

Impact of COVID-19 in early breast cancer management: a summary of the current evidence

Francisco Pimentel Cavalcante^{1,2}, Edson Abdala³, Leonardo Weissmann^{4,5,6}, Carlos Eduardo dos Santos Ferreira^{7,8}, Gilberto Amorim^{9,10}, Gustavo Aguiar Campana^{8,11}, Vilmar Marques de Oliveira^{2,12,13}, Gisah Guilgen^{10,14,15}, Luciana Landeiro¹⁶, João Renato Rebello Pinho^{7,17}, Álvaro Pulchinelli Jr^{8,18,19}, Heber Ribeiro^{20,21}, Rafael Souza²², and Daniela Dornelles Rosa^{10,23,24}

¹Fortaleza General Hospital, Breast Surgery

²Brazilian Society of Mastology

³USP, School of Medicine, Department of Infectious and Parasitic Diseases

⁴Emílio Ribas Infectious Disease Institute

⁵Unaerp Medicina, Guarujá

⁶Brazilian Society of Infectology

⁷Albert Einstein Hospital

⁸Brazilian Society of Clinical Pathology/Laboratory Medicine

⁹Oncologia D'Or

¹⁰GBECAM

¹¹DASA

¹²Santa Casa de São Paulo Hospital

¹³Santa Casa de São Paulo School of Medical Sciences

¹⁴Curitiba Cancer and Transplant Institute

¹⁵Nossa Senhora das Graças Hospital

¹⁶Núcleo de Oncologia da Bahia (NOB) - Oncoclínicas Group

¹⁷Hospital das Clínicas, School of Medicine, University of São Paulo, Medical Research

¹⁸UNIFESP, School of Medicine (EPM)

¹⁹Fleury Group

²⁰Brazilian Society of Oncology Surgery

²¹AC Camargo Cancer Center

²²Cancer Treatment Institute (ITC)

²³Moinhos de Vento Hospital

²⁴Federal University of Health Sciences of Porto Alegre (UFCSPA)

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Abstract

Purpose: An Expert Panel on Breast Cancer and COVID-19 was convened to address the impact of the COVID-19 pandemic for early breast cancer management.

Methods: In order to ensure the most clinically relevant information was addressed, essential information was drawn from several of the latest national and international guidelines and another technical document. The Expert Panel met in five virtual

closed sessions from November 2020 to May 2021 to consult on the relevant data from evidence-based results. The data gathered were discussed on an online platform (Within3 [®]).

Results: This paper reports the Expert Panel's highlights of these meetings' discussions. In addition, it provides practical recommendations covering topics regarding diagnosis, treatment, and management of breast cancer patients in clinical settings routinely encountered by HCPs amid the COVID-19 pandemic.

Conclusions: It was provided guidance on several topics regarding eBC management amid the COVID-19 pandemics to inform safer care practices.

Introduction

In 2020, the predicted number of new breast cancer cases was 2.3 million worldwide, with an estimated age-standardized rate (ASR) incidence of 47.8 per 100,000 person-years and ASR mortality of 13.6 per 100,000 person-year with 684,996 deaths predicted ¹. The COVID-19 pandemic has challenged the medical community on many fronts, having a significant impact on access to cancer diagnosis and treatment ². The fear of becoming infected while using healthcare facilities, fueled by the rising number of infected individuals seeking medical care, is one of the main factors delaying cancer diagnosis and treatment ³⁻⁵. A significant decrease in cancer diagnoses has been observed during the COVID-19 pandemic, with the most marked decline seen in breast cancer care (51.8%) ⁶.

Surgery remains the main curative treatment for breast cancer ⁷. However, due to the COVID-19 pandemic, breast cancer teams have been forced to review triage for surgical procedures in a bid to optimize clinical resource usage. This move has entailed assessing risks and deciding which surgery cases should be postponed ⁸, such as elective surgeries ⁹ and taking preventive measures for potentially infected non-deferrable surgery candidates ^{10,11}. Brazil is currently facing one of the worst moments of the pandemic, with almost 500,000 deaths registered ¹². The purpose of this review is to provide an evidence-based update of the management of early breast cancer during COVID-19 outbreak, with a particular emphasis on avoiding risks to both patients and healthcare professionals (HCP).

