Disclaimer about preliminary version

The following article has been accepted after peer review for publication in *JCO Oncology Practice*. This preliminary version has been posted with author permission and will be replaced with the final published manuscript, after which this preliminary version will be removed. This version, including any author disclosures should be considered preliminary and may contain errors.

Suggested citation: Sheng, J.Y., Santa-Maria, C. A., Mangini, N.

Management of Breast Cancer During the Covid-19 Pandemic: A Stage and Subtype-Specific Approach

DOI: 10.1200/OP.20.00364 *JCO Oncology Practice*
Title: Management of Breast Cancer During the Covid-19 Pandemic: A Stage and Subtype-Specific Approach

Running head: Breast Cancer Treatment During Covid-19

Authors: Jennifer Y. Sheng MD\textsuperscript{1,2}, Cesar A. Santa-Maria MD MSC\textsuperscript{1,2}, Neha Mangini PharmD\textsuperscript{2}, Haval Norman PharmD\textsuperscript{2}, Rima Couzi MD\textsuperscript{1,2}, Raquel Nunes MD\textsuperscript{1,2}, Mary Wilkinson MD\textsuperscript{1,2}, Kala Visvanathan MD\textsuperscript{1,3}, Roisin M. Connolly MB BCh\textsuperscript{4}, Evanthia Torres MD PhD\textsuperscript{5}, John H. Fetting MD\textsuperscript{1,2}, Deborah K. Armstrong MD\textsuperscript{1,2}, Jessica J. Tao MD\textsuperscript{1,2}, Lisa Jacobs MD\textsuperscript{1,2}, Jean L. Wright MD\textsuperscript{1,2}, Elissa D. Thörner BS MHS\textsuperscript{2}, Christine Hodgon MS\textsuperscript{6}, Samantha Horn MPA\textsuperscript{7}, Antonio C. Wolff MD\textsuperscript{1,2}, Vered Stearns MD\textsuperscript{1,2}, and Karen L. Smith MD MPH\textsuperscript{1,2}

Affiliations:
(1) The Johns Hopkins University School of Medicine, Baltimore, MD.
(2) The Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD.
(3) The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.
(4) Cancer Research @UCC, College of Medicine and Health, University College Cork, Ireland.
(5) Norris Comprehensive Cancer Center, Keck School of Medicine of University of Southern California, Los Angeles, CA.
(6) Clinical Trials Consultant, Quantum Leap Health Care Collaborative, San Francisco, CA.
(7) LifeBridge Health, Alvin and Lois Lapidus Cancer Institute, Baltimore, MD.

Corresponding Author:
Karen Lisa Smith MD MPH
Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital
Building B, First Floor
5255 Loughboro Rd, NW
Washington, DC 20016
Phone: (202) 660-6500
Fax: (202) 660-6501
Email: ksmith60@jhmi.edu

Keywords: Breast Cancer, COVID-19, HER2-positive, Triple Negative, Hormone Receptor-Positive, Guideline

Acknowledgement of research support: Funding for this was made possible (in part) by the Centers for Disease Control and Prevention. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services, nor does the mention of trade names, commercial practices, or organizations endorsed by the U.S. Government.
ABSTRACT

The COVID-19 pandemic has rapidly changed delivery of cancer care. Many non-urgent surgeries are delayed in order to preserve hospital resources and patient visits to healthcare settings are limited to reduce exposure to SARS-CoV-2. Providers must carefully weigh risks and benefits of delivering immunosuppressive therapy during the pandemic. For breast cancer, a key difference is increased use of neoadjuvant systemic therapy due to deferral of many breast surgeries during the pandemic. In some cases, this necessitates increased use of genomic tumor profiling on core biopsy specimens to guide neoadjuvant therapy decisions.

Breast cancer treatment during the pandemic requires multi-disciplinary input and varies according to stage, tumor biology, comorbidities, age, patient preferences and available hospital resources. We present here the Johns Hopkins Women’s Malignancies Program approach to breast cancer management during the COVID-19 pandemic. We include algorithms based on tumor biology and extent of disease that guide management decisions during the pandemic. These algorithms emphasize medical oncology treatment decisions and demonstrate how we have operationalized the general treatment recommendations during the pandemic proposed by national groups, such as the COVID-19 Pandemic Breast Cancer Consortium. Our recommendations can be adapted by other institutions and medical oncology practices in accordance with local conditions and resources. Guidelines such as these will be important as we continue to balance treatment of breast cancer against risk of SARCS-CoV-2 exposure and infection until approval of a vaccine.
INTRODUCTION

On March 11, 2020, the World Health Organization declared a pandemic in the setting of over 100,000 cases of a new respiratory illness, Coronavirus Disease-19 (COVID-19), caused by infection with a novel coronavirus, SARS-CoV-2. Data regarding COVID-19 and cancer is limited, but reports suggest individuals with cancer, especially those who receive systemic anti-cancer therapy within 14 days of COVID-19 diagnosis, are more likely to develop severe disease. Furthermore, individuals with metastatic cancer are more likely to require admission for intensive care, undergo mechanical ventilation and die from COVID-19. Data also implicate healthcare settings as a source for SARS-CoV-2 transmission, a finding concerning to cancer patients who frequent cancer centers.

Many countries have implemented strategies to avoid surges of COVID-19 cases, conserve resources, and protect vulnerable populations from infection. Cancer centers have rapidly changed models of care by delaying non-urgent surgeries, increasing home-based therapies and expanding telemedicine. Numerous organizations and institutions have issued general and disease-specific guidelines for cancer care. Although COVID-19 cases have already peaked in some locations, they are increasing in others, and secondary surges are anticipated, suggesting that changes in cancer care will not be short-lived.

