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LETTER TO THE EDITOR

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Breast oncology and the COVID-19 pandemic: Recommendations from the Brazilian Society of Clinical Oncology (SBOC)

Câncer de mama na pandemia de COVID-19: Recomendações da Sociedade Brasileira de Oncologia Clínica (SBOC)

Gilberto Luiz da Silva Amorim[1], Daniele Xavier Assad[2], Bruno Lemos Ferrari[3], Daniela Dornelles Rosa[4], Bruno Pacheco Pereira[5], Renan Orsati Clara[6], Clarissa Maria de Cerqueira Mathias[6]

ABSTRACT

The current pandemic moment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has completely changed health services, with most services being directed to the treatment of affected patients. Even during this critical period, cancer patients need to be treated, as delayed treatment can compromise the chances of a cure. The Brazilian Society of Clinical Oncology (SBOC) has developed recommendations to guide decisions in breast cancer treatment during the SARS-CoV-2 pandemic through their Breast Tumors Committee. Due to the scarcity of relevant data, discussions on systemic treatment and surgical decisions related to breast cancer biological sub- types, chemotherapy schemes, anti-HER2 therapy, adjuvant endocrine therapy, breast surgery, radiotherapy, follow-up and routine exams, long-term central venous catheters, bisphosphonate and denosumab, genetic counseling and metastatic disease were evaluated and recommendations were issued. For newly diagnosed breast cancer, if appropriate, start systemic treatment with neoadjuvant endocrine therapy or neoadjuvant chemotherapy (NACT) with anti-HER2 blockage if HER2 positive disease. Surgery should be promptly considered if disease progression during NACT, malignant phyllodes tumor or breast sarcoma. These recommendations should be adjusted according to the reality of each service (private or public) and according to the epidemiological issues COVID19 presents in each area and revised recommendations may arise at any time.

Keywords: Breast Neoplasms; Pandemics; Coronavirus.

1. Oncologia D'Or RJ e Clínica São Vicente - Rio de Janeiro - Rio de Janeiro - Brazil.
2. Hospital Sírio-Libanês, Oncology - Brasília - Distrito Federal - Brazil.
3. Grupo Oncoclínicas, Oncology - Belo Horizonte - Minas Gerais - Brazil.
4. Hospital Moinhos de Vento, Oncology - Porto Alegre - Rio Grande do Sul - Brazil.
5. Multihemo Oncoclinicas Group, Medical Oncology Department - Recife - Pernambuco - Brazil.

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Correspondence author: Gilberto Luiz da Silva Amorim, Oncologia D'Or RJ e Clínica São Vicente - Rio de Janeiro - Rio de Janeiro - Brazil.
E-mail: gilberto.oncologista@gmail.com

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has challenged the medical community, including those in the field of clinical oncology, which has always required priority in the diagnosis and treatment of patients.

The Breast Tumors Committee of the Brazilian Society of Clinical Oncology (SBOC) brought to light some relevant decisions to guide medical oncologists during this pandemic, pointing out that there is a scarcity of scientific data related to this scenario. The following recommendations for systemic treatment and surgery decisions are based on biological subtypes of breast cancer.

RECOMMENDATIONS ON BREAST CANCER TREATMENT ACCORDING TO BIOLOGICAL SUBTYPES[1-8]

LUMINAL A INVASIVE BREAST CANCER

These recommendations include luminal A-type cancers (immunohistochemistry profile of high expression of estrogen receptor [ER] and progesterone receptor [PR], negative human epidermal growth factor receptor 2 [HER2], and low Ki-67) and luminal A breast cancers assessed by genomic tests.

