

# Management of early breast cancer during the COVID-19 pandemic in Brazil

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## Research Article

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# Abstract

**Purpose:** The COVID-19 pandemic has impacted early breast cancer (EBC) treatment worldwide. This study analyzed how Brazilian breast specialists are managing EBC.

**Methods:** An electronic survey was conducted with members of the Brazilian Society of Breast Specialists between April 30 and May 11, 2020. Bivariate analysis was used to describe changes in how specialists managed EBC at the beginning and during the pandemic, according to molecular subtype and oncoplastic surgery.

**Results:** The response rate was 34.4% (503/1,462 specialists). At the beginning of the pandemic, 43% changed their management approach. As the outbreak progressed, this proportion increased to 69.8% ( $p < 0.001$ ). For hormone receptor-positive tumors with the best prognosis ( $Ki67 < 20\%$ ), 47.9% and 17.7% of specialists would recommend neoadjuvant endocrine therapy for postmenopausal and premenopausal women, respectively. For tumors with poorer prognosis ( $Ki67 > 30\%$ ), 34% and 10.9% would recommend it for postmenopausal and premenopausal women, respectively. Menopausal status significantly affected whether the specialists changed their approach ( $p < 0.00001$ ). For tumors  $\geq 1.0$  cm, 42.9% of respondents would recommend neoadjuvant systemic therapy for triple-negative tumors and 39.6% for HER2+ tumors. Overall, 63.4% would recommend immediate total breast reconstruction, while only 3.4% would recommend autologous reconstruction. In breast-conserving surgery, 75% would recommend partial breast reconstruction; however, 54.1% would contraindicate mammoplasty. Furthermore, 84.9% of respondents would not recommend prophylactic mastectomy in cases of BRCA mutation.

**Conclusions:** Important changes occurred in EBC treatment, particularly for hormone receptor-positive tumors, as the outbreak progressed in each region. Systematic monitoring could assure appropriate breast cancer treatment, mitigating the impact of the pandemic.

## Introduction

A novel coronavirus (SARS-COV-2) has led to a global health emergency, with the World Health Organization (WHO) ultimately declaring it a pandemic [1]. The transmission and progression of this disease (COVID-19), which first appeared in Wuhan, China, imply that a great number of infected individuals will need hospitalization and possibly admission to intensive care units for mechanical ventilation [2,3]. On May 13, more than four million individuals had confirmed COVID-19 infection and around 290,000 had died from the disease [4]. Recognition of the seriousness of the situation, with the risk of overwhelming healthcare systems, and the absence of any confirmed effective treatment or vaccine for COVID-19, resulted in the implementation of social distancing measures, with a consequently negative effect on the management of various different diseases [5].

The management of early breast cancer (EBC), a disease with well-established treatment protocols [6-8], also had to be adjusted in order to free up hospital beds and vital hospital supplies for individuals infected by COVID-19 and to minimize the risk to healthcare professionals and patients undergoing

treatment of contracting the disease. Cancer patients are at a greater risk of acquiring COVID–19, of developing severe symptoms and of dying compared to the rest of the population, possibly due to their state of immunosuppression resulting from cancer treatment [9–11]. Consequently, expert groups have drawn up novel protocols [12–14]. The treatment of EBC with a low risk of progression such as ductal carcinoma in situ or invasive hormone-positive tumors could begin, for example, with neoadjuvant endocrine therapy (NET) during the pandemic [15], with surgery being postponed with no negative effect on disease outcome [16–18]. Other suggestions include extending the use of neoadjuvant chemotherapy (NACT) to tumors of adverse biology, using strategies to minimize immunosuppression [19–20], and avoiding major or prophylactic surgeries.

Cancer treatment during the pandemic has been much debated in Brazil and worldwide [21,22]. EBC is a curable disease at an initial stage. Multimodal treatment, including upfront surgery associated with adjuvant therapy in most cases, improves prognosis [23]. Changes in these protocols may negatively affect outcomes in cases of EBC. Many argue that there may be regional differences in a country of continental dimensions such as Brazil and that the decision should be made case by case, taking into consideration the rapid changes in local conditions and the available resources. Although the Brazilian medical societies drew up recommendations [24,25], little is known regarding how Brazilian breast specialists have complied with these guidelines. This online survey study aimed to evaluate how Brazilian breast specialists have managed EBC (stage I/II and clinically negative axilla) following publication of emergency treatment protocols [12–14,24,25], both at the beginning and during the COVID–19 pandemic, as a function of EBC molecular subtypes [26] and with regards to oncoplastic surgery.

