# COVID-19 Pandemic Breast Cancer Consortium's Considerations for Re-entry


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## INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is the most widespread coronavirus pandemic in history, wreaking havoc across the globe as governments work to limit its transmission and mortality, primarily through social distancing. The causative agent, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) results in a spectrum of clinical presentations including fulminant COVID-19, whose fatality rate varies by age and comorbidities.[1,2]

In the United States, elective medical procedures have been postponed in order to conserve personal protective equipment (PPE), create hospital capacity, and protect patients needing non-urgent surgery and other procedures from exposure to the virus in the hospital setting. The latter aim is particularly relevant to cancer patients, whose immune systems may be compromised by both disease and treatment, placing them at increased risk of COVID-19 infection and its serious complications.

While some reports suggest that cancer itself may be a risk factor for developing severe COVID-19, the evidence is conflicting. A series of 105 hospitalized Chinese patients who underwent surgery for breast and thyroid cancer while testing positive for COVID-19 infection experienced no mortality, had fewer critical symptoms, and did not require mechanical ventilation.[3] In contrast, a smaller series of 34 infected patients undergoing a variety of elective surgeries reported an increase in intensive care unit admissions and an increased mortality rate of 20.5%.[4] The study suggested that “surgery may accelerate and exacerbate disease progression of COVID-19”, although no association specific to cancer surgery and COVID-19 mortality was inferred.

As knowledge develops about the risks for cancer patients during the pandemic, major considerations for management include that both the cancer condition itself and its treatment may increase risk of serious COVID-19 complications. This has created a difficult dilemma for the cancer community, including those focused on the treatment of breast cancer. We have been forced to make difficult risk-benefit decisions weighing concerns that treatment of cancer may increase the risk of serious COVID-19 infection against the risk that delay in treatment until the pandemic subsides may compromise oncologic outcomes. This was the focus of a prior publication from our group that suggested recommendations for the prioritization, treatment, and triage of breast cancer patients during the current COVID-19 pandemic.[5]

The pandemic is currently at different phases across the United States with geographic variations in the stages, infection rates and success in ‘flattening the curve’.[6] Breast cancer is the most common cancer among women globally and in the U.S[7] and reintroduction of medical services to this population is critical as the pandemic subsides. As regions begin to emerge from the initial wave of COVID-19 cases, each center will need to consider how to safely reintroduce routine breast cancer services; these decisions should be made on a local level based on the best knowledge and resources available.

This manuscript offers recommendations on how we can safely resume the multidisciplinary care of breast cancer patients whose treatment has been put on hold or otherwise modified. The management of patients with breast cancer who are currently infected with SARS-CoV2 or being treated for COVID-19 is beyond the scope of this document and should follow guidelines developed by experts at the local institution. In general, however, most early stage breast cancer patients can have surgery and chemotherapy deferred until the viral infection is cleared, which typically occurs within 20 to 30 days, and the patient has clinically recovered.

This document uses vignettes to illustrate the risks and benefits of resuming treatment of breast cancer as the pandemic resolves. The 5 clinical questions addressed are:

- How do we care for our asymptomatic but high-risk patients presenting for office visits in the post-COVID era?
- How do we handle the backlog of patients whose surgical treatment was delayed due to the pandemic?
- As our operating rooms reopen, how should patients who were placed on endocrine therapy prior to definitive surgery be managed?
- As we emerge from the pandemic, how do we manage patients who have already begun neoadjuvant chemotherapy?
- How do we manage a patient who is not a candidate for breast conserving surgery but is ready for their operation?

These vignettes, presented in tumor board fashion, are based on expert opinion and published literature when available.

## SCENARIO 1

Clinical Question: How do we care for our asymptomatic but high-risk patients presenting for office visits in the post-COVID era?

Background:
As the COVID-19 pandemic begins to subside, breast cancer patients will be able to return to outpatient clinics and offices. However, it is likely that some of the restrictions imposed during the pandemic will persist into the near future. In this “new normal”, it will remain important to follow physical distancing practices to minimize patient-patient contact in waiting rooms and patient-medical staff interactions in exam and procedure rooms. Many visits can still be conducted by telehealth with necessary tests ordered remotely. However, as physical exam findings can impact the recommendations for type of surgery and reconstruction, in-person visits will still be necessary. Local infection control policies should be followed and may include screening patients for COVID-19 symptoms by phone prior to their appointment and upon arrival to clinic, along with other risk mitigation strategies.

Case presentation:

Your region has passed its peak of COVID-19 cases and your hospital is easing restrictions on surgical cases. A 32 year old woman is referred to you due to a strong family history of breast cancer and a positive BRCA-2 mutation. She is interested in having bilateral nipple sparing mastectomies but plans to have children and would like to postpone oophorectomies.

Discussion:
This patient will benefit from an in-person visit for a physical exam. Baseline screening imaging should be obtained prior to the consultation and include both bilateral mammogram (with tomosynthesis, if available) and bilateral breast MRI prior.[8] Access to imaging will depend on regional availability of screening appointments for high risk patients. Decisions between diagnostic versus screening designation should follow pre-COVID-19 guidelines. Radiologic evaluation of high-risk women with mammography and MRI should be prioritized in scheduling templates over screening for non-high risk patients. If a patient needs an image-guided biopsy, she should be evaluated for COVID-19 symptoms and tested if illness is suspected. If positive, the biopsy should be delayed if possible, to avoid exposure to staff and other patients, and to ensure that the patient's COVID-19 illness, should it develop, is not further complicated. If there are no signs or symptoms of COVID-19 or if a test performed is negative, image-guided biopsy can proceed. Prior to reinstating screening exams and image-guided biopsies, radiology facilities should institute processes and procedures similar to those above to protect patients and staff. The timing of surgery will be based on each institution's OR priority system. This patient was considered Priority C (low) in the original guidance (See Dietz, et al [5]) and Priority A and B patients should have their operations before this patient. As noted in the mastectomy section below, the reconstruction plan should enable recovery as an outpatient.

