care delivery reviews

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

Jennifer Y. Sheng, MD[1,2]; Cesar A. Santa-Maria, MD, MSCI[1,2]; Neha Mangini, PharmD[2]; Haval Norman, PharmD[2]; Rima Couzi, MD[1,2]; Raquel Nunes, MD[1,2]; Mary Wilkinson, MD[1,2]; Kala Visvanathan, MD, MHS[1-3]; Roisin M. Connolly, MB, BCh, MD[4]; Evanthia T. Roussos Torres, MD, PhD[5]; John H. Fetting, MD[1,2]; Deborah K. Armstrong, MD[1,2]; Jessica J. Tao, MD[1,2]; Lisa Jacobs, MD, MSPH[1,2]; Jean L. Wright, MD[1,2]; Elissa D. Thorner, MHS[2]; Christine Hodgdon, MS[6]; Samantha Horn, MPA[7]; Antonio C. Wolff, MD[1,2]; Vered Stearns, MD[1,2]; and Karen L. Smith, MD, MPH[1,2]

abstract

The COVID-19 pandemic has rapidly changed delivery of cancer care. Many nonurgent surgeries are delayed to preserve hospital resources, and patient visits to health care 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 multidisciplinary 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 SARS-CoV-2 exposure and infection until approval of a vaccine.

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INTRODUCTION

On March 11, 2020, the World Health Organization declared a pandemic in the setting of > 100,000 cases of a new respiratory illness, coronavirus disease 2019 (COVID-19), caused by infection with a novel coronavirus, SARS-CoV-2.[1] Data regarding COVID-19 and cancer are limited, but early reports suggest individuals with cancer, especially those who receive systemic anticancer therapy within 14 days of COVID-19 diagnosis, are more likely to develop severe disease.[2-7] Furthermore, individuals with metastatic cancer are more likely to require admission for intensive care, undergo mechanical ventilation, and die as a result of COVID-19.[6] Data also implicate health care settings as a source for SARS-CoV-2 transmission, a finding concerning to patients with cancer who frequent cancer centers.[8]

Many countries have implemented strategies to avoid surges of COVID-19 cases, conserve resources, and protect vulnerable populations from infection.[9] Cancer centers have rapidly changed models of care by delaying nonurgent surgeries, increasing home-based therapies, and expanding telemedicine.[10,11] Numerous organizations and institutions have issued general and disease-specific guidelines for cancer care.[12-17] 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.[18]

For patients with breast cancer, preliminary management recommendations have been proposed by the COVID-19 Pandemic Breast Cancer Consortium.[15] These tiered guidelines prioritize surgery, radiation, and systemic therapy interventions by urgency. As in nonpandemic circumstances, treatment decisions must consider stage and tumor biology within the context of comorbidities and individual patient goals.[19] Acknowledging the uncertainties of cancer outcomes

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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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 multidisciplinary 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

In accordance with recommendations from the American College of Surgeons and COVID-19 Pandemic Breast Cancer Consortium, we recommend deferring surgery for ductal carcinoma in situ (DCIS) during the pandemic in the absence of microinvasion or of high suspicion of invasive cancer.[13,15] 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 postmenopausal women[20] and tamoxifen for premenopausal women.[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.[22-24] Omission of radiation is an option for good-risk disease (low to intermediate grade, < 2.5 cm, surgical margins ≥ 3 mm).[25] These recommendations are summarized in Appendix Table A1 (online only).

Early-Stage Invasive Breast Cancer (Stages I-III)

We recommend early multidisciplinary 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 up-front surgery and/or who are not appropriate candidates for neoadjuvant systemic therapy. Because 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 1A and Appendix Table A2 (online only) summarize our approach to newly diagnosed early-stage triple-negative breast cancer (TNBC). If available, we recommend up-front 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 up-front surgery, we initiate adjuvant chemotherapy within the standard time frame. 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. Although addition of carboplatin to neoadjuvant AC-T increases likelihood of pathologic complete response, 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, because of associated adverse events.[31] On completion of neoadjuvant chemotherapy (NACT), surgery should be performed within 4-6 weeks.[32] If surgery is delayed because of the pandemic, we do not recommend additional 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.[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 because of risk of locoregional recurrence.[24,34,35]

