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COVID-19 Pandemisi Sırasında Hipofraksiyone Meme Kanseri Işınlaması ve Erken Sonuçları; Tek Merkez Deneyimi

Hypofractionated Breast Cancer Irradiation and Early Results During the COVID-19 Pandemic; Single Center Experience

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ÖZ

Amaç: COVID-19 pandemisi sırasında meme radyoterapisi uygulanan hastalarda hipofraksiyone radyoterapinin dozimetrik olarak analizi ve erken klinik sonuçlarının değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Meme kanseri nedeniyle radyoterapi alan on yedi kadın hasta çalışmaya dahil edilmiştir. Hedef hacme 42,55 Gray (Gy) tedavi dozu tanımlanarak, toplamda 16 fraksiyonda uygulandı. Hastaların COVID-19 belirtileri ve akut yan etkileri takip edilmiştir.

Bulgular: On yedi meme kanseri hastasına hipofraksiyone radyoterapi uygulanmıştır. Hedef volümlerin % 95'inin aldığı doz ve kritik organların dozları 25 fraksiyonda 50 Gy Radyoterapi tedavi dozuna normalize edilerek değerlendirilmiştir. Tüm planlar 50 Gy' lik tedavi dozuna normalize edildikten sonra medulla spinalisin maksimum dozunun <45 Gy ve Kalp için ortalama dozun <5 Gy olması sağlanmıştır. Akciğer için 20 Gy veya daha fazlasını alan akciğer hacmi ortalama 20,19 Gy olarak elde edilmiştir. Ortalama 5 aylık takip süresince sadece 5 hastada grad 1 cilt reaksiyonu görülmüştür.

Sonuç: Meme kanseri tedavisinde hipo-fraksiyonasyone radyoterapi, pandemi döneminde hastaların tedavi sürelerinin kısaltılması ve daha az riske maruz kalınılması açısından daha uygundur. Aynı zamanda, tedavi süresi kısaldığı için de tedavi maliyeti daha düşük olmaktadır.

Anahtar Kelimeler: COVID-19, hipofraksiyone, meme kanseri, radyoterapi

ABSTRACT

Objective: We aimed to the dosimetric analysis of hypofractionated radiation therapy and early clinical results of patients who received breast radiation therapy during the COVID 19 pandemic.

Materials and Methods: Seventeen women who received breast cancer radiotherapy were included in the study. For target volumes, the prescription dose was applied 42.55 Gray (Gy) in 16 fractions. COVID-19 symptoms and acute side effects of the patients were followed.

Results: Seventeen breast cancer patients were treated with hypofractionated radiotherapy. Dose of 95% of target volumes and critical organ doses were evaluated by normalizing to 50 Gy in 25 fractions. When all plans were evaluated by normalizing to 50 Gy, the maximum dose of medulla spinalis was <45 Gy. The mean dose of heart was <5 Gy. The volume for the lung receiving 20 Gy or more was averaged 20.19. Grade 1 skin reaction was observed in only 5 patients during a mean follow-up of 5 months.

Conclusion: In the treatment of breast cancer, hypofractionated radiotherapy is more suitable in terms of shortening the treatment period of patients in the pandemic period and being exposed to less risk. At the same time, the treatment cost is lower as the treatment time is shortened.

Keywords: COVID-19, breast cancer, hypo-fractionate, radiotherapy

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INTRODUCTION

Breast cancer is the most frequently diagnosed and the leading cause of cancer deaths in women worldwide. Treatment of newly diagnosed, nonmetastatic breast cancer requires a multidisciplinary approach that includes surgery, radiation therapy, and chemotherapy. The purpose of adjuvant radiotherapy (RT) is to eliminate residual tumor residues after surgery for patients treated with breast-conserving surgery and mastectomy.[1] Thus, the risk

