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Epidemiological and clinicopathological parameters related to the neoadjuvant chemotherapy for breast cancer during the COVID-19 crisis

Maria Fernanda da Motta Sperotto Valadares Gontijo[1]*, Letícia Martins de Araújo Campos Linhares[1], Luisa Lazarino de Souza Campos[1], Marcela de Oliveira Sá[1], Caroline Cançado Avelar[1], João Pedro Costa Apolinário[1], Paulo Henrique Costa Diniz[1], José Tadeu Campos de Avelar[1]

ABSTRACT

Introduction: Breast cancer, the second-leading cause of cancer-related deaths among women worldwide, is a complex and heterogeneous disease. Its socioeconomic aspects are recognized as determinants of clinical outcomes. The COVID-19 crisis negatively affected millions, particularly in impoverished macroregions like Brazil. Thus, influences on breast cancer patients' journey may occur, particularly in the neoadjuvant settings, in which a coordinated and multidisciplinary approach is mandatory. The present study aimed to analyze the epidemiological and clinicopathological profile of breast cancer patients who underwent neoadjuvant chemotherapy during the pandemic in Brazil. **Methods:** This is a unicentric, retrospective, and descriptive cross-sectional study conducted by analyzing data obtained from electronic medical records of breast cancer patients who underwent neoadjuvant chemotherapy. **Results:** From March 2020 to December 2022, 55 patients underwent neoadjuvant chemotherapy. They presented an average age of 50.0 years (range 43.9–47.6). About 83.6% of the tumors were invasive ductal carcinomas, and the most prevalent molecular subtype was hormone receptor-positive. T2 tumors accounted for 50.9%, while compromised N1 axillary lymph nodes represented 52.7%. The most commonly used neoadjuvant chemotherapy combined anthracyclines, cyclophosphamide, and sequential taxane. Regarding postoperative pathological response, 42.2% showed a partial response after neoadjuvant treatment, and a complete pathological response of as high as 40.0% occurred. The luminal and hybrid luminal subtypes were those that achieved the greatest response to neoadjuvant therapy. The lack of pathological response was only found in the luminal molecular subtype. **Conclusions:** This study demonstrated the impacts of the COVID-19 pandemic on breast cancer patients' journey. During this period of disruption in healthcare assistance, the disease presented at more advanced stages, but the pathologic complete response was higher than expected, and influences on chemotherapy decisions were not relevant. Overall, there were efforts to keep patients in the best breast cancer care.

KEYWORDS: breast neoplasms; breast; neoadjuvant therapy; COVID-19.

INTRODUCTION

Breast cancer, the second-leading cause of cancer-related deaths among women worldwide, is a major public health issue. Considering the complexity of this malignancy, socioeconomic inequalities may impact its relevant clinical outcomes. During the COVID-19 pandemic, whose beginning was recognized by the World Health Organization on March 20, 2020, approximately 90% of countries experienced setbacks in healthcare services, particularly in elective outpatient care, routine examinations, and complementary propaedeutics, focusing on emergency care[1]. It was even more evident in the most vulnerable populations, which includes Brazil, a continental developing country[2].

As a result of delays in the cancer patients' journey, from screening to treatment, it was reported an increase in the diagnosis of breast cancer in locally advanced stages, which requires multimodal therapies, notably the combination of neoadjuvant chemotherapy, surgery, and radiation therapy[3].

By addressing micrometastases early, neoadjuvant chemotherapy aims to downstage the tumor to enable conservative surgery, evaluate *in vivo* response to systemic therapy, obtain

[1]Hospital Mater Dei – Belo Horizonte (MG), Brazil.
***Corresponding author:** mariafernandasperotto@gmail.com
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prognostic information, reduce the need for axillary dissection in cases of clinically positive axilla at the initial diagnosis, and provide time for surgical planning and genetic counseling[4]. Randomized prospective studies have shown the benefits of neoadjuvant systemic therapy compared to adjuvant therapy in operable tumors (T1–T3, N0–N1, M0), but with no differences in overall survival.

In the decision-making process involved in breast cancer, phenotypic subtype, histopathological aspects, and epidemiological data such as age and menopausal status should be considered. As these data might have changed significantly during the pandemic, this study analyzes clinical, epidemiological, and histopathological aspects of breast cancer patients treated with neoadjuvant chemotherapy in the COVID-19 pandemic period in Brazil.