Human epidermal growth factor receptor 2–positive breast cancer. Figure 1B and Appendix Table A3 (online only) summarize our approach to newly diagnosed early-stage human epidermal growth factor receptor 2 (HER2)–positive breast cancer during the pandemic. Although the COVID-19 Pandemic Breast Cancer Consortium suggests up-front surgery only for T1N0 HER2-positive breast cancer, we also favor up-front 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.[36,37] For pathologic stage T1bN0 HER2-positive breast cancer, we discuss pros and

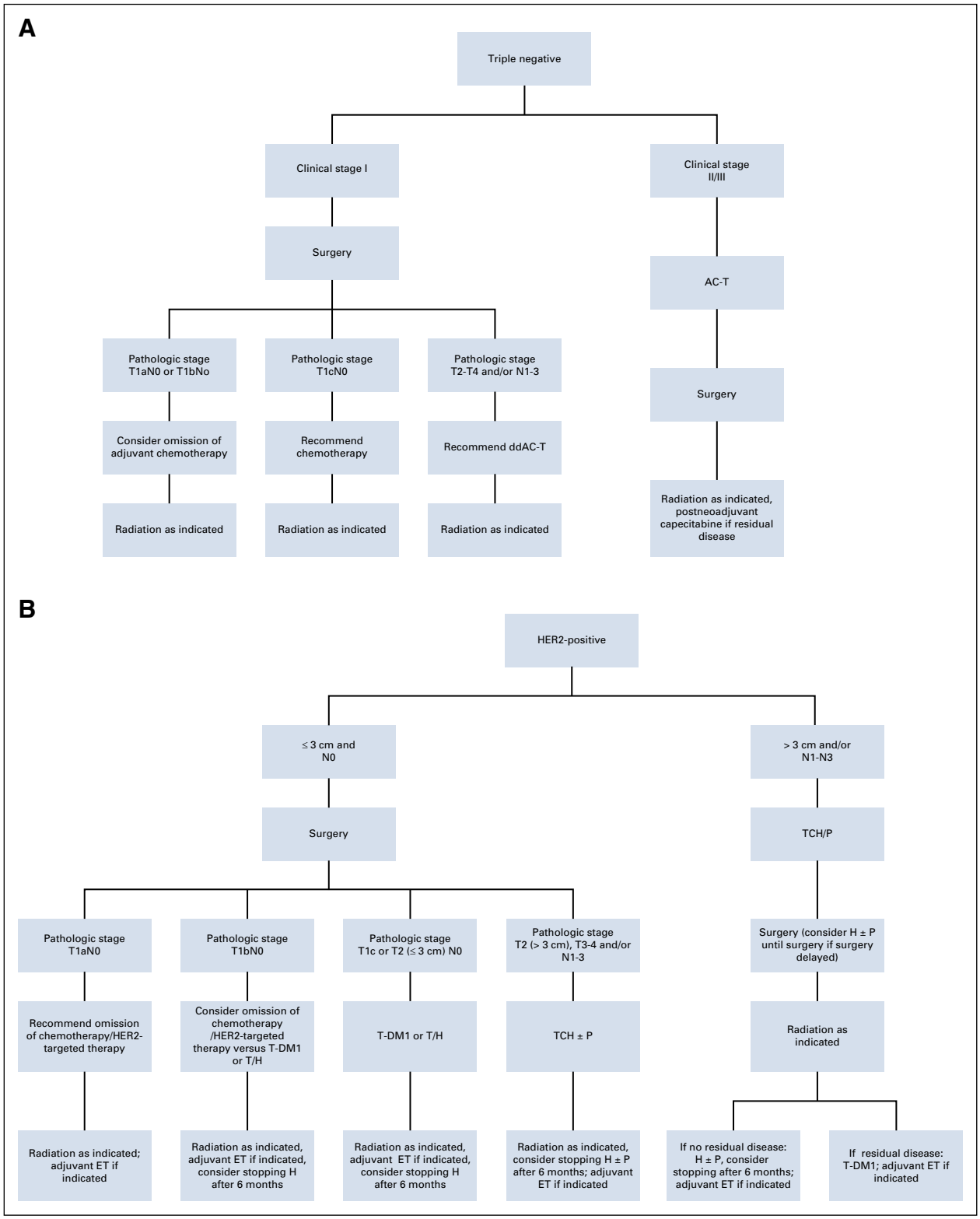

FIG 1. (A) Johns Hopkins recommended approach to multidisciplinary care for stage I-III triple-negative invasive breast cancer during the COVID-19 pandemic. (B) Johns Hopkins recommended approach to multidisciplinary care for stage I-III HER2-positive invasive breast cancer during the COVID-19 pandemic. (C) Johns Hopkins recommended approach to multidisciplinary care for stage I-III hormone receptor–positive invasive breast cancer during the COVID-19 pandemic. (*) 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

