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Radiation Therapy for Breast Cancer During the COVID-19 Pandemic in Low Resource Countries: Consensus Statement from the Iranian Society of Radiation Oncology

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Abstract

Context: COVID-19 pandemic has resulted in considerable overloading of health care systems in almost all regions of the world. Among different malignancies, breast cancer can be considered as a typical example of how the decision-making process for radiation treatment can be adapted to unusual situations. There exist several international guidelines in order to modify radiotherapy treatments during the COVID-19 pandemic, however, some of their recommendations are not applicable in regions with limited resources. In this manuscript, we provided guidance to deliver radiotherapy to patients with breast cancer during the COVID-19 pandemic based on our available nationwide resources.

Evidence Acquisition: A team of expert radiation oncologists convened multidisciplinary and cross-institutional meetings and reviewed the major internationally published guidelines and relevant literature in the field of breast radiotherapy during the COVID-19 pandemic in order to establish recommendations for the safe application of radiation regimens based on the national limited resources.

Results: Practical guidance in order to deliver radiotherapy to patients with breast cancer during the COVID-19 pandemic based on available nationwide resources was developed.

Conclusions: Many of the international recommendations on the breast cancer radiotherapy during COVID-19 outbreak are not applicable in countries with limited resources. Therefore, modifying the guidelines based on the available resources is mandatory in order to achieve the best possible results.

Keywords: Breast Cancer, Radiotherapy, COVID-19, Limited Resources

1. Context

COVID-19 pandemic has resulted in considerable overloading of health care systems in almost all regions of the world. Previous reports have shown that, compared to the normal population, patients with cancer are more prone to develop COVID-19 complications and death as these frail populations have a higher risk of developing severe respiratory manifestations and requiring invasive ventilation (1).

Radiation therapy is the main treatment modality of cancer. Previous reports have estimated that among those patients with cancer who are cured, 49% are cured by surgery, 40% by radiotherapy alone or combined with other modalities, and 11% by chemotherapy alone or combined with other modalities (2). Therefore, radiotherapy as a "life-saving" procedure should be accessible for all patients with cancer.

However, due to the fractionated nature of radiotherapy treatments, the risk-benefit ratio might be different in a critical situation such as the COVID-19 pandemic (1). In such situations, interdisciplinary and shared decision-making seem to be essential in order to reduce the hospital visits of patients, ease pressure on the workforce, and achieve the best possible outcome for the patients (1, 3).

Besides, the pandemic situation has put a heavy burden on many radiotherapy departments worldwide, which has resulted in changing the allocation of resources, selec-

tively screening the patients on a daily basis, and dealing with the workforce shortage (1).

Among different malignancies, breast cancer can be considered as a typical example of how the decision-making process for radiation treatment can be adapted to unusual situations (1).

It is estimated that breast radiotherapy accounts for 30 percent of delivered radiotherapy fractions, and as a result, it has a high impact on the workload of the radiotherapy departments (3).

Managing this critical situation in regions with limited radiotherapy resources and facilities is troublesome. Breast cancer is the most common malignancy among Iranian women (4), however, based on international standards, there is still a large gap between available radiation therapy units and facilities in Iran compared to developed countries. A large number of centers in Iran mainly use the 3DCRT technique, and access to advanced technologies, such as intensity-modulated radiation therapy (IMRT), tomotherapy, and stereotactic body radiation therapy (SBRT) and CyberKnife is extremely limited (5). Besides, many populated areas are considerably far from the radiotherapy centers, and generally, those centers are not able to provide accommodation or transportation for the patients and their families. This, in turn, increases the risk of exposure and disease contraction.

As a result, some recommendations from international guidelines tending to modify the radiation treatment are not applicable in many parts of the country. In this manuscript, we aimed to provide guidance to deliver radiotherapy to patients with breast cancer during the COVID-19 pandemic based on our available nationwide resources. Obviously, centers that are equipped with modern facilities and experienced staff can comply with the international guidelines.

2. Evidence Acquisition

A team of radiation oncologists (all active members of the Iranian Society of Radiation Oncology) from different university hospitals and large referral centers convened multidisciplinary and cross-institutional meetings and reviewed the major internationally published guidelines and relevant literature in the field of breast radiotherapy during the COVID-19 pandemic. After data collection and re-evaluating the available facilities, they established recommendations for the safe application of radiation regimens based on the national limited resources.