METHODS

Patients undergoing neoadjuvant chemotherapy for breast cancer treatment at Mater Dei Hospital, a private referral center in Belo Horizonte, Brazil, between March 2020 and December 2022, were selected. Demographic and clinical data, such as age, menopausal status, family history of cancer, axillary staging, chemotherapy regimen, and pathological response to chemotherapy were gathered from electronic medical records. Histopathological data were obtained, including information on histology subtype, histological grade, tumor size, expression of hormonal receptors, human epidermal growth factor receptor-type 2 (HER2) status, Ki67 protein, molecular subtype, and degree of histological response to neoadjuvant treatment. No pathological review was performed for this analysis.

Inclusion criteria were female gender, age 18 and above, histologically confirmed diagnosis of breast cancer, multifocal disease, availability of data in electronic medical records, and neoadjuvant chemotherapy. Synchronic carcinomas were excluded, according to Figure 1.

Descriptive statistics were used to summarize the data. Normality tests (Shapiro-Wilk) were performed for each continuous variable. Categorical variables were presented as numbers and percentages, and continuous variables as medians and interquartile ranges. Statistical analysis was conducted using Statistical Package for Social Sciences - SPSS® software, version 20 (SPSS, Chicago, IL).

The study was approved by an independent Ethics Committee (CAAE 73246223.8.0000.5128), and the protocols followed the 1975 Helsinki Declaration ethical guidelines. Due to the retrospective nature of this study, the local Human Subjects Committee approved the waiver of participants' free and informed consent.

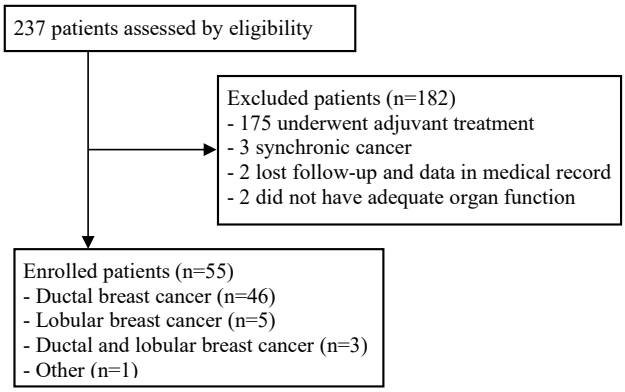

Figure 1. Trial profile.

RESULTS

Demographic data, clinical characteristics, and histopathological parameters of patients and their respective tumors were summarized in Table 1. Among the patients included in the study (n=237), 55 (22.0%) underwent neoadjuvant chemotherapy, with an average age of 50 years (range 43.9–47.6). Approximately 60% of these patients did not have a relevant family oncologic history, such as a history in first-degree relatives with breast, ovarian, or intestinal cancer. High penetrance gene mutations were found in two patients (TP53 and BRCA 2), and one had a variant of uncertain significance in the POLD1 gene.

Regarding histological aspects, approximately 83.6% of the tumors were invasive ductal carcinomas, and the most prevalent molecular subtype was hormone receptor-positive tumors. The luminal subtype (either A or B) comprised about 45.4% of the analyzed cases. T2 tumors (> 2 to 5 cm) accounted for 50.9%, followed by T3 tumors (larger than 5 cm) at 29.0%. Axillary involvement was found in 52.7% of patients, with mobile and fixed lymph nodes in the axilla ipsilateral to the tumor (respectively, N1 and N2), the majority classified as clinical staging II B. The most commonly used neoadjuvant regimen was a combination of anthracyclines, cyclophosphamide, and sequentially taxane (52.7%).

Partial pathological response after neoadjuvant treatment was seen in 42.2%, and complete pathological response (pCR) in 40.0%. When analyzing molecular subtypes, HER2-positive and hybrid luminal, patients had the highest complete response rates (80% and 50%, respectively), as show in Figure 2. The absence of pathological response to chemotherapy was found only in patients with the luminal molecular subtype, accounting for 20% of all analyzed luminal subtype patients.

