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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Treatment Results and Dosimetric Comparison of Synchronous Bilateral Breast Cancer with Helical Tomotherapy and Volumetric-Modulated Arc Radiotherapy

Senkron Bilateral Meme Kanserinde Helikal Tomoterapi ve Volumetrik Yoğunluk-ayarlı Ark Radyoterapi Tekniklerinin Dozimetrik Karşılaştırması ve Tedavi Sonuçlarımız

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ABSTRACT

Objective: The aim of this study is to present the short-term treatment results and dosimetric comparison of patients with synchronous bilateral breast cancer (SBBC) with helical tomotherapy (HT) and volumetric-modulated arc therapy (VMAT) by actual treatment plans.

Material and Method: Twelve patients with SBBC who were diagnosed between June 2015 and June 2018, received adjuvant bilateral breast or chest wall RT were retrospectively analyzed. Seven of the patients were irradiated in helical Tomotherapy (Hi-Art ® Version 5.1.3) (HT) and the remaining 5 patients in Elekta Versa-HD v4.0 with VMAT. HT and VMAT plans were compared based on dose-volume histograms (DVH).

Results: The median follow-up period of the patients was 19 months (range, 3-37 months). Nine (75%) patients had a locally advanced stage. Neoadjuvant chemotherapy was applied to 5 (41.6%) patients. One of 12 SBBC patients died due to systemic progression. Local control was achieved in other patients. Acute grade 1-2 dysphagia was observed in 5 and acute grade 1-2 radiodermatitis in 7 cases. When comparing VMAT and HT plans, statistically significant difference was revealed only in PTV Dmin and Lung V5 values. Lung V5 was found statistically better in favor of HT and PTV Dmin in favor of Elekta Versa-VMAT.

Conclusion: Various RT techniques as VMAT and HT can be approached in the management of rare cancers such as SBBC, and the patient-specific optimal plan should be selected.

Keywords: Synchronous bilateral breast cancer, helical tomotherapy, volumetric-modulated arc therapy, radiotherapy

ÖZ

Amaç: Bu çalışmanın amacı, senkron bilateral meme kanseri (SBMK) hastalarının helikal tomoterapi (HT) ve volumetrik yoğunluk-ayarlı ark radyoterapisi (VMAT) ile kısa dönem tedavi sonuçlarını ve gerçek tedavi planları ile dozimetrik karşılaştırmalarını sunmaktır.

Gereç ve Yöntem: Adjuvan bilateral meme veya göğüs duvarı RT'si alan on iki SBMK'li hasta retrospektif olarak analiz edildi. Hastaların yedisine HT (Hi-Art® Sürüm 5.1.3) (HT) ile, geri kalan beş hastaya VMAT (Elekta Versa-HD v4.0) ile RT uygulandı. HT ve VMAT planları, doz-hacim histogramlarına (DVH) göre karşılaştırıldı.

Bulgular: Hastaların ortanca takip süresi 19 aydı (3-37 ay). Dokuz (% 75) hasta lokal olarak ileri evre idi. Neoadjuvan kemoterapi 5 (% 41,6) hastaya uygulandı. 12 SBMK hastasından biri sistemik progresyon nedeniyle ex oldu. Diğer hastalarda lokal kontrol sağlandı. Akut grad 1- 2 yutma güçlüğü 5 olguda ve akut grad 1- 2 radyodermit 7 olguda görüldü. VMAT ve HT planları karşılaştırıldığında sadece PTV Dmin ve Lung V5 değerlerinde istatistiksel olarak anlamlı fark ortaya çıktı. Lung V5 değeri HT lehine ve PTV Dmin de Elekta Versa-VMAT lehine istatistiksel olarak daha iyi bulundu.

Sonuç: Senkron bilateral meme kanseri gibi nadir görülen kanserlerin radyoterapisinde VMAT ve HT tekniklerinin her ikisi de kullanılabilir.

Anahtar Kelimeler: Senkron bilateral meme kanseri, helikaltomoterapi, volumetrik yoğunluk-ayarlı ark radyoterapisi, radyoterapi

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INTRODUCTION

Synchronous bilateral breast cancer (SBBC) can be defined as the development of malignancy in both breasts with a maximum interval of 6 months (1). It constitutes 0.4-2.8% of all breast cancer (BC) cases (2). SBCC is very rare but it has been shown that the number of diagnoses tends to increase day by day (3). However, a clear optimal radiotherapy (RT) technique has not yet been described for SBBC. The RT of SBBC is much more complex and difficult than unilateral BC. Having an overlap-junction area on the skin, excessive entry of lungs and heart to the field of RT are troublesome situations in SBCC radiotherapy (4-6). In this case, it is necessary to find the best RT technique by making various plans.