3. Results

3.1. Omitting Breast Radiotherapy

3.1.1. Ductal Carcinoma Insitu

As adjuvant radiotherapy for ductal carcinoma insitu (DCIS) generally does not improve the overall survival, even in normal situations, it might be reasonable to omit radiotherapy in selected patients with DCIS, including patients with older age, significant comorbidities, or small foci of low-grade disease resected with wide negative margins (e.g., patients with low- to intermediate-grade DCIS, $<$ 2.5 cm in size with margins $\geq$ 2 - 3mm) (3, 6).

However, caution is warranted in omitting radiotherapy in patients under 40 years of age (7).

3.1.2. Invasive Carcinoma

Adjuvant breast radiotherapy might be omitted in select patients older than 65 - 70 years of age.

A retrospective analysis of patients with clinically node-negative breast cancer aged 70 years or older did not show any improvements in survival with the use of adjuvant radiotherapy or axillary dissection. They suggested that breast-conserving surgery without axillary dissection and adjuvant radiotherapy can be considered as a feasible treatment modality for this group of patients (8). It must be mentioned, however, that ipsilateral breast tumor recurrence was higher in the patients who did not receive axillary surgery or radiotherapy compared to other patients who received the standard treatment (5.3% and 1.6% respectively, P = 0.005) (8).

PRIME II phase 3 trial by evaluating 1326 patients suggested that adjuvant radiotherapy can be omitted in patients 65 years old of age and older with node-negative; grade 1 or 2 invasive breast cancer less than 3 cm with clear margins, positive estrogen receptor, and negative human epidermal growth factor receptor 2 (HER2) who are planned to receive endocrine therapy (9). Based on these data, it seems reasonable to omit adjuvant breast radiotherapy in some elderly patients with invasive cancer who meet the above- mentioned criteria (3, 7).

3.1.3. Mastectomy

Currently, nine provinces (out of 31) with a total population of more than 10 million do not have an active radiotherapy center (5). Modified radical mastectomy remains the surgical treatment of choice in regions where postoperative radiotherapy is not available (10, 11).

3.1.4. Deferring Breast Radiotherapy (DCIS)

In patients who are planning to receive adjuvant radiotherapy, the treatment can be delayed up to 12 weeks

after the surgery without a significant increase in recurrence rate (7). In a study on 1323 patients, the 10-year ipsilateral rate of tumor recurrence for radiotherapy starting less than 8 weeks, 8 - 12 weeks, and more than 12 weeks after the surgery was 13%, 7.6%, and 23%, respectively (12).

3.1.5. Invasive Carcinoma

A study on 6428 women who had T1 to 2, N0 to 1, M0 breast cancer found that outcomes were statistically similar for patients who started their adjuvant radiotherapy sooner than 20 weeks after the surgery, but they were inferior for intervals beyond 20 weeks (13). Therefore, in patients with early-stage and hormone positive breast cancer, radiotherapy can safely begin 8 to 12 weeks after breast-conserving surgery without compromising disease control or survival. In an appropriate subset of patients, even a delay up to 20 weeks may be safe (7).

Limited evidence exists regarding the interval from chemotherapy to radiotherapy and in most cases, radiotherapy is initiated 4 to 6 weeks after chemotherapy. By extrapolating data from surgical literature, an interval of up to 12 weeks from chemotherapy to radiotherapy might be reasonably safe (7).

3.2. Accelerated Partial Breast Irradiation

A large body of evidence has shown that accelerated partial breast irradiation (APBI) can be considered a suitable technique for select patients with breast cancer. These patients include individuals older than 50 years of age with T1, estrogen receptor-positive and node-negative disease, and in the case of DCIS, those with low/intermediate grade tumors smaller than 2.5 cm in size (7, 14, 15). The rational is that defining a smaller target volume allows shorter regimens to be utilized (7). Various fractionations and techniques exist for accelerated external beam partial breast radiation using 3-dimentional conformal radiation therapy (3D-CRT). One well-studied regimen is 38.5 Gy in 10 fractions delivered twice daily, however, twice-daily treatment is not possible in the majority of our centers, as the daily number of treated patients far exceeds the current international standards. Another attractive regimen would be 30 Gy in 5 fractions every other day (7), which cannot be utilized in the majority of our centers since the lack of facilities to use intensity-modulated radiation therapy (IMRT). Two feasible options for our limited resources include 40 Gy in 10 or 15 daily fractions using 3D-CRT (7).