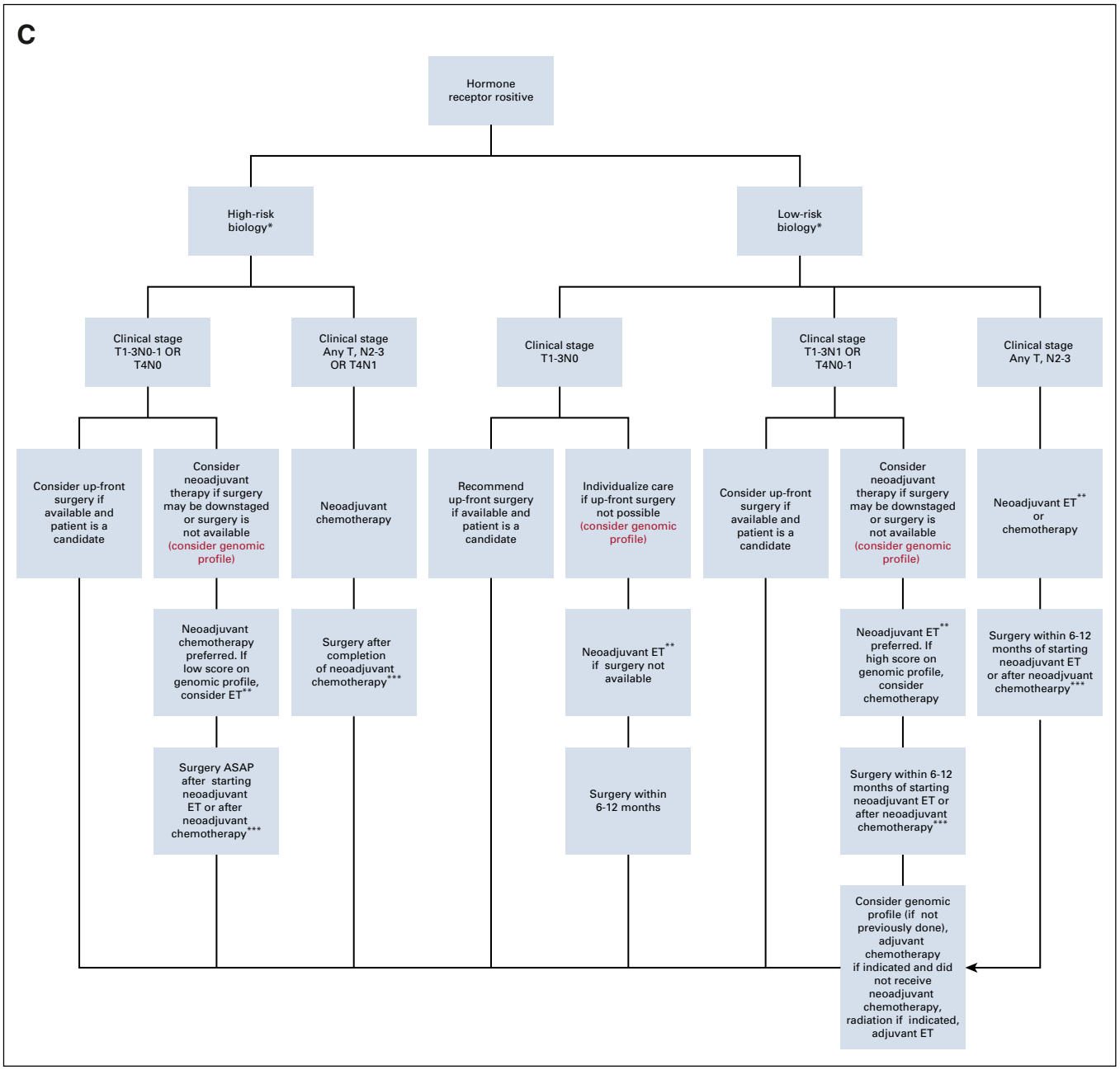

FIG 1. (Continued) in which biologic risk features are neither clearly high nor low risk and genomic profiling is not performed, we recommend following low-biologic-risk arm. (**) The preferred neoadjuvant regimen for postmenopausal women is aromatase inhibitor (AI). The preferrred neoadjuvant regimen for premenopausal women is ovarian function suppression with tamoxifen followed by transition to AI once estradiol is suppressed. (***) If surgery is not available after completion of planned course of neoadjuvant chemotherapy, may initiate neoadjuvant endocrine therapy (ET) until surgery is available. AC-T, doxorubicin and cyclophosphamide followed by paclitaxel; ASAP, as soon as possible; ddAC-T, dose-dense AC-T; H, trastuzumab; P, pertuzumab; T, paclitaxel; TCH, docetaxel/carboplatin/trastuzumab; T-DM1, ado-trastuzumab emtansine.

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 disease-free survival and minimal hematologic toxicity.[38,39] A potential advantage of adjuvant T-DM1 over T/H during the pandemic is the every-3-week dosing interval. For individuals found to have more extensive disease after up-front surgery, we recommend standard adjuvant chemotherapy/HER2-targeted therapy with docetaxel/carboplatin/trastuzumab (TCH) ± pertuzumab (P).[40,41] As per

routine, we initiate adjuvant systemic therapy within 60 days of surgery for HER2-positive breast cancer.[42]

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 we consider de-escalation with paclitaxel/trastuzumab/pertuzumab.[43]

After completion of NACT/HER2-targeted therapy, surgery should be performed within 4-6 weeks.[32] 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 postneoadjuvant T-DM1.[44] 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 weeks to 4 weeks.[45,46] Although there is interest in subcutaneous trastuzumab, there are challenges with implementation, including requirement for administration by a health care provider and insurance coverage.

After completion of primary therapy for HER2-positive early breast cancer, we refer to radiation oncology per standard guidelines.[47] As is the case for TNBC, we do not recommend delaying radiation for HER2-positive breast cancer because of risk of locoregional recurrence.[24,34] After completion of primary therapy, we initiate adjuvant ET per usual care for individuals with HR-positive and HER2-positive breast cancer.[48,49]

