

Breast cancer patients with delayed radiotherapy during the pandemic process

 Muzaffer Bedri Altundağ,  Can Azak,  Gülçin Ertaş,  Cafer Atar

University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Radiation Oncology, Ankara, Turkey

Cite this article as: Altundağ MB, Azak C, Ertaş G, Atar C. Breast cancer patients with delayed radiotherapy during the pandemic process. *Anatolian Curr Med J* 2022; 4(2); 158-161.

ABSTRACT

Aim: In this study; We wanted to examine the changes and delays in radiotherapy of all our breast cancer patients diagnosed with COVID-19

Material and Method: Radiotherapy delays of our breast cancer patients who had COVID-19 infection before and during radiotherapy between March 2020 and March 2021 were evaluated retrospectively.

Results: Sixteen of a total of 642 breast cancer patients, 472 operated and 165 metastatic, who underwent radiotherapy were diagnosed with COVID-19. All patients were women, ages were between 40 and 77 (mean 54.6). Five patients had a mastectomy, 8 had breast-conserving surgery, and 3 had breast cancer with bone metastases. Different radiotherapy schemes were applied at different treatment duration according to the clinical stage and disease status. The first breast cancer patient with COVID-19 infection was diagnosed on 27 June 2020. Our other patients were diagnosed from June to December (n=15) in 2020. Treatment of patients infected during radiotherapy was interrupted after a mean of 10 fractions (2-24 fractions) and treatment was started after a mean of 25 days (21-44 days). Post-operative patients who could not start treatment because they were SARS-CoV-2 PCR positive were able to start treatment after a mean of 22 days (14-30 days).

Conclusion: Radiotherapy could not be started at the recommended times for breast cancer patients infected with COVID-19 during the pandemic and the treatments had to be interrupted. Therefore, more care should be taken in the follow-up of these patients; should be considered as patients at risk for local recurrence and metastasis.

Keywords: Breast cancer, radiotherapy, COVID-19, pandemic

The study presented as an oral presentation in "Ankara Hematoloji ve Onkoloji Günleri 2021", Ankara, 4-6 February 2021.

INTRODUCTION

COVID-19 outbreak; caused unwanted delays in cancer diagnosis and treatment (1,2). Radiation therapy of breast cancer patients is also affected by up to 30% of the pandemic (3). It is shown that interruption of radiotherapy is related to lower local control (4). However, it takes some time to evaluate the scale and consequences of this pandemic. Various recommendations and guidelines have been prepared for each disease group. Health associations and authorities made different recommendations for general surgery, medical oncology, and radiation oncology clinics to treat breast cancer and started to be applied in a short time. The first COVID-19 case was diagnosed in Turkey on March 11, 2020. In our clinic, recommendations of national and international guidelines have been followed (5). Our aim in arranging

the clinical approach was to evaluate and treat cancer patients' radiotherapy indications while preventing exposure to hospital-acquired COVID-19 infection. This study retrospectively examined the changes and delays in radiotherapy of all breast cancer patients diagnosed with COVID-19 after March 11, 2020.

MATERIAL AND METHOD

Our study was approved by the COVID-19 Scientific Research Evaluation Commission within the General Directorate of Health Services of our Ministry and Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital Ethics Committee (Date: 2021, Decision No:2021-04/1139). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Breast cancer patients who had COVID-19 infection between March 2020 and March 2021 in the Radiation Oncology Clinic of -censored- hospital were identified from the records kept by the COVID-19 pandemic unit of our clinic. Both clinical and radiotherapy plan characteristics of each patient were recorded. Delays in patients infected before and during radiotherapy and treated/quarantined were evaluated retrospectively.

When calculating the delay time, the weekend is added to the total delay time for delays that include the weekend. For example, the 4 days from Thursday to Sunday were calculated as the delay period for the patient who could not enter treatment on Thursday and Friday. Otherwise, only the day without treatment was evaluated as the delay time.

All data were analyzed using SPSS (version 22) and Microsoft Excel programs. Descriptive statistics were used to determine the general characteristics of the groups. Frequency tables were used for ordinal variables, median and minimum/maximum values were used for non-parametric variables. Conformity of variables to normal distribution was analyzed using visual and analytical (Kolmogorov-Smirnov/Shapiro-Wilk) methods.