of locoregional recurrence decreases, and breast cancer-specific and overall survival increases. We apply either whole-breast RT (WBRT) or chest wall RT (CWRT) to most women treated with breast-conserving surgery or mastectomy. Moreover, additional doses were applied as RT boost to the tumor bed to reduce the risk of intra-breast tumors in most women who take WBRT. Regional node RT can also be added for women with lymph node metastasis and high-risk tumor. Traditionally, conventional fraction breast RT (CF-BRT) is applied to the entire breast/chest wall for 5 to 6 weeks in fractions of 1.8 to 2 Gray (Gy) in a conventional fraction of 45 to 50 Gy in total. However, another option is the preferred hypo fractionation breast RT (HF-BRT), which is associated with equivalent tumor control and less toxicity. Generally, the hypo-fractionated scheme yields a higher radiation dose per fraction, but the overall treatment time is shorter (40 to 42.5 Gy in about three to five weeks).[2-5]

After HF-BRT studies, in our clinical protocol, HF-BRT was started to be applied to early-stage patients over 60 years of age with T1 tumors, grade 1-2, and hormone receptor-positive patients with no lymphatic radiotherapy indication. However, the COVID-19 pandemic process changes the scope of treatment modality. Since cancer patients suffer from low immune systems, shortening the treatment period is crucial in terms of reducing exposure to coronavirus. (HF-BRT) was applied to all patients who were diagnosed with breast cancer without Mamaria Interna RT indication and whose desired dose-volume histogram was provided.

In our study, we aimed to analyze dosimetric data of HF- RT and early clinical results of patients who received hypo-fractionated breast RT during the COVID 19 pandemic.

MATERIALS AND METHODS

This study was approved by the Clinical Researches Ethical Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 18/ 05/ 2020, decision no: 2020/ 213). Consent was obtained from the patients and the study was conducted according to Helsinki and other international declarations.

Seventeen breast cancer patients who received breast/chest wall ± axilla radiotherapy with HF-RT from March to June 2020 were included in our study. The planning Computed Tomography (CT) datasets at 3 mm slice thickness were generated with Toshiba Aquilian simulation (Toshiba, Japan). All CT images were imported to the Monaco treatment planning system (CMS Inc, Version 5. 1, St. Louis, MO) to outline all target volumes and critical structures located on both sides.

According to the report by the International Commission on Radiation Units and Measurements, gross tumor volume (GTV) and clinical target volume (CTV) were determined. Target volumes and organs at risk were manually delineated by a single radiation oncologist. The planning target volume (PTV) were generated from the respective CTVs adding a 3 mm margin with all expansion for setup uncertainties. The prescription dose of the PTVs is 42.55 Gy in a total of 16 daily fractions in 3 weeks. Contoured critical structures were the heart, lungs, medulla spinalis, and contralateral breast. The manual contours of these structures were drawn according to the breast cancer consensus multicenter guidelines. Two different treatment planning namely Conformal Radiation Therapy (CRT) and Intensity Modulated Radiation Therapy (IMRT) plans were applied for all patients. 6 MV photon beams generated by Elekta Synergy linear Accelerator (Elekta Oncology, UK) was used to design both plans and patients were treated based on these plans. IMRT includes various gantry positions and speed, leaf, and jaw positions simultaneously. IMRT plans were generated with Monaco which offers equivalent uniform dose (EUD) based on biological optimization. EUD based cost functions are applied for critical structures in this optimization. During the delivery, the couch angle was 0o, treatment delivered from 7 fields with a fixed collimator rotational position at 0o. Moreover, the gantry angle was the patient's specific and was determined based on the tumor site. Target cost functions (target penalty and quadratic overdose) were defined for PTVs. Final dose calculations were done with a voxel-based Monte Carlo algorithm. All treatment plans generated based on both approaches aimed to cover 95% of the prescription dose defined for PTVs while protecting critical structures as much as possible. Dose constraints for two approaches were modified based on the Radiation Therapy Oncology Group (RTOG) 0615 Protocol. The data obtained from Dose Volume Histograms (DVH) of all plans were normalized to standard breast cancer treatment plan which delivers 50 Gy in 25 daily fractions to determine the dosimetric difference between the two approaches. The following items were evaluated for the plan comparisons: D95% defined as the dose received by 95% of target volumes to provide tumor coverage were evaluated. Additionally, the maximum dose (Dmax) for