DISCUSSION

The present study shows that, during the COVID-19 pandemic period, roughly 22.0% of all breast cancer patients underwent neoadjuvant therapy. Most (83.6%) presented as T2 or above, and clinical axillary involvement was detected in approximately 63.7%. Despite the challenges of keeping the patients at home in this period, the most used chemotherapy regimen

Table 1. Patients with analyzed outcomes, in which the information was available, expressed as absolute numbers and percentage.

Characteristic	Number (n=55)	%
Age		
<40	11	20.0
40–49	18	32.7
50–64	19	34.5
≥65	7	12.7
Family History		
Positive	22	40.0
Negative	33	60.0
Histology		
Ductal	46	83.6
Lobular	5	9.0
Ductal and Lobular	3	5.4
Others	1	1.8
Molecular Subtype		
Luminal	25	45.4
HER2	5	9.0
Triple Negative	10	18.1
Hybrid Luminal	15	27.2
Tumor Size		
T1	9	16.3
T2	28	50.9
T3	16	29.0
T4	2	3.6
Lymph Node Status		
N0	20	36.3
N1	29	52.7
N2	6	10.9
N3	0	0
Therapy		
ddAC-T	29	52.7
ddAC –THP	10	18.1
ddAC	7	12.7
AC-TC	4	7.2
THP	3	5.4
TCHP	2	3.6
Pathological Response		
Complete	22	40
Luminal	7	27.2
HER2	4	18.1
Triple Negative	3	13.6
Hybrid Luminal	8	36.3
Partial	26	47.2
Luminal	13	50
HER2	1	3.8
Triple Negative	5	19.2
Hybrid Luminal	7	29.9
Absent		9.0
Unknown		3.6

HER2: human epidermal growth factor receptor-type 2; ddAC-T: dose--dense anthracycline plus cyclophosphamide and sequential paclitaxel; ddAC-THP: dose-dense anthracycline plus cyclophosphamide and sequential paclitaxel plus double blockade of trastuzumab and pertuzumab; AC-TC: anthracycline plus cyclophosphamide and sequential paclitaxel plus carboplatin; THP: paclitaxel plus double blockade of trastuzumab and pertuzumab; TCHP: paclitaxel plus carboplatin plus double blockade of trastuzumab and pertuzumab,

was ddAC-T, instead of those that required fewer days for infusions, such as a combination of taxanes and carboplatin or cyclophosphamide. Moreover, the frequency of HER2 tumors was higher than usual, and pathological response rates (partial or complete) in this subgroup were more common than the other molecular subtypes.

Breast cancer is the leading cause of cancer-related deaths in Brazil, except in the Northern, considered a socioeconomic less favorable geographic region[5]. Many epidemiological and clinicopathologic characteristics are associated with relevant clinical outcomes of this malignancy and need to be pointed out.

First, breast cancer incidence rises with age, thus being less common among younger women. Most cases are diagnosed in women aged 50–64, consistent with the predominant age group in our study (34.54% of patients)[6].

Approximately 10–15% of breast cancers are associated with genetic alterations[7]. The Breast Cancer Association Consortium publication demonstrated an association between nine genes and breast cancer risk. Genes considered high-risk include BRCA1, BRCA2, PALB2, and TP53[8]. In our cohort, 40% had a family history of cancer in first-degree relatives, but only three had genetic mutations, two in high-risk genes (TP53 and BRCA2).

Over the last years, with a greater understanding of tumor molecular biology, breast cancer treatment has become increasingly complex, primarily guided by the subtype. A multidisciplinary approach becomes fundamental for treatment decisions for locally advanced cancer cases, defined as a tumor measuring over 2 cm (T2) and involving lymph nodes (N+). Almost 23% of patients underwent neoadjuvant therapy. Of those, 84.43% had T2, T3, or T4 tumors, and approximately 64% had clinically positive axilla. Due to screening failure or delay in searching for non-COVID-19-related medical assistance, we would expect a higher number of locally advanced tumors under neoadjuvant treatment. However, it is essential to mention the existence of different waves of COVID-19 cases[9]. This profile would probably be worse before vaccinations or when more new cases were reported. The resistance of patients and doctors to undergo chemotherapy during uncontrolled phases of the pandemic may also explain these findings.