Clinical Stage I-II disease

- Treat with neoadjuvant endocrine therapy (ET).
- Perform surgery after 3-4 months or when appropriate if responding to ET (Stage I and II luminal tumors are usually indolent and respond very well to ET).
- Surgery may be postponed with apparently no impact on survival.[9-11]

Clinical stage III disease

- Discuss neoadjuvant chemotherapy (NACT) or neoadjuvant ET.
- Perform surgery after 4-6 months of neoadjuvant treatment as appropriate (In stage III luminal breast cancer, neoadjuvant ET is a reasonable approach with significantly improved surgical outcomes.[12]

LUMINAL B HER2-NEGATIVE INVASIVE BREAST CANCER

This includes luminal B-type cancers (ER-positive, HER2-negative and one of the following: high Ki-67 or low/negative PR by immunohistochemistry) and luminal B breast cancers assessed by genomic tests.

Clinical Stage I-II disease

- Discuss NACT or neoadjuvant ET.
- Perform surgery after 4-6 months of neoadjuvant treatment as appropriate.

Clinical stage III disease

- Administer NACT
- Perform surgery after 4-6 months of neoadjuvant treatment as appropriate (Oncotype DX™ can be performed in the core-biopsy prior to surgery, and can guide the therapeutic decision between the choice of neoadjuvant ET or NACT, or whether surgery should be prioritized[13]).

TRIPLE NEGATIVE BREAST CANCER (TN)

This includes breast cancers that are ER-negative, PR-negative, and HER2- negative.

cT1a, cN0

- Surgery is recommended as the principle treatment at the earliest favorable moment, considering risks versus benefits.

cT1b, cN0

- Discuss with the multidisciplinary team: NACT is advised for invasive TN disease > 6 mm; otherwise, prompt surgical intervention is recommended (at the earliest favorable moment, considering risks versus benefits).

≥ cT1c, N0 or N+

- Administer NACT
- Perform surgery after 4-6 months of neoadjuvant treatment as appropriate.

HER2-POSITIVE BREAST CANCER

This includes invasive breast tumors that are:

- ER-positive, HER2 over-expressed or amplified, any Ki-67 and any PR or,

- HER2 over-expressed or amplified, ER-negative and PR-negative

cT1a, cN0

- Surgery is recommended as the principle treatment at the earliest favorable opportunity, considering risks versus benefits.

cT1b, N0

- Discuss with the multidisciplinary team: NACT with anti-HER2 if invasive HER2 positive breast cancer > 6 mm (given that in pT1b lesions, adjuvant CT + anti-HER2 blockage is indicated).
- If NACT is not considered, recommend surgery as soon as possible (if initial surgery is required, select the earliest option available, considering risks versus benefits.

≥cT1c, N0 or any N+

- Administer NACT with anti-HER2 therapy (double blockage with trastuzumab and pertuzumab if available).
- Perform surgery after 4-6 months of neoadjuvant treatment as appropriate.

RECOMMENDATIONS ON CHEMOTHERAPY SCHEMES[1-8]

- There are no CT schemes of choice during the pandemic period, but it may be suitable to favor exceptional schemes every 14 days or 21 days instead of weekly schemes that will result in multiple visits and consequently increased risk of infectious exposure. If possible, medical appointments should occur on the same day as the chemotherapy infusion, to reduce the number of patient visits to the hospital or clinic.
- Schemes with lower risk for gastrointestinal toxicity or febrile neutropenia and consequent lower risk of hospitalization are favored in order to avoid health system overload and risk of individual exposure.
- In cases where CT indications are borderline, a genomic test like Oncotype DX™ or MammaprintT™ is suggested to increase the chance of avoiding unnecessary CT during the pandemic. In the absence of genomic tests, we suggest using the MINDACT clinical risk criteria to avoid unnecessary CT. In exceptional circumstances, Oncotype DX™ can be performed during the core- biopsy in luminal B-type tumors (see above).
- In cases where colony-stimulating factors are required, the pegylated form should be used, given that it is administered in a single dose. If the pegylated formula is unavailable, offer filgrastim and guide patients on how to store it and how to perform multiple shots at home.