RESULTS

Sixteen (2.5%) of 642 breast cancer patients, including 472 operated breast cancer and 165 metastatic breast cancer, were diagnosed with COVID-19 on the specified dates. Of the patients with a mean age of 54.6 (40-77), 5 were mastectomized, 8 had breast-conserving surgery, and 3 had bone metastatic breast cancer. One patient was Stage 0, 2 patients were Stage I, 4 patients were Stage IIA, 2 patients were Stage IIB, 1 patient was Stage IIIA, 2 patients were Stage IIIB, 1 patient was Stage IIIC, and 3 patients were Stage IV. Nine patients had invasive breast carcinoma, 3 had invasive lobular carcinoma, 3 had medullary carcinoma, and 1 had ductal carcinoma in situ histopathology. Thirteen patients were hormone positive, 4 patients were HER2 positive. Only hormone therapy was started in 5 patients. Postoperative chemotherapy was applied to 7 patients, and neoadjuvant chemotherapy was applied to 4 patients. In mastectomized patients (n=5); to chest wall +/- lymph nodes 50 Gy/25 fractions in 5 weeks, in breast-conserving surgery patients; In 6 patients, the breast +/- lymph nodes 50 Gy/25 fractions in 5 weeks and the tumor bed 10-16 Gy/5-7 fractions boost, 1 patient 48 Gy/20 fractions to the breast and 12.5 Gy to the tumor bed/5 fractions boost and 1 patient 48 Gy/18 fractions and 16 Gy/6 fraction boost adjuvant radiotherapy was planned to the tumor bed. Palliative radiotherapy (RT) was planned 20 Gy/5 fractions in 1 week for metastatic patients (Table 1).

Table 1. Patients Characteristics (n=16)

Age	Median Age 55 (40-77)
Type of Surgery	Mastectomy (n=5) Breast-Conserving Surgery (n=8)
Staging (TNM)	Stage 0 (n=1) Stage I (n=2) Stage II (n=6) Stage III (n=4) Stage IV (n=3)
Histopathology	Invasive breast carcinoma (n=9) Invasive lobular carcinoma (n=3) Medullary carcinoma (n=3) Insitu Ductal carcinoma (n=1)
Chemotherapy/Hormonotherapy	Postoperative chemotherapy (n=7) Neoadjuvant chemotherapy (n=4) Hormonotherapy (n=5)
Radiotherapy Dose/Fractionization/Duration	50 Gy/25 fx (5 Wk) (n=5) 50 Gy/25 fx (5 Wk) + 10-16 Gy/5-8 fx (2 Wk) (n=6) 48 Gy/20 fx (4 Wk) + 12.5 Gy/5 fx (1 Wk) (n=1) 48Gy/18 fx (4 Wk) + 16 Gy/6 fx (1 Wk) (n=1) 20 Gy/5 fx (1 Wk) (n=3)
*fx: fraction, Wk: week, n: patient number	

The first patient with COVID-19 infection was a breast cancer patient with fever and sore throat on June 27, 2020. Our other patients were found in June (n=1), August (n=2), September (n=1), October (n=3), November (n=5) and December (n=4) 2020. 8 of the patients were diagnosed with COVID-19 during RT and 8 before radiotherapy. The treatment of patients infected during radiotherapy was prolonged after the 10th fraction, as the median (2-24 fractions) and a mean of 25 days (21-44 days). Patients who were scheduled for postoperative radiotherapy but infected before radiotherapy were able to start treatment after a mean of 22 days (14-30 days) (Table 2). Three patients with bone metastases were diagnosed before RT and started treatment after a mean of 20 days (14-30 days). The treatment was discontinued since 1 patient infected in the 18th fraction of RT (25 fractions were planned) and 1 infected in the 27th fraction (33 fractions were planned) did not want the remaining treatments. It was determined that a patient who was infected in the 5th fraction of RT completed his remaining treatment in another center after about 4 months. Other patients (n=5) completed their treatment as planned. The mean follow-up period of the patients was 11.6 months (4-17 months). Three patients with bone metastases were alive with metastatic disease in a mean follow-up of 8 months (4-13 months), and non-metastatic patients were alive without disease with a mean follow-up of 12.3 months (6-17 months).

