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Modifications in Breast Cancer Guidelines in COVID-19 Pandemic; An Iranian Consensus

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ABSTRACT

Background: In March 2020, the World Health Organization declared the novel COVID-19 infection a pandemic. Among high-risk patients infected by the virus, breast cancer patients are vulnerable to present more severe infections. Iran is among the countries with a high incidence of COVID-19, and most of the routine activities of medical centers are affected by the epidemic disease. Thus, there is a need to make some modifications to international protocols for dealing with breast cancer in the affected countries.

Methods: The headings of breast cancer management protocols have been discussed among the university-affiliated professors in different disciplines involved in breast cancer management. The discussions were done through a “WhatsApp” group considering the titles and the latest news about COVID-19. Under each title, we provide the consensus of all members in the related disciplines.

Recommendations and Conclusion: In each specialty, all members agreed to choose minimal intervention. The modifications aim to reduce the workload of the medical centers as well as to provide the least interface of the patients with the medical centers. The members know that some recommendations may interfere with the routine best-practice recommendations and decrease the quality measures in the patient's outcome. Therefore, these recommendations are valid just in epidemic COVID-19 situation in the country.

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Introduction

Coronavirus disease (COVID-19)

In March 2020, the World Health Organization declared the novel Coronavirus infection a pandemic.¹ Although all people are susceptible to infection, mortality rate is significantly higher in patients with



older age, immunocompromised status, or severe comorbid diseases, most notably cancer.^{2,3} On the other hand, there is not enough evidence to make a conclusive association between cancer and COVID-19.^{4,5} Breast cancer is the most common cancer in women with treatment ranging from surgery, systemic chemotherapy, hormonal therapy and radiation therapy to more novel targeted immunotherapies. These patients face higher likelihood of exposure to the virus due to their frequent visits to medical centers and imaging centers. Furthermore, the immune suppression associated with most cancer directed therapies confers greater risk of serious complications and mortality from infection with COVID-19.⁶⁻⁸

As the pandemic continues, the national health system of the country will be increasingly engaged in the management of this critical and potentially life-threatening infection. On the other hand, medical centers admit patients who show more severe presentation of COVID-19. Therefore, the risk of involvement of patients referred for other diseases is higher.

According to official statistics, Iran is in a dire situation as a result of the outbreak. As of 21 March 2020, about 20000 people have been infected by COVID-19 and about 2000 people have died due to the infection, based on the reports by the Iranian Ministry of Health.⁹

In this paper, we present modifications in the approved breast cancer guidelines in an effort to reduce the frequency of hospital visits for breast cancer patients as the outbreak continues. The new guidelines will allow us to save the limited health care resources only for urgencies and emergencies and more importantly to protect our vulnerable breast cancer patients against COVID-19. A large group of Iranian medical physicians involved in the care of breast cancer patients in large academic centers have contributed to this project through a virtual discussion platform.

Methods

The headings of breast cancer management protocols were discussed among university-affiliated professors in different disciplines (multidisciplinary approach) involved in breast cancer management. The discussions were done through a “WhatsApp” group considering the titles and the latest news about COVID-19. Regarding each title, we considered the consensus of all members in the related disciplines. The admin of the group (first author) asked the members to comment on each title by direct questions and case presentations. Also, some items were added according to Frequently Asked Questions (FAQ) banks and databases asked by patients and health care professionals.

Discussion and Recommendations

1. Infection prevention and control

In order to diminish the spread of the novel

Coronavirus (COVID-19), health care professionals should engage in rigorous handwashing and advise their patients to do the same. Social distancing should be reinforced for patients and their families until the pandemic subsides. Information regarding these preventative measures must be distributed among patients through social media or other online outlets and during every medical encounter. Maximum protective care for health care professionals and hospital employees who are in contact with cancer patients is crucial. Clinic staff may need additional training on the use of personal protective equipment (PPE). Breast cancer patients who refer to the hospitals are advised to protect themselves by personal protective equipment like masks and gloves.^{10,11}

2. Breast cancer screening

For minimizing unessential visits to medical facilities it is advisable that screening procedures, such as mammography and clinical breast examinations, be postponed. This measure will help to reserve human resources available in hospitals and clinics for COVID-19 patients in need of urgent help.¹⁰

3. Breast cancer staging

Standard diagnostic procedures should still be pursued for diagnosis and staging of the disease prior to surgery. However, we recommend forgoing the placement of markers at the site of axillary lymph nodes and breast biopsies in advanced-stage disease given that this decision may lead to a higher mastectomy rate. We can minimize staging procedures before adjuvant therapy, especially for T0-T3, N0-N1, M0.¹² These measures will decrease the burden on radiologic centers, minimize contacts and transports and save human resources.