Methods

With the aim of pooling information on the host of clinical scenarios in which early breast cancer patients may present during the COVID-19 pandemic, a group of specialists in Brazil were invited to join an expert panel. In order to ensure the most clinically-relevant information was addressed, essential information was drawn from several of the latest national and international guidelines and from other technical documents 4,9,10,13–31. The data gathered were discussed on an online platform (Within3 ®) covering topics regarding diagnosis, treatment, and management of breast cancer patients in clinical settings routinely encountered by HCPs amid the COVID-19 pandemic.

Fourteen recognized experts joined an online expert panel and worked collaboratively in five virtual closed sessions from November 18th to May 25th, 2021, in five virtual closed sessions. A three-step process was conducted: [1] Prewrite, in which all relevant material was shared, and notes on crucial aspects acknowledged; [2] Steering Committee meeting, where participants discussed and shared clinical expertise, drafting recommendations; [3] Meeting convening all experts, in which a comprehensive review of all evidence provided was performed online, and resultant recommendations discussed and refined.

Clinical Presentation of Breast Cancer

Breast cancer (BC) is a heterogeneous disease with different subtypes. Most patients with breast cancer are asymptomatic (findings from screening mammography) while others may present with a palpable lump at diagnosis. Early breast cancer (eBC; stages I and II) represents more than 75% of cases in most parts of the world ³². The management of eBC is well-defined according to international protocols ^{13,14,33}. HER2-positive and triple negative (TN) BC are biologically more aggressive tumors whereas luminal cancers (which express hormone receptors) are more indolent ³⁴. Based on the Ki-67 proliferation index, the St Gallen Consensus defines two luminal subtypes: luminal A (better prognosis) and luminal B (more aggressive disease)³⁴. Surgery is the mainstay treatment for eBC, and the procedure may be performed upfront or after neoadjuvant therapy (chemotherapy or endocrine therapy). As a rule, HER2-positive, luminal B and TN patients are priority categories for urgent breast cancer therapy ³³.

Pathophysiology

Cancer patients have dysregulated immunity with depleted immune cells, such as CD8+ Tcells, CD4+ Tcells, NK cells and others ³⁵. COVID-19 infection in cancer patients significantly increases inflammatory factors and cytokines (high-sensitivity C-reactive protein, procalcitonin, IL-2, IL-6, IL-8), possibly explaining the poorer prognosis in individuals with cancer relative to those without cancer ³⁶. SARS-CoV-2 can enter the cell by mediating spike proteins using the angiotensin-converting enzyme 2 (ACE2) receptor via plasma membrane fusion or endosomes ³⁷. SARS-CoV-2 stimulates the innate immune system and antigen-specific responses of B and T cells through a mechanism similar to that seen for the influenza virus ³⁸. The development of virus-neutralizing antibodies is essential for protection against viral infections, and clinical studies of SARS-CoV-2 vaccines have been pursuing this therapeutic target ³⁹.

Management

Assessment and Diagnosis

In the context of the COVID-19 pandemic, the management of patients with eBC has become more complex, as patients can present in any of three clinical situations: asymptomatic patients with no known exposure to SARS-CoV-2, asymptomatic patients exposed to SARS-CoV-2, and symptomatic patients with suspected SARS-CoV-2 infection (Table 1) ⁴⁰.

The diagnosis of SARS-CoV-2 can be established based on the RT-PCR test for symptomatic or asymptomatic patients exposed within 5-10 days to SARS-CoV-2 infected patients ^{41,42}. Serological tests, such as ELISA IgM, can be employed for screening symptomatic patients after day 10 of symptoms as an alternative method to RT-PCR for COVID-19 diagnosis (gold standard) ⁴². However, the use of serological tests alone is not recommended because they are less sensitive before 10 days of symptom onset and given the possibility of false positives ^{23,24}.

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Table 1- Early breast cancer patients with surgery planned and SARS-CoV-2 clinical status.jpg available at <https://authorea.com/users/420763/articles/527023-impact-of-covid-19-in-early-breast-cancer-management-a-summary-of-the-current-evidence>

Another practical approach is to assess eBC management in those cases with SARS-CoV-2 test results available (positive or negative) and a more controversial clinical scenario (Table 2).