medulla spinalis limited to < 45 Gy, Dmax for contralateral breast limited to < 10 Gy. Moreover, the mean dose (Dmean) for the heart was limited to < 5 Gy and Volume receiving 5 Gy or more (V5) of heart was limited to < 25%. Additionally, V5, V10, V20 of each lung volume, and total lung volumes were evaluated. V20 of the lung was limited to < 30 Gy, V10 of the lung was limited to <40 Gy, V5 of the lung was limited to <60 Gy for the ipsilateral lung.

The data obtained were analyzed by using SPSS 18.0 statistical software (SPSS Inc., Chicago, USA). Descriptive statistical methods (mean, median, minimum, maximum) were used when evaluating the study data.

RESULT

Patients' Characteristics: The average age of patients was 53 (range 32-74). 3 patients (17.6%) had hypertension and others had no comorbid disease. Of the patients included in the study, 47% (8) were right side breast cancer patients, and 58.8% (10) were left side breast cancer. When the patients were classified according to the tumoral stage (T stage), 5 patients (29.4%) were T1, 8 patients (64.7%) were T2, 1 patient (5.8%) were T3. When the tumor grades of the patients were analyzed, 12 patients (70.5%) had grade 2, 5 patients (29.4%) had grade 3 tumors. All the patients were treated with breast surgery, 15 patients had (88.23%) breast-conserving surgery, and 2 patients (11.7) had modified radical mastectomy. Twelve of the patients had chemotherapy before radiation treatment. An additional dose of 10 Gy boost was applied to the tumor bed in 15 patients (88.23%) who underwent breast-conservation surgery. While 10 patients underwent axillary lymphatic irradiation, none of the patients received Interna lymphatic irradiation. The general

Table 1. Patient'characteristics.

Patient ID	Tumor Location	Histological Type	Grade	LVI	PNI	T Stage	N Stage	Chemo-therapy	Skin Reaction
1	Right	IDC	2	-	-	2	1	-	1
2	Right	IDC	2		-	2	-		-
3	Left	IDC	2		-	1	1		-
4	Left	IDC	2	-	-	2	1		-
5	Right	IDC	3	-	-	2	-		-
6	Right	IDC	3			3	2	-	-
7	Left	IDC	2	-	-	2	1		-
8	Right	ILC	2	-	-	2	-		-
9	Left	IDC	2		-	2	2		1
10	Left	IDC	3	-	-	1	-	-	1
11	Left	IDC	2	-	-	1	-		1
12	Left	IDC	2	-	-	2	1		1
13	Right	IDC	1	-	-	1	-	-	-
14	Left	IDC	2	-	-	2	1	-	-
15	Left	IDC	2	-	-	2	1		-
16	Right	IDC	2	-	-	1	-		-
17	Left	IDC	3		-	2	1		-

IDC: Invasive ductal carcinoma; ILC: Invasive lobuler carcinoma; LVI: Lymphovascular invasion; PNI: Perineural invasion; T: Tumoral; N: Nodal.

Table 2. Dose constraints for target volumes for hypofractionated radiation therapy.