HR-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 1C and Appendix Table A4 (online only) 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.[50-54] Low-risk biologic features suggest low likelihood of response and/or small benefit from (neo)adjuvant chemotherapy, whereas high-risk biologic features suggest the converse (Table 1). We typically consider premenopausal women as clinically high risk (irrespective of other characteristics).[55]

If available, we prefer up-front surgery for clinical stage T1-3N0 HR-positive breast cancer with low-risk biologic features who are operative candidates.[47] If up-front surgery or the desired procedure is not available, neoadjuvant ET can be initiated and surgery delayed for up to 6-12 months.[56,57] We also consider up-front 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 the patient is an operative candidate. If up-front 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.[58-60]

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 up-front surgery if the patient is a candidate and the desired surgery is available. As for low-biologic-risk tumors, if up-front 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 postmenopausal women.[56] For neoadjuvant ET in premenopausal women, we favor ovarian function suppression (OFS) with tamoxifen followed by transition to AI once estradiol is suppressed; however, data supporting this approach are limited, and careful monitoring is required.[57] 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.[56,57] 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.[26,28,29] On completion of NACT, surgery should be performed within 30-60 days.[32] If surgery cannot be performed within that time frame, 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 up-front surgery, we recommend genomic profiling on the surgical specimen per usual indications if not previously performed.[29,51-54] If indicated, we offer adjuvant chemotherapy with TC or AC-T as per routine care.[26-29] 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

TABLE 1. Biologic Risk Classification for Hormone Receptor–Positive Breast Cancer

Low-Risk Biologic Features	High-Risk Biologic Features
Favorable pathology (pure tubular, pure mucinous, pure cribiform, or papillary carcinoma)[53]	Clearly unfavorable pathology (metaplastic, excluding low-grade adenosquamous and low-grade fibromatosis-like carcinoma)[53]
Low score on genomic profile[a][53]	High score on genomic profile
Strong hormone receptor expression[53]	Weak hormone receptor expression (eg, ER < 20%[50])
Low grade[50]	High grade[50]
Lobular[87,88]	Premenopausal[55,89]
Luminal A subtype (HER2-negative, low Ki-67)[53]	