RECOMMENDATIONS ON ANTI-HER2 THERAPY[1-8]

- Always favor trastuzumab and pertuzumab schemes every 21 days. Consider exchanging intravenous (IV) for subcutaneous (SC) trastuzumab to reduce the time spent at the chemotherapy unit.
- In selected cases where weekly paclitaxel for 12 weeks with trastuzumab for 1 year (APT scheme)[14] is indicated, consider switching to adjuvant trastuzumab emtansine (T-DM1) every three weeks, despite there being no label indication for T-DM1 in this scenario[15]. This may reduce patient exposure compared to the APT scheme.
- The indication for adjuvant T-DM1 in residual disease after NACT remains valid[16] and routine hepatic tests and platelet blood counts can be spaced and/or evaluated remotely by tele-medicine, thereby reducing the number of visits, according to the recent regulations of the Brazilian Federal Council of Medicine.

RECOMMENDATIONS ON ADJUVANT ENDOCRINE THERAPY[1-8]

- ET must continue to be carried out during the pandemic period using either tamoxifen or aromatase inhibitors. Medical appointments may be postponed and patient questions can be handled by tele-medicine.
- Patients at high risk for recurrent disease, who have indicators of suppression of ovarian function (SOF) or who are already receiving monthly LHRH agonist therapy, can start or switch to schemes that are applied every 12 weeks, thereby reducing the number of patient visits to the clinic. When tamoxifen is combined with SOF, the later may be temporarily suspended.

RECOMMENDATIONS ON BREAST SURGERY[2,3,5,8,17,18]

CONSIDER DELAYING SURGERY WITHOUT IMPACT ON PROGNOSIS IN THE FOLLOWING CASES:

- Benign nodules
- Delayed breast reconstruction

- Mastectomies (in general and in cases of metastatic cancer) and hygienic surgery, except in rare cases of bleeding refractory to radiotherapy

In the case of pathological fractures, a multidisciplinary discussion of the risks and benefits of surgery in a pandemic environment should take place. The decision must take into account the potential for functional recovery with good quality of life.

CONSIDER DELAYING SURGERY WITH VERY MILD IMPACT ON PROGNOSIS IN THE FOLLOWING CASES:

- Prophylactic surgeries (patients with pathogenic genetic variants)
- Resections of atypical findings and/or precursor lesions (atypical ductal hyperplasia; atypical lobular hyperplasia; lobular carcinoma in situ)

CASES OF IN-SITU DUCTAL CARCINOMA (DCIS) CASES WITH NO SUSPECTED ASSOCIATED INVASIVE DISEASE:

The cases of low risk DCIS are defined by the criteria of LORIS:

-Age > 45 years;

- Low grade DCIS with biopsy;

- Microcalcifications in the image as the only finding;

- Extension < 5 cm;

- No palpable lesions; or

- Paget papillary discharge.

- In cases that are hormone receptor (HR)-positive, consider initial pharmaco- prophylaxis.
- In cases that are HR-negative, pharmaco-prophylaxis is not indicated (consider the statement below).
- Consider postponing surgery for 3-4 months or performing surgery once it is deemed safe.

CASES OF DCIS WITH SUSPECTED ASSOCIATED INVASIVE DISEASE:

High-risk DCIS is defined as extensive/ palpable lesions accompanied by the possibility of invasive disease, or which do not meet the above criteria for low- risk DCIS.

- In cases that are HR-positive, consider initial pharmaco-prophylaxis.
- In cases that are HR-negative, there is no indication for pharmaco-prophylaxis (consider the statement below)
- Consider surgery promptly.

SURGERY AFTER NEOADJUVANT TREATMENT:

- Consider delaying surgery after neoadjuvant treatment as long as possible (technical limit of 4-8 weeks or until improvement of logistics and adequate safety conditions).
- If NACT is concluded and the disease is HR-positive, consider ET as a bridging measure with or without SOF until surgery may be safely performed (it is not recommended to increase the number of NACT cycles).
- In cases of HER2-positive disease, consider maintaining double-blockade if available (or at least trastuzumab) for a few additional doses after completion of NACT, based on the previous argument.
- In cases of TN disease, prompt surgery is recommended, considering the risk vs benefit, 4-6 weeks after NACT. In exceptional cases where surgery is not available within a reasonable period of time, consider neoadjuvant radiotherapy (RT).