Consider using Point of Care (POC) antigen tests if PCR unavailable? In what situations?

Antigen-detection for the diagnosis of SARS-CoV2 using point-of-care tests (POC) provides a workable solution that could enable patients to self-isolate earlier and reduce the spread of infection ¹⁷, representing an option which is accessible to most outbreak areas compared with standard nucleic acid amplification tests (NAATs), such as RT-PCR assays ¹⁸. However, the trade-off is a loss of sensitivity compared to NAATs, particularly among asymptomatic patients ⁴⁴. These tests should be carried out by trained professionals.

The POC antigen test is a viable when RT-PCR is unavailable in the following scenarios ¹⁸:

- * Patients presenting with 5–7-day onset of symptoms;
- * Positive results need confirmation by RT-PCR assays (ideally);
- * Outbreak areas and remote settings, where POC testing constitute an alternative to RT-PCR.

Consider using Point of Care (POC) antibody tests if PCR was unavailable? In what situations?

Serology tests have limited application diagnosis-wise, particularly in the acute phase⁴⁵, as most patients will develop an antibody response within 1 to 3 weeks after infection¹⁹. Crucial windows of opportunity for clinical intervention and isolation measures may have already been missed¹⁹.

There is also a possibility of cross-reaction with other pathogens, such as other human coronaviruses, increasing the odds for false positives⁴⁵. There was no consensus among the experts regarding the clinical utility of POC antibody tests. Some authors agreed this technology could be considered in some situations, despite its limitations in order to¹⁹:

- * determine the extent of infection in patients not diagnosed using RT-PCR
- * determine infection fatality rate
- * support the development of vaccines

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Table 2- SARS-CoV-2 test results in specific eBC clinical scenarios.jpg available at <https://authorea.com/users/420763/articles/527023-impact-of-covid-19-in-early-breast-cancer-management-a-summary-of-the-current-evidence>

Treatment

Neoadjuvant therapy to allow delay of surgery

The clinical management guidelines for breast cancer were recently updated in the COVID-19 era. Clinical cases eligible for neoadjuvant treatment are^{9,24}:

- * Triple-Negative Breast Cancer (TNBC), HER2-positive and luminal B tumors \geq 2cm and/or with positive axilla ([?]N1).
- * Luminal A tumors stages T1-T2 and N0-N1 (neoadjuvant endocrine therapy [NET] may be recommended, especially in postmenopausal patients).
- * Inflammatory and locally advanced breast cancer (NET or neoadjuvant chemotherapy [NCT]).
- * Any type – to complete NCT that has already been initiated.

Specifically, for ER-positive and HER2-negative patients, both ESMO and ACS have stated that NET is an option to enable deferral of surgery by 6 to 12 months in clinical stage I or II breast cancers according to menopausal status^{9,24}.

Although constraints are often present in terms of resources, workforce, and hospital bed availability in the COVID-19 pandemic, causing a delay in procedures, both NET and NCT appear to be safe choices to postpone surgery in non-urgent indications of ER-positive early-stage breast cancer, also potentially contributing to a reduction in outpatient visits.

Managing axilla after neoadjuvant systemic therapy

According to the panel, if the sentinel lymph node (SN) is negative at the time of surgery, axillary dissection (AD) is not recommended, even in previously positive axilla. If the SN is positive, however, then course of action should be discussed on a case-by-case basis, especially after NET ⁴⁸.

There has been increasing interest in omitting AD after NCT in past years, even in those with residual disease on sentinel lymph node biopsy (SNB). A recent American study ⁴⁹ demonstrated that the use of isolated positive SN after NCT has an upward trend after the publication of the results of ACOSOG Z0011 ⁵⁰. In fact, the Z0011 study demonstrated excellent local and locoregional control with isolated SLNB but excluded patients who underwent neoadjuvant systemic treatment (NCT or NET) ⁵⁰. In women undergoing NCT, residual axillary disease can be associated with resistance, and there is no data on cancer safety when omitting axillary dissection at this time.