**SCENARIO 2**

Clinical Question: How do we handle the backlog of patients whose surgical treatment was delayed due to the pandemic?

Background:
Many early stage breast cancer patients have been placed on neoadjuvant endocrine therapy or chemotherapy. As operating rooms across the country begin to open, we will be competing for OR time with other services. Constant communication with hospital leadership on a staggered opening based on a rational priority system would be helpful to ensure on-time treatment of the most urgent cases, including some breast cancers.

Case Presentation:
You are a member of a busy breast practice and your hospital is beginning to see the end of your COVID-19 surge. You are told your group can have two OR days next week. Imagine there are 120 patients on your list of delayed breast surgery patients. How will you decide which patients have surgery next week?

Your breast imaging department calls you to ask how many tags/seeds/markers they should order to be ready for your marker localized breast cases over the next few months. What will you need?

Discussion:
In most settings, OR schedules and case volume will only gradually return to pre-COVID baselines. It is likely that mammogram and MRI screening will also resume during this re-entry phase, adding patients with newly diagnosed cancers and other lesions to the pool of postponed patients. In larger practices, there may be hundreds of patients waiting for surgery. Keeping track of a large number of delayed patients with enough individual detail for safe and rational assignment to limited OR slots is a daunting task.

The COVID-19 Breast Cancer Consortium recommendations stratify newly diagnosed breast cancer patients as high, intermediate and low priority for treatment based on their diagnosis and the acuity of their disease process.[5] Other considerations to determine priority for surgery include overall patient health, COVID-19 risk, and expected hospital resource utilization.[9]

Additional tools will be useful when implementing these guidelines into clinical practice. There will be many early stage patients with ER+ invasive cancers or DCIS, and many patients with atypical or benign conditions for whom guidelines recommended postponing surgery. There will be a smaller number of patients who will complete preoperative chemotherapy while OR resources remain limited. It will be necessary to characterize individual patients in these groups with enough granularity to accurately assess risk of delay and prioritize patients for surgery. Assignment of one patient to surgery while another continues to wait must be done with objective criteria in an equitable and transparent manner.

The consortium recommendations assign patients receiving neoadjuvant chemotherapy highest priority, early stage ER+ cancers and DCIS intermediate priority and atypical and benign lesions lowest priority for surgery when OR resources are limited. Other factors may be considered to rank patients within these larger priority categories.

A tool was developed at Massachusetts General Hospital to assist surgeons and administrators in the difficult task of prioritizing individual patients for surgery (see Appendix). This tool uses a mathematical model to prioritize delayed breast cancer patients for surgery. It uses the patient, tumor and delay factors described above to assign a numerical priority score to each delayed patient, with higher scores indicating a higher priority for surgery (Table 1 in Appendix). The assumptions used in assigning scores are consistent with those of the recently published Consortium priority schema.[5] Although the tool will likely be most useful for large programs with large numbers of delayed patients, it can also be used to prioritize smaller groups of patients for surgery. It is also useful as a means to track patients waiting for surgery. Versions of the tool

were prepared in both REDCap[10] and Microsoft Excel formats for ease of use by different centers.

The tool and risk score assignments are described in the Appendix. Copies of the tool may be obtained for personal or institutional use at: https://www.massgeneral.org/surgical-oncology/about/news-and-events/re-entry-tool-for-breast-surgeons/

In developing the algorithm behind the tool, the following considerations were employed:

**Patients completing neoadjuvant chemotherapy**: It is recommended that patients completing neoadjuvant chemotherapy proceed with surgery approximately 3-6 weeks after their last dose of chemotherapy. Although some ER+ patients could receive endocrine therapy and HER2+ patients could receive additional antibody therapy to postpone surgery, the safety of this additional delay is unknown. Neoadjuvant chemotherapy patients are given highest priority for surgery, with ER- patients more urgent than ER+ or HER2+ patients.

**Early stage ER+ cancers and DCIS:** Among early stage and ER+ breast cancers, tumor properties, patient factors, and duration of delay may be used to assign priority for surgery. When assigning patients to neoadjuvant endocrine therapy rather than surgery, T-stage, tumor grade, degree of endocrine sensitivity, and nodal status are important factors to consider. Invasive cancers are given higher priority than DCIS. For patients with similar tumors, it is reasonable to give higher priority to those who have waited longest.

Data suggest that surgery for ER+ tumors can be safely delayed for 6-12 months with neoadjuvant endocrine therapy. Patient age is relevant in this decision as there is ample data on the efficacy of neoadjuvant endocrine therapy in postmenopausal women[11], but limited data in premenopausal women.[12]

Careful monitoring of patients and their tumors during neoadjuvant endocrine therapy is important as some tumors will progress on treatment. Patients are generally evaluated for side effects and compliance with medication after 4-6 weeks of treatment. Careful assessment of response with repeat physical examination by the surgeon after approximately 3 months of endocrine therapy, with imaging as appropriate, is warranted. Patients whose tumors progress on endocrine therapy should proceed directly to surgery or consider chemotherapy.

**Positive lumpectomy margins, axillary staging:** Multidisciplinary review is important for patients with positive lumpectomy margins and those for whom additional axillary surgery is being considered. Radiation and systemic therapy without additional surgery or delayed surgery may be considered. In some cases, re-excision may be considered after chemotherapy. During COVID-19 resource restrictions, surgeons should make every effort to avoid positive margins by taking reasonable gross specimen margins and performing careful specimen imaging. Sentinel node biopsy can be performed for large

DCIS lesions or DCIS with microinvasion to reduce the need for second axillary procedures.