3.2.1. Hypofractionated Regimens for Whole-Breast Radiotherapy

In many countries, hypofractionation is the standard of care for patients who require whole-breast radiotherapy without nodal irradiation (3, 7). Delivering radiotherapy in 5 fractions only as per the FAST (28 - 30 Gy in once weekly fractions over 5 weeks) and FAST Forward (26 Gy in 5 daily fractions over 1 week) trials (16, 17) is not feasible in Iran as the lack of the facilities for IMRT treatment and besides in majority of centers, there exists complexities regarding patient fixation (eg. lack of breast fixators) and daily set ups.

Two well-established regimens with moderate hypofractionation include 42.56 Gy in 16 fractions and 40 Gy in 15 fractions (7). These regimens that utilize the 3D-CRT technique, are suitable for areas with limited resources, and their use is encouraged.

3.2.2. Postmastectomy and/or Regional Nodal Irradiation

Regional nodal irradiation can reduce the risk of distant recurrence and improve disease-free survival (DFS), even among patients with a limited axillary involvement (7). Many studies have demonstrated the safety of hypofractionated nodal irradiation (18, 19), however, in many centers worldwide including the majority of centers in Iran, this approach is not widely employed. Recent studies have shown the safety of moderate hypofractionation (e.g., 40 Gy in 15 fractions) in the treatment of breast, chest wall, and regional lymph nodes if the supraclavicular hot points could be kept below 105% (20, 21). As a result, it is recommended that centers with limited resources adopt the policy to employ moderate hypofractionation to treat breast, chest wall, and regional lymph nodes (3).

One international guideline (3) has suggested that radiation oncologists omit nodal irradiation in women with low-risk disease (post-menopausal, T1, estrogen receptor-positive, HER2 negative, and grade 1 or 2 with 1 - 2 macrometastases) in order to treat them in 5 fractions based on FAST trial (16). As mentioned before, employing the FAST trial protocol is not feasible in Iran, and therefore, omitting nodal irradiation cannot be recommended as it does not reduce the overall treatment time.

3.3. Boost to the Tumor Bed

3.3.1. DCIS

Tumor bed boost dose in DCIS has less than 2% local control benefit following whole breast radiation with no overall survival benefit (7). As a result, it seems reasonable to omit boost dose in patients with DCIS. However, care must be taken in patients with positive margins or younger than 45 years of age, in whom boost dose has been shown to have a significant benefit in local control (10% improvement at 72 months) (22).

3.3.2. Invasive Carcinoma

Following whole breast radiation during the pandemic, tumor bed boost can be considered only in pa-

tients with high risk of local recurrence including patients younger than 60 years of age and those with a high-grade tumors or inadequate margins (23). Some international guidelines and published papers have suggested using simultaneous integrated boost (SIB) (7). As mentioned before, the majority of centers in Iran mainly use the 3DCRT technique, and access to IMRT is limited (5). Therefore, SIB cannot be considered a valid option for the majority of our centers. Besides, many of our centers do not have access to electron beams and in daily practice, they either deliver the boost dose with photons or refer the patients to another center (which can put the patients and carers at excess risk of contracting COVID-19 infection). Therefore, in this regard, we recommend that the radiation oncologists make decisions after discussing risks and benefits with the patients.

3.3.3. Brachytherapy and Intra-operative Radiotherapy

Very few radiotherapy centers in Iran have access and expertise in breast brachytherapy or intra-operative radiotherapy. For this reason and the fact that the use of brachytherapy could result in increased opportunities for exposure and infection (7), their use cannot be recommended.

4. Discussion

There is a large gap between available radiation therapy units and facilities in Iran and that of developed countries (5). Table 1 shows some of the published international recommendations for adjuvant breast radiotherapy during the COVID-19 pandemic. As mentioned in the results and the table, some of the international recommendations are not feasible in our country. Main obstacles in providing radiotherapy treatment include:

Limited number of radiotherapy centers: Based on 2015 data, there are 54 operational external beam radiotherapy centers for about 80 million population in Iran; a figure which is far below the international standards (5). The embargo before 2015 and the sanctions afterward have restricted the country's ability to purchase the adequate number of radiotherapy machines and equipment (5, 24, 25).

Unequal distribution: unequal geographical distribution has made access to radiotherapy facilities a big challenge for the patients. While the access in some big cities is reasonably easy, 9 provinces with a population of 10 million do not have access to radiotherapy facilities (5). As a result, patients either have to commute a long distance every day to the radiotherapy center, or to stay in a hotel or with their relatives in another city where the radiotherapy center is located. Apart from imposing a huge economic burden on the patients and their families, this problem put them at a higher risk of exposure with the COVID-19. This situation should be considered while making treatment decisions for the patients during the pandemic.