Table 2. Parameters of Delays in COVID-19 Infection (n=16)

SARS Cov-2-PCR + Timing
During RT (n=8)
Before RT (n=8)
SARS Cov-2-PCR + time interval
June 2020 (n=1)
August 2020 (n=2)
September 2020 (n=1)
October 2020 (n=3)
November 2020 (n=5)
December 2020 (n=4)
SARS Cov-2-PCR + delay time during radiotherapy
25 days (21-44 days) Median after 10th fx (2-24 fx)
SARS Cov-2-PCR + delay time before radiotherapy
22 days (14-30 days) post-op RT
20 days(14-30 days) palliative RT
*fx: fraction n=patient number

DISCUSSION

The diagnosis of COVID-19 with polymerase chain reaction (PCR) was made in November and December 2020 in routine examinations, one of which was symptomatic during radiotherapy and eight asymptomatic patients before radiotherapy. Our hospital was a clean hospital which means SARS Cov-2-PCR positive patients were referred to another pandemic hospital and clean hospital precautions were taken (6). As in other radiation oncology clinics in Turkey, the treatment of patients was not interrupted or clinically delayed during any period of the pandemic. Therefore, more often seen as the cause of this date, the number of cases occurring in Turkey increased, and before radiotherapy, the decision to have a negative result of the SARS Cov-2-PCR test of the patients was applied (7). Performing a SARS Cov-2-PCR test before treatment for every radiotherapy patient is controversial. Some publications suggest that cancer patients and their staff need SARS Cov-2-PCR testing twice a week (8). Our clinical approach is to perform a SARS Cov-2-PCR test the day before starting treatment and to repeat the test if it is symptomatic for COVID-19 during radiotherapy and similar to other clinics that practice it caused a delay of up to 1 day per patient (9). The rationale for routine SARS Cov-2-PCR testing before radiotherapy is that cancer patients are more susceptible to infections, more than one cancer patient is present in the same room and device at the same time or one after the other, and the risk of transmission of infection to the hospital personnel who are in constant contact with the patient is reduced.

It is estimated that failure to complete radiotherapy within the specified time due to the COVID-19 pandemic will reduce local control (10,11). In our study, patients with COVID caused a break in radiotherapy for at least 2 weeks of breast cancer patients. Bese et al. (12) study shows that the 5-year local control was reduced by 5% if the radiotherapy interval was longer than 1 week. It means two weeks of

COVID-19 quarantine duration is affected radiotherapy efficacy more than 5%. In this case, an additional dose may be considered at the end of the treatment.

Radiotherapy increases the risk of infection of patients and hospital staff in COVID-19 because it is a form of treatment that requires an extended visit to the hospital (13). During this period, suggestions of hypofractionated radiotherapy came to the fore. Long-term results of randomized controlled studies such as START and FAST, which were conducted to investigate the side effects and local control of hypofractionated radiotherapy, especially in early-stage breast cancer, showed that radiotherapy for a shorter time is possible without reducing local control rates (14-17). The use of hypofractionated treatment regimens has increased in our clinic in patients with clinical suitability. Hypofractionated radiotherapy studies in locally advanced breast cancer are still ongoing and are not used in our clinic despite the COVID-19 pandemic. Treatments with fractions of 5 or less are routinely preferred for palliation of metastases (18).

COVID-19 was detected in 2.5% of the patients we applied radiotherapy during this period. This rate is shallow, and the measures we have taken are effective. The pandemic risk assessment determined that the patients had external contact, and there was no intra-clinical transmission. Radiotherapy should be started 1-2 months after surgery in patients with early-stage breast cancer who are not given chemotherapy and patients with locally advanced breast cancer who are operated on after neoadjuvant chemotherapy. In breast cancer patients in whom chemotherapy is started postoperatively, radiotherapy should be started within 7 months after surgery (19,20). One of our patients who received SARS Cov-2-PCR + before radiotherapy and received post-mastectomized chemotherapy 8 months later, and 2 patients who were operated on after neoadjuvant chemotherapy started radiotherapy 2 months later. Treatment continued after a mean of 3 weeks (21, 21, 22, 24, and 44 days) due to the prolonged quarantine period and recovery of those infected during radiotherapy. No dose change was made in patients for whom treatment was interrupted. All patients were treated at the planned doses.