For patients with breast cancer, preliminary management recommendations have been proposed by the COVID-19 Pandemic Breast Cancer Consortium. These tiered guidelines prioritize surgery, radiation and systemic therapy interventions by urgency. As in non-pandemic circumstances, treatment decisions must consider stage and tumor biology within the context of comorbidities and individual patient goals. Acknowledging the uncertainties of cancer outcomes and SARS-CoV-2 infection risk associated with treating breast cancer, we present here the John Hopkins Women’s Malignancies Program approach to breast cancer management during the pandemic. These stage and subtype-specific algorithms, endorsed by
our multi-disciplinary team and patient advocates, represent our strategy to apply available evidence to optimize breast cancer management during this time.

EARLY STAGE BREAST CANCER

Ductal Carcinoma In Situ (DCIS)

In accordance with recommendations from the American College of Surgeons and COVID-19 Pandemic Breast Cancer Consortium, we recommend deferring surgery for DCIS during the pandemic in the absence of microinvasion or of high suspicion of invasive cancer.\textsuperscript{13,16} For newly diagnosed estrogen receptor (ER)-negative DCIS, we defer intervention for up to 3-6 months and until after the peak of the pandemic when surgical supplies are more available. For ER-positive DCIS, we recommend a telemedicine consultation with medical oncology and neoadjuvant endocrine therapy (ET) for up to 6 months. We prefer an aromatase inhibitor (AI) for post-menopausal women\textsuperscript{20} and tamoxifen for pre-menopausal women.\textsuperscript{21} For individuals who previously underwent breast-conserving surgery (BCS) for DCIS, we consider delaying or omitting radiation for those who are ER-positive and are able to initiate ET.\textsuperscript{22-24} Omission of radiation is an option for good-risk disease (low-intermediate grade, < 2.5 cm, surgical margins $\geq 3$ mm).\textsuperscript{25} These recommendations are summarized in Supplementary Table (ST) 1.

Early Stage Invasive Breast Cancer (Stages I-III)

We recommend early multi-disciplinary evaluation for most individuals with newly diagnosed clinical stage I-III invasive breast cancer. At Johns Hopkins, surgery is currently available for patients with early stage invasive breast cancer completing neoadjuvant systemic therapy and for select patients with newly diagnosed invasive breast cancer who desire upfront surgery and/or who are not appropriate candidates for neoadjuvant systemic therapy. Since availability of surgery is fluid, based on resources within the institution and COVID-19 incidence in the community, our surgeons use tiered criteria to prioritize patients for surgery. When
possible, we recommend BCS. Contralateral procedures and reconstruction with an expander or immediate implant are currently available on a case-by-case basis after assessment of COVID-19 risk and comorbidity. Limitations in available surgeries may necessitate a staged approach, with BCS of the affected breast performed first and additional surgery after the pandemic. If the desired reconstruction procedure is not immediately available, we consider neoadjuvant systemic therapy to allow deferral of mastectomy.

**Triple Negative Breast Cancer**

*Figure 1, Panel A* and *ST-2* summarize our approach to newly diagnosed early stage triple negative breast cancer (TNBC). If available, we recommend upfront surgery for clinical T1N0 TNBC and do not recommend adjuvant chemotherapy for pathologic small (T1a-b), node-negative disease. For those with pathologic T1a-bN0 TNBC who desire adjuvant chemotherapy and for those with more advanced pathologic stage after upfront surgery, we initiate adjuvant chemotherapy within standard timeframe. Whenever possible, we administer non-anthracycline-containing regimens such as docetaxel/cyclophosphamide (TC) for adjuvant treatment of pathologic stage T1cN0 TNBC as the added benefit of an anthracycline-containing regimen is small in this population and TC requires fewer clinic visits. For pathologic T2-4 and/or N1-3 TNBC, we recommend adjuvant dose dense doxorubicin/cyclophosphamide followed by weekly or dose dense paclitaxel (AC-T). 26–29

For clinical prognostic stage II-III TNBC, we recommend neoadjuvant AC-T. While addition of carboplatin to neoadjuvant AC-T increases likelihood of pathologic complete response (pCR), we do not typically include carboplatin as there is no definite survival benefit and hematologic toxicity increases. 30 We likewise have reservations regarding neoadjuvant immunotherapy, especially during the pandemic, due to associated adverse events. 31 Upon completion of neoadjuvant chemotherapy (NACT), surgery should be performed within 4-6 weeks. 32 If surgery is delayed due to the pandemic, we do not recommend further
chemotherapy; these patients should be prioritized for surgery when available. If residual disease is identified at surgery after NACT, we consider post-neoadjuvant capecitabine as per routine.\textsuperscript{33}

After completion of (neo)adjuvant chemotherapy and surgery, we refer individuals with stage I-III TNBC to radiation oncology per usual criteria. Despite the risk of SARS-CoV-2 exposure with daily radiation visits, we do not recommend delaying radiation for TNBC due to risk of locoregional recurrence.\textsuperscript{24,34,35}

\textbf{HER2-Positive Breast Cancer}

\textbf{Figure 1, Panel B} and \textbf{ST-3} summarize our approach to newly diagnosed early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer during the pandemic. While the COVID-19 Pandemic Breast Cancer Consortium suggests upfront surgery only for T1N0 HER2-positive breast cancer, we also favor upfront surgery for small T2 (≤ 3 cm) N0 disease with the goal of de-escalating adjuvant systemic therapy (and the attendant risks of visits to the cancer center and immunosuppression) if early stage is confirmed pathologically. If surgery reveals pathologic T1aN0 disease, we do not recommend adjuvant chemotherapy/HER2-targeted therapy given low recurrence risk.\textsuperscript{36,37} For pathologic stage T1bN0 HER2-positive breast cancer, we discuss pros and cons of adjuvant chemotherapy/HER2-targeted therapy, but consider it most strongly for individuals with hormone receptor (HR)-negative and/or grade 3 disease. For individuals with pathologic T1bN0 disease who opt for adjuvant chemotherapy/HER2-targeted therapy and for those with pathologic T1cN0 or small T2N0 (≤ 3 cm) disease, we recommend paclitaxel/trastuzumab (T/H) or trastuzumab emtansine (T-DM1). Although toxicity profiles differ, both adjuvant T/H and T-DM1 are associated with favorable DFS and minimal hematologic toxicity.\textsuperscript{38,39} A potential advantage of adjuvant T-DM1 over T/H during the pandemic is 3-weekly dosing interval. For individuals found to have more extensive disease after upfront surgery, we recommend
standard adjuvant chemotherapy/HER2-targeted therapy with
docetaxel/carboplatin/trastuzumab (TCH) +/- pertuzumab (P). As per routine, we initiate
adjuvant systemic therapy within 60 days of surgery for HER2-positive breast cancer.