4. Breast cancer surgery

4.1. Avoid hospital admissions

COVID-19 continues to spread faster than expected. Therefore, we need to reserve our limited hospital wards for COVID-19 patients. Most of our surgery wards are currently closed in order to provide care to COVID-19 patients. Our surgeons teams have reduced their elective surgeries to minimize the risk of their patients and health care workers contracting the infection. This is also due to considerable shortage of available non-Covid-19 ward beds and personnel in the hospitals across the country including the major referral centers in Tehran.

Breast cancer patients requiring surgery after neoadjuvant chemotherapy are relatively immunodeficient, which increases their risk of infection with COVID-19 and developing serious complications. Considering the fact that surgery is still a crucial part of breast cancer therapy, it should continue to be performed following standard protocols as long as it is within the hospital policies for pandemic crisis. It is



essential that we refrain from admitting patients in hospitals overnight. Therefore, it is strongly advisable that all breast surgeries be performed in a Day-Care unit except for patients with severe comorbidities.^{10,13,14}

4.2. Tumor localization at the time of surgery in advance stages

In the case of non-palpable early breast tumors, it is advisable to use markers to localize the tumors, as usual. However, routine preoperative wire or radioactive seed placement in patients who are scheduled for the operation after neoadjuvant therapies would raise the risk of COVID-19 infection by increasing the number of referrals to the hospital as well as the workload of hospitals. The latter also could exhaust hospital resources required to tend to COVID-19 patients.

4.3. Risk reducing surgeries

We strongly recommend to stop all risk reducing surgeries for the patients even if there is a known genetic mutation (e.g. BRCA, CHECK, etc.) These operations can be done some months after subsiding the pandemic situation.

4.4. Mastectomy in DCIS and T1-2 N0 patients

Although in most references, breast-conserving surgery (BCS) followed by radiation has the same efficacy as mastectomy in the treatment of Ductal Carcinoma In situ, during COVID-19 outbreak, the surgeon can consider mastectomy more frequently. The surgeon should fully inform the patients of the potential risk of contracting COVID-19 through frequent visits to medical centers to receive radiation following BCS. Overall, to decrease the frequency of hospital visits in early-stage node-negative invasive cancers as well as DCIS, we recommend substituting “mastectomy” for “breast-conserving surgery plus radiotherapy”

We can consider Breast Conserving Surgery (BCS) followed by Accelerated Partial Breast Irradiation (APBI) or Intraoperative Radiation Therapy (IORT) for appropriated low risk patients. If the patient need whole breast irradiation it is recommended to do mastectomy in place of BCS or postpone radiotherapy up to 20 weeks after surgery. The latter is indicated in patients who are not high risk for local recurrence (microscopic positive margin, age less than 40 years).¹⁵

4.5. Breast Reconstruction:

Immediate breast reconstruction should be avoided in the epidemic situation of COVID-19 regardless of the type of breast reconstruction. Flap reconstructions require 1-5 days of hospital admission, and the implant and expander reconstructions will slightly increase the risk of complications, which is not acceptable in a viral epidemic situation. All secondary breast

reconstructions should be canceled or postponed when the COVID-19 outbreak has subsided.

5. Neoadjuvant /Adjuvant systemic therapy

Coming soon, all of our wards must provide services to COVID-19 patients. We must choose less toxic systemic therapy for breast cancer patients given that toxicity predisposes them to COVID-19 infection and that controlling the complications will become increasingly difficult due to limited human and medical resources. However according to ASCO recommendation “withholding critical anti-cancer therapy is not currently recommended”.¹⁰

According to previous studies and ASCO recommendation, we don't postpone adjuvant chemotherapy and begin therapy as soon as possible. In advanced stages, triple negative patients and HER2 positive cases, there is survival benefit to start adjuvant chemotherapy sooner (especially under 30 days).¹⁶⁻²¹ Hormone therapy, with or without anti HER2 treatment, is less toxic and can therefore be started earlier.

