



MANAGEMENT POLICIES OF BREAST CANCER SURGERY, CHEMOTHERAPY AND RADIOTHERAPY DURING COVID-19 OUTBREAK IN IRAN

H. MAHMOODZADEH^{1,2}, F. HADJILOOEI^{2,3}, R. OMRANIPOUR^{1,2}, E. ESMATI^{1,4}, S. ALIPOUR^{2,5}, F. SHAHI^{1,2}

¹Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran

²Breast Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

³Fellowship of Radiation Oncology from Princess Margaret Cancer Center, University of Toronto, ON, Canada

⁴Radiation Oncology Research Center, Tehran University of Medical Sciences, Tehran, Iran

⁵Department of Surgery, Arash Women's Hospital, Tehran, Iran

Abstract – Objective: *Introducing a modified guideline to save medical and human resources during COVID-19, and suggesting modifications to cancer treatment procedures during COVID-19 with the aim of reducing patients' exposures to medical centers.*

Materials and Methods: *Breast cancer management protocols were discussed among our colleagues in Cancer Institute of Tehran University of Medical Sciences through interactive applications (WhatsApp and Skype). We have provided the consensus of all opinions under relevant headings. Our recommendations will be modified as pandemic severity changes.*

Results: *Surgery is restricted to patients whose survival is likely to be compromised if surgery is not performed. As for systemic therapy, we prefer to prescribe less toxic regimens and choose tri-weekly cycles instead of bi-weekly or weekly ones. In the case of radiotherapy, hypofractionated schedules are preferred schedules.*

Conclusions: *COVID-19 pandemic put cancer patients, physicians, and health care systems in a challenging situation. All our colleagues agreed to choose less invasive and minimal interventions at this time because it is imperative to spare medical resources and workforce, and decrease patients' contact with medical environments. We know that some of our suggestions may interfere with standard and routine practice, but our recommendations will be changed when COVID-19 pandemic severity changes.*

KEYWORDS: *Breast cancer, Chemotherapy, Coronavirus, COVID-19, Iran, Pandemic, Radiotherapy, Surgery.*

INTRODUCTION

The World Health Organization (WHO) declared the Coronavirus Disease 2019 (COVID-19) outbreak to be a public health emergency of international concern on January 30, 2020 and recognized it as a pandemic on March 11, 2020¹. The first confirmed case of COVID-19 in Iran was reported

on February 19, 2020². Mortality rate is higher in patients with older age, severe comorbid disease, or immunosuppressed status^{3,4}. Mortality rate for a confirmed infected cancer patient is 7.6% compared to 3.8% for overall patients without comorbid condition. COVID-19 pandemic put the cancer patients, physicians, and health care systems in a challenging situation. As COVID-19 outbreak is



This work is licensed under a [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/)



a new event, we do not have enough information about how this infection can affect cancer patients. However, cancer patients are categorized as a high-risk group more vulnerable to COVID-19³.

Breast cancer is the most prevalent cancer among females in Iran⁵ and is one of the common cancers with treatments ranging from surgery and radiotherapy to systemic therapy. Our center, Cancer Institute, established in 1949 in Tehran, and Affiliated with Tehran University of Medical Sciences, is the oldest and biggest institute for diagnosis, research, and treatment of cancerous disease in Iran. Cancer institute of TUMS is the oldest and the most referral center in Iran and has an essential role in assigning standards and protocols of therapy and caring for cancerous patients in the country. While more than 350 breast cancer operations are performed annually, about 500 patients receive radiotherapy per year, and more than 500 breast cancer patients undergo chemotherapy per month. In this paper, we recommend our modifications in the approved breast cancer protocols to reduce the frequency of clinic visits and hospitalizations, and to manage our resources during this pandemic while providing patients with the best possible treatment.

MATERIALS AND METHODS

Breast cancer management protocols were discussed in our weekly breast tumor board, converted to a virtual board after COVID-19, in various relevant disciplines in Cancer Institute through interactive applications (WhatsApp and Skype). We studied guidelines provided by Breast Cancer Organizations of other countries to investigate their modifications to their standard guidelines and their scientific rationale for those changes, and we have provided the consensus of all opinions under each following heading.