In general, we recommend NACT/HER2-targeted therapy for those with tumor size >3
cm and/or clinically positive axillary lymph node(s). Our preferred neoadjuvant regimen is
TCH+/-P, but in select circumstances consider de-escalation with
paclitaxel/trastuzumab/pertuzumab (THP).

After completion of NACT/HER2-targeted therapy, surgery should be performed within 4-
6 weeks. If surgery is not available, we recommend additional cycles of HER2-targeted
therapy (H+/-P) until surgery is available. If residual disease is identified at surgery, we treat
with standard post-neoadjuvant T-DM1. If there is no residual disease at surgery, we
administer adjuvant H+/-P. To limit clinic visits during the pandemic, we consider shortening
HER2-targeted therapy with H+/-P from 12 to 6 months and extending the dosing interval from 3
to 4 weeks. While there is interest in subcutaneous trastuzumab, there are challenges with
implementation including requirement for administration by a healthcare provider and insurance
coverage.

After completion of primary therapy for HER2-positive early breast cancer, we refer to
radiation oncology per standard guidelines. As is the case for TNBC, we do not recommend
delaying radiation for HER2-positive breast cancer due to risk of locoregional recurrence.

After completion of primary therapy, we initiate adjuvant ET per usual care for individuals with
HR-positive and HER2-positive breast cancer.

**Hormone Receptor-Positive Breast Cancer**

Treatment decisions for newly diagnosed clinical stage I-III HR-positive breast cancer
are complicated as pandemic conditions sometimes necessitate diversion from commonly used
therapeutic paradigms. Figure 1, Panel C and ST-4 summarize our approach to newly
diagnosed early stage HR-positive breast cancer according to biologic risk. We recommend considering biologic risk features when making treatment decisions for newly diagnosed early stage HR-positive breast cancer. Low risk biologic features suggest low likelihood of response and/or small benefit from (neo)adjuvant chemotherapy while high risk biologic features suggest the converse (Table 1). We typically consider pre-menopausal women as clinically high risk (irrespective of other characteristics).

If available, we prefer upfront surgery for clinical stage T1-3N0 HR-positive breast cancer with low risk biologic features who are operative candidates. If upfront surgery or desired procedure is not available, neoadjuvant ET can be initiated and surgery delayed for up to 6-12 months. We also consider upfront surgery for newly diagnosed clinical stage T1-3N1 or T4N0-1 HR-positive breast cancer with low risk biologic features if surgery is available and patient is an operative candidate. If upfront surgery is unavailable or not preferred (especially for larger tumors or nodal involvement if neoadjuvant therapy can reduce extent of breast and/or axillary surgery), we consider genomic profiling on the core biopsy specimen. If genomic profiling confirms low risk, we favor neoadjuvant ET for up to 6-12 months; if it indicates high risk, we consider NACT.

We use a slightly different approach for newly diagnosed early stage HR-positive breast cancer with high risk biologic features. For clinical stage T1-3N0-1 or T4N0 disease, we favor upfront surgery if the patient is a candidate and the desired surgery is available. As for low biologic risk tumors, if upfront surgery is unavailable or not preferred, we suggest neoadjuvant therapy and genomic profiling may be performed to clarify tumor biology and aid the choice between neoadjuvant ET and NACT. If genomic profiling confirms high risk, we favor NACT. If genomic profiling demonstrates low risk despite the other high risk biologic features, we discuss pros and cons of neoadjuvant ET and NACT and individualize the approach.

For patients with newly diagnosed clinical N2-3 HR-positive breast cancer, we generally favor neoadjuvant systemic therapy regardless of biologic risk. For those with high risk biologic
features, we recommend NACT and for those with low risk biologic features, we individualize the approach after discussing pros and cons of neoadjuvant ET and NACT.

As per usual, we recommend AI over tamoxifen for neoadjuvant ET in post-menopausal women. For neoadjuvant ET in pre-menopausal women, we favor ovarian function suppression (OFS) with tamoxifen followed by transition to AI once estradiol is suppressed; however data supporting this approach is limited and careful monitoring is required. Surgery can usually be safely deferred for up to 6-12 months in individuals receiving neoadjuvant ET; however, we favor careful monitoring and surgery as soon as possible in high biologic risk. If surgery is delayed beyond 6-12 months, neoadjuvant ET should be continued until surgery is available.

For selection of NACT in early HR-positive breast cancer, we favor AC-T, especially for node positive disease. Upon completion of NACT, surgery should be performed within 30-60 days. If surgery cannot be performed within that timeframe, we recommend neoadjuvant ET until surgery is available, but such patients should be prioritized for surgery.

For individuals with HR-positive breast cancer who have upfront surgery, we recommend genomic profiling on the surgical specimen per usual indications if not previously performed. If indicated, we offer adjuvant chemotherapy with TC or AC-T as per routine care. We favor omitting chemotherapy if the expected benefit is small, even in limited node positive disease. For individuals receiving neoadjuvant ET followed by surgery with residual disease, we consider genomic profiling on the core biopsy specimen if not already performed. We recommend adjuvant chemotherapy if high risk, although clear selection criteria in this scenario are unavailable. We consider delaying adjuvant chemotherapy for HR-positive breast cancer for up to 90 days after surgery with the hope that risk of COVID-19 will decrease prior to initiation; however we recommend caution delaying care given uncertainties about the time course of the pandemic.
After completion of surgery with or without adjuvant chemotherapy for HR-positive early breast cancer, we refer to radiation oncology per usual criteria. Radiation can be deferred for several months in select patients with low risk HR-positive breast cancer receiving adjuvant ET. Based on low local recurrence risk in women >65-70 years with small, N0, HR-positive breast cancer after BCS in the setting of adjuvant ET, radiation may be omitted. Adjuvant ET should be offered per standard care, although we consider deferring initiation of OFS until after the pandemic in appropriate individuals. To minimize clinic visits, we offer individuals already receiving monthly OFS the options of monthly home self-administration or every 3 month injections in clinic.