SCENARIOS IN WHICH SURGERY SHOULD BE PROMPTLY CONSIDERED:

- Patients with disease progression during NACT
- Malignant phyllodes tumor
- Breast sarcoma

RECOMMENDATIONS ON RADIOTHERAPY (RT)[1, 2, 4, 5, 18]

- For patients with stages I and II low-risk luminal tumors where adjuvant CT is not indicated and who are candidates for adjuvant ET, consider delaying the start of RT to 3-6 months from the date of surgery. Additionally, consider hypo-fractionation (40 Gy in 15 fractions in 3 weeks) or the lowest possible number of treatment days.
- Omit RT in elderly patients (> 65-70 years) with low-risk disease and negative axilla or in younger patients with low-risk disease and negative axilla with serious co-morbidities.
- Patients with DCIS can also avoid adjuvant radiotherapy after assessment of risk versus benefit.
- Patients with negative axilla who do not require a boost can be candidates for hyper-fractioning (28-30 Gy/single weekly dose in 5 weeks or 26 Gy in 5 daily sessions in one week) if the technique is available.
- Hypo-fractionation (40 Gy/15 days/3 weeks) can be used in all cases of breast, chest wall and drainage chains radiation therapy.

- For patients with luminal tumors who have newly undergone surgery after NACT and who are candidates for adjuvant ET, RT can be delayed for up to 3 months after surgery.
- For patients with stages I and II HER2-positive tumors who have undergone surgery after NACT where follow-up with adjuvant treatment and anti-HER2 blockade is indicated, RT can be delayed for up to 3 months after the end of chemotherapy.
- For patients with stage III HER2-positive tumors who have undergone surgery after NACT and for whom adjuvant treatment and anti-HER2 blockade are indicated, RT can be delayed for up to 3 months after the end of chemotherapy, especially when a pathological complete response (pCR) is achieved. Consider earlier RT in cases where pCR is not achieved.
- For patients with TN tumors after adjuvant CT, RT can be postponed for 3 months after completion of CT
- For patients with TN tumors, when there is residual disease and indication of adjuvant capecitabine after NACT, RT may be considered immediately following completion of adjuvant CT, due to the high risk of recurrence.
- For patients with TN tumors who have achieved pCR after NACT, RT can be delayed for up to 2-3 months.
- In cases of metastatic breast cancer, consider bone antialgic single dose radiotherapy if possible; for other indications of RT in metastatic sites (e.g. whole brain, anti-hemorrhagic), consider the minimum number of fractions possible.

RECOMMENDATIONS OF FOLLOW-UP AND ROUTINE EXAMS[1-8]

- To avoid unnecessary medical office visits, some follow-up exams should be postponed until the end of the pandemic period, without increasing patient risks or influencing prognosis; consider tele-medicine if available.
- Screening tests for patients with suspected metastatic disease and biopsies in new cases or in suspected cases of recurrence should be performed when feasible, still aiming to avoid multiple visits and unnecessary patient exposure to the risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Imaging tests to assess the response of metastatic disease in patients with clear clinical benefits and oligo/asymptomatic disease may be postponed at the clinician's discretion.

RECOMMENDATIONS ON LONG-TERM CENTRAL VENOUS CATHETERS[1, 2, 4, 5, 18]

- Consider cleaning long-term central venous catheters every 12 weeks.
- Withdrawal of these catheters should be postponed until the pandemic period has passed.
- Catheter placement should be avoided if possible, after discussing the risks and benefits according to the treatment protocol.

RECOMMENDATIONS ON INJECTABLE BISPHOSPHONATES AND DENOSUMAB[1-8]

- Consider postponing these treatments during the pandemic period if the indication is for adjuvant use or prevention and / or treatment of osteoporosis.
- In the case of metastatic disease, delay infusion of zoledronic acid to every 12 weeks; if zoledronic acid is used monthly, consider switching to every 12 weeks. • Space monthly denosumab as needed if the patient has oligo/asymptomatic, low-volume disease without high risk of skeletal events, and no hypercalcemia.