## Methods

Between April 30 and May 11, 2020, a survey was conducted by e-mailing a questionnaire to 1,462 actively practicing physicians affiliated to the Brazilian Society of Breast Specialists (SBM). A previous pilot test involving 10 associates evaluated the time required to complete the questionnaire and the response rate, with any necessary changes then being incorporated. The American Association for Public Opinion Research recommendations were taken into consideration when constructing and applying the questionnaire and evaluating response. In view of the rapid changes triggered by the pandemic, the deadline for returning the questionnaires was short.

The questionnaire dealt with demographic aspects, changes in EBC management at the beginning and during the pandemic, and EBC management as a function of molecular subtypes and the oncoplastic surgery performed (see addendum). The first part of the questionnaire focused on the respondent's demographic data including sex, age, board-certification as a breast specialist (yes or no) and workplace (general hospital or cancer center). The following aspects of the respondent's workplace were also evaluated: region of the country; type of city (state capital or other city/town); number of inhabitants; confirmed cases of COVID–19 and availability of dedicated COVID-free hospitals/wards for treating other diseases.

To evaluate changes in treatment plans, this survey dealt only with EBC (stages I and II), with clinically negative axilla, since these patients are normally submitted to primary surgery. Classification according to molecular subtype was based on immunohistochemical findings. Patients with HER2 3+ or HER2 2+ and FISH/SISH-positive tumors were classified as HER2 irrespective of hormone receptor (HR) status. Tumors that were HR-negative and HER2-negative were considered triple-negative (TN), while those expressing HR but that were HER2-negative were considered luminal. The Ki-67 proliferation index was used to sub-classify luminal tumors based on the 2015 St. Gallen Consensus, which suggested a cut-off point of between 20% and 30% [27]: a low proliferation index was considered luminal A (Ki-67 <20%), while a Ki-67 index >30% was classified as luminal B. Questions also dealt with menopausal status and its impact on EBC management. The final questions concerned oncoplastic and prophylactic surgery. The questionnaire ended by asking whether the individual had changed their management approach to EBC over the course of the pandemic, since the outbreak occurred at different times and at different degrees of intensity in the different geographical regions of the country, generating social restrictions that increased or decreased as a function of how the outbreak progressed and of the policies implemented in the different states.

The questions allowed a single answer to be selected. The SBM's internal review board approved the study protocol prior to commencement and waived the requirement for informed consent, since the returned survey forms were unidentified.

The statistical analysis was conducted using the Statistical Package for the Social Sciences, version 24.0 (IBM SPSS). To analyze the responses, frequencies and percentages were calculated. The chi-square test was used in the bivariate analysis to evaluate possible management changes at the beginning and during the pandemic. Significance level was set at 5% with a 95% confidence interval (95%CI).

## Results

The survey was sent to 1,462 physicians affiliated with the SBM, with 503 (34.4%) returning a completed questionnaire. Of these, 271 (53.9%) were male and 229 (45.5%) were female. The most common age group was 31–40 years (172; 34.2%), followed by 41–50 years (157; 31.2%) and 51–60-years (110; 21.9%). Most (324; 64.4%) lived in a state capital city, were board-certified as breast specialists (395; 78.5%) and either worked in an academic institute or one associated with breast cancer treatment (390; 77.5%). The best response rate was from the southeast of the country (240; 47.7%), followed by the northeast (128; 25.4%), south (85; 16.9%), Midwest (35; 7%) and north (15; 3%). Most respondents (355, 70.6%) lived in large cities with over 500,000 inhabitants, while 12 respondents (2.4%) lived in towns with 50,000–100,000 inhabitants and 9 (1.8%) lived in towns with fewer than 50,000 inhabitants. Non-respondents were younger than respondents. Regarding their geographical distribution in the country, more respondents compared to non-respondents came from the northeast and fewer from the southeast. However, there is no statistically significant difference when the southeastern and northeastern regions, those most affected by COVID-19 in Brazil, are evaluated together ( $p = 0.746$ ) (Table 1). No other statistically significant differences were found between the groups.