METASTATIC BREAST CANCER

In general, we agree with recommendations for metastatic breast cancer (MBC) management proposed by the COVID-19 Pandemic Breast Cancer Consortium. We recommend that patients receiving early line palliative systemic therapy that is likely to improve outcomes continue therapy, but risks and benefits of later line therapy must be considered carefully. As per routine, we assess tumor genomics with next generation sequencing (NGS) when indicated. For HER2-positive MBC with minimal disease burden and an extended period of stability, we consider holding therapy with surveillance for progression every 3-6 months. To decrease frequent visits for those receiving H+/-P, we offer extending the dosing interval from 3 to 4 weeks, especially if receiving other treatments every 4 weeks.

We advise caution in the use of therapies with high risk of pulmonary toxicity such as immunotherapy for metastatic TNBC or trastuzumab deruxtecan for HER2-positive MBC. For HR-positive MBC, we generally continue ET and targeted therapies that are well-tolerated. However, we weigh risks and benefits of administering targeted agents with ET for newly diagnosed or progressing HR-positive MBC and for elderly individuals with comorbidities due to potential toxicities.
With the exception of patients with high risk for skeletal related events or symptomatic hypercalcemia, we defer or extend dosing intervals for denosumab and zoledronic acid in individuals with bone metastases until after the peak of the pandemic. While consideration of oral bisphosphonates for bone metastases is appealing, we are unaware of data to support this. Lastly, in individuals with MBC who are clinically stable, we recommend delaying routine restaging scans, monitoring tumor markers, and lengthening intervals between laboratory studies if safe. (ST-5)

**GENERAL CONSIDERATIONS**

Despite risk of exposure to SARS-CoV-2 for patients and providers, we recommend in-person clinic visits in the setting of suspected oncologic emergencies, progression, recurrence, new diagnoses, and unstable or symptomatic MBC. In the neoadjuvant setting, we recommend baseline in-person evaluation followed by alternating in-person and telemedicine visits. In the metastatic setting, we favor intermittent in-person evaluations to assess disease and toxicities.

For most other scenarios, we recommend care via telemedicine. While we had not established telemedicine prior to the pandemic, we were forced to implement it rapidly. Despite steep patient and provider learning curves, telemedicine has proven to be user friendly and compatible with billing, especially with relaxation of state licensing requirements. Routine survivorship visits can be conducted by telemedicine or deferred until after the pandemic. Most ET side effects including hot flashes, arthralgias and sexual concerns can be managed via telemedicine and remote education.

To further limit the risk of SARS-CoV-2 transmission, we recommend extending intervals for routine monitoring (e.g. follow-up echocardiograms and electrocardiograms in the absence of known cardiac problems and bone mineral density evaluation) and deferring bone-modifying therapy in the adjuvant setting until after the pandemic. We continue to offer germline testing to eligible candidates, especially if results will impact treatment decisions. Additionally, we
continue to offer fertility preservation to eligible interested young women prior to systemic therapy.

Regardless of stage, we recommend modifying treatment to reduce immunosuppression and frequent visits if possible. Oral or intravenous regimens with less frequent dosing and immunosuppression should be utilized, although there may be trade-offs between these factors. Prophylactic growth factor should be considered with regimens for which it would not typically be recommended.\textsuperscript{75} When possible, we administer pegfilgrastim on-body-injector the day of chemotherapy or arrange home administration of growth factor afterwards. We recommend minimizing steroid use to mitigate immunosuppression. To do so, we have implemented olanzapine-based anti-emetic regimens for moderate-highly emetogenic chemotherapy.\textsuperscript{76,77} Additionally, we eliminate dexamethasone pre-medication for weekly paclitaxel after the second dose in the absence of hypersensitivity and use single dose intravenous dexamethasone prior to docetaxel instead of multiple oral doses.\textsuperscript{29,78–80} (ST-6)

CONCLUSIONS

During the COVID-19 pandemic, delivering breast cancer care necessitates balancing risks associated with delay or pursuit of less aggressive cancer therapy with risks of COVID-19 exposure and infection in limited resource environments and with much uncertainty.\textsuperscript{3,81,82} We are currently only able to test asymptomatic cancer patients before surgery and interventional radiology procedures. As testing capabilities for COVID-19 expand, testing prior to delivery of chemotherapy may be considered.

Our experiences treating breast cancer during the pandemic have given us greater appreciation of the modest benefits of toxic therapies and comfort in using genomic platforms to guide neoadjuvant therapy and remote systems of care delivery. However, the pandemic has highlighted weaknesses within our healthcare system including disparities, lack of insurance, inadequate supplies, poorly validated diagnostic biomarkers and inadequate contingency
planning. This guideline, while immediately applicable to breast cancer care during the COVID-19 pandemic, may serve as a template for selection and sequencing of breast cancer therapies during future crises.