RECOMMENDATIONS ON GENETIC COUNSELING [1, 2, 4, 5, 18]

- Consider postponing genetic counselling if there is no clear impact on medical practice for the next 3-6 months; consider tele-medicine if there is an urgent need for an appointment.
- Consider performing genetic testing for the evaluation of pathogenic variants of BRCA 1 and BRCA 2 for possible indication of platinum and/or olaparib; the tests should be performed using a simple salivary home-based test kit, if available, to avoid unnecessary visits to the laboratory.

RECOMMENDATIONS FOR METASTATIC DISEASE[1-8]

- Do not stop treatments that provide a clear clinical benefit such as chemotherapy, endocrine treatment, immunotherapy or biological anti-HER2 treatments. If feasible, consider spacing medical visits and exams. Use tele- medicine whenever possible.
- Whenever possible, choose treatments with fewer toxicities to minimize visits to the emergency department and facilitate fewer clinical appointments and evaluations.
- Whenever possible, prescribe fewer cycles of chemotherapy, concluding CT after 4-6 cycles

or upon improved response, utilizing anti-HER2 therapy, bevacizumab, atezolizumab or single ET (in HR-positive tumors) as maintenance therapy, thus reducing the duration of exposure to immunosuppressive chemotherapy and steroid treatments.

- Preferentially prescribe monotherapy in cases of palliative CT; in HR-positive disease, consider single endocrine treatment, avoiding initiation of treatments with increased risk of pulmonary toxicity such as everolimus. In cases where alpelisib is used, perform an endocrinologic assessment to better control blood glucose in order to reduce the risk of grade III hyperglycemia (and therefore the risk of hospitalization). Patients using everolimus or alpelisib with adequate responses and good tolerance must be carefully evaluated for continuation of these treatments.
- Cyclin inhibitors can be started and continued in combination with ET, due to the robust increase in overall survival associated with these combinations. Patients must be closely monitored for hematological, gastrointestinal and other side effects and exams can be performed and shared with the medical team electronically by tele-medicine.
- Patients with advanced disease and life expectancy less than 3 months should be referred to palliative care, avoiding futile treatments that overwhelm the health system with toxicities, unnecessary hospitalizations and possible mechanical ventilators aimed at use in terminally ill patients.
- Delays in cycles, dates of treatment, and routine visits in the context of the pandemic and in the context of a non-curative treatment are perfectly acceptable.
- Patients with good performance status, irrespective of age, should receive appropriate cancer treatment notwithstanding the pandemic. In most cases it will not be possible to delay the start of treatment for 3-4 months, therefore, a shared decision should be proposed, respecting the patient's opinion and considering limitations and difficulties in the access and availability of emergency services.

RECOMMENDATIONS FOR PATIENTS WITH FEVER, RESPIRATORY SYMPTOMS (COUGH, CORYZA, DIFFICULTY IN BREATHING) OR WITH SUSPECTED OR CONFIRMED COVID-19 DIAGNOSIS[6]

- Advise patients to always contact their medical team. If there is no shortness of breath, they are advised to stay at home in social isolation for 14 days unless the medical team can provide a COVID-19 test, and to maintain contact with the doctor by tele-medicine throughout this period.
- Cases with warning symptoms (shortness of breath, respiratory distress, O2 saturation <95%, worsening in the clinical conditions of pre-existing disease, severe abdominal pain) should seek emergency service.
- Patients with fever and respiratory symptoms should discontinue any systemic cancer treatments until symptoms are resolved.

FINAL CONSIDERATIONS:

These are general recommendations. All cases should be discussed on an individual basis with the multidisciplinary team and shared decisions between the medical team and the patient must be guided. It is strongly recommended to maintain multidisciplinary meetings through web conferences for the optimal management of all cases. It is also recommended that these recommendations be adjusted according to the reality of each service (private or public) and according to the epidemiological issues COVID19 presents in each area. Revised recommendations may arise at any time.

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