	HF-RT for Target Volume						
Patients	**TM**	**PTV D95 (Gy)**	**PTV D98 (Gy)**	**PTV D2 (Gy)**	**PTV Dmean (Gy)**	**PTV Dmax (Gy)**	**HI**
1	CRT	40.73	39.74	44.77	43.06	45.43	1.05
2	CRT	40.27	39.03	44.51	42.36	45.62	1.10
3	IMRT	41.15	39.60	44.02	42.68	45.93	1.06
4	CRT	41.39	40.67	44.90	43.31	45.61	1.00
5	CRT	40.52	38.79	45.05	43.20	45.68	1.11
6	IMRT	41.10	39.96	43.92	42.52	45.95	1.06
7	IMRT	40.15	38.16	45.22	43.56	45.63	1.12
8	CRT	40.80	39.98	44.92	43.11	45.56	1.10
9	IMRT	40.23	37.85	44.97	42.79	45.85	1.10
10	IMRT	41.87	41.10	45.10	43.88	45.42	1.07
11	CRT	40.33	39.68	45.48	43.26	45.94	1.12
12	IMRT	39.71	37.55	44.79	42.85	45.48	1.12
13	IMRT	40.54	39.75	44.86	42.48	46.08	1.10
14	IMRT	40.75	40.12	44.67	42.70	45.32	1.09
15	IMRT	41.15	3934	45.83	43.86	46.23	1.11
16	IMRT	41.60	40.34	45.04	43.74	45.53	1.08
17	IMRT	40.51	39.76	44.84	42.67	45.63	1.10
Mean		40.753	39.495	44.875	43.06	45.699	1.08

HF-RT: Hypofractionated radiation therapy; TM: Treatment modality; CRT: Conformal radiation therapy; IMRT: Intensity modulated radiationtherapy; PTV: Planning target volume; D95: Dose received by 95% of target volumes; D2: Dose received by 2% of target volumes; D98: Dose received by 98% of target volumes; Dmax: Maximum dose; Dmean: Mean dose; Gy: Gray; HI: Homogenity index.

characteristics of the patients are summarized in Table 1.

Dose constrains for HF-RT: Patients' treatment plans were generated to deliver 42.5 Gy in 16 daily fractions.

Six patients were treated with hypo-fractionated CRT and the rest of the patients were treated with hypofractionated IMRT. Dose constraints for target volume were shown in Table 2. Additionally, critical organ doses were shown in Table-3. In the second part, hypo-fractionated radiotherapy (HF-RT) plans were converted to the standard radiotherapy plans, in which 50 Gy was given in 25 daily fractions, to evaluate critical organs' doses based on the Radiation Therapy Oncology Group (RTOG) 0615 Protocol. The converted dose of target volumes and OARs from HF-RT to the standard plan was shown in Table 4 and Table 5 respectively. According to these results, all plans were clinically acceptable for tumor coverage and respected planning objectives. The data analysis of PTV coverage was done based on D95% in all plans, it was reached the goal to treat a maximum dose of less than 45 Gy to the medulla spinalis. Dmean for the heart was limited to < 5 Gy. These dose criteria are provided except for one patient. The average mean dose of the heart is 3.15 Gy. Dmean for contralateral breast was limited <1 Gy. The average mean dose of the contralateral breast was 0.95 Gy. The mean V20 of the lung was 20.19 Gy, V10 of the lung was 28.32 Gy, V5 of the lung was 35.36 Gy for the ipsilateral lung. All of them are provided.

Patient follow-up during and after treatment: Seventeen breast cancer patients had hypofractionated radiotherapy. Daily temperature measurement and symptomatic evaluation were performed in all patients. A polymerase chain reaction (PCR) test was requested in case of fever or symptoms. PCR positivity was not detected in any patient during the treatment. The mean follow-up period of the patients was 5 months. During hypo-fractionated radiotherapy, patients' complaints were asked weekly for 3 weeks ± 1 week. Also, the degree of skin reactions was noted at the end of each week by maintaining social distance and providing polyclinic ventilation. On the 10th day after treatment, side effects were evaluated with teleconference again. Grad 1 acute skin toxicity was seen in only 5 patients during treatment. Also, when evaluated at an average of 20 weeks, skin toxicity was observed in patients. There were no skin side effects, breast side effects, and fatigue 6 weeks after the start of treatment.