RESULTS AND DISCUSSION

General Preventive Measures

To minimize the spread of COVID-19, we have converted more than 50% of our clinic visits to virtual ones. Patients are encouraged to wash their hands with soap for at least 15-20 seconds and if soap is not available, they should use hand sanitizer at the first entry to the clinic, before they leave the clinic, and at regular intervals while they are waiting for a long time or during their hospitalization. We do not have any special policy for patients' shoes protection in surgery inpatient wards and outpatient clinics, but patients must wear plastic shoe covers in

chemotherapy and radiotherapy wards. We consider a private locker for each patient in chemotherapy, radiotherapy, and surgery wards to handle their bags and belongings, and it is sanitized after each patient is discharged. To ensure social distancing, all patients are advised to sit with at least one and preferably two chairs between them in waiting areas. We have restricted the presence of patients' companions in the waiting areas only to patients who need physical assistance or emotional support at the physicians' discretion. Instructions related to wearing protective items such as masks and gloves, not touching the surface of any equipment or furniture, and not touching face and eyes are repeatedly given to all patients. All health care providers must wear surgical masks, sleeves, and gloves; however, the anesthesia team must wear N95 masks in the operation room. Due to shortage of N95 masks, not all patients can have it, but we recommend N95 masks without valve to patients who can obtain it. In order to reduce the risk of in-hospital acquisition of COVID-19, we decreased the wards' capacity to half, and decreased diagnostic imaging, laboratory assays and external consultations as far as possible. Additionally, all on-site coffee shops and restaurants have been shut down since the first days of the outbreak. Almost all the follow-up visits are done through phone or video calls, but if a concerning issue arises, patients should be seen. Follow-up procedures are deferred unless the patient has a concerning complaint.

Systemic therapy

During this pandemic we should adjust our routine guidelines to reduce the frequency of clinic visits and hospitalizations, and manage our resources. We prefer less toxic chemotherapy regimens and opt for tri-weekly regimens over bi-weekly and weekly. Before each cycle we check fever and other symptoms such as dyspnea, cough, and myalgia in patients and their companions. Because of the current shortage of blood supplies, we prefer to adjust the chemotherapy agent's dose in patients with borderline serum hemoglobin. Based on ASCO recommendations, prophylactic G-CSF (Granulocyte Colony-Stimulating Factor) should be used in high risk chemotherapy regimens, while Dexamethasone prescription should be limited, if appropriate, to reduce immunosuppression. In a neoadjuvant setting, for patients with strongly hormone receptor-positive tumors, we recommend endocrine neoadjuvant therapy rather than chemotherapy. For patients with hormone receptor-negative, HER-2 negative breast cancer we prefer tri-weekly regimens to dose dense bi-week-

ly or weekly regimens. Paclitaxel + Trastuzumab regimen is recommended for patients with HR-negative early stage (node negative), HER-2 positive breast cancer, and for locally advanced disease we recommend Docetaxel + Carboplatin + Trastuzumab regimen. In adjuvant setting, for early stage, HER-2-negative, ER-positive node negative breast cancer, we recommend “Adjuvant Online” (www.adjuvantonline.com) computer based model to estimate outcome with local treatment only, and the absolute benefit from systemic adjuvant endocrine therapy and chemotherapy. If an adjuvant chemotherapy is indicated, we prefer tri-weekly regimens to dose dense bi-weekly or weekly regimens, and we suggest four courses of Docetaxel plus Cyclophosphamide instead of routine eight courses of Anthracycline-based regimen for hormone-receptor positive early stage patients. In a metastasis setting, for hormone receptor-positive patients without visceral crisis and symptomatic visceral disease, we recommend hormone therapy with aromatase inhibitors or tamoxifen without CDK4/6 inhibitors or Trastuzumab and for hormone receptor-negative breast cancer or symptomatic visceral disease, we recommend oral chemotherapy regimens like Capecitabine or oral Vinorelbine, alone or in combination. Based on NHS recommendations, prescribing Denosumab, Zoledronic acid (except for hypercalcemia) and CDK4/6 inhibitors can be deferred, with consideration to add later. In patients with low risk HER-2 positive disease, shortening of the duration of adjuvant Trastuzumab to less than 12 months will be considered, based on the data from the PHARE and PERSEPHONE trials⁶.