**Atypical and benign lesions, risk reducing and cosmetic procedures**: Patients with ADH on core biopsy have an approximately 20% risk of upgrade to DCIS or invasive cancer on excisional biopsy and should have the highest priority for surgery in this group. Other atypical lesions (ALH, LCIS, FEA (flat epithelial atypia), radial scars, etc.) have lower rates of upgrade and have the next highest priority. Unexpected malignancy is found in up to 3-4% of prophylactic mastectomies performed for BRCA and other risk gene mutations. Prophylactic mastectomies in high risk patients have priority over symmetry surgery and surgery for benign lesions.

Other considerations
It is important for breast surgeons to create and manage the algorithm used to prioritize breast patients for surgery. However, resumption of breast surgery will be concurrent with resumption of many other hospital activities. Access to the operating room and use of other hospital resources will need to be balanced across specialties and with consideration of anesthesia, nursing, and other OR personnel and resource constraints. For each surgical procedure, the patient's health status, including risk of having or acquiring a COVID-19 infection must be considered. Prioritization of breast surgery in this environment will require ongoing multidisciplinary discussion.

All departments of the hospital or outpatient facility have experienced COVID-19 disruption of routines. Collaboration and strategic thinking will be needed to return to pre-COVID clinical capacity.

**SCENARIO 3:**

Clinical Question: As our operating rooms reopen, how should patients who were placed on endocrine therapy prior to definitive surgery be managed?

Background:
Early-stage hormone receptor positive patients usually have definitive surgery followed by adjuvant radiation and endocrine therapy. Many patients have had their surgery delayed due to the pandemic and have been placed on hormonal therapy preoperatively.

Surgeons now need to decide on how each patient should be prioritized to go to the operating room taking into account age, comorbid conditions, the risk of coronavirus infection, response to systemic therapy as well as local OR and resource availability.

Case Presentation:
The patient is a 62 year old female with 36 C cup size who self-palpated a mass in February 2020. Diagnostic mammogram showed heterogeneously dense breasts and a 2.0 cm suspicious mass at the 11:00 o'clock position in the right breast.

Right axillary ultrasound, in addition to characterizing the index lesion, demonstrated a minimally prominent lymph node adjacent to a normal-appearing lymph node. There was no associated palpable lymphadenopathy on clinical examination.

Ultrasound-guided biopsy of the right breast mass showed grade 2 infiltrating ductal carcinoma. ER+ 98 %, PR+ 68 %, HER-2 2+ (equivocal), FISH non-amplified and Ki-67 24%.

Breast MRI demonstrated a "1.6 cm mass in the upper outer quadrant of the right breast consistent with biopsy-proven malignancy without suspicious enhancement elsewhere. The left breast is normal. A low right axillary lymph node demonstrates mild cortical thickening compared with contralateral lymph nodes."

Molecular profiling suggests a low recurrence risk indicating little likely benefit from chemotherapy.

Due to the pandemic, the patient initiated neoadjuvant endocrine therapy with an aromatase inhibitor one month ago. Now, the OR schedule is open for this type of operation. How should you proceed?

Discussion:

Radiology

The degree of suspicion regarding this patient's lymph nodes calls for careful review with the radiologist, consideration of the clinical scenario, and physical exam. While it is entirely possible that she has an involved lymph node, "mild cortical thickening" is rather non-specific and can be seen in reactive nodes.[13] Since this is a nonspecific finding, biopsy at the time of diagnosis or now, one month into neoadjuvant endocrine therapy, is not necessary, unless it would affect recommendations regarding systemic therapy. The patient has a low recurrence score and even if she was found to be node-positive, treating with endocrine therapy without chemotherapy is reasonable. She would be classified as cN0 based on her physical exam at presentation.

If the decision is to keep her on endocrine therapy for several more months, repeat imaging is not needed until just before surgery, unless there is concern about progression based on self-reported symptoms or physical examination during her course of treatment. If her operation remains delayed and she continues on preoperative endocrine therapy until surgery one could perform a follow-up ultrasound 4 weeks following initiation of neoadjuvant endocrine therapy, with the possibility of re-core biopsy to assess for drop in Ki67[14]; however, this is not standard practice in the U.S. An MRI immediately prior to surgery would be the imaging study of choice if there is ambiguity.

Surgery

This patient was a candidate for breast conserving surgery at the time of presentation. She would also have been a candidate for intraoperative radiation therapy, assuming the LN is negative at the time of surgery, or other forms of accelerated partial breast irradiation. Some surgeons would have initiated the endocrine therapy while others

would refer to medical oncology. Either way, it is reasonable to initiate short term preoperative endocrine therapy without the need for specific labs or bone density evaluation. It is important to reassure the patient that there is no concern regarding immunosuppression with endocrine therapy. Once the option for surgery is available, the surgeon must consider prioritization of his or her other cancer patients. Patients may come off neoadjuvant endocrine therapy "early" if desired and feasible to undergo their excision based upon resources and availability.

In hormone receptor positive patients undergoing neoadjuvant endocrine therapy who are now going to the OR and are clinically node negative, it is reasonable to apply ACOSOG Z0011 criteria and perform sentinel lymph node biopsy alone although this is controversial.

Medical Oncology

Based on high level evidence, the use of neoadjuvant endocrine therapy was appropriate in this patient whose operation was delayed. Her clinical history and demographic profile is well matched to the TransNEOS trial of neoadjuvant endocrine therapy in which women received 6 months of an aromatase inhibitor.[15] In the group of patients with recurrence scores <18, 55% had a clinical response, 45% had stable disease, and <1% had disease progression. The patient in this scenario was already a candidate for breast-conserving surgery and can therefore undergo lumpectomy at any time that local public health and hospital conditions allow. However, had she not been a candidate for breast conservation, a full 6 months of neoadjuvant endocrine therapy could be considered, as breast conservation eligibility increased from 62% to 79% with the use of preoperative endocrine therapy in the TransNEOS study. For women with luminal A or low genomic risk cancers, multiple studies suggest that responses continue even beyond 6 months. Though a pathologic complete response (pCR) is unlikely, if disease appears stable or slowly responding, endocrine therapy could be continued.