Overall, 498 respondents (99%) lived/worked in a city/town with confirmed cases of COVID-19 and 258 (51.3%) reported that there were COVID-free medical establishments in their cities. Overall, 217 (43%) changed their management approach at the beginning of the pandemic, while 351 (69.8%) made changes during the pandemic ( $p < 0.001$ ) (Fig. 1).

The southeast of the country ( $p = 0.005$ ) and the state capital cities ( $p < 0.001$ ) were associated with changes at the beginning of the pandemic, while being female ( $p = 0.001$ ) was associated with changes during the pandemic. Being board-certified, having COVID-free hospitals available and working in an academic institute associated with cancer treatment had no significant effect either at the beginning or during the pandemic (Table 2).

In cases of HR-positive breast cancer tumors with the best prognosis ( $Ki-67 < 20\%$ ), 241 physicians (47.9%) would recommend NET for 3–6 months for postmenopausal patients compared to 251 (49.9%) who would recommend upfront surgery and 7 (1.4%) who would recommend NACT. While 89 (17.7%) respondents would recommend NET for premenopausal women, 390 (77.5%) would recommend upfront surgery and 20 (4%) would recommend NACT. In the case of HR-positive tumors with a higher proliferation index ( $Ki-67 > 30\%$ ), 171 (34%) specialists would recommend NET for postmenopausal women and 55 (10.9%) for premenopausal women. For postmenopausal women, 63 (12.5%) specialists would recommend NACT and 264 (52.5%) would recommend surgery, while for premenopausal women, 103 (20.5%) would recommend NACT and 338 (67.2%) would recommend surgery. Menopausal status significantly affected specialists' decision regarding whether to recommend NET in cases of EBC with  $Ki-67 < 20$  and in tumors with a higher proliferation index ( $p < 0.00001$ ) (Fig. 2).

In HER2 breast cancer, 107 specialists (21.3%) would recommend neoadjuvant systemic therapy for all cases compared to 132 (26.2%) who would recommend upfront surgery. Overall, 199 specialists (39.6%) would recommend initial systemic therapy in cases of tumors  $\geq 1.0$  cm, while for 59 (11.7%) the cut-off point for neoadjuvant treatment would be  $\geq 0.5$  cm.

In cases of triple-negative tumors, 96 (19.1%) would recommend NACT for all cases compared to 108 (21.5%) who would recommend upfront surgery. Overall, 216 (42.9%) specialists believed that NACT is the most appropriate option only for tumors  $\geq 1.0$  cm, while 77 (15.3%) would recommend neoadjuvant therapy in cases of tumors  $\geq 0.5$  cm (Fig. 2).

Overall, 319 (63.4%) participants would recommend immediate total breast reconstruction. A definitive implant would be the preferred method of reconstruction for 273 (54.3%) participants, while 201 (40%) would recommend temporary tissue expanders and 17 (3.4%) would recommend reconstruction using autologous tissue.

A total of 377 respondents (75%) would perform breast-conserving surgery with partial reconstruction, while 272 (54.1%) would contraindicate mammoplasty associated with breast-conserving surgery. Finally, 427 (84.9%) would not recommend risk-reducing mastectomy, even for patients with BRCA deleterious mutations (Fig. 3).

## Discussion

The immunohistochemical classification of breast cancer into luminal (HR+), HER2 and TN tumors [26–28] allows different treatment strategies to be adopted. In TN and HER2 tumors, NACT regimens and/or associated target therapy, even in EBC, have contributed to minimizing surgical morbidity and to identifying patients with residual disease for additional adjuvant therapy [29–31]. On the other hand, the approach with luminal tumors is generally upfront surgery, with the need for chemotherapy being defined according to histopathology, immunohistochemistry and genomic assay [27]. In general, the use of NET has been restricted to exceptional cases [28].