In the past 40 years, medications and therapies have been developed to improve the quality of life and long-lasting outcomes for breast cancer patients. In this context, neoadjuvant treatment has emerged as a therapeutic strategy for surgical downstaging, *in vivo* assessment of systemic therapy response, and prognostic evaluation[10]. A study at the Memorial Sloan Kettering Cancer Center, between 2013 and 2019, revealed that of breast cancer patients with clinical stage I to III undergoing neoadjuvant chemotherapy, 75% presented a conversion from infeasible to feasible conservative surgery[11].

Subsequently, two major studies conducted in the United States in the 1990s demonstrated the non-inferiority of

neoadjuvant compared to adjuvant therapy regarding overall survival and progression-free survival. It was shown that patients achieving pCR had a better prognosis than those with residual disease[4]. The evaluation of this surrogate outcome as a reliable parameter was conducted in a meta-analysis published in 2014, correlating pCR with increased overall survival. This association became even more statistically evident in HER2+ patients, regardless of hormonal status, and triple-negative cases, confirmed in our study, where this group represents 84.4% of patients achieving pCR[12]. Another critical point to be explored is the high frequency of HER2+ patients in our cohort. Possibly, these patients were more often referred to neoadjuvant treatment due to advances in antiHER2 treatment in this scenario.

Today, the standard therapy for initial HER2+ subtype breast cancer patients is neoadjuvant therapy, comprising different chemotherapy regimens associated with trastuzumab with or without pertuzumab[13-15]. In our institution's study, 36.6% of patients were hybrid luminal or HER2+ types. Of these patients, 50% underwent neoadjuvant treatment with ddAC-THP, while the others were treated with de-escalated neoadjuvant protocols such as THP or TCHP, with 54.4% achieving pCR. Interestingly, these data point to the fact that the COVID-19 period did not interfere with medical decisions for regimens requiring fewer infusions despite the attempts to keep patients at home.

For triple-negative breast cancer (TNBC), current evidence indicates that treatments used in adjuvant therapy are also suitable for neoadjuvant settings. Based on the Anthracycline in Breast Cancer study, neoadjuvant treatment in TNBC patients is recommended for at least T1c and N+ using anthracycline and taxane-based chemotherapy[16,17]. In our study, ten patients (18.8%) had TNBC in our institution.

None of the TNBC patients received neoadjuvant immunotherapy despite the data from the KEYNOTE-522 study. Published in 2020, this phase 3 trial demonstrated that combining pembrolizumab with carboplatin and paclitaxel followed by anthracycline in stage II or III TNBC patients resulted in higher pCR rates (64.8% *vs.* 51.2%)[18]. However, pembrolizumab in this scenario