A retrospective review evaluated residual disease burden in positive SN after NCT and demonstrated an additional high disease burden, regardless of whether it was micrometastasis (59%) or macrometastases (63%), possibly an indication for AD ⁵¹. Another analysis showed that the likelihood of non-SLN-centered metastasis at axillary lymph node dissection (ALND) was high across all tumor subtypes ⁵². The core point is whether AD would play a role in residual lymph node disease cases or whether axillary radiation therapy could replace surgery in such cases. For instance, a retrospective study using data from the National Cancer Database (NCDB), with 1617 women with N1 disease after NACT, compared patients who received AD associated with nodal radiotherapy with those who received only SNB and radiotherapy, similar to the design of an ongoing randomized study of ALLIANCE group (A11202) ⁵³ showing increased survival in women undergoing AD ⁵⁴. However, in an exploratory analysis, the authors found that SN was comparable to AD in luminal tumors with single metastases. The panel recommends caution in omitting AD in such cases.

On the other hand, after NET, pathologic complete response (pCR) is generally not expected following systemic treatment ⁵⁵. The question is whether these patients match the ACOSOG Z0011 study profile or otherwise. The data in this scenario is limited. A study using the NCDB and Dana-Farber/Brigham and Women's Cancer Center database evaluated tumor burden after NET and the type of axillary surgery performed (SNB or AD): more than 90% of patients who had cN0 axilla at initial presentation, in both cohorts, they had <3 positive lymph nodes in the final pathology, with no difference in overall survival regardless of the type of axillary surgery ⁴⁸. In another study, using the NCDB, for stages 2 and 3, SNB use after NET was similar to that for upfront surgery and, among those with pN1 disease, the NET patients were less likely to undergo AD ⁵⁶. In this scenario, the panel recommended a case-by-case assessment, with the possibility of omitting axillary dissection, especially in initially clinically negative axilla.

Breast conservative surgery and risk of infection by COVID-19

BCS is associated with lower rates of hospital stay and visits after surgery and hospitalization than mastectomy ⁵⁷: a study with patients undergoing nipple-sparing mastectomy (NSM) had total complication rates of 47% and reoperations around 9% ⁵⁸. Regarding the use of oncoplastic surgery, complication rates also tend to be higher than in BCS. In a study using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database, complications within 30 days were greater in patients undergoing oncoplastic surgery compared to BCS (3,8% vs. 2.6%; $p < 0.001$) ⁵⁹. Another prospective cohort (TeaM Study) identified a reoperation rate of 2.8% ⁶⁰. In a survey conducted during the pandemic among mastologists from the Brazilian Society of Mastology (SBM), 75% of surgeons would recommend partial reconstruction after BCS; however, 54% of those would contraindicate mammoplasty techniques during the pandemic period ⁶¹. The panel recommends caution in recommending major surgery during the pandemic.

Although there are still limited data on this subject, it is possible to infer that the risk of contamination for less invasive surgeries, such as BCS, is low because risks of procedure complications and surgery times are lower. In addition, all precautions mentioned previously should also be taken for this surgical procedure.

Elective surgeries that cannot be delayed

Elective surgeries, by definition, can be postponed for up to 8 weeks. There are a few elective situations that are considered essential and require planned or immediate medical assistance surgery-wise. Emergency or urgent surgeries are those that, if not performed might compromise patient survivorship. Examples of this type of surgery are revision of an ischemic mastectomy flap, surgical evacuation of breast hematoma, drainage of breast abscess and revascularization of an autologous tissue flap ⁹.

Bilateral mastectomy

Regarding patients with contralateral prophylactic mastectomy in unilateral breast cancer indication, although there is still limited data on this subject, historically these cases have a longer hospital stay compared to breast-conserving surgery or unilateral mastectomy, and also have more post-surgery visits and higher rates of hospitalization⁵⁷. This potential increase in patient exposure could lead to a greater risk of infection by COVID-19 ²⁵. The expert panel suggested that a contralateral prophylactic mastectomy is not recommended during this period and conservative breast surgery, or even unilateral mastectomy should be carried out instead. The panel recommended that immediate breast reconstruction should be evaluated on a case-by-case basis, according to the local conditions or resource availability due to the pandemics.