The COVID–19 pandemic has affected the world at different moments, requiring the reorganization of health structures [2–4]. Cancer patients are at an increased risk of contagion, infection, morbidity and death [9–11]. Emergency guidelines for breast cancer treatment [13–15,32,33] have suggested postponing surgery when the risk of progression is low (luminal tumors), initiating NET, extending the application of NACT and/or target therapies to subtypes of adverse biology (TN and HER2), minimizing the extent of surgery, including avoiding the use of autologous tissue in breast reconstruction, and postponing prophylactic surgery.

Brazil is a country of continental dimensions, with widely differing distribution of human and technical resources. The availability of hospital supplies and beds is greater in the southeast of the country where the concentration of COVID–19 cases is greater [34,35]. The concentration of physicians affiliated to the SBM is also greater in the southeast, with the highest response rate in the present study (48%) being from that region, followed by the northeast, the south, the Midwest and finally the north, with only 3%. In agreement with the SBM database, most respondents live in state capitals or in cities with more than 500,000 inhabitants, which are also those most affected by COVID–19 [36].

The onset of the COVID–19 epidemic in Brazil occurred relatively late compared to Europe and North America. Whereas the incidence of the disease was high in Italy and Spain in March, it was only beginning to appear in Brazil at that time, first in the city of São Paulo (southeast), and then spreading unevenly throughout the country [34]. This heterogenous pattern of spread may have resulted in poorer initial compliance by Brazilian breast specialists with the guidelines issued in those countries. Accordingly, 57% of participants had not changed EBC management at the beginning of the pandemic, while 70% had changed management during the course of the pandemic. At the beginning of the pandemic, changes in management occurred similarly in both sexes and in the different age groups, and irrespective of board certification or workplace. The demographic characteristics most associated with change in management at the beginning of the pandemic were living in the southeast of the country and in a state capital city, coinciding with the areas in which the incidence of COVID–19 infection was greatest, with increasing demand for hospital beds and implementation of government restrictive measures. On the other hand, during the pandemic, various state capital cities made an effort to reserve COVID-free hospitals or wards so as to guarantee the admission of elective patients, particularly cancer patients. These initiatives, however, had no effect on the results of this survey.

NET was more commonly indicated for postmenopausal women, both in the case of luminal A (48%) and luminal B tumors (34%). For premenopausal women, the specialists were more likely to recommend NET for cases of luminal A (18%) compared to luminal B tumors (11%). Menopausal status had a significant effect on how these specialists manage EBC. Conversely, although a considerable proportion of respondents suggested a different approach with respect to luminal tumors, upfront surgery remained the most common choice. For premenopausal women, 77.5% of respondents recommended upfront surgery for luminal A tumors and 67% for luminal B tumors. For postmenopausal patients, fewer respondents would recommend upfront surgery, either for luminal A tumors (50%) or for luminal B tumors (52.5%). The pandemic and the emergency recommendations for EBC treatment impacted on the management strategies of Brazilian breast specialists. According to these recommendations [13–15,24,32,33], HR-positive EBC should preferentially be treated using NET. Some societies have suggested that recommendations for the treatment of EBC should be classified by degree of priority according to the advice provided in the Ontario Health Pandemic Planning Clinical Guideline for Patients with Cancer [37], with cases of luminal tumors being classified as Priority B and surgery being postponed for 3–6 months. Another cancer organization also suggested that luminal A tumors should be treated initially with NET, while in the case of luminal B tumors, particularly those in which the axilla is positive or clinical stage II, the use of genomic assays could be useful in making this decision [33,38,39]. On the other hand, despite the partial compliance of Brazilian breast specialists with NET, particularly in cases in which the proliferation index is low, it is clear that a good proportion of those interviewed are still reluctant to use this strategy, even in exceptional conditions such as during a pandemic. However, although NET is a treatment that remains under debate, its use has increased in recent years with the publication of studies showing its safety [16–18,40,41].

In HER2 and TN tumors, considerable variations were found in the protocols from the different organizations. In one, TN and HER2 tumors are classified as Priority B1, suggesting NACT for tumors over 2 cm or with affected axillae [13]. Others also suggest NACT without specifying the cut-off point for treatment [32,33]. The Brazilian Society of Clinical Oncology suggests NACT for tumors over 5 mm or in the case of positive axillae [24].