We eagerly await the achievements of massive global efforts to overcome COVID-19 and ongoing national efforts to collect data in cancer patients with COVID-19 to characterize determinants of susceptibility and outcomes.83–86 Meanwhile, as hospitals commit resources to fight COVID-19, the oncology community will continue to provide quality care for those who carry the burden of cancer during the pandemic.
REFERENCES


83. Ong MBH. Lowy: “Our patients are counting on us, and we must not let them down” [Internet]. Cancer Lett. [cited 2020 Apr 20];Available from: https://cancerletter.com/articles/20200417_1/


<table>
<thead>
<tr>
<th>Low Risk Biologic Features</th>
<th>High Risk Biologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable pathology (pure tubular, pure mucinous, pure cribiform, or papillary carcinoma)</td>
<td>Clearly unfavorable pathology (metaplastic excluding low grade adenosquamous and low grade fibromatosis-like carcinoma)</td>
</tr>
<tr>
<td><em>Low score on genomic profile</em></td>
<td>High score on genomic profile</td>
</tr>
<tr>
<td>Strong hormone receptor expression</td>
<td>Weak hormone receptor expression e.g. ER&lt;20%</td>
</tr>
<tr>
<td>Low grade</td>
<td>High grade</td>
</tr>
<tr>
<td>Lobular</td>
<td>Pre-menopausal</td>
</tr>
<tr>
<td>Luminal A subtype (Her2-, low Ki-67)</td>
<td></td>
</tr>
</tbody>
</table>

*At our institution, we consider low likelihood of high Oncotype Dx Recurrence Score on the Breast Cancer Recurrence Score Estimator as a low risk biologic feature\(^7\) (http://www.breastrecurrenceestimator.onc.jhmi.edu/).

REFERENCES


Figure 1, Panel A: Johns Hopkins Recommended Approach to Multi-Disciplinary Care for Stage I-III Triple Negative Invasive Breast Cancer During the COVID-19 Pandemic

Triple Negative

Clinical Stage I
- Surgery
  - Pathologic Stage T1aN0 or T1bNo
    - Consider omission of adjuvant chemotherapy
    - Radiation as indicated
  - Pathologic Stage T1cN0
    - Recommend chemotherapy
    - Radiation as indicated
  - Pathologic Stage T2-T4 and/or N1-3
    - Recommend ddAC-T
    - Radiation as indicated

Clinical Stage II/III
- AC-T
  - Surgery
    - Radiation as indicated, post neoadjuvant capecitabine if residual disease
Figure 1, Panel B: Johns Hopkins Recommended Approach to Multi-Disciplinary Care for Stage I-III HER2-Positive Invasive Breast Cancer During the COVID-19 Pandemic

HER2-positive

- **≤3cm and N0**
  - Surgery
  - Pathologic Stage T1aN0
    - Recommend omission of chemo/HER2 targeted therapy
    - Radiation as indicated; adjuvant ET if indicated

- **Pathologic Stage T1bN0**
  - Consider omission of chemo/HER2 targeted therapy versus T-DM1 or T/H
  - Radiation as indicated, adjuvant ET if indicated, consider stopping H after 6 months

- **Pathologic Stage T1c or T2 (≤3 cm) N0**
  - T-DM1 or T/H
  - Radiation as indicated, consider stopping H after 6 months

- **Pathologic Stage T2 (>3cm), T3-4 and/or N1-3**
  - TCH+/-P
  - Radiation as indicated, consider stopping H+/-P after 6 months; adjuvant ET if indicated

- **>3cm and/or N1-N3**
  - TCH/P
  - Surgery (consider H+/-P until surgery if surgery delayed)
  - If no residual disease: H+/-P, consider stopping after 6 months; adjuvant ET if indicated
  - If residual disease: T-DM1; adjuvant ET if indicated
Figure 1, Panel C: Johns Hopkins Recommended Approach to Multi-Disciplinary Care for Stage I-III Hormone Receptor-Positive Invasive Breast Cancer During the COVID-19 Pandemic

1. See Table 1 for definitions of low and high risk biology. For patients with biologic risk features that are neither clearly high nor low risk, genomic profile may be performed on the core biopsy specimen to guide classification. In cases in which biologic risk features are neither clearly high nor low risk and genomic profiling is not performed, recommend following low biologic risk arm.

2. Preferred neoadjuvant regimen for post-menopausal women is AI. Preferred neoadjuvant regimen for pre-menopausal women is OFS/Tamoxifen→Al once estradiol suppressed.

3. If surgery is not available after completion of planned course of neoadjuvant chemotherapy, may initiate neoadjuvant ET until surgery is available.
**SUPPLEMENTARY MATERIALS**

### Table 1: Recommendations for Ductal Carcinoma In Situ (DCIS) during the COVID-19 Pandemic

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Newly diagnosed ER-negative DCIS  | - Defer intervention until after pandemic unless high suspicion for invasive cancer
  - Schedule follow-up with surgeon for physical exam +/- imaging (to plan for surgery) |
| Newly diagnosed ER-positive DCIS  | - Medical oncology and surgery evaluation at diagnosis
  - Initiate neoadjuvant endocrine therapy (ET) for up to 6 months
  - Defer surgery and radiation, if indicated, until after the peak of pandemic
  - Schedule follow-up with medical oncologist and surgeon for toxicity assessment on ET, physical exam +/- imaging (to plan for surgery) |
| Surgically resected DCIS          | - Obtain radiation oncology consultation if breast conserving surgery performed
  - Consider delay or omission of radiation, especially if ER-positive and able to initiate ET $^{2,3}$ |

### Table 2: Subtype Specific Recommendations for Early Stage Triple Negative Breast Cancer (TNBC) during the COVID-19 Pandemic