[a]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.[90,91]

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 before initiation; however, we recommend caution delaying care, given uncertainties about the time course of the pandemic.[42]

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.[24,61] On the basis of low local recurrence risk in women > 65-70 years of age with small, N0, HR-positive breast cancer after BCS in the setting of adjuvant ET, radiation may be omitted.[24,62,63] 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 injections in clinic every 3 months.[64]

METASTATIC BREAST CANCER

In general, we agree with recommendations for metastatic breast cancer (MBC) management proposed by the COVID-19 Pandemic Breast Cancer Consortium.[15] 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 when indicated.[47] 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.[65,66] To decrease frequent visits for those receiving H ± P, we offer extending the dosing interval from 3 weeks to 4 weeks, especially if receiving other treatments every 4 weeks.[67]

We advise caution in the use of therapies with high risk of pulmonary toxicity, such as immunotherapy for metastatic TNBC[68] or trastuzumab deruxtecan for HER2-positive MBC.[69] 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, because of 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.[70,71] Although consideration of oral bisphosphonates for bone metastases is appealing, we are unaware of data to support this. Last, 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 (Appendix Table A5, online only).

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. Although we had not established telemedicine before 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.[72,73] Routine survivorship visits can be conducted by telemedicine or deferred until after the pandemic. Most ET adverse 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 (eg, follow-up echocardiograms and ECGs 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 affect treatment decisions.[74] In addition, we continue to offer fertility preservation to eligible interested young women before 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 used, 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.[75] When possible, we administer pegfilgrastim on-body injector the day of chemotherapy or arrange home administration of growth factor afterward. We recommend minimizing steroid use to mitigate immunosuppression. To do so, we have implemented olanzapine-based antiemetic regimens for moderate to highly emetogenic chemotherapy.[76,77] In addition, we eliminate dexamethasone premedication for weekly paclitaxel after the second dose in the absence of hypersensitivity and use single-dose intravenous dexamethasone before docetaxel instead of multiple oral doses (Appendix Table A6, online only).[29,78-80]

In conclusion, 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.[3,81,82] We are currently only able to test asymptomatic patients with cancer before surgery and interventional radiology procedures. As testing capabilities for COVID-19 expand, testing before 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 health care system, including disparities, lack of insurance, inadequate supplies, poorly validated diagnostic biomarkers, and inadequate contingency planning. This guideline, although 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 patients with cancer 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.

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 at 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]Quantum Leap Health Care Collaborative, San Francisco, CA
[7]LifeBridge Health, Alvin and Lois Lapidus Cancer Institute, Baltimore, MD

CORRESPONDING AUTHOR

Karen L. Smith, MD, MPH, Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital, Building B, First Floor, 5255 Loughboro Rd, NW, Washington, DC 20016; Twitter: @hopkinskimmel, @JHBreastGyn; e-mail: ksmith60@jhmi.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/OP.20.00364.

AUTHOR CONTRIBUTIONS

Conception and design: Cesar A. Santa-Maria, Rima Couzi, Raquel Nunes, Mary Wilkinson, John H. Fetting, Lisa Jacobs, Elissa D. Thorner, Antonio C. Wolff, Vered Stearns, Karen L. Smith, Jennifer Y. Sheng, Neha Mangini, Haval Norman, Roisin M. Connolly, Evanthia T. Roussos Torres, Jean L. Wright
Provision of study material or patients: Deborah K. Armstrong, Lisa Jacobs, Vered Stearns, Jennifer Sheng, Cesar Santa-maria, Neha Mangini, Haval Norman, Rima Couzi, Raquel Nunes, Mary Wilkinson, Kala Visvanthan, Roisin Connolly, Evanthia Roussos Torres, John Fetting, Jessica Tao, Jean Wright, Antonio Wolff, Karen Smith
Collection and assembly of data: Jennifer Y. Sheng, Cesar A. Santa-Maria, Neha Mangini, Haval Norman, Jessica J. Tao, Antonio C. Wolff, Vered Stearns, Karen L. Smith, Rima Couzi, Raquel Nunes, Mary Wilkinson, Kala Visvanthan, Roisin M. Connolly, Evanthia Roussos Torres, John H. Fetting, Deborah Armstrong, Lisa Jacobs, Jean Wright
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Jennifer Y. Sheng
Travel, Accommodations, Expenses: Nutramax