These differences were reflected in this survey, with 21% of participants recommending NACT for all cases of HER2 tumors and 19% for all TN tumors. Overall, 40% of respondents considered the cut-off point of 1 cm for an indication of NACT to be appropriate in the case of HER2 tumors, while 43% deemed it appropriate for TN tumors. Conversely, 12% considered a cut-off point of 0.5 cm to be appropriate for NACT in HER2 tumors and 15% for TN tumors. In these subtypes, compliance with the recommendations would appear to be greater, although it is impossible to affirm that there was indeed any change. The prediction of a better pathological response to cytotoxic drugs and targeted therapy, as well as the possibility of selecting cases of residual disease for additional adjuvant therapy, had already rendered neoadjuvant therapy the standard treatment in many cases before the pandemic [29,30,42]. Likewise, in our understanding, the fact that one-third of respondents opted for NACT in cases of tumors <1 cm may represent overtreatment, since there are safe options of de-escalating treatment, as occurs in cases of HER2 tumors [43].

Breast reconstruction constitutes the basic principle in the present-day surgical treatment of breast cancer, reducing the patient's sensation of mutilation and improving their quality of life [44,45]. Approximately 60% of the participants would recommend total immediate breast reconstruction, with the most commonly suggested technique being definitive implants, followed by tissue expanders and autologous tissue. For breast-conserving surgery, 75% would recommend partial reconstruction, whereas 54% would contraindicate mammoplasty. Finally, 85% of respondents would not recommend risk-reducing mastectomy for patients with BRCA deleterious mutations. These data agree with the recommendations to avoid or delay major surgery that could prolong hospitalization and increase complications or require further hospital admissions [46–52].

There are some limitations associated with the present study. Since the data originate from a survey, it is impossible to affirm that the behavior encountered in these results would be completely applicable in practice. In addition, the deadline established for the responses to the questionnaires to be received was short; however, the dynamics of the progression of the pandemic could have affected the results if this time had been longer. Nevertheless, the short deadline may have affected the response rate of 34.4%, increasing the likelihood of bias. On the other hand, no significant differences were found between the different geographical regions of the country, or between the SBM database and our sample population, leading us to believe that the sample was indeed representative.

## Conclusions

The present findings highlight important changes in the management approach of these breast specialists at the beginning of the pandemic and throughout, particularly with respect to HR-positive tumors. These data may provide further information on EBC treatment in Brazil during the COVID–19 pandemic and may be useful in the perception of treatment and its consequences, permitting adaptation and a return to the conventional guidelines as the outbreak progresses in each region of the country.

## Declarations

*Conflicts of interest:* None.

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## Tables

**Table 1. Characteristics of the members of the Brazilian Society of Breast Specialists**

	Total N (%)	Respondents N (%)	Non-respondents N (%)	p-value <sup>a</sup>
<b>Members</b>	1462	503	959	
<b>Sex</b>				0.080
<b>Men</b>	746 (51)	271 (54)	475 (49.5)	
<b>Women</b>	716 (49)	229 (46)	487 (50.5)	
<b>Data Missing</b>	-	3 (0.6)	-	
<b>Age</b>				<0.000
<b>&lt;40 years</b>	461 (31.6)	178 (35.4)	283 (29.5)	
<b>41-50 years</b>	393 (26.9)	157 (31.2)	236 (24.6)	
<b>51-60 years</b>	291 (19.9)	110 (21.9)	181 (18.9)	
<b>&gt;60 years</b>	241 (16.5)	58 (11.5)	183 (19.1)	
<b>Data missing</b>	76 (5.1)	0 (0)	76 (7.9)	
<b>Region</b>				0.007
<b>Southeast</b>	756 (51.7)	240 (47.7)	516 (53.8)	
<b>Northeast</b>	306 (20.9)	128 (25.4)	178 (18.5)	
<b>South</b>	228 (15.6)	85 (16.9)	143 (14.9)	
<b>Midwest</b>	127 (8.7)	35 (7)	92 (9.6)	
<b>North</b>	45 (3)	15 (3)	30 (3.1)	

<sup>a</sup> Chi-square test.