Surgery

Surgery is restricted to patients whose survival will be compromised without surgery, e.g. malignant phyllodes tumors, sarcomas, discordant histologic exam suspicious for cancer, patients who completed their neoadjuvant chemotherapy, and excision of malignant recurrence (6). Decision about proceeding with surgery and best surgical option should be made through our virtual multidisciplinary tumor board. Every patient who is planned to undergo elective surgery should be assessed in terms of the possibility of COVID-19. History of exposure to an infected case or a seriously infected area should be asked, and signs and symptoms of the disease should be investigated. If any suspicion arises, laboratory assessment of COVID-19 and/or chest CT scan should be performed. If positive, the surgery should be postponed until complete clearance of symptoms.

Other preoperative assessments are carried out via telemedicine⁷. We prefer surgeries with less complications and early discharge of patient, so BCS is prioritized over mastectomy. Also, we prefer to postpone procedures with little or no significant risk, such as axillary sentinel lymph node biopsy if cancer is identified after excisional biopsy in a clinically lymph node negative patient and re-excision surgery due to positive margin until control of the outbreak. Locally advanced and inflammatory breast cancer patients and all metastatic cases are referred to the oncology team in order to consider systemic treatment if appropriate. Surgery for DCIS will be delayed. Given the fact that a small percentage of these patients may have a component of invasive disease, patients with ER+ DCIS should be considered for endocrine therapy during the delay and an excision by vacuum-assisted biopsy is recommended for small ER negative DCIS⁸; however, surgery should be performed in extensive DCIS with suspect microinvasive or invasive component as soon as it is feasible. Bilateral prophylactic mastectomies for mutation carriers without a cancer diagnosis will be delayed^{6,7}.

Radiotherapy

All the radiation treatment unit staff must use personal protective equipment (PPE). Our patients are advised to wear mask, gown, and gloves. Before radiation treatment each patient is questioned about signs and symptoms of COVID-19, and if there is any of them, radiation therapy will be postponed, and infectious referral will be requested. After each treatment, the entire room is cleaned with disinfectants. Adjuvant breast radiotherapy is a standard part of standard treatment and there are strong data supporting it in most patients⁷. We prefer hypofractionated schedules (42.4 Gy in 16 fractions or 40 Gy in 15 fractions) to standard regimen (50 Gy in 25 fractions). However, we prescribe standard regimen in patient whose regional lymph nodes must be treated. Although a radiotherapy boost may reduce locoregional recurrence in breast cancer, the survival benefit is negligible, and the possibility of omission should be considered⁹. We omit radiotherapy boost in patients older than 50 years old with ER positive, HER-2 negative invasive type tumor without other adverse pathologic features^{10,11}. Following BCS in women over 70 with small, grade 1-2, and hormone-receptor positive tumor, strong consideration will be given to the omission of standard radiation if a patient is planning to take endocrine therapy^{6,12}. Strong consideration will be given to



the omission of radiation after excision for low to intermediate grade DCIS, particularly in women over 60⁶. In patients receiving radiotherapy with palliative intent, we prefer smallest number of radiation sessions; e.g. in painful bone metastases a single 8 Gy fraction is recommended¹³.