Cesar A. Santa-Maria
Consulting or Advisory Role: Polyphor, Genomic Health, Halozyme, Bristol Myers Squibb, Athenex
Research Funding: MedImmune, Pfizer, Tesaro (Inst)

Rima Couzi
Stock and Other Ownership Interests: Cellunova, (I)
Consulting or Advisory Role: Precision Biosciences (I)
Research Funding: Pharmacyclics (I)
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Raquel Nunes
Research Funding: bioTheranostics
Uncompensated Relationships: Agendia

Kala Visvanathan
Patents, Royalties, Other Intellectual Property: Licensing of patent with Cepheid (Inst)

Roisin M. Connolly
Research Funding: Genentech/Roche (Inst), Puma Biotechnology (Inst), Novartis (Inst), Merck (Inst), Macrogenics (Inst)
Travel, Accommodations, Expenses: Genentech/Roche

Deborah K. Armstrong
Consulting or Advisory Role: Cue Biopharma, AbbVie, Eisai
Research Funding: Clovis Oncology (Inst), AstraZeneca (Inst), Advaxis (Inst), Syndax (Inst), Pfizer (Inst), Tesaro (Inst), Eisai (Inst)
Other Relationship: AstraZeneca

Jean L. Wright
Employment: Johns Hopkins Hospital
Honoraria: ASTRO
Research Funding: Oncospace

Elissa D. Thorner
Consulting or Advisory Role: Solace

Christine Hodgdon
Honoraria: Roche/Genentech
Consulting or Advisory Role: Roche/Genentech
Travel, Accommodations, Expenses: Lilly

Antonio C. Wolff
Consulting or Advisory Role: Ionis Pharmaceutical
Research Funding: Biomarin (Inst), Celldex (Inst)
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Vered Stearns
Research Funding: AbbVie, Pfizer, MedImmune, Novartis, Puma Biotechnology, Biocept
Other Relationship: Immunomedics

Karen L. Smith
Stock and Other Ownership Interests: AbbVie (I), Abbott Laboratories (I)
Honoraria: AsiM CME
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APPENDIX

TABLE A1. Recommendations for DCIS During the COVID-19 Pandemic

Clinical Scenario	Recommendation
Newly diagnosed ER-negative DCIS	Defer intervention until after pandemic unless high suspicion for invasive cancer
	Schedule follow-up with surgeon for physical examination ± imaging (to plan for surgery)
Newly diagnosed ER-positive DCIS	Medical oncology and surgery evaluation at diagnosis
	Initiate neoadjuvant ET for up to 6 months[20]
	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 examination ± 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[24,25]

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; ET, endocrine therapy.

TABLE A2. Subtype-Specific Recommendations for Early-Stage TNBC During the COVID-19 Pandemic

Clinical Scenario	Recommendation
Newly diagnosed clinical stage I TNBC	Recommend up-front surgery, if possible, within 60 days of diagnosis[a]
	Note: May consider NACT if up-front surgery is not possible or if NACT is preferred
Pathologic stage T1aN0 or T1bN0 TNBC after up-front surgery	Consider omission of adjuvant chemotherapy
	Note: If omission of chemotherapy is not desired, recommend non–anthracycline-based regimen (TC)[26,27]
	If adjuvant chemotherapy is planned, initiate within 60 days of surgery[42]
Pathologic stage T1cN0 TNBC after up-front surgery	Recommend adjuvant chemotherapy with TC within 60 days of surgery
	Note: May consider anthracycline-taxane based regimen (AC-T)[26,28,29]
Pathologic stage T2-T4, N1-3 TNBC after up-front surgery	Recommend adjuvant chemotherapy with AC-T within 60 days of surgery[42]
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 up-front surgery is preferred and surgery is available, may proceed to surgery first
Progression during NACT	Consult multidisciplinary team to consider alternate therapy (eg, switch chemotherapy, surgery if patient is a candidate and it is possible, and/or radiation)
Completion of NACT	Recommend surgery within 4-6 weeeks[32]
Completion of NACT, but surgery unable to be performed	Do not extend NACT
	Note: Prioritize these patients for surgery as soon as possible
Residual disease at surgery after NACT	Consider postneoadjuvant capecitabine[33]
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 PMRT are present

Abbreviations: AC-T, doxorubicin and cyclophosphamide followed by paclitaxel; NACT, neoadjuvant chemotherapy; PMRT, postmastectomy radiation; TC, docetaxel and cyclophosphamide; TNBC, triple-negative breast cancer.