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Newly diagnosed clinical stage I TNBC      | - Recommend upfront surgery, if possible, within 60 days of diagnosis $^4$
  Note: May consider neoadjuvant chemotherapy (NACT) if upfront surgery is not possible or if NACT is preferred |
| Pathologic stage T1aN0 or T1bN0 TNBC after upfront surgery | - Consider omission of adjuvant chemotherapy
  Note: If omission of chemotherapy is not desired, recommend non-anthracycline-based regimen [Docetaxel and Cyclophosphamide (TC)] $^{5,6}$
  - If adjuvant chemotherapy is planned, initiate within 60 days of surgery $^7$ |
| Pathologic stage T1cN0 TNBC after upfront surgery | - Recommend adjuvant chemotherapy with TC within 60 days of surgery
  Note: May consider anthracycline-taxane based regimen [Doxorubicin and Cyclophosphamide followed by Paclitaxel (AC-T)] $^{5,8,9}$ |
| Pathologic stage T2-T4, N1-3 TNBC after upfront surgery | - Recommend adjuvant chemotherapy with AC-T within 60 days of surgery |
| Newly diagnosed clinical stage II-III TNBC | - Recommend NACT with AC-T
  Note: If patient has operable breast cancer and is not a candidate for NACT and/or if upfront surgery is preferred and surgery is available, may proceed to surgery first |
| Progression during NACT                 | - Consult multi-disciplinary team to consider alternate therapy (e.g. switch chemotherapy, surgery if patient is a candidate and it is possible, and/or radiation) |
| Completion of NACT                       | - Recommend surgery within 4-6 weeks $^{10}$ |
| Completion of NACT, but surgery unable to be performed | - Do not extend NACT
  Note: Prioritize these patients for surgery as soon as possible |
<p>| Residual disease at surgery after NACT    | - Consider post-neoadjuvant capecitabine $^{11}$ |
| After completion of surgery +/- adjuvant chemotherapy | - Refer to radiation oncology if breast conserving surgery was performed or if mastectomy was performed and usual criteria for consideration of post-mastectomy radiation (PMRT) are present |</p>
<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Newly diagnosed ≤ 3 cm and node negative                                         | - Recommend upfront surgery within 60 days of diagnosis\(^4\)  
Note: If surgery is not possible or neoadjuvant systemic therapy is preferred), initiate neoadjuvant therapy as per recommendations for newly diagnosed > 3 cm and/or node positive |
| Pathologic stage T1aN0 after upfront surgery                                    | - Recommend omission of adjuvant therapy \(^7\)  
Note: If chemotherapy/HER2 targeted therapy is desired, recommend paclitaxel/trastuzumab (T/H) or ado-trastuzumab emtansine (T-DM1)\(^12,13\) within 60 days of surgery |
| Pathologic stage T1bN0 after upfront surgery                                   | - Consider omission of adjuvant therapy  
- Consider adjuvant T/H or T-DM1 within 60 days of surgery more strongly in setting of higher risk features such as hormone receptor-negative and/or grade 3 disease |
| Pathologic stage T1c or T2 (≤3 cm) and N0 after upfront surgery                | - Recommend adjuvant therapy with T/H or T-DM1 within 60 days of surgery                                                                                                                                     |
| Pathologic stage T2 (>3 cm), T3-4 and/or N1-3 after upfront surgery            | - Recommend adjuvant therapy with Docetaxel/Carboplatin/Trastuzumab (TCH) +/- Pertuzumab (P)\(^14,15\) within 60 days of surgery                                                                              |
| Newly diagnosed > 3 cm and/or node positive                                     | - Recommend neoadjuvant TCH/P\(^18\)  
Note: In some cases, consider de-escalating neoadjuvant regimen to paclitaxel/trastuzumab/pertuzumab (THP)\(^17\)  
Note: If patient has operable breast cancer and is not a candidate for NACT/HER2-targeted therapy and/or if upfront surgery is preferred and available, may proceed to surgery first |
| Progression during neoadjuvant therapy                                         | - Consult multi-disciplinary team to consider alternate therapy (e.g. switch chemotherapy/HER2-targeted therapy, surgery if patient is a surgical candidate and surgery is possible, and/or radiation) |
| Completion of neoadjuvant therapy                                               | - Recommend surgery within 4-6 weeks of completion of therapy\(^10\)                                                                                                                                      |
| Completion of neoadjuvant therapy, but surgery not able to be performed        | - If surgery is not available at the time of completion of neoadjuvant therapy, consider additional cycles of HER2-targeted therapy (H+/-P) until surgery is available  
Note: Prioritize these patients for surgery if possible                          |
| Residual disease identified at surgery after neoadjuvant therapy               | - Recommend post-neoadjuvant T-DM1\(^16\)                                                                                                                                                                   |
| No residual disease identified at surgery after neoadjuvant therapy             | - Recommend adjuvant therapy with H+/-P                                                                                                                                                                      |
| Completion of surgery +/- neoadjuvant therapy                                   | - Refer to radiation oncology if breast conserving surgery was performed or if mastectomy was performed and usual criteria for consideration of PMRT are present  
Note: Radiation may be delivered concurrently with H+/-P or T-DM1 and at the same time as ET                                                                                           |
| Duration and frequency of HER2-targeted therapy                                | - Consider shorter course of H+/-P from 12 to 6 months in patients treated with T/H, THP or TCH+/-P\(^19,20\)  
- Consider extending dosing interval from 3 to 4 weeks for H and P               |
| Hormone receptor-positive stage I-III after completion of surgery +/- neoadjuvant therapy | - Initiate adjuvant ET as per usual care\(^21,22\)  
Note: May initiate adjuvant ET prior to, during or after radiation  
Note: May initiate adjuvant ET while HER2-targeted therapy (H, H/P or T-DM1) is ongoing after completion of chemotherapy |
<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Risk assessment in newly diagnosed hormone receptor-positive breast cancer     | - Classify patient into low or high biologic risk group:  
  - Low risk biologic features suggest low likelihood of response to chemotherapy and include characteristics such as favorable pathology, low score on genomic profile, strong hormone receptor expression, low grade, lobular, and luminal A subtype\(^{23-27}\)  
  - High risk biologic features suggest high likelihood of response to chemotherapy and include characteristics such as clearly unfavorable pathology, high score on genomic profile, weak hormone receptor expression, high grade, and premenopausal  
  Note: Pre-menopausal women may be considered high risk clinically (irrespective of other characteristics)  
  - For a patient with biologic risk features that are neither high nor low risk, genomic profiling may be performed on the core biopsy specimen from diagnosis to guide classification into low or high biologic risk group |
| Newly diagnosed clinical stage T1-3N0 with low risk biologic features          | - Recommend upfront surgery within 60 days of diagnosis\(^4\)  
  - If upfront surgery is not available, initiate neoadjuvant ET                                                                                                                                                                                                                      |
| Newly diagnosed clinical stage T1-3N1 or T4N0-1 with low risk biologic features | - Consider upfront surgery within 60 days of diagnosis if available and patient is a candidate  
  - Consider neoadjuvant therapy to downstage or if surgery is not an option  
  - If neoadjuvant therapy is indicated, individualize care:  
    - Consider genomic profiling on core biopsy specimen  
    - If genomic profile is low or intermediate risk, neoadjuvant ET is preferred  
    - If genomic profile is high risk, consider NACT                                                                                                                                                                        |
| Newly diagnosed clinical stage any T, N2-3 with low risk biologic features     | - Individualize care and initiate neoadjuvant ET or chemotherapy                                                                                                                                                                                                                       |
| Newly diagnosed clinical stage T1-3N0 with high risk biologic features OR T1-3N1 with high risk biologic features OR T4N0 with high risk biologic features | - Recommend upfront surgery within 60 days of diagnosis  
  - If upfront surgery is not possible, individualize care:  
    - Consider genomic profiling on core biopsy specimen  
    - If genomic profile is low or intermediate risk, neoadjuvant ET is preferred; Note: Monitor closely for progression and prioritize these patients for surgery when possible  
    - If genomic profile is high risk, NACT is preferred                                                                                                                                                                      |
| Newly diagnosed clinical stage T4N1 or any T,N2-3 with high risk biologic features | - Initiate NACT                                                                                                                                                                                                                                                                       |
| Selection of neoadjuvant endocrine therapy regimen                              | - Recommend an aromatase inhibitor (AI) is for post-menopausal women\(^{28}\)  
  - Recommend Tamoxifen and Ovarian Function Suppression (OFS) for pre-menopausal women, although data limited  
  Note: Transition to an AI once estradiol is suppressed\(^{29}\)                                                                                                                                                           |
| Selection of NACT regimen                                                       | - Consider regimens such as AC-T\(^{5,7,8}\) or TC\(^{5,7}\)  
  - Prefer AC-T especially if node positive disease                                                                                                                                                                         |
| Evaluation during neoadjuvant ET or chemotherapy                                | - Perform periodic physical exam +/- imaging to assess for toxicity and to assess response to therapy                                                                                                                                                                                   |
| Duration of neoadjuvant ET                                                      | - Delay surgery for up to 6-12 months\(^{28,29}\)  
  - Continue neoadjuvant ET until surgery can be performed (in the event of delay beyond 6-12 months)                                                                                                                                                                                  |
<table>
<thead>
<tr>
<th>Completion of NACT</th>
<th>- Recommend surgery within 30-60 days(^{10})</th>
</tr>
</thead>
</table>
| NACT complete, but surgery cannot be performed | - Initiate neoadjuvant ET until surgery is available  
Note: Prioritize these patients for surgery |
| Progression during neoadjuvant ET or chemotherapy | - Consult multi-disciplinary team to consider alternate neoadjuvant systemic therapy regimen, surgery if the patient is a candidate and surgery if available, and/or radiation. |
| Adjuvant systemic therapy after surgery | - Consider genomic profiling if not previously done\(^{5,24-27}\) Perform on surgical specimen if no neoadjuvant treatment was administered. Perform on core biopsy specimen if neoadjuvant treatment was administered.  
- Consider adjuvant chemotherapy with TC or AC-T\(^{5,6,8,9}\) (if indicated and if NACT was not administered)  
- Adjuvant chemotherapy should be started within 90 days of surgery\(^{7}\)  
- Continue or initiate adjuvant ET as per usual care\(^{21,30}\) prior to, during or after radiation. Consider deferring initiation of OFS until after peak of pandemic |
| Sequencing of adjuvant chemotherapy and radiation therapy | - Individualize the optimal sequencing of radiation and chemotherapy (e.g. consider administering radiation prior to adjuvant chemotherapy if it facilitates patient safety)\(^{31}\) |
| After surgery and adjuvant chemotherapy (if administered) | - Consult radiation oncology to determine if radiation is required and, if so, whether it can be deferred  
Note: Ensure follow-up appointment with radiation oncology if plan to defer radiation until after pandemic |
| Ongoing adjuvant oral endocrine therapy | - Continue ongoing AI or tamoxifen  
- Manage side effects by telemedicine when possible  
- Defer routine survivorship visits or perform via telemedicine until after the peak of the pandemic |
| Ongoing Ovarian Function Suppression (OFS) | - Continue OFS administered in conjunction with an AI or tamoxifen.  
- Switch to every 3 month injection at clinic or to monthly self-injection at home to reduce clinic visits. |
### Table 5: Recommendations for Metastatic Breast Cancer during the COVID-19 Pandemic