**Table 2. Bivariate analysis for the association between management change at the beginning of the pandemic and during its course according to the characteristics of the breast specialists**

Management Change	Beginning of the Pandemic			During the Pandemic		
	Yes N (%)	No N (%)	p- value	Yes N (%)	No N (%)	p- value
<b>Total N = 503 respondents</b>						
<b>Region</b>			0.005			0.020
<b>Midwest</b>	14 (6.5)	21 (7.4)		20 (5.7)	15 (10)	
<b>Southeast</b>	87 (40.1)	153 (53.9)		159 (45.3)	81 (54)	
<b>South</b>	46 (21.2)	38 (13.4)		62 (17.7)	23 (15.3)	
<b>North</b>	4 (1.8)	11 (3.9)		9 (2.6)	6 (4)	
<b>Northeast</b>	66 (30.4)	61 (21.5)		101 (28.8)	25 (16.7)	
<b>State capital city</b>			<0.001			0.002
<b>Yes</b>	159 (73.3)	163 (57.3)		241 (68.7)	81 (54.4)	
<b>No</b>	58 (26.7)	120 (42.4)		110 (31.3)	68 (45.6)	
<b>Board-certified</b>			0.137			0.345
<b>Yes</b>	177 (81.6)	216 (76.1)		280 (79.8)	114 (76)	
<b>No</b>	40 (18.4)	68 (23.9)		71 (20.2)	36 (24)	
<b>Cancer Institution</b>			0.200			0.846
<b>Yes</b>	174 (80.2)	214 (75.4)		271 (77.2)	117 (78)	
<b>No</b>	43 (19.8)	70 (24.6)		80 (22.8)	33 (22)	