[a]Bleicher RJ, Ruth K, Sigurdson ER, et al: Time to surgery and breast cancer survival in the United States. JAMA Oncol 2:330-339, 2016.

TABLE A3. Subtype-Specific Recommendations for Early-Stage HER2-Positive Breast Cancer During the COVID-19 Pandemic

Clinical Scenario	Recommendation
Newly diagnosed ≤ 3 cm and node negative	Recommend up-front surgery within 60 days of diagnosis.[a]
	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 up-front surgery	Recommend omission of adjuvant therapy
	Note: If chemotherapy/HER2-targeted therapy is desired, recommend T/H or T-DM1[38,39] within 60 days of surgery[42]
Pathologic stage T1bN0 after up-front 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 HR-negative and/or grade 3 disease
Pathologic stage T1c or T2 (≤ 3 cm) and N0 after up-front 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 up-front surgery	Recommend adjuvant therapy with TCH ± P[40,41] within 60 days of surgery
Newly diagnosed > 3 cm and/or node positive	Recommend neoadjuvant TCH/P[b]
	Note: In some cases, consider de-escalating neoadjuvant regimen to paclitaxel/trastuzumab/pertuzumab (THP)[43]
	Note: If patient has operable breast cancer and is not a candidate for NACT/HER2-targeted therapy and/or if up-front surgery is preferred and available, may proceed to surgery first
Progression during neoadjuvant therapy	Consult multidisciplinary team to consider alternate therapy (eg, 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[32]
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 postneoadjuvant T-DM1[44]
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 adjuvant HER2-targeted therapy	Consider shorter course of H ± P from 12 to 6 months in patients treated with T/H, THP, or TCH ± P.[45,46] Consider extending dosing interval from 3 weeks to 4 weeks for H and P
Hormone receptor–positive stage I-III after completion of surgery ± (neo) adjuvant therapy	Initiate adjuvant ET as per usual care.[48,49] Note: May initiate adjuvant ET before, during, or after radiation. May initiate adjuvant ET while HER2-targeted therapy (H, H/P, or T-DM1) is ongoing after completion of chemotherapy

Abbreviations: ET, endocrine therapy; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; NACT, neoadjuvant chemotherapy; P, pertuzumab; PMRT, postmastectomy radiation; TCH, docetaxel/carboplatin/trastuzumab; T-DMI, ado-trastuzumab emtansine; T/H, paclitaxel/trastuzumab.

[a]Bleicher RJ, Ruth K, Sigurdson ER, et al: Time to surgery and breast cancer survival in the United States. JAMA Oncol 2:330-339, 2016.

[b]Schneeweiss A, Chia S, Hickish T, et al: Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 24:2278-2284, 2013.

TABLE A4. Subtype-Specific Recommendations for Early-Stage HR-Positive Breast Cancer during the COVID-19 Pandemic

Clinical Scenario	Recommendation
Risk assessment in newly diagnosed HR-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 HR expression, low grade, lobular, and luminal A subtype[50-54]
	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 HR expression, high grade, and premenopausal
	Note: Premenopausal 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 up-front surgery within 60 days of diagnosis[a]
	If up-front surgery is not available, initiate neoadjuvant ET
Newly diagnosed clinical stage T1-3N1 or T4N0-1 with low-risk biologic features	Consider up-front 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 up-front surgery within 60 days of diagnosis
	If up-front 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 AI in postmenopausal women.[56] Recommend tamoxifen and OFS for premenopausal women, although data are limited
	Note: Transition to an AI once estradiol is suppressed[57]
Selection of NACT regimen	Consider regimens such as AC-T[27,28,42] or TC[27,42a]
	Prefer AC-T, especially if node-positive disease
Evaluation during neoadjuvant ET or chemotherapy	Perform periodic physical examination ± imaging to assess for toxicity and to assess response to therapy
Duration of neoadjuvant ET	Delay surgery for up to 6-12 months[56,57]
	Continue neoadjuvant ET until surgery can be performed (in the event of delay beyond 6-12 months)
Completion of NACT	Recommend surgery within 30-60 days[32]
NACT complete, but surgery cannot be performed	Initiate neoadjuvant ET until surgery is available
	Note: Prioritize these patients for surgery