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Considerations:</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Early line palliative chemotherapy that is likely to improve outcomes | - Continue chemotherapy  
- Consider oral regimens (e.g. capecitabine) or tailoring intravenous regimens to decrease number of visits to cancer center (e.g. paclitaxel every 21 days, liposomal doxorubicin every 28 days) |
| Later line palliative chemotherapy that is less likely to improve outcomes | - Individualize use of chemotherapy  
- Consider best supportive care if risks of chemotherapy due to visits to cancer center and immunosuppression outweigh potential benefits |
| Anti-resorptive therapy for bone metastases | - Defer denosumab and zoledronic acid until after pandemic unless high risk for skeletal related events or needed urgently for hypercalcemia  
Note: If unable to defer, consider less frequent dosing intervals |
| Restaging scans | - Defer restaging scans until after pandemic or lengthen intervals between scans if clinically stable  
- Consider using tumor markers to assess disease and guide timing of scans in select patients |
| Port flush | - Extend interval between port flushes to 12 weeks or longer |
| Genomic testing | - Proceed with next generation sequencing (NGS) as per usual care, if indicated |
| **Triple Negative Disease:** | |
| Immunotherapy | - Exercise caution in use of immunotherapy due to risk of pneumonitis[^32] |
| HER2-Positive Disease: | |
| Trastuzumab Deruxtecan | - Exercise caution in use of trastuzumab deruxtecan due to due to risk of interstitial lung disease[^33] |
| HER2-targeted therapy | - Individualize decision to continue or hold HER2-targeted therapy during pandemic for individuals with metastatic HER2-positive breast cancer who have minimal disease burden and who have been stable > 2 years  
Note: If therapy is held, follow for progression every 3-6 months |
| HER2 antibody therapy | - Consider extending dosing interval from 3 to 4 weeks for H and P |
| **Hormone Receptor-Positive Disease:** | |
| Oral endocrine therapy or fulvestrant | - Continue AI, tamoxifen or fulvestrant  
- Consider options other than fulvestrant if feasible in order to avoid visits to cancer center |
| Use of targeted therapies in combination with endocrine therapy | - Consider delaying the addition of a targeted agent (CDK4/6i, PIK3CA inhibitor, mTOR inhibitor) in first line with minimal disease burden or when ET alone is controlling disease  
Note: Weigh expected benefit of adding targeted agent against risk of immunosuppression and increased visits to cancer center for required monitoring.  
- Continue targeted therapies that have already been initiated and are currently well-tolerated  
- Consider lowering dose of targeted agent to optimize tolerability and reduce toxicity  
- Consider increasing laboratory monitoring intervals if tolerating targeted therapies well |