With such a low recurrence score the benefit from chemotherapy would likely be minimal, even if there were limited nodal involvement at surgery.[16,17] For that reason, additional nodal evaluation prior to definitive surgery can be deferred, and sentinel node biopsy can be performed at the time of lumpectomy. Repeating receptors is recommended after 6-12 months of standard of care neoadjuvant endocrine therapy, and the utility of repeat testing for shorter courses is undefined, though may be done.

When genetic testing is warranted, telemedicine and a home-based saliva test can be leveraged.

Radiation Oncology

In our patient with minimal or no axillary disease, treatment would typically consist of tangential fields (with or without inclusion of the low axilla in the case of a positive node) as in ACOSOG Z0011. Hypofractionated, whole breast radiation should be utilized with consideration of a boost. Various regimens have been previously described.[5] Regarding the use of APBI, while the patient may have been a suitable candidate for APBI with upfront surgery, neoadjuvant therapies complicate our understanding of the target volume, and there are little-to-no data of APBI after neoadjuvant systemic

therapies. Since there was limited exposure to neoadjuvant endocrine therapy, if the radiation therapy program has experience delivering APBI and was intending on APBI for this patient prior to the pandemic, it can be considered, particularly if the sentinel lymph node is negative. For all other scenarios, external beam whole breast radiation would be preferred using one of several (previously described) hypofractionated regimens that provide equivalent toxicity and efficacy.

**SCENARIO 4**:

Clinical Question: As we emerge from the pandemic, how do we manage patients who have already begun neoadjuvant chemotherapy?

Background:
During the COVID-19 pandemic, there are several factors to consider in determining when a patient receiving chemotherapy should undergo surgery. Some factors are extrinsic to the cancer or patient, and are related to the current extent of the pandemic in the local region, the local and institutional regulatory restrictions on surgery, and local institutional resource constraints. Other factors are intrinsic to breast cancer and its treatment and include the subtype of breast cancer (hormone receptor [HR]+, triple negative breast cancer [TNBC], HER2+), whether the patient has completed or is currently receiving therapy, the treatment response, patient comorbidities, and potential complications from chemotherapy. Taken together in multidisciplinary discussion, each of these factors will inform when a patient may undergo surgery following neoadjuvant chemotherapy. In general, patients who are progressing on therapy or who have no effective alternative treatment options are high priority for surgery.[5] In addition, although the pandemic may necessitate alternative approaches for patients undergoing neoadjuvant chemotherapy, standard of care is preferred if circumstances allow.

Case Presentation:
A 42 year old female presents with a 4 cm left breast lump. Diagnostic imaging with sonography and MRI reveals a suspicious left axillary lymph node. A sonographic-guided core biopsy of the mass and axillary node showed invasive ductal carcinoma of the breast, grade 3, ER+ 80%, PR+ 10%, Ki67 60%, HER2 1+, and metastatic carcinoma in the node. The patient preference was for breast conservation surgery. She started neoadjuvant chemotherapy with doxorubicin plus cyclophosphamide with growth factor support, achieving a partial reduction of the mass on clinical exam with no other complications from treatment. Sequential weekly paclitaxel was planned to follow when the COVID-19 pandemic emerged and restrictions on surgery were imposed. She initiated therapy as planned, and towards the end of her planned course of paclitaxel discussions about lifting restrictions on surgery were initiated. How should you proceed?

Discussion:

<u>Medical Oncology:</u>

The patient described above has appropriately initiated neoadjuvant chemotherapy with a standard regimen of dose dense doxorubicin plus cyclophosphamide followed by paclitaxel (AC-T). The rationale for selecting neoadjuvant chemotherapy in this setting and the choice of regimen is beyond the scope of this manuscript, but this standard approach is well-supported by numerous studies over several decades.[17-19] The patient's cancer in the scenario is HR positive and although molecular subtyping is not available, the tumor has characteristics suggesting a more proliferative (or luminal B-like) subtype further supporting the use of chemotherapy in this setting. Midway through the planned course of chemotherapy, the emergence of the pandemic resulted in restrictions on surgery at her institution.

The limited data on outcomes of patients with cancer who contract COVID-19 suggests higher rates of severe events and mortality compared to the general population.[20-23] However, such data are limited by including only a small number of breast cancer patients and very few patients who contracted COVID-19 while undergoing active chemotherapy. For patients with otherwise curable disease who are undergoing neoadjuvant chemotherapy during the pandemic, we recommend completing the planned course uninterrupted. However, available measures should be taken to minimize the risk of contracting, or developing complications from, COVID-19. The overall approach should aim to minimize potential exposures to the virus, by reducing the number of clinic visits and the number of exposures once in the clinic, and minimize immunosuppression and other toxicity from chemotherapy. For example, the chemotherapy regimen may be adjusted based on a careful assessment balancing the risk of potential toxicities with opportunities to reduce the number of hospital visits. Weekly paclitaxel, for example, may offer less immunosuppression whereas paclitaxel every two weeks, nab-paclitaxel every 3 weeks, or docetaxel every 3 weeks may offer fewer clinic visits. Additional measures to minimize risks include maximizing opportunities for telehealth virtual visits prior to chemotherapy to allow patients to proceed directly to infusion rooms, and liberal use of growth factors to reduce the risk of neutropenia.

Patients completing neoadjuvant chemotherapy are considered a high priority for surgery.[5] However, if access to surgery is not available at the end of planned neoadjuvant chemotherapy, then consideration of initiating endocrine therapy according to menopausal status is an option. (The use of neoadjuvant endocrine therapy is described in more detail in scenario 3). Although neoadjuvant endocrine therapy has been well-studied as an effective approach, it is not routinely used immediately following neoadjuvant chemotherapy and less data exist. This patient has a high grade cancer and completion of standard surgery should be pursued first, with a change to neoadjuvant endocrine therapy used only if absolutely necessary if surgery cannot be scheduled. If the switching approach is used, as noted above, and the patient subsequently experiences progression of disease, surgery should be pursued urgently.