It is clear that we must strictly follow safety precautions including personal protection, checking fever and other symptoms like cough and dyspnea for both patients and their families before each cycle of chemotherapy. We need better time management to shorten waiting times before chemotherapy and minimize the number of allowed visitors for each patient.¹⁰

In Luminal A breast cancer patients, we recommend to follow “predict online” instead of “NCCN guideline” which minimizes the use of chemotherapy.²² We believe that intensive regimens are not suitable during epidemic days; therefore, we can use shorter chemotherapy regimens such as Docetaxel plus Cyclophosphamide instead of routine 8 courses anthracycline based regimens for low risk patients such as those with node-negative, hormone receptor-positive breast cancer or for the triple-negative breast cancer patients (T<10mm) with negative nodes.^{10,23,24}

We recommend to substitute every 3 weeks regimens instead of dose dense or weekly protocols. During chemotherapy, as per ASCO recommendation, using primary GCSF prophylaxis and even prophylactic antibiotics may make our patients less vulnerable to COVID-19 related complications. It is reasonable to use less glucocorticoid base premedication for chemotherapy induced nausea and vomiting prophylaxis.¹⁰

There is no evidence that bisphosphonate use can affect COVID-19 infection. However, we decided to stop adjuvant bisphosphonate injections (every 6 months) or even substitute by oral or subcutaneous forms. We made this decision as a means of minimizing contact between patients and health care professionals and not because of the side effects of bisphosphonate. Besides, we currently do not have



adequate staff and resources to provide this service to our patients. We continue bisphosphonate use for metastatic patients as per the guidelines.

We should consider the general situation of the patient if the home infusion is socially feasible for the patients, and the medical center has enough equipment and human resources to securely cover the substitution of IV in-hospital chemotherapy by oral or at-home chemotherapy.

There is no need to stop hormone therapy during the COVID-19 epidemic, even if COVID-19 infection is proven or suspected, especially in an outpatient setting. For hormone-positive patients with comorbidities, we can offer neoadjuvant/adjuvant hormone therapy instead of chemotherapy in cases with proven or suspected COVID-19 infection.¹⁰

6. Radiation therapy

Radiation therapy can be pursued following routine local guidelines and protocols. However, we endorse considering more conservative radiation techniques such as hypofractionation or IORT for proper patients. After neoadjuvant chemotherapy, all favorable “clinically complete responder” patients can be potential candidates for more conservative radiation therapy. We can also omit tumor bed boost in older patients with sufficient clear margin and good prognostic factors.^{15,25-28}

Radiotherapy will significantly increase the number of referrals to hospitals and, therefore, the risk of contracting COVID-19. Although it is not the standard of care, many T1-T2, N0 patients can be treated by mastectomy instead of BCT to avoid the 25-30 days visits required for radiation treatment. For patients receiving chemotherapy before RT, time interval does not influence survival rates. However, the possible interplay between the timing of chemotherapy and timing of RT needs further elucidation. In addition, the results should be evaluated further in different subgroups. Overall, we conclude that starting RT as soon as possible after BCS may not be necessary and delaying it up to 20 weeks is reasonable.²⁹ We must refer to local guidelines before making this decision to make sure that the patient is a suitable candidate for this option.²⁸

7. Treatment of metastasis

In metastatic patients, it is highly recommended to use less aggressive and toxic treatment if possible. For negative hormone patients, oral chemotherapy drug administration is recommended instead of IV administration and single agent therapy is preferred over combination therapy. Holiday policy is more acceptable than maintenance chemotherapy. We should also try to minimize hospitalizing our patients especially for palliative treatments. For hormone-positive patients, hormone therapy is the preferred treatment except for catastrophic metastatic crisis.¹⁰ We recommend delayed use of CD4/6 inhibitors,

given their risk of neutropenia. If a metastatic patient receives radiotherapy as a palliative treatment, it is highly recommended to use hypofractionated or single fraction radiation therapy. (20 Gy in 5 or 8 Gy in single fraction)