Table 3. Dose constraints for organs at risks for hypofractionated radiation therapy.

	HF-RT for Organs at Risks										
	Heart	Lung				Total Lung			Contralateral Breast		Medulla Spinalis
Patients	Dmean (Gy)	V5 (Gy)	V5 (Gy)	V10 (Gy)	V20 (Gy)	V5 (Gy)	V10 (Gy)	V20 (Gy)	Dmean (Gy)	Dmax (Gy)	Dmax (Gy)
1	1.19	0	53.50	41.62	31.80	28.38	22.17	17.03	0.90	7.41	16.99
2	1.04	0	28.26	20.91	15.64	14.81	11.02	8.30	0.84	9.30	0.82
3	3.06	7.44	58.29	36.57	17.92	30.05	16.70	8.25	1.23	7.55	19.54
4	3.72	9.91	42.89	34.75	27.86	19.52	15.81	12.68	0.89	8.16	8.97
5	1.18	0	35.55	28.46	23.12	19.36	15.56	12.69	1.09	9.20	0.82
6	3.14	10.84	58.13	32.03	19.55	34.51	18.64	11.46	1.37	6.2	13.15
7	3.68	10.80	38.54	28.60	20.39	16.99	12.68	9.10	1.00	10.55	8.85
8	1.06	0	26.44	19.40	14.30	15.19	11.20	8.30	0.93	9.71	0.74
9	4.10	11.99	39.54	30.31	22.74	18.05	13.84	10.38	0.86	7.28	8.36
10	3.56	10.16	34.04	27.18	21.57	14.15	11.28	8.96	0.87	7.52	7.41
11	2.16	5.35	15.73	10.48	6.30	7.13	4.75	2.85	0.99	7.94	0.59
12	3.93	0.12	48.88	39.22	29.17	23.61	18.99	14.19	0.99	5.93	12.26
13	1.14	6.04	35.41	26.75	20.79	20.41	15.50	12.12	0.75	7.61	4.24
14	4.09	11.52	48.62	36.78	26.95	23.40	17.76	13.08	0.76	5.53	13.87
15	2.62	5.96	54.19	41.15	28.50	24.62	18.69	12.95	1.01	7.15	1.01
16	1.12	0	30.41	21.29	14.78	17.31	12.11	8.41	1.04	8.89	4.75
17	4.48	13.76	45.65	34.20	24.77	19.02	14.30	10.43	0.78	6.93	44.67
Mean	2.663	5.764	35.36	28.32	20.19	19.25	13.85	9.251	9.588	7.45	9.825

HF-RT: Hypofractionated radiation therapy; Dmax: Maximum dose; Dmean: Mean dose; Gy: Gray; V5: Volume receiving 5 Gy or more; V10: Volume receiving 10 Gy or more; V20: Volume receiving 20 Gy or more.

Table 4. Converted dose from hypofractionated radiation therapy to standard radiation therapy for target volume.

	Dose Conversion of Target Volume				
Pa-tients	PTV D95 (Gy)	PTV D98 (Gy)	PTV D2 (Gy)	PTV Dmean (Gy)	PTV Dmax (Gy)
1	47.79	46.64	52.50	50.52	53.54
2	47.58	46.11	52.58	50.05	53.89
3	48.52	46.69	51.91	50.33	54.16
4	48.81	47.96	52.96	51.08	53.78
5	47.90	45.91	53.29	51.29	53.87
6	48.46	47.12	51.79	50.14	54.18
7	47.95	45.59	54.04	52.03	54.50
8	47.44	45.57	52.78	50.55	53.52
9	47.37	44.58	52.97	50.39	54.00
10	49.31	48.41	53.13	51.69	53.50
11	47.50	46.79	53.63	51.00	54.17
12	47.14	44.85	52.96	50.69	53.78
13	47.70	46.77	52.77	49.98	54.21
14	47.87	46.72	52.88	50.49	53.68
15	48.47	46.33	53.98	51.66	54.45
16	49.10	47.69	53.14	51.61	53.71
17	47.86	47.00	53.05	50.44	53.89
Mean	48.045	46.513	52.962	50.82	53.931

HF-RT: Hypofractionated radiation therapy; PTV: Planning target volume; D95: Dose received by 95% of target volumes; D2: Dose received by 2% of target volumes; D98: Dose received by 98% of target volumes; Dmax: Maximum dose; Dmean: Mean dose, Gy: Gray.