The patient in this scenario had HR+, HER2- disease. However, another common scenario is a similar patient with TNBC. Neoadjuvant chemotherapy is standard for patients with Stage II or III TNBC with regimens including anthracyclines,

cyclophosphamide and taxanes.[17] As with the HR+HER2- patient above, patients with TNBC who initiate chemotherapy should complete the planned regimen uninterrupted. Some institutions also add carboplatin to anthracycline-taxane regimens or may use the combination of docetaxel plus carboplatin.[24-26] The addition of carboplatin results in increased toxicity which should be carefully considered during the COVID-19 pandemic. Surgery after completion of neoadjuvant chemotherapy for TNBC is a high priority. However, if local conditions do not permit timely surgery in this setting, additional strategies may be employed as a temporary bridge to surgery. Data from the CREATE-X study support the use of adjuvant capecitabine in patients with TNBC who do not achieve a pathologic complete response to standard anthracycline and taxane neoadjuvant chemotherapy.[27] If necessary in extenuating circumstances due to the pandemic, extrapolating data from the CREATE-X study provides a rationale to consider neoadjuvant capecitabine after standard neoadjuvant chemotherapy until surgery is possible. However, because adjuvant capecitabine monotherapy is less effective than standard polychemotherapy, capecitabine as a bridge to surgery in this setting should be used after, but not instead of, standard polychemotherapy.[28] Alternatively, if the tumor is clinically responding and the patient is not experiencing significant toxicity from chemotherapy, additional cycles of non-anthracycline chemotherapy, such as paclitaxel or the other options described above, may be offered until surgery. The decision to use additional chemotherapy beyond the standard regimen in this setting is pragmatic rather than data-driven.

A third common scenario is a similar patient but with HER2+ disease. Similar to TNBC, neoadjuvant chemotherapy is standard for Stage II or III HER2+ breast cancer.[17,29,30] Several standard regimens exist and incorporate combinations of trastuzumab (H) and pertuzumab (P) with chemotherapy. As with the prior two patient scenarios, patients with HER2+ breast cancer who initiate neoadjuvant chemotherapy should complete the intended regimen uninterrupted. If surgery is not available after completing neoadjuvant therapy, the treatment options depend on response to neoadjuvant therapy. Continued treatment with trastuzumab and pertuzumab (HP) as maintenance therapy is a reasonable option to bridge to surgery for patients achieving a clinical complete response or significant partial response. Alternatively, data from the neoadjuvant and metastatic setting support extended taxane-based HER2 therapy in patients, with careful monitoring for taxane related toxicity.[31,32] Patients with no response or a less robust clinical response are a high priority for surgery. However, such patients may consider switching to neoadjuvant trastuzumab emtansine (T-DM1) as a bridge to surgery in extenuating circumstances, and may subsequently complete the course of adjuvant T-DM1. This suggestion is based on data from the KATHERINE study which showed that in patients who did not achieve a pCR after neoadjuvant trastuzumab-based therapy, switching to T-DM1 had more favorable outcomes compared to continuing trastuzumab in the adjuvant setting.[33] It should be noted, however, that anti-HER2 regimens incorporating traditional cytotoxic chemotherapy (e.g. taxane+HP or docetaxel/carboplatin+HP) have higher response rates than those without (e.g. HP or T-DM1+P), so these “bridging” strategies should be considered short-term and with careful monitoring for progression.[29,34]

**SCENARIO 5:**

Clinical Question: How do we manage a patient who is not a candidate for breast conserving surgery and is ready for their operation?

Background:
As breast surgical oncology determines its priorities on re-entry into the operating theater, thought must be given to not only minimize the risk of COVID-19 to the patient, healthcare team and hospital but also to maintain our overall principles of patient care and safety.

In general, breast conserving surgery (BCS), even with sentinel node biopsy is an outpatient operation. However, there will be patients who will not be candidates for BCS. Whether or not the patient undergoes immediate reconstruction will also influence the time that has traditionally been spent recuperating in the hospital. For those patients it is imperative that we find ways to minimize their exposure to the inpatient setting.

There are several factors to consider in a patient needing a mastectomy with or without reconstruction. In the era of COVID-19, mastectomy, in general, should be performed alone or with immediate expander/implant reconstruction and should be limited to the affected breast. Consideration for bilateral mastectomy may be given for those at high-risk for developing metachronous contralateral breast cancer (because of factors such as young age, inherited predisposition, ER-negative disease). Autologous reconstruction in most cases should not be offered until operating rooms and services return to the new normal.

Enhanced Recovery After Surgery (ERAS) is an approach designed to 1) enable the patients to recover more quickly and 2) minimize the time spent in the hospital.[35,36] In this Case Scenario we will review some of the considerations that will allow the care team to decrease the need for the inpatient setting.

Case presentation:
A 43 year old woman underwent a screening mammogram that revealed a unicentric right breast mass measuring 2.9 cm, with 6 cm of suspicious calcifications. Ultrasound shows a 3.2 cm irregular mass. A core biopsy was performed and clip placed with a finding of a 3.5 cm right breast invasive ductal carcinoma, TNBC, T2 N0 M0 clinical Stage IIA. A stereotactic biopsy of the calcifications shows high grade ductal carcinoma in situ. Bilateral MRI shows a unicentric 3.5 cm mass, with no other areas of abnormality, except for suggestion of slightly enlarged single right axillary node. Right axillary ultrasound shows a 1.6 cm node with cortical bulge, core biopsy and clip placed. Biopsy reveals lymphocytes but no malignancy. Genetic testing was negative for genetic predisposition to breast and ovarian cancer in panel testing. Dose-dense AC-T was given and the patient has completed treatment. She had a complete clinical response. Post neoadjuvant chemotherapy imaging shows no residual mass, however 6

cm of calcifications remain and she is an A cup breast. She desires bilateral mastectomy with reconstruction.