Limited number of modern radiotherapy machines: The number of modern radiotherapy units in Iran is limited. Many centers are not equipped with high-energy radiotherapy machines, and some of them lack some ordinary facilities including multi-leaf collimators, fixators, or portal imaging devices. This makes it very improbable to use the application of modern treatment techniques. The majority of international recommendations for breast radiotherapy during COVID-19 pandemic are based on hypofractionation techniques and IMRT that cannot be applied in many centers in Iran.

Staff shortage: There is a shortage of radiotherapy staff including radiation oncologist, radiation physicist, and radiotherapy technician especially in small towns (5). This problem prevents the use of complicated techniques which need more accurate patients' set up and increases the risk of treatment errors that are more prominent in hypofractionated techniques.

In conclusion, many of the international recommendations on the breast cancer radiotherapy during COVID-19 outbreak are not applicable in countries with limited resources. Therefore, modifying the guidelines based on the available resources is mandatory in order to achieve the best possible results.

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Footnotes

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Table 1. International Recommendations for Adjuvant Breast Radiotherapy During COVID-19 Pandemic

	Braunstein et al.; from MSKCC (2020) (7)	Coles et al.; from RCR (Onc) of England (2020) (3)	Coles et al. (2020) (3)	Dietz et al. (2020) (26)	Curigliano et al. (2020) (27)	Franco et al (2020) (1)	Iranian Consensus (Present Guideline) from ISRO
DCIS	Omit (all criteria must be met): Mammographically detected lesions < 2.5 cm; Low or intermediate grade; ≥ 2 mm margins, (Be cautious in patients younger than 40 years of age). Delay: RT can be delayed up to 12 weeks after BCS	Omit: Not mentioned. Delay: Not mentioned	Omit: Not mentioned; Delay: Not mentioned	Omit: Not mentioned. Delay: Defer RT until pandemic is over, except for ER-negative DCIS with positive margin	Omit: In low-risk patients. Delay: Not mentioned	Omit: In low-risk disease. Delay: Not mentioned	Omit: omit RT in selected patients with older age, significant comorbidities, or small foci of low-grade disease resected with wide negative margins: Low- to intermediate-grade; <2.5 cm; ≥2-3mm surgical margins, (Be cautious in in patients under 40 years of age). Delay: RT can be delayed up to 12 weeks after BCS.
Invasive cancer	Omit (all criteria must be met): ≥ 70 years of age; ER positive tumors ≤ 3 cm; Negative resection margins; No involved nodes; Eligible to receive endocrine therapy. Delay: RT can be delayed up to 8 - 12 weeks in patients with early-stage, node negative, ER positive breast cancer after BCS	Omit (all criteria must be met): ≥ 65 years of age; ER positive tumors that are ≤ 3 cm; HER2 negative; Negative resection margins; Grade 1 or 2; No involved nodes; Eligible to receive endocrine therapy. Delay:Not mentioned	Omit (all criteria must be met): ≥ 65 years of age; ER positive tumors that are ≤ 3 cm; HER2 negative; Negative resection margins; Grade 1 or 2; No involved nodes; Eligible to receive endocrine therapy. Delay: Not mentioned	Omit or Delay (all criteria must be met): >65 years; Early-stage; Node negative; ER positive; HER2 negative; Eligible for adjuvant endocrine therapy	Omit: Elderly patients at low risk of recurrence. Delay: Postpone RT up to 3 months for high-risk patients; Postpone RT and up to 6 months for low-risk patients	Omit (all criteria must be met): ≥65 years of age; ER positive tumors ≤3 cm; HER2 negative; Clear resection margins; Grade 1 or 2; No involved nodes; Eligible to receive endocrine therapy. Delay: Not mentioned	Omit (all criteria must be met): ≥65-70 years of age; ER positive tumors ≤3 cm; Negative resection margins; No involved nodes; Eligible to receive endocrine therapy. Delay: RT can be delayed up to 8-12 weeks in patients with early-stage, node negative, ER positive breast cancer after BCS.
Positive regional lymph nodes	Omit: Not recommended	Omit (all criteria must be met): Post-menopausal; T1 disease; ER positive; HER2 negative; Grade 1 or 2; Presence of 1 - 2 macrometastases	Omit (all criteria must be met): Post-menopausal; T1 disease; ER positive; HER2 negative; Grade 1 or 2; Presence of 1 - 2 macrometastases	Omit: Not recommended. Delay: Not recommended	Omit: Not recommended	Omit (all criteria must be met): Post-menopausal; Size ≤2 cm; ER positive; HER2 negative; Grade 1 or 2; Presence of 1-2 macrometastases	Omit: Not recommended