8. Follow-up and supportive care

According to our local guideline published by Iranian Society of Endocrine and Metabolism and Iranian Rheumatology Society, it is advisable to prescribe 50000 units of oral vitamin D per week for only 4 weeks in persons who did not check their plasma vitamin D level recently.³⁰ According to ASCO recommendation “there is no evidence to use prophylactic antiviral therapy for COVID-19 in cancer patients”.¹⁰ We must inform our patients that they should seek medical attention in the event of fever ($T > 37.3$), tachypnea ($RR > 20$), dyspnea, hypoxia ($O_2 \text{ sat} < 93\%$) or dry cough although ASCO does not recommend COVID-19 testing in all cancer patients.^{10,31,32}

It is recommended to restrict follow-up visits and para clinic activities such as blood testing (especially tumor markers) and imaging except in the presence of symptoms. To reduce the number of hospital/clinic visits and relieve patients' anxiety, healthcare professionals are encouraged to be in touch with them via telephone or web-mediated consulting to support patients remotely and meet their needs. It is possible to learn about symptoms and solve many of our patients' problems without necessarily meeting them in person.¹⁰

9. Sharing data among patients and health care providers

Unfortunately, before the COVID-19 epidemic, Cyberspace and the Internet were underutilized in our healthcare system and both patients and healthcare providers were unaware of the benefits of communication through these platforms. This epidemic has taught us the importance of developing sufficient infrastructure to improve the status of cyber networking in our healthcare system. Currently, many clinicians use social media platforms such as “WhatsApp”, “Telegram” and “Instagram” to communicate with their patients.

Nonetheless, we need to move forward and promote more specialized platforms or the so called “Telemedicine Apps” such as “Virtual Breast Clinic-<http://rubanapp.com/>”, which is currently being used in our center. In order to support our patients and control their anxiety, we can share with them the latest news on COVID-19 and published government guidelines on cyberspace. We can also share educational media and information concerning stress management, nutrition, early detection methods, self-protection and prevention measures such as proper hand washing techniques.³¹⁻³⁵ We have summarized the recommendations in Table 1.

**Table 1.** Recommendations to deal with breast cancer during COVID-19 pandemic outbreak

Title	Recommendation	References
Infection prevention and control	<p><i>Educate patients, health care providers to:</i></p> <ul style="list-style-type: none"> - Correct handwashing, avoid touching the eyes, nose, and mouth - Social distancing - Use of personal protective equipment (PPE) according to local guidelines - Home quarantine according to local guidelines - Cover mouth and nose with a tissue during cough and wear a facemask if you are sick - Clean and disinfect frequently touched surfaces - Inform patients as well as healthcare professionals about the symptoms of COVID-19 <p><i>Drug therapy:</i></p> <ul style="list-style-type: none"> - Prescribe 50000 units of vitamin D per week for 4 weeks for all breast cancer patients (Suggested by our local guideline) - No need to prophylactic antiviral therapy 	<p>ASCO¹⁰ CDC guidelines³¹⁻³³ Local guidelines³⁴ NHS³⁵ ESMO²⁴</p>
Screening	<ul style="list-style-type: none"> - Postpone screening procedures, such as mammography and clinical breast examinations 	<p>ASCO¹⁰ Suggested</p>
Breast cancer staging	<ul style="list-style-type: none"> - Minimize staging procedures before adjuvant therapy 	<p>NCCN¹² Suggested</p>
Surgery	<p><i>General Rules:</i></p> <ul style="list-style-type: none"> - Reschedule elective surgeries as necessary - Limit visits to hospitals and day care clinics - It is recommended not to postpone surgery - Breast surgeries should be performed in a Day-Care unit except for patients with severe comorbidities <p><i>Risk reducing surgery:</i></p> <ul style="list-style-type: none"> - postpone risk reducing surgery some month after subsiding pandemic outbreak <p><i>Surgery for DCIS and early stage T1-2, N0:</i></p> <ul style="list-style-type: none"> - Consider mastectomy more frequently to avoid radiotherapy (after full discussion with patients) - Substitute IORT or APBI instead of whole breast RT in appropriated patients or omission of RT in older patients (>70 years) with good prognostic factor and good peripheral margins <p><i>Tumor localization:</i></p> <ul style="list-style-type: none"> - Avoid routine preoperative wire or radioactive seed placement except for non-palpable tumors <p><i>Breast Reconstruction:</i></p> <ul style="list-style-type: none"> - Avoid immediate breast reconstruction - Do not use implant and expander reconstructions - Delay secondary breast reconstructions 	<p>ASCO¹⁰ CDC¹¹ ACS¹³⁻¹⁴ Suggested</p>
Neoadjuvant/Adjuvant Chemotherapy	<p><i>Timing:</i></p> <ul style="list-style-type: none"> - Do not delay anti-cancer therapy - Initiate or continue systemic cancer treatment as your curatives plans. - Begin chemotherapy as soon as possible (<30 days) in advanced stages, triple-negative patients and HER2 positive cases - Screen patients for possible COVID-19 infection sign and symptoms before each course of chemotherapy 	<p>ASCO¹⁰ NHS³⁵ Uptodate Predict online²² Suggested</p>