Discussion:

Surgery:

The above described young patient with TNBC who has undergone neoadjuvant chemotherapy with a good clinical response and desires bilateral mastectomy presents unique surgical management challenges, some of which can be magnified by the COVID-19 pandemic.

Given that the patient has TNBC and has completed a standard neoadjuvant chemotherapy regimen (dose-dense AC-T) with clinical complete response, no further neoadjuvant chemotherapy is required outside of clinical trial. Adjuvant chemotherapy may be recommended after surgery if the patient does not achieve pathologic complete response in the breast and/or axilla. The extensive area of microcalcifications that harbors DCIS excludes breast conserving surgery as a viable option.

The next step for the management of this patient is to proceed with surgical extirpation of the tumor, in this case a mastectomy, along with surgical assessment of the axilla. Typically, surgery for patients who complete neoadjuvant chemotherapy should occur around 3-6 weeks from the last dose of chemotherapy (provided that the patient has recovered from chemotherapy-related toxicity and has adequate blood counts). At this point of the COVID-19 pandemic, if the patient needs or desires mastectomy with reconstruction (implant/expander), she should be able to undergo the desired procedure within the above time frame.

Given that the patient is young (with long-life expectancy) and has TNBC (thus she would not receive adjuvant endocrine therapy), her lifetime risk for contralateral breast cancer is high (likely over 30%) and thus considering contralateral prophylactic mastectomy is not unreasonable should COVID-19 conditions in the local institution allow this procedure to proceed. However, the emphasis should be on the side of known malignancy (even with positive genetic testing).[37,38] If, because of an institutional case backlog, coordination with the plastic surgery team would result in substantial delays, alternative options would include 1) performing ipsilateral mastectomy/axillary staging with implant/expander reconstruction or unilateral mastectomy/axillary staging with delayed reconstruction (along with the contralateral mastectomy, if the patient desires) or 2) performing a lumpectomy/axillary staging and postponing the mastectomy for a later date or after completion of adjuvant chemotherapy (if indicated). A partial mastectomy is not the best alternative in this case due to the large area of residual calcifications and the original stereotactic biopsy confirming the presence of extensive DCIS. If the patient would not require adjuvant radiation post mastectomy (given the pathologic findings at surgery), then if a temporizing lumpectomy is performed, the completion mastectomy should take place before any breast radiotherapy is to be given. In order to decrease the inpatient stay and risk of complications that might prolong the hospitalization, if the patient undergoes mastectomy with immediate reconstruction

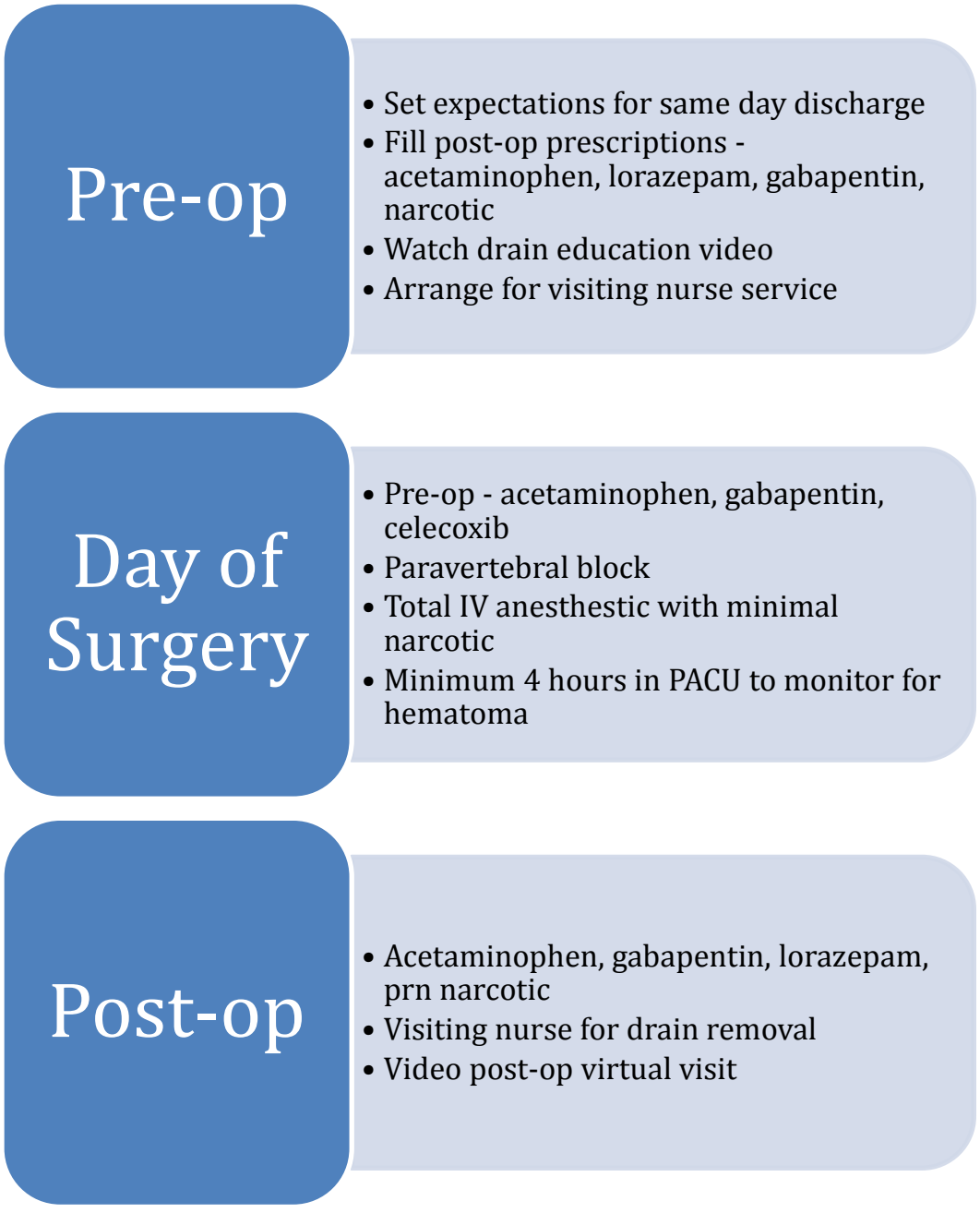
(unilateral or bilateral) the initial reconstruction should be limited to insertion of expander/implants. Whether to eventually undergo implant based or autologous reconstruction after the pandemic should be based on the need for postmastectomy radiation, and patient preference.