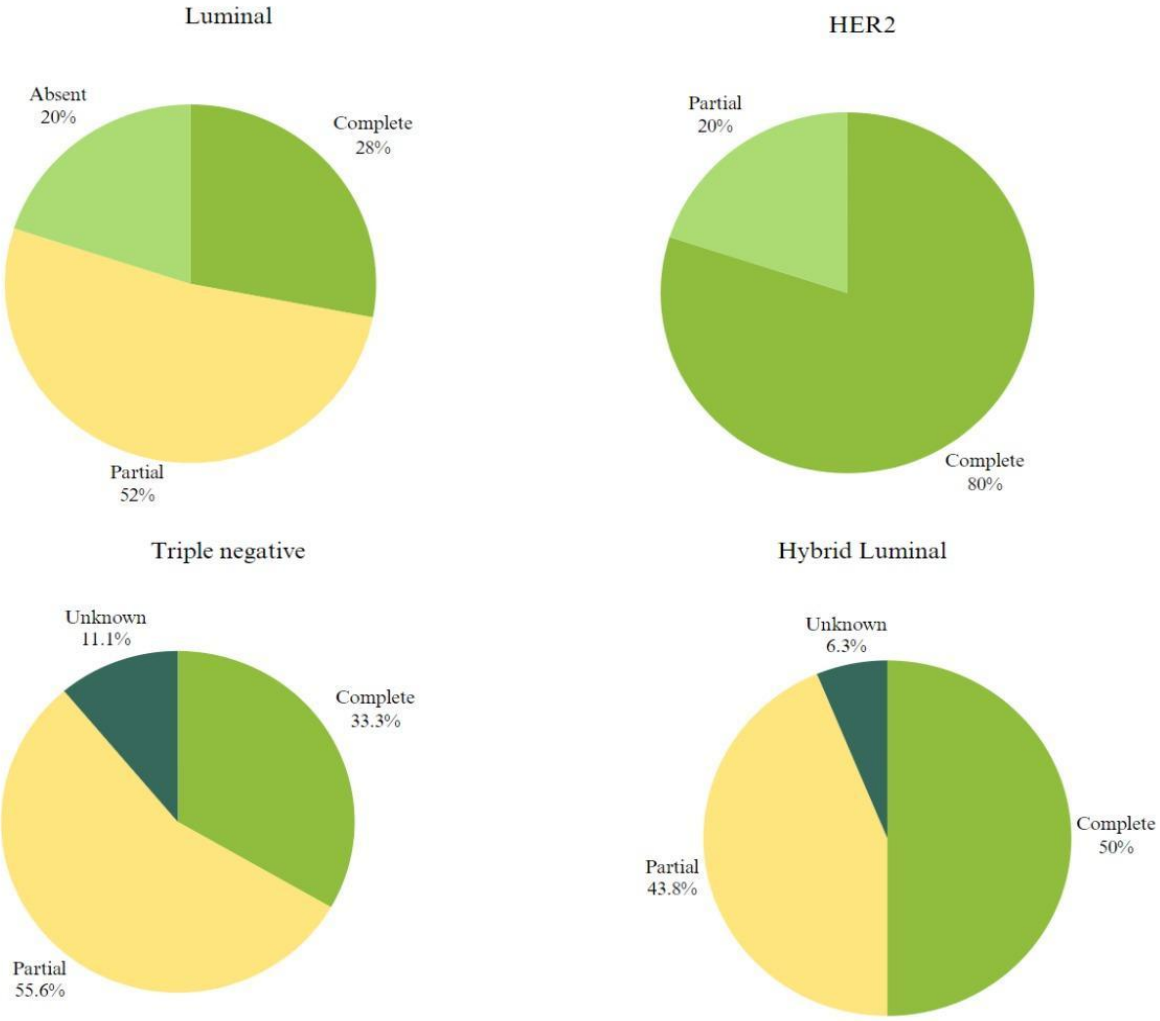

Figure 2. Analysis of pathological response according to molecular subtypes.

was only approved in May 2022 by regulatory agencies in Brazil. It needs to be clarified whether the pandemic delayed our country's approval process.

Hormone receptor-positive (HR+) and HER2- tumors, despite their high prevalence, have more restricted indications for neoadjuvant therapy compared to other histological subtypes. However, it was a useful strategy worldwide during the COVID-19 period, when temporary contraindications for surgery were required. Despite that, we expected more patients with this condition at our center. Concerns regarding virus exposition during chemotherapy may have been balanced.

It is known that neoadjuvant chemotherapy is less effective in achieving pCR in luminal tumors, especially in the luminal A subtype, compared to more aggressive histologies[19]. However, our data showed that a pCR rate of around 25% was observed, surpassing global data of around 6–11% in the literature[20]. Another intriguing finding is the absence of neoadjuvant endocrine therapy among our cohort, despite data showing pCR at least equivalent to chemotherapy ones[21].

Our study has some limitations. It was retrospective and performed in a single center, not reflecting our population's sociodemographic and genetic diversity. Moreover, information and selection bias may have occurred. However, it was an important study to assess the impact of the COVID-19 crisis among our patients, which analyzed epidemiologic and clinical pathological aspects.

CONCLUSION

The study contributed to a better understanding of the epidemiological profile of breast cancer patients who underwent neoadjuvant chemotherapy during the COVID-19 crisis when there was a disruption in healthcare assistance. Despite concerns regarding the pandemic itself, it was shown the effort to keep patients on the best assistance directed to breast cancer.

AUTHORS' CONTRIBUTION

MFMSVG: Conceptualization, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. LMACL: Data curation, Writing – original draft, Writing – review & editing. LLSC: Data curation, Formal analysis, Writing – original draft, Writhing – review & editing. MOS: Formal analysis, Investigation, Writing – review & editing. CCA: Formal analysis, Investigation. JPCA: Data curation, Validation. PHCD: Formal analysis, Investigation, Methodology, Project administration, Visualization. JTCA: Conceptualization, Methodology, Project administration, Visualization.

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