Nowadays, by the use of advanced RT techniques, satisfying results can be achieved. It may be possible to reduce toxicity by minimizing lung and heart doses using breath-controlled RT (7-9). Similarly, breath holding method in deep inspiration can provide better protection of organs at risk (lung and heart) (10,11). In the RT of unilateral BC, if the patient's anatomy is also suitable, the most preferred technique is tangential field in field technique. In more complex cases, when an optimal plan cannot be achieved with tangential field in field technique, intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) techniques can be used (4-9).

Concerning the low incidence of SBBC, there is no clarity regarding the most effective RT technique for adjuvant setting. Our study is a clinical study that presents the dosimetric data comparing adjuvant RT techniques (VMAT and HT) for SBBC. We aimed to present short-term results and dosimetric comparison of patients with SBBC with HT and VMAT by actual treatment plans.

MATERIAL AND METHODS

Patients and Volume Delineation

Twelve patients with SBBC from two institutions who were diagnosed between June 2015 and June 2018, received adjuvant bilateral breast or chest wall RT were retrospectively analyzed. Approval for the study was granted by the Ethics Committee of Ankara City Hospital (Decision no: E1-20-1434). Informed consent was obtained from all the patients. All patients were immobilized with the Computed Tomography (CT) simulator in supine position with hands up by utilising the breast board at free-breathing. Seven of the patients were irradiated with helical Tomotherapy (Hi-Art ® Version 5.1.3) at Ankara City Hospital and the remaining 5 patients with Elekta Versa-HD v4.0 at Ankara Memorial Hospital. A total of 24 breasts or chest walls ± regional lymph node regions were irradiated.

Clinical Target volume (CTV) for the breast or chest wall ± regional lymph node was contoured according to Radiation Therapy Oncology Group Contouring Atlas (12). Planning Target Volume (PTV) was created by expanding to CTV with a 3-5 mm margin. Bilateral lung, heart, spinal cord were determined as organ at risk (OAR). Target volume for boost was defined as the volume involving surgical clips and scar.

Treatment Planning

IMRT with Helical Tomotherapy: The RT plans of 7 patients were designed as IMRT in Tomotherapy version 5.1.3 treatment planning system (Accuray ® planning station). In these plans 5.02 field width and 0.287 pitch factor were used. The prescribed dose was a total of 50 Gy in 25 fractions with a 2 Gy fraction dose for the chest wall and regional lymph nodes. The same doses were delivered for whole breast irradiation and median 10 Gy RT was applied as a boost dose.The RT plans of 12 chest wall + regional lymph nodes (n: 6) and 2 whole breast + regional lymph nodes (n: 1) were made with Tomotherapy. These plans were evaluated based on dose-volume histograms (DVH). PTV Dmin (minimum dose), PTV Dmax (maximum dose), V95% (volume covered by 95% of the prescribed dose) ve V105% (volume covered by 105% of the prescribed dose) for PTV; V20 (volume of the received dose of 20 Gy) and V5 (volume of the received dose of 5 Gy) for lung; V25 (volume of the received dose of 25 Gy), Dmean (mean dose) and Dmax for heart; V35 (volume of the received dose of 35 Gy) for esophagus were analyzed. During treatment, daily MVCT (Mega Voltage Cone Beam CT) images were taken as image guided radiotherapy.

VMAT with Elekta Versa HD: The RT plans of 5 patients were designed with partial arcs in Eclipse v13.1, the treatment planning system of Elekta Versa HD device. Optimization was performed by selecting appropriate treatment angles for the target volumes with five partial arcs in a single isocenter. The 7 Chest walls + regional lymph nodes and 3 whole breast ± regional lymph nodes irradiation were performed with Elekta Versa HD. As at the Tomotherapy plan, similar DVH parameters were analyzed in the VMAT plan and the same RT doses were prescribed. During treatment, daily electronic portal imaging and weekly cone-beam computed tomography (CBCT) images were taken as image guided radiotherapy.

Statistical Analysis

The SPSS version 24 (IBM SPSS Corp.; Armonk, NY, USA) statistical package software was used for the analysis. Dmax, Dmin, V95%, V105% values for target organ (PTV); whole lung V20% and V5%; heart Dmean, Dmax and V25%; esophagus V35% values for organ at risk (OAR) were examined. Descriptive statistics for continuous (quantitative) variables are expressed as mean, standard deviation (SD), minimum and maximum values, and categorical variables are expressed as number (n) and ratio (%). The demographic characteristics of the patients were calculated with the Chi-square and Fisher's exact test. Spearman's rank correlation test was used for univariate correlation analysis. Significance was evaluated with the

Mann-Whitney U test for analysis of two independent groups. Statistical significance limit was accepted as less than 0.05.

RESULTS

Treatment Outcomes

The median follow-up period of the patients was 19 months (range, 3-37 months) and the median age was 45 years (range, 29-72 years). Radiotherapy was applied postoperatively to all except one patient who did not accept surgery. Nine (75%) patients had a locally advanced stage. Neoadjuvant chemotherapy was applied to 5 (41.