Regarding axillary management, the patient had an enlarged axillary lymph node that was biopsied and was negative for malignant cells. Thus, the patient is a good candidate for sentinel lymph node biopsy after neoadjuvant chemotherapy. Given that the biopsied node has been clipped, it is prudent to use dual tracer and remove the clipped node to rule out a false-negative core biopsy as well as to look for chemotherapy treatment effect, if the node is negative.

Radiation Oncology:
The need for radiotherapy in this patient will depend on the pathology findings. If the axillary nodes are negative and the residual tumor in the breast is T0/is-T2 with negative margins, postmastectomy radiotherapy is generally not indicated. Had the previously biopsied lymph node (and/or other lymph nodes) been positive and post neoadjuvant chemotherapy shows evidence of treatment effect, the case for postmastectomy radiotherapy could be entertained concluding that the axillary lymph nodes were converted to negative by the neoadjuvant chemotherapy. If there are positive lymph nodes at the time of surgery, post-mastectomy radiation with inclusion of comprehensive lymph node regions will be recommended.

When proceeding with mastectomy with or without reconstruction in the post-COVID era, decreasing length of stay and potential complications requiring use of more resources and exposure is critical. Figure 1 shows an example of an ERAS procedure developed by Mass General Brigham Health Care that can be useful in achieving these goals. Table 2 in the Appendix describes in detail an example ERAS procedure to assist with outpatient mastectomy.

**Figure 1**. Sample ERAS same day surgery protocol for mastectomy with or without reconstruction



## CONCLUSION

There will be regional differences in how individual providers and institutions will begin to normalize the care of breast patients. These will depend on the incidence and prevalence of COVID-19 cases in the region and factors specific to the facility itself; the resources available including PPE, ventilators, operating rooms and staff to care for patients as well as the ability to create a virus-free space for the safety of patients. The main principles for re-entry include providing standard of care treatment, when resources allow, weighed against the risks of virus exposure to the patient from the effects of treatment, to the patient from staff and to the staff from patient. We urge that clinicians communicate with the multidisciplinary team, make group treatment decisions, and record the priority level and severity of pandemic at the time of the decision. This should include an assessment of your institution's ability to test and practice safe physical distancing during treatments. Patients should be informed of the risks of delayed treatment and the risks of virus exposure during surgery, intubation, treatment visits and of their immunocompromised state from cancer therapies. Follow safe practices put forward by the institution or local government to reduce the risk of virus transmission. Make an extra effort to maintain the doctor/patient relationship, hear the patients concerns and preferences and participate in shared-decision making for the best patient experience during these difficult times.

COVID-19 has transformed the way we practice medicine. We are using more telemedicine, reducing the number of patient visits and being more efficient with resources. Clinicians are striving to deliver more care in an outpatient setting and delay or even eliminate tests and treatments while avoiding compromising patient outcomes. Many of these practices may be shown to improve the value of our care due to decreased costs and improved efficiencies and will become the standard, even in a post-COVID world. We must take extra care to ensure that the populations most affected by the COVID-19 pandemic, including those in underserved areas and the elderly, in particular, are included in our modified practice patterns. Time and careful documentation will tell if outcomes and patient experience are compromised because of the altered treatment patterns that have emerged out of necessity during this pandemic.

## APPENDIX

MGH Tool for Risk Stratification of Breast Cancer Surgeries Delayed by the COVID-19 Pandemic

Purpose:

1. To allow a group practice or individual surgeon to create an objective, risk-stratified list of all breast operations delayed during the COVID-19 pandemic to prioritize assignment of surgery dates
2. To create a system with enough granularity to create clinically rational ranking among the expected large number of delayed breast surgery patients
3. To create a user-friendly interface that works for large or small breast surgery practices
4. To allow customization of the ranking system by users
5. To create an optional database of outcomes in delayed breast surgery patients including:
    - rates of response vs. progression in early stage neoadjuvant endocrine patients
    - pathology findings at definitive surgery in delayed patients
    - changes in uptake of risk reducing surgery, benign surgery and cosmetic procedures after the COVID-19 delay

Ranking principles:

1. Neoadjuvant chemotherapy patients should proceed to surgery on schedule except in the most extreme situations (ER+ patients might transition to neoadjuvant endocrine therapy if severe limitations in surgery access, HER2+ patients might transition to antibody therapy alone if severe limitations in access to surgery).
2. Most T1-2N0, ER+ patients receiving neoadjuvant endocrine therapy can safely defer surgery for at least 3-6 months, or potentially longer if local conditions require
3. Delayed ER+ patients should be monitored for disease response and should proceed urgently to surgery or other systemic therapy if progression is found
4. Most operations for 1) positive breast conserving surgery margins, 2) risk reduction, 3) benign lesions and 4) non-reconstruction cosmetic reasons can safely be deferred until more urgent cancer-related COVID-19 delays have been resolved

Infrastructure: REDCap and Excel platforms were created. Each site will own and manage its own data, and sites can utilize this tool as an aid to clinical decision making. It is important to note that this tool is not a substitute for clinical judgement and multidisciplinary input in patient care.

There is an option to pool data for analysis across institutions. IRB review for research projects derived from data or for sharing data outside institutions should be obtained by interested parties.