CONCLUSION

Radiotherapy could not be started at the recommended times for patients with breast cancer infected with COVID-19 during the pandemic period, and the treatments had to be interrupted. Therefore, more care should be taken in the follow-up of these patients; they should be considered risky patients in terms of local recurrence and metastasis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the COVID-19 Scientific Research Evaluation Commission within the General Directorate of Health Services of our Ministry and Dr. Abdurrahman Yurtaslan Ankara Onkoloji Training and Research Hospital Ethics Committee (Date: 2021, Decision No:2021-04/1139).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

- Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. *Nat Cancer* 2020; 1-3.
- Lee S, Heo J. COVID-19 pandemic: a new cause of unplanned interruption of radiotherapy in breast cancer patients. *Med Oncol* 2021; 39: 5.
- Papautsky EL, Hamlish T. Patient-reported treatment delays in breast cancer care during the COVID-19 pandemic. *Breast Cancer Res Treat* 2020; 184: 249-54.
- Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. *Int J Radiat Oncol Biol Phys* 2007; 68: 654-61.
- Coles CE, Aristei C, Bliss J, et al. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic. *Clin Oncol (R Coll Radiol)* 2020; 32: 279-81.
- Göksel F, Güzle Adaş Y. Management of a radiation oncology clinic in a clean oncology hospital during the COVID-19 outbreak. *J Surg Med* 2020; 4: 925-9.
- Anacak Y, Onal C, Ozyigit G, et al. Changes in radiotherapy practice during COVID-19 outbreak in Turkey: A report from the Turkish Society for Radiation Oncology. *Radiother Oncol* 2020; 150: 43-5.
- Marschner S, Corradini S, Rauch J, et al. SARS-CoV-2 prevalence in an asymptomatic cancer cohort-results and consequences for clinical routine. *Radiat Oncol* 2020; 15: 165.
- Ning MS, McAleer MF, Jeter MD, et al. Mitigating the impact of COVID-19 on oncology: Clinical and operational lessons from a prospective radiation oncology cohort tested for COVID-19. *Radiother Oncol* 2020; 148: 252-7.
- Benk V, Joseph L, Fortin P, et al. Effect of delay in initiating radiotherapy for patients with early stage breast cancer. *Clin Oncol (R Coll Radiol)* 2004; 16: 6-11.
- Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review 2003; 21: 555-63.
- Bese NS, Sut PA, Ober A. The effect of treatment interruptions in the postoperative irradiation of breast cancer. *Oncology* 2005; 69: 214-23.
- Gemici C, Yaprak G. Covid-19 outbreak in a major radiation oncology department; which lessons should be taken? *Radiother Oncol* 2020; 149: 107-8.
- Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013; 14: 1086-94.
- Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: a randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol* 2020; 38: 3261-72.
- Brunt AM, Wheatley D, Yarnold J, et al. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol* 2016; 120: 114-8.
- de Azambuja E, Trapani D, Loibl S, et al. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. *ESMO Open* 2020; 5.
- Lutz ST, Chow EL, Hartsell WE, Konski AA. A review of hypofractionated palliative radiotherapy. *Cancer* 2007; 109: 1462-70.
- Tsoutsou PG, Koukourakis MI, Azria D, Belkacemi Y. Optimal timing for adjuvant radiation therapy in breast cancer: a comprehensive review and perspectives. *Crit Rev Oncol Hematol* 2009; 71: 102-16.
- Abdel-Rahman O. Impact of timeliness of adjuvant chemotherapy and radiotherapy on the outcomes of breast cancer; a pooled analysis of three clinical trials. *Breast* 2018; 38: 175-80.