Boost to tumor bed	DCIS: Omit. Invasive cancer: Consider only in the presence of significant local recurrence risk factors: ≤ 60 years of age; High grade tumors; Inadequate margins	DCIS: Not mentioned. Invasive cancer: Consider in patients ≤ 40 years of age, or with > 40 years of age and significant risk factors for local relapse. Any boost should be either simultaneous and integrated or hypofractionated sequential	DCIS: Not mentioned. Invasive cancer: Consider in patients ≤ 40 years of age, or with > 40 years of age and significant risk factors for local relapse. Any boost should be either simultaneous and integrated or hypofractionated sequential	DCIS: Not mentioned. Invasive cancer: 10 Gy/4F	DCIS: Not mentioned. Invasive cancer: Consider in patients ≤40 years of age, or with >40 years of age and significant risk factors for local relapse.	DCIS: Not mentioned. Invasive cancer: should be omitted unless for young patients (≤40 years) and/or for those having high-risk factors for local recurrence	DCIS: omit, (Be cautious in patients with positive margins or ≤45 years of age). Invasive cancer: discuss the risks and benefits with the patients.
Recommended doses and schedules	Partial breast (node negative): 30 Gy/5F every other day or daily; 40 Gy/10F daily. Whole breast (node negative): 26 Gy/5F daily [a]; 40 Gy/15F daily; 42.4 Gy/16F daily. Postmastectomy (node negative): 42.56 Gy/16F. Breast and regional lymph nodes: 42.56 Gy/16F with SIB to tumor bed; 48 Gy/16F; 40 Gy/15F with SIB to tumor bed; 48 Gy/15F	Partial breast (node negative): 26Gy/5F daily [a]; 28-30 Gy/5 once weekly [b]. Whole breast (node negative): 26Gy/5F daily [a]; 28-30 Gy/5F once weekly [b]. Postmastectomy (node negative): Not mentioned. Breast and regional lymph nodes: 26Gy/5 daily [a]	Partial breast (node negative): 26Gy/5 daily [a]; 28-30 Gy/5F once weekly [b]. Whole breast (node negative): 26Gy/5F daily [a]; 28-30 Gy/5F once weekly [b]. Postmastectomy (node negative): 40 Gy/15F daily. Breast and regional lymph nodes: 40 Gy/15F daily	Whole breast: 40.05 Gy/15F; 42.56 Gy/16F; 28.5 Gy/5F once weekly [b]; 26–27 Gy/5F daily [a]. Post-mastectomy: 37.5 Gy/15F to chest wall, 35 Gy/14F to regional nodes (including IMN). 43.5 Gy/15F to chest wall, supraclav and Level III axilla (not IMN). 42.56 Gy/16F to chest wall and regional nodes (including IMN). 40.05 Gy/15F to chest wall, 37.38 Gy/14 to regional nodes	Partial breast: 30 Gy/5 over 2 weeks. Whole breast (node negative): 40 Gy/15F daily. 26 Gy/5F daily [a]. 28-30Gy/5F once weekly [b]. Postmastectomy (node negative): 40 Gy/15F daily. Breast and regional lymph nodes: 40 Gy/15F daily	Whole breast (node negative): 26 Gy/5F daily [a]. 28-30Gy/5F once weekly [b]. Postmastectomy (node negative): Not mentioned. Breast and regional lymph nodes: Not mentioned	Partial breast (node negative): 40 Gy/15F; 40 Gy/10F. Schedules with 5 total fractions are not recommended. Whole breast (node negative): 42.5 Gy/16F; 40 Gy/15F; Schedules with 5 total fractions are not recommended. Postmastectomy (node negative): 42.5 Gy/16F; 40 Gy/15F; Schedules with 5 total fractions are not recommended. Breast and regional lymph nodes: 42.5 Gy/16F; 40 Gy/15F; Schedules with 5 total fractions are not recommended.

Abbreviations: CIS, ductal carcinoma insitu; RT, radiotherapy; ER, estrogen receptor; BCS, breast conserving surgery; Gy, Gray; F, fraction; HER2, human epidermal growth factor receptor 2; IMN, internal mammary nodal chain; SIB, simultaneous integrated boost dose; MSKCC, memorial sloan kettering cancer center; RCR, royal college of radiologists (clinical oncology) of England; ISRO, Iranian Society of Radiation Oncology.

[a] Patients must fulfill the eligibility criteria of FAST FORWARD trial (17).

[b] Patients must fulfill the eligibility criteria of FAST trial (16).