Table 1. Score assignments for factors related to risk of delaying breast surgery: higher score gets to OR sooner

| Risk Factor | Risk Score |
|---|---|
| | |
| INDICATION PRIORITY SCORE - ALL PATIENTS | |
| INDICATION SCORE | |
| Cancer - neoadjuvant chemotherapy | 30 |
| Cancer - neoadjuvant endocrine therapy | 10 |
| Re-excision, positive lumpectomy margin | 4 |
| ADH | 3 |
| Other atypia/probably benign | 2 |
| High-risk gene mutation | 1 |
| Symmetry/cosmetic | 0 |
| | |
| SCORED ONLY FOR CANCER PATIENTS RECEIVING NEOADJUVANT ENDOCRINE THERAPY | |
| ENDOCRINE SENSITIVITY SCORE | |
| | |
| If genomic risk testing done | |
| GENOMIC RISK TEST SCORE – Oncotype DX | |

| | |
|---|---|
| <18 | 0 |
| ≥18, <31 | 1 |
| ≥31 | 5 |
| GENOMIC RISK TEST SCORE – MammaPrint, EndoPredict, or other | |
| Low risk | 0 |
| High risk | 5 |
| | |
| If no genomic risk testing done | |
| ER STRENGTH SCORE | |
| ≥ 50% strong/moderate | 0 |
| 11-49% strong/moderate | 1 |
| Any % faint or 1-10% strong/moderate | 4 |
| PR STRENGTH SCORE | |
| Strong/moderate | 0 |
| Weak/negative | 1 |
| | |
| TUMOR GRADE SCORE | |
| 1 | 1 |
| 2 | 2 |

| | |
|---|---|
| 3 | 3 |
| | |
| TUMOR SIZE (cm) SCORE | |
| DCIS | 0 |
| Microinvasion (≤0.1) | 1 |
| >0.1, ≤1.0 | 1 |
| >1.0, ≤2.0 | 2 |
| >2.0, ≤3.0 | 3 |
| >3.0 | 4 |
| | |
| PATIENT AGE SCORE | |
| ≥70 | 0 |
| ≥50, <70 | 1 |
| ≥35, <50 | 3 |
| <35 | 4 |
| | |
| DELAY SCORE | |
| Time since biopsy | |
| ≥0, <3 months | 0 |

| | |
|---|---|
| ≥3, <4 months | 1 |
| ≥4, <6 months | 2 |
| ≥6 months | 3 |
| | |
| IMAGING RESPONSE SCORE | |
| Responding | 0 |
| Stable | 1 |
| Progressing any site | 4 |
| | |
| PHYSICAL EXAM RESPONSE SCORE | |
| Not palpable and not palpable at diagnosis | 0 |
| Responding | 0 |
| Stable | 1 |
| Progressing any site | 5 |
| | |
| SCORED ONLY FOR CANCER PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY | |
| ER SCORE - NEOADJUVANT CHEMOTHERAPY PATIENTS | |
| ER strong/moderate or low genomic risk | 0 |

| | |
|---|---|
| ER weak/negative or high genomic risk | 10 |
| | |
| TOTAL RISK SCORE | |
| TOTAL SCORE | |

TABLE 2: Enhanced Recovery for mastectomy with or without reconstruction: (Adapted from Mass General Brigham Health Care, ERAS protocols):

1. Enhanced utilization of ERAS especially for mastectomy patients who undergo +/- reconstruction patients (see Figure 1).
2. Setting clear expectations prior to the day of surgery for same day home discharge. Pre-operative education by either the surgeon or advanced practice provider should include postoperative pain management, early mobilization, and drain management.
3. Pre-operative non-alcohol based skin prep to be used by the patient at home
4. Clear liquids up to 2 hours before surgery with carbohydrate liquids
5. Holding area pre-medication with Gabapentin, Acetaminophen, Celecoxib
6. Consideration of anesthesia block (see block recommendations below)
7. Maintain normoglycemia during operation.
8. IV antibiotics prior to incision and goal-directed fluid therapy
9. Plastic surgery team prepare for their portion of the procedure with a separate table for implant/expander with or without an acellular dermal matrix while oncologic breast surgery is being performed. For bilateral mastectomy procedures, plastic surgery starts on the completed mastectomy side while contralateral mastectomy is performed by the breast surgery team.
10. Limit postoperative IV fluids, IV narcotics, maintain normothermia, normoglycemia, aim for early mobilization and early feeding.
11. For all patients consider acetaminophen, celecoxib, gabapentin for pain control prior to using narcotics. Tramadol may also be used instead of opioids.
12. Consider hospital-directed home remote monitoring for discharged patients and visiting nurse (VNA) directed drain removal with remote postoperative checks via telemedicine
13. Minimize postoperative narcotic utilization and narcotic need during the perioperative period

There are a number of nerve blocks that can be used to minimize the need for opiate analgesics in the post-operative period. Techniques include:

- Thoracic Paravertebral Block (PVB)
- Pectoral Never (PECS) I
- Pectoral Nerve (PECS) II
- Erector Spinae Plane (ESP)

This is not an exhaustive list,[39] but it includes the most common blocks that are done in the modern era in the United States. Almost every patient undergoing a mastectomy with or without a reconstruction procedure is a candidate. Because the paravertebral block is so close to the epidural space, teams should note that there is a bleeding risk in these patients. We would apply the same criteria for anticoagulants and coagulopathies

to a PVB as we do to an epidural or spinal. Teams should be set up to educate patients regarding these blocks before they come in on the day of surgery. Often many patients decline these blocks if they haven't been given prior education or guidance. In addition, administration of some PECS blocks may result in temporary paralysis of the motor nerves of the axilla. This should be considered when offering these blocks to patients undergoing mastectomy with lymph node removal.

Many of these techniques will be useful in the post-COVID era but certainly now more than ever avoiding prolonged hospital stay or returning to healthcare facilities for treatment of complications will be important to avoid unnecessary exposure to the virus.

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