[^32]: p. 32  
[^33]: p. 33
<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| In-person visit versus telemedicine visit | - Engage in multi-disciplinary approach to weigh the risk/benefit of in-person visits to cancer center and of each modality of cancer therapy against risks of COVID-19 in each individual, especially if older or with comorbidities.  
- Consider schedules that require less frequent visits if possible  
- Defer visits for patients on adjuvant ET until after the peak of the pandemic (or have telemedicine visits)  
- Conduct visits via telemedicine when possible, but may alternate in-person evaluation to assess toxicity and response (e.g. active chemotherapy +/- HER2-targeted therapy)  
- Evaluate all patients receiving NACT +/- HER2-targeted therapy in-person prior to initiation of therapy  
- Evaluate patients with concerning clinical change in person:  
  - Unstable of symptomatic metastatic breast cancer  
  - Suspected oncologic emergency, intractable symptoms during therapy or suspected progression on therapy  
  - Suspected recurrence or newly diagnosed metastatic breast cancer |
| Patient communication            | - Utilize messaging within the electronic medical record, phone calls and mailed letters to update patients about changes in hospital procedures and care                                                                                                                                                                                                                                                                                                                                 |
| Medical emergencies              | - Provide care as usual for neutropenic fever, severe pain, intractable nausea, symptomatic malignant effusions, and cord compression                                                                                                                                                                                                                                                                                                                                         |
| Steroids                         | - Minimize dexamethasone use to reduce immunosuppression whenever possible  
- Use olanzapine-based anti-emetic regimens  
- Reduce dexamethasone premedication prior to docetaxel and eliminate dexamethasone after docetaxel  
- Eliminate dexamethasone premedication prior to paclitaxel for third dose onwards in patients without hypersensitivity reactions with two doses  
- Consider using prophylactic growth factor to reduce risk of neutropenic fever with regimens for which growth factor would not typically be recommended (i.e. regimens associated with < 20% risk of neutropenic fever)  
- Avoid visits to the cancer center for growth factor the day after chemotherapy by using pegfilgrastim on-body-injector the day of chemotherapy or arranging home administration of growth factor after chemotherapy |
| Growth factor                    | - Consider using prophylactic growth factor to reduce risk of neutropenic fever with regimens for which growth factor would not typically be recommended (i.e. regimens associated with < 20% risk of neutropenic fever)  
- Avoid visits to the cancer center for growth factor the day after chemotherapy by using pegfilgrastim on-body-injector the day of chemotherapy or arranging home administration of growth factor after chemotherapy |
| Prescriptions                    | - Prescribe a 90 day supply of medications instead of a 30 day supply, if possible  
- Encourage patients to use mail order or pharmacy delivery services                                                                                                                                                                                                                                                                                                                                             |
| Ovarian Function Suppression (OFS) | - Continue OFS administered in conjunction with an AI or tamoxifen  
- Consider changing from monthly injection at cancer center to monthly self-injection at home or to or to every 3 month injection at cancer center  
- For individuals who have not started adjuvant OFS, consider tamoxifen alone until after the peak of the pandemic.                                                                                                                                                                                                                                                                               |
| Cardiac monitoring               | - Defer follow-up echocardiograms/electrocardiograms for routine monitoring until after pandemic or lengthen intervals between cardiac assessments if clinically stable in those with no known cardiac issues                                                                                                                                                                                                                                                                                      |
| Bone density                     | - Defer bone mineral density assessment until after peak of the pandemic                                                                                                                                                                                                                                                                                                                                                                                                         |
| Anti-resorptive therapy in adjuvant setting | - Defer adjuvant zoledronic acid or denosumab until after the peak of the pandemic                                                                                                                                                                                                                                                                                                                                                                                   |
| Fertility preservation           | - Refer eligible patients as per routine                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Genetic testing                  | - Perform germline testing as per routine                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Screening patients for COVID-19  | - Implement calls the day before visits to prescreen COVID-19 symptoms  
- Screen for COVID-19 symptoms on site on the day of visit or treatment                                                                                                                                                                                                                                                                                                                                         |
| Treatment modifications for patients with COVID-19 | - Follow institutional guidelines for when patients may return to cancer center  
- Consider modifying treatment after recovery from COVID-19 using the same principles as when modifying therapy in the setting of other adverse events                                                                                                                                                                                                                                                                 |

*Table 6: General Principles of Cancer Care During the COVID-19 Pandemic*
REFERENCES