DISCUSSION

In studies, The Early Breast Cancer Trialists' Collaborative Group [6,7] reported in two systematic meta-analyses that radiotherapy applied after primary surgery reduced regional cancer recurrence and breast cancer-related deaths. For the past half-century, adjuvant radiotherapy has been given for 5-7 weeks in a fractionation called CF-BRT in 2 Gy, 25 fractions. Long-term randomized controlled trials have confirmed that HF-BRT with a lower total dose is at least as safe and effective as international standard conventional fractionation.[8-10]

Gupta et al.11 compiled long-term European and Canadian studies comparing HF-BRT and CF-BRT schemes. For locally advanced disease, lymph node and/or post-mastectomy radiotherapy is also presented in the evaluation of evidence supporting hypofractionation.[4,8-14] Tumor controls equivalent to CF-BRT of HF-BRT for early breast cancer have been shown to result in the same or better acute and late toxicity, and better breast cosmetology. Also, early data of HF-RT requiring regional lymph node treatment and/or post-mastectomy have been suggested to support the use of the hypo-fractionated regimen, but its wide adoption should await long-term results.[15,16]

Radiation oncology is a special department with a highly specialized team and types of treatment. The treatment equipment is special and fixed, treating patients sequentially, increasing the likelihood of cross-contamination. Treatments are affected by intervals and delay. It can be used in conjunction with systemic chemotherapy or sequentially, which increases the risk of infection. During the COVID-19 pandemic throughout the world, breast RTs were adopted by international recommendations, some centers did not apply adjuvant RT in ductal carcinoma in situ (DCIS) and early-stage breast cancer with low risk. Some centers used hypofraction and accelerated partial breast radiation (APBI) instead. Previously, hypofractionation was the preferred standard for full breast RT without nodal therapy in the United States and was used in all patients, including the axilla after a pandemic.[17] We aimed to protect our patients and healthcare workers from exposure to COVID-19 with hypo-fractionated treatments and to reduce the workload for healthcare services in cases where resources are difficult.

We applied 42. 5 Gy HP-RT at 16 fractions to 17 breast cancer patients admitted to our clinic. While 15 patients received HF-BRT after breast-conserving surgery, 2 patients received HF chest wall RT after mastectomy. Also, regional lymphatic irradiation was added to 10 patients. Target tissue doses and organ doses at risk were achieved in the desired dose volume range. Early acute adverse effects were not seen except for grade 1 skin reaction. Small patient population and short-term follow-up is limitation of our study.

Early results in the pandemic period were reported with this study and we plan new study for the future to compare the long-term results of standard fractionated radiotherapy and hypofractionated radiotherapy.

In conclusion, during the early days of the pandemic period, hypo-fractionated radiotherapy is essential to reduce the total treatment time and it is more suitable for patients since they expose the riskless. For the same reason, hypo-fractionated radiation therapy represents high-quality and high-value care that is not only more convenient for patients but also more cost-effective and resourceful.

Ethics Committee Approval: This study was approved by the Clinical Researches Ethical Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Date: 18/05/2020, decision no: 2020/213).

Conflict of Interest: The authors declare that they have no competing interests.

Author Contributions: Concept-EEO; Supervision-EEO, GPS; Materials-EEO, GPS, SC; Data Collection and/or Processing- EEO, GPS, SC; Analysis and/ or Interpretation-SC, EEO; Writing-EEO.

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