CONCLUSIONS

Physicians should weigh benefits of cancer treatment against the risk of morbidity and mortality of COVID-19. Additionally, there are shortages in terms of human resources. Presently, each country should have its own field-specific treatment guideline based on available resources to provide patients with best possible emotional and medical care. During this pandemic, we should adjust our routine guidelines to reduce the frequency of clinic visits and hospitalizations and manage our resources. Accordingly, for systemic therapy, we choose less toxic chemotherapy regimens and tri-weekly regimens are preferred to bi-weekly and weekly when appropriate. In the case of radiotherapy, we prefer hypofractionated schedules. We omit radiotherapy boost in patients over 50 with ER positive, Her-2 negative invasive type tumor without other adverse pathologic features^{10, 11}. We may omit whole breast standard irradiation following BCS in a patient over 70 with a small, grade 1-2, hormone-receptors positive, and HER-2 negative tumor^{6, 12}. In case of surgery, in the non-metastatic setting, cases that should be postponed consist of: axillary sentinel lymph node biopsy after excisional biopsy of a malignant mass, small ER negative DCIS which has been excised by vacuum-assisted biopsy, ER positive DCIS or early luminal tumors that should undergo hormone therapy during the delay as well as triple negative, HER-2 positive, locally advanced luminal, and inflammatory breast cancer for which neoadjuvant chemotherapy will be initiated. As well, delayed reconstruction, risk-reducing surgeries and oncologic surgical revisions for cosmetic purpose should all be deferred. In metastatic breast cancer, every surgery including resection of the breast tumor or the metastasis should be deferred except for life-threatening complications or those that severely disturb quality of life that need surgery^{6, 7}. Lastly, to minimize the spread of COVID-19, almost all follow-up visits are done through phone or video calls, but if a concerning issue arises, the patient should be seen. Follow-up procedures are deferred unless patients have a concerning complaint.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

REFERENCES

1. WHO announces COVID-19 outbreak a pandemic. Available at: www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19. Accessed March 12, 2020.
2. Iranian Ministry of Health and Medical Education medical guidelines, Infographic /Existing Statistics of COVID-19 Patients. Available at: www.behdasht.gov.ir
3. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; 21: 335-337.
4. Wang H, Zhang L. Risk of COVID-19 for patients with cancer. *Lancet Oncol* 2020; 21: e181.
5. Shirzadi A, Mahmoodzadeh H, Qorbani M. Assessment of sentinel lymph node biopsy after neoadjuvant chemotherapy for breast cancer in two subgroups: initially node negative and node positive converted to node negative. *J Res Med Sci* 2019; 24: 18.
6. Suggested Treatment Modifications in Multidisciplinary Breast Cancer in the Setting of COVID-19, Breast Oncology Center, Dana-Farber/Brigham and Women's Cancer Center, March 30, 2020- version 1.0. Available at: https://www.dana-farber.org/uploadedFiles/Pages/For_Patients_and_Families/Care_and_Treatment/Coronavirus_COVID-19_Information/breast-cancer-treatment-and-covid-19.pdf
7. American College of Surgeons (ACS). COVID 19: Elective Case Triage Guidelines for Surgical Care. Available at: www.facs.org/covid-19/clinical-guidance/elective-case. Accessed April 7, 2020.
8. Omranipour R, Mahmoodzadeh H, Hadjilooei F, Alipour S. Recommendations for Breast Surgical Care during COVID-19 Outbreak in Iran: Setting Priorities of Management. *WCRJ* 2020; 7: e1588.
9. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR. The UK Standardization of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer. *Lancet Oncol* 2013; 14: 1086-1094.
10. Naoum GE, Salama L, Ho A, Horick NK, Oladeru O, Aboueglyah M, Daniell K, MacDonald S, Arafat WO, Smith BL, Colwell AS, Taghian AG. The impact of chest wall boost on reconstruction complications and local control in patients treated for breast cancer. *Int J Radiat Oncol Biol Phys* 2019; 105: 155-164.
11. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagl D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L; European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet Oncol* 2015; 16: 47-56.

12. Simcock R, Thomas TV, Estes C, Filippi AR, Katz MA, Pereira IJ, Saeed H. COVID-19: Global radiation oncology's targeted response for pandemic preparedness. *Clin Transl Radiat Oncol* 2020; 22: 55-68.
13. Chow R, Hoskin P, Schild SE, Raman S, Im J, Zhang D, Chan S, Chiu N, Chiu L, Lam H, Chow E, Lock M. Single vs multiple fraction palliative radiation therapy for bone metastases: Cumulative meta-analysis. *Radiother Oncol* 2019; 141: 56-61.