	<ul style="list-style-type: none"> - Delay or modify treatment in a patient with active infection - Collect routine lab samples needed before each chemotherapy at home 	
	<p><i>Choosing protocol:</i></p> <ul style="list-style-type: none"> - Minimize chemotherapy in Luminal A patients by following “predict online” instead of “NCCN guideline” - Substitute every-3-weeks regimens instead of dose dense or weekly protocols - Four courses Docetaxel plus Cyclophosphamide instead of routine 8 courses Anthracycline-based regimens in low risk patients such as: those with node-negative, hormone receptor-positive breast cancer or smaller than 10 mm in triple-negative breast cancer with negative nodes - Consider home-care chemotherapy if it is feasible for the patient and the health system - Continue hormone therapy during the COVID-19 epidemic even if COVID-19 infection is proven or suspected 	<p>ASCO¹⁰ NHS³⁵ Suggested</p>
	<p><i>Supportive treatments:</i></p> <ul style="list-style-type: none"> - Minimize glucocorticoids use for prevention of nausea and vomiting - Use GCSF as primary prophylaxis. - Minimize infectious complications by using prophylactic antibiotics - Defer supportive zoledronic acid treatments - Consider oral or subcutaneous form if home infusion is medically and logistically feasible specially for anti Her-2 	
Palliative/ Metastatic	<ul style="list-style-type: none"> - Change intravenous treatments to subcutaneous or oral if there are alternatives - Consider deferring supportive therapies such as denosumab and zoledronic acid treatments (except for hypercalcaemia) preferably by home care if feasible - Consider treatment breaks for long-term treatments (Holiday policy) - Delay using CD4/6 inhibitors given their risk of neutropenia 	<p>NHS³⁵ Suggested</p>
Radiotherapy	<ul style="list-style-type: none"> - Use more conservative radiation technique such as IORT or APBI techniques if available - Delaying radiation therapy up to 20 weeks after surgery if the patients have no high risk of local recurrence (positive margin) age less than 40 years or if no systemic treatment is given - Radiation can postpone in low risk patients as long as the COVID-19 outbreak is kept to a minimum or the risk for patients involvement is reasonably reduced - For adjuvant breast RT use hypofractionated RT (42.6 Gy in 16 fractions) instead of conventional RT (50 GY in 25 fractions) specially in node negative breast cancer - Omit boost in patients with more than 50 years old and clean surgical margins - Offer omission of adjuvant breast radiotherapy to those patients with low risk breast cancer who fulfil the NICE Early Breast Cancer Guideline (2018) criteria 	<p>ASCO¹⁰ NHS³⁵ NCCN¹²</p>
Followup	<ul style="list-style-type: none"> - Identify alternative arrangements to minimize patient exposure/remote monitoring/follow-up - Minimize face-to-face appointments - Postpone routine follow-up visits - Better schedule appointments to reduce waiting times (not to arrive early –consider measures such as texting them when ready 	<p>NHS³⁵ Suggested</p>



to see them so they can wait in their car)

Sharing data between patients and health care providers

- Virtual attendance at MDT meetings
- Have discussions about patients and make decisions in specific situation via cyberspace
- Encourage our teams to be in touch with patients via internet such as “WhatsApp”, “Telegram” or “Instagram”
- Share educational media and information concerning stress management, nutrition etc.
- Gather Frequently Asked Questions (FAQ) data banks and educate nurses to answer our patients properly.
- Use “Telemedicine Apps” such as “Virtual Breast Clinic-<http://rubanapp.com/>”

Conflict of Interests

There is no conflict of interest to declare.

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