COVID-19 vaccines and breast cancer

According to the panel, breast cancer patients should receive the COVID-19 vaccine as soon as it becomes available, since benefits are likely to outweigh the risks of adverse effects from SARS-CoV-2 vaccination⁶². The National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology recently reinforced this position ^{26,27}. It is essential to point out that there is limited clinical data supporting COVID-19 vaccination in cancer patients ⁶³. A multicenter, observational, prospective study has shown that SARS-CoV-2 specific IgG antibody response does not differ in cancer patients and HCP ⁶⁴. It is uncertain, however, whether long-term immunization can be achieved in the oncologic population ⁶³. In the same vein, data from influenza vaccinations indicates the development of immune protective response in cancer patients and, although, potentially, not the same level as compared to the general population, it is generally safe ^{28,65–67}. Again, there are long-term uncertainties, and the protection may vary depending on antineoplastic therapies, administration timing, disease stage, and comorbidities ⁶⁸.

It is important to note that patients who received monoclonal antibodies or convalescent plasma as part of COVID-19 treatment should defer vaccination for at least 90 days as stated by CDC recommendations ²⁹. After the final dose is received, an individual is considered fully vaccinated after a minimum of two weeks ³⁰. If the patient is asymptomatic and has not been in close contact with someone with SARS-CoV-2 infection in the prior 14 days, the panel deemed it safe to conduct a surgical procedure. The expert panel recommendation for vaccination against COVID-19 for eBC is presented in Figure 1. Table 3 summarizes the main vaccines approved worldwide as of April 14th, 2021.

Recently, an unexpectedly high incidence of axillary adenopathy findings after Moderna and Pfizer-BioNTech COVID-19 vaccines occurred⁶⁹. For patients receiving the Moderna vaccine, a solicited adverse event was reported in 11.6% vs 5.0% for placebo following dose 1, and 16.0% vs 4.3% for placebo following dose 2 ⁷⁰. Adenopathy occurred in the arm and neck 2-4 days after vaccination with a median duration of 1-2 days ⁶⁹. For those receiving the Pfizer-BioNTech vaccine, resultant lymphadenopathy lasted for a mean of 10 days.

However, in the Pfizer-BioNTech study, adenopathy was only reported as an unsolicited adverse event ⁶⁹. A single institution report found similar findings and the authors are considering “MRI-detected isolated unilateral lymphadenopathy ipsilateral to the vaccination arm to be most likely COVID-19 vaccine-related if within four weeks of either dose” ⁷¹.

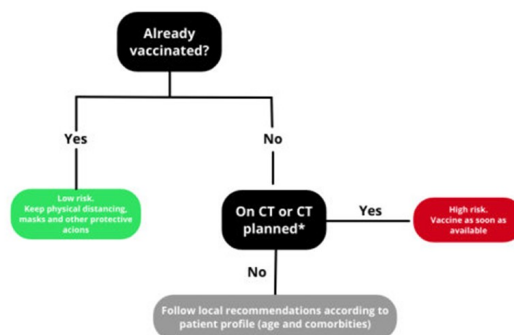


Figure 1: Vaccination against COVID-19 for eBC. CT: chemotherapy; * Planned within 8 weeks

What is the role of post-vaccine antibody quantification tests in eBC patients?

The current evidence supports that seroconversion rates among patients with cancer are similar to those without the disease, particularly in solid tumors like breast cancer ⁷². Vaccine-wise, serological tests can often be misinterpreted as they might not distinguish between past infection and post-vaccination immunological response ²³. Furthermore, serologic testing does not evaluate cellular immune response. When performed against nucleocapsid protein, these tests will not detect immune responses resulting from vaccination, and are not suitable for vaccine decision-making ²⁹. Most experts do not see a clinical application for these tests.

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Table 3-\selectlanguage{ngerman} COVID-19 vaccine candidates approved.jpg available at <https://authorea.com/users/420763/articles/527023-impact-of-covid-19-in-early-breast-cancer-management-a-summary-of-the-current-evidence>

Conclusion

We have provided guidance on several topics regarding eBC management amid the COVID-19 pandemic to inform safer care practices for both patients and HCPs.

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