(continued on following page)

TABLE A4. Subtype-Specific Recommendations for Early-Stage HR-Positive Breast Cancer during the COVID-19 Pandemic (continued)

Clinical Scenario	Recommendation
Progression during neoadjuvant ET or chemotherapy	Consult multidisciplinary team to consider alternate neoadjuvant systemic therapy regimen, surgery if the patient is a candidate and surgery is available, and/or radiation
Adjuvant systemic therapy after surgery	Consider genomic profiling if not previously done.[29,51-54] 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[26-29] (if indicated and if NACT was not administered)
	Adjuvant chemotherapy should be started within 90 days of surgery[42]
	Continue or initiate adjuvant ET as per usual care[48,49] before, 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 (eg, consider administering radiation before adjuvant chemotherapy if it facilitates patient safety)[b]
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 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

Abbreviations: AC-T, doxorubicin and cyclophosphamide followed by paclitaxel; AI, aromatase inhibitor; ET, endocrine therapy; HR, hormone receptor; NACT, neoadjuvant chemotherapy; OFS, ovarian function suppression; TC, docetaxel and cyclophosphamide.

[a]Bleicher RJ, Ruth K, Sigurdson ER, et al: Time to surgery and breast cancer survival in the United States. JAMA Oncol 2:330-339, 2016.

[b]Bellon JR, Come SE, Gelman RS, et al: Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: Updated results of a prospective randomized trial. J Clin Oncol 23:1934-1940, 2005.

TABLE A5. Recommendations for Metastatic Breast Cancer during the COVID-19 Pandemic

Clinical Scenario	Recommendation
General considerations	
Early-line palliative chemotherapy that is likely to improve outcomes	Continue chemotherapy
	Consider oral regimens (eg, capecitabine) or tailoring intravenous regimens to decrease number of visits to cancer center (eg, 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
Antiresorptive therapy for bone metastases	Defer denosumab and zoledronic acid until after peak of 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 peak of 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 every 12 weeks or longer
Genomic testing	Proceed with next-generation sequencing as per usual care, if indicated
Triple-negative disease	
Immunotherapy	Exercise caution in use of immunotherapy because of risk of pneumonitis[68]
HER2-positive disease	
Trastuzumab deruxtecan	Exercise caution in use of trastuzumab deruxtecan because of risk of interstitial lung disease[69]
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 weeks to 4 weeks for H and P
HR-positive disease	
Oral endocrine therapy or fulvestrant	Continue AI, tamoxifen, or fulvestrant. Consider options other than fulvestrant if feasible 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

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; H, trastuzumab; HER2, human epidermal growth factor receptor-2; HR, hormone receptor; P, pertuzumab.

TABLE A6. General Principles of Cancer Care During the COVID-19 Pandemic

Clinical Scenario	Recommendation
In-person visit *v* telemedicine visit	Engage in multidisciplinary 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[5]
	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 (eg, active chemotherapy ± HER2-targeted therapy)
	Evaluate all patients receiving NACT ± HER2-targeted therapy in-person before initiation of therapy
	Evaluate patients with concerning clinical change in person:
	Unstable 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	Use 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 antiemetic regimens[76]
	Reduce dexamethasone premedication before docetaxel and eliminate dexamethasone after docetaxel[79,80]
	Eliminate dexamethasone premedication before paclitaxel for third dose onward in patients without hypersensitivity reactions with 2 doses[29,78]
Growth factor	Consider using prophylactic growth factor to reduce risk of neutropenic fever with regimens for which growth factor would not typically be recommended (ie, 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
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 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/ECGs for routine monitoring until after peak of 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
Antiresorptive therapy in adjuvant setting	Defer adjuvant zoledronic acid or denosumab until after the peak of the pandemic

(continued on following page)

TABLE A6. General Principles of Cancer Care During the COVID-19 Pandemic (continued)

Clinical Scenario	Recommendation
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[12,16]
	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

Abbreviations: AI, aromatase inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor-2; NACT, neoadjuvant chemotherapy; OFS, ovarian function suppression.