds importance in order to predict future response to adjuvant treatments (3-5).

Since the beginning of 2020, SARS-CoV-2 infection dramatically spread worldwide, disturbing daily life, strongly impairing public health and penalizing patients with non-COVID-19 related disease (6-8). During the pandemic, many health resources have been shifted towards COVID-19 patients (7). Furthermore, management of oncological patients suffered a significant slow-down with the reduction in dedicated hospital bed, operation rooms, and healthcare professionals (6). In addition, temporary suspension of screening programs and the refusal to access healthcare due to COVID-19 anxiety led to delays in breast cancer treatments with consequent more advanced staging (6, 10, 11, 16). Beyond advanced stages, many studies reported a reduction in the absolute number of procedures or access to health services (8, 10, 11, 17, 18). Similarly, during the

pandemic we report a significant reduction in the absolute number of cases evaluated for breast cancer.

In order to avoid further delays, many oncological scientific committees issue recommendations for the management of breast cancer during the COVID-19 pandemic (7, 19-22). Moreover, the role of neoadjuvant chemo and endocrine therapy was rediscussed, and many oncological societies further proposed new indications as a bridging therapy in patients with concomitant SARS-CoV-2 infection or when up front surgery could be not be performed due to pandemic associated effects (13, 23, 24). In our study, only one case underwent a neoadjuvant endocrine therapy as a bridging strategy for concomitant COVID-19. Despite the novel indication for neoadjuvant chemo and endocrine therapy, we report an absolute reduction in the number of NACT during the pandemic. Moreover, we also observed a reduction of approximately 2.5% in the incidence of cases undergoing NACT in the COVID-19 group. This reduction in incidence could be related to the increase in extremely advanced cases, as we reported in a previous study, in addition to the reluctancy of the physicians to abandon conventional care, when possible, during the pandemic (11, 25-27).

We did not observe a variation of indication or of breast cancer staging clinical presentation in patients undergoing NACT. Indications for NACT, despite the new proposal as bridging treatment, are well established with entrenched guidelines, and breast physicians are probably reluctant to abandon conventional standard care (3, 4, 14, 20, 21, 27-33).

Additionally, therapeutic schedules did not change during the pandemic; we can attribute this result to the indications and types of neoadjuvant treatment which are correlated with the tumor type, subtype, staging and predictive and prognostic breast cancer risk factors (1, 3, 5).

During the pandemic, we reported a significant increase in vascular adverse events during NACT. Two of these had a previous history of SARS-CoV2 infection and both received NACT with a monoclonal antibody. On the one hand, many studies pointed towards the association between COVID-19 and ischemic and thrombotic disease, including following virus infection resolution (34-38). On the other hand, cases of vascular disease are reported in association with cancer drugs as well (30-42). Due to similar schedule of NACT and no cases of such adverse events in the Pre-COVID-19 group, we may postulate an association of vascular disease with COVID-19; however, due to small sample of cases we could not confirm this hypothesis. Despite the higher number of vascular adverse events, all cases of NACT suspension were comparable between the two periods.

Factors influencing tumor response are well established in the literature (*e.g.* phenotype and biomarkers) (43-45). Both radiological and pathological responses did not change during the pandemic. This is an expected result due to the comparability of tumor type, sub-type, clinical presentation and schedule of NACT in the two periods analyzed.

Surgical strategies, including conservative or invasive breast surgery, did not change during the pandemic period as reported in our previous published studies (10, 11). As for indications and schedule of NACT; surgical strategy is correlated with tumor characteristics and follow the good clinical practices and guidelines (3, 4, 14, 20, 21, 25, 26). Additionally, a drastic reduction of immediate breast reconstructions is reported. Avoiding an immediate and preferring a temporary reconstruction could lead to a higher availability of operation rooms and hospital beds allowing to perform more oncological surgeries and preventing delays, as suggested by many recommendations (6, 20, 46-49). In addition, the surgical procedure was not impacted by the pandemic according to standard clinical practices (21, 25, 26, 50, 51).

Administration of breast cancer adjuvant and radiation therapies during the pandemic did not show statistically significant differences. This finding stems from the fact that the indications for adjuvant treatments are strongly supported by other features such as breast cancer biomarkers, prognostic and predictive factors (14, 20-22).

Conclusion

While the COVID-19 pandemic disturbed daily life, and many scientific committees proposed NACT bridging therapy as a novel strategy, in our study, we did not observe any differences in terms of NACT indications and breast cancer clinical presentation. We observed a reduction in the absolute number of patients undergoing NACT during the pandemic. Furthermore, we reported an increase in vascular events in patients undergoing NACT during the COVID-19 era. Nevertheless, due to the small number of cases, we could not confirm this hypothesis. Further studies on this aspect with a larger number of patients are required.

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. Francesca Combi, Simona Papi, Marco Materazzo, Silvia Segattini, Stefano Rizza, Marcello Chiocchi, Tommaso Perretta, Rosaria Meucci, Ilaria Portarena,: statistical analysis. Francesca Combi, Simona Papi, Marco Materazzo, Silvia Segattini, Stefano Rizza, Marcello Chiocchi, Tommaso Perretta, Rosaria Meucci, Ilaria Portarena, Chiara Adriana Pistolese, Benedetto Ielpo, Michela Campanelli, Giorgio Lisi, Agostino Chiaravalloti data collection and

curation. Giovanni Tazzioli and Oreste Claudio Buonomo: Supervision. All the Authors reviewed and approved the manuscript.

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