## Figures

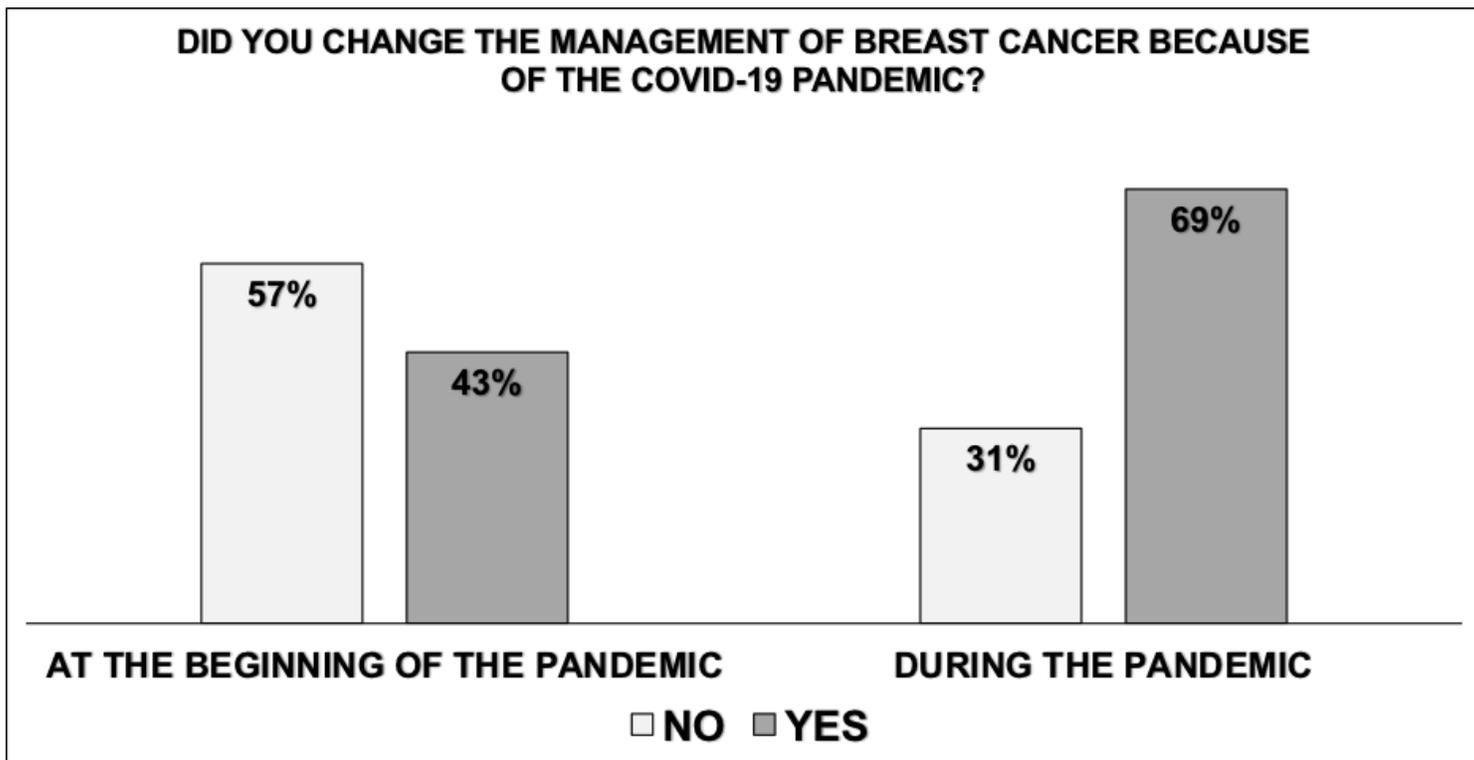


Figure 1

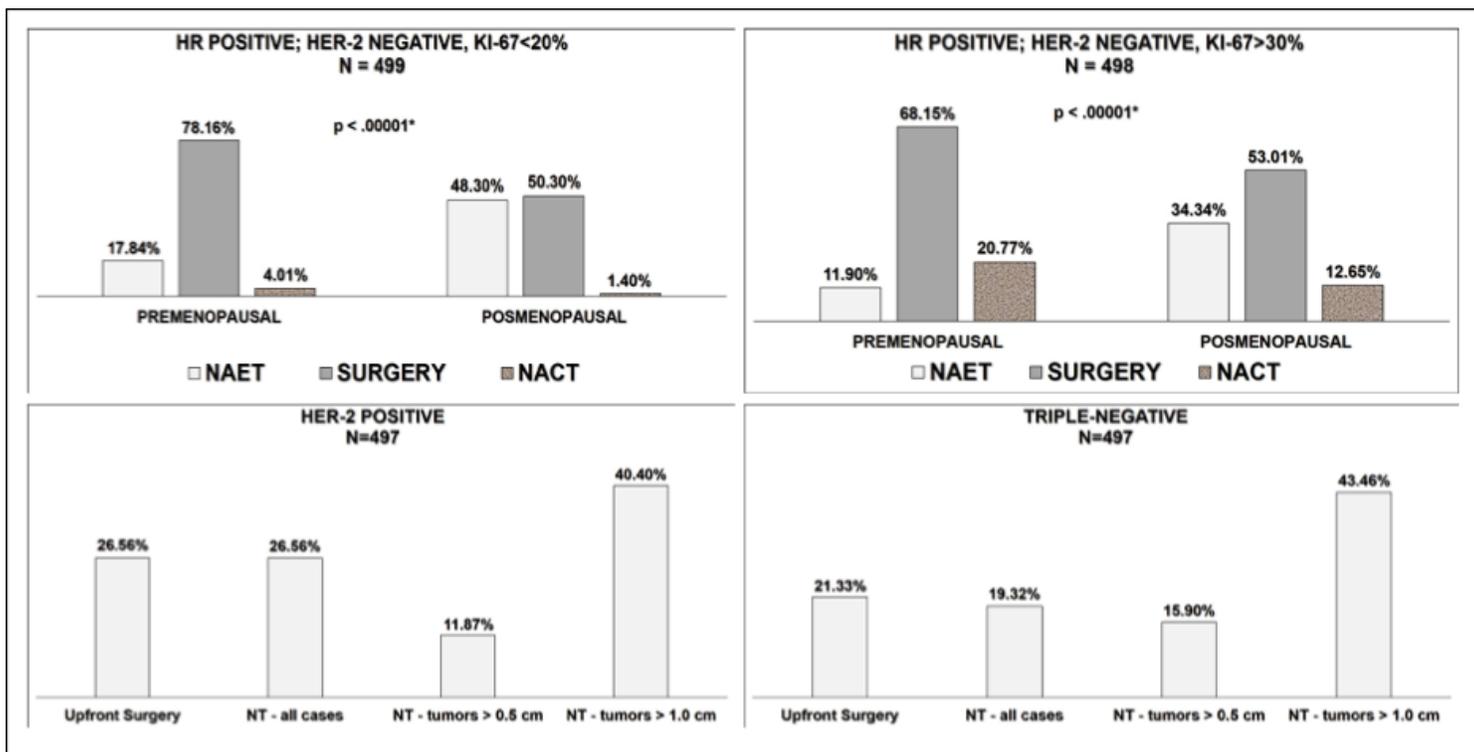
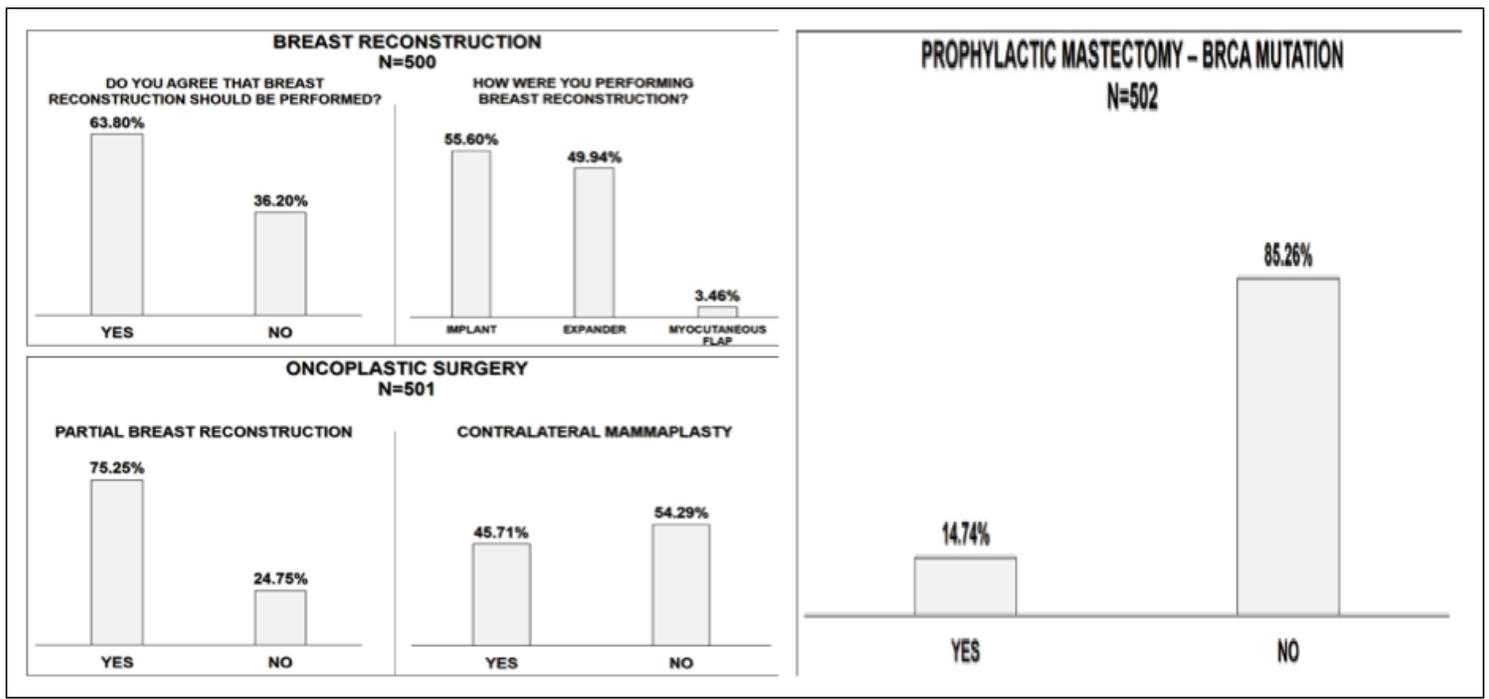


Figure 2

Decision making on treatment according to tumor biology NET: neoadjuvant endocrine therapy, NACT: neoadjuvant chemotherapy, NT: neoadjuvant therapy, N: number of answers in the survey, HR: hormone receptor; \* Chi-square test



**Figure 3**

Changes in the types of surgery performed due to the COVID-19 pandemic

## Supplementary Files

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- [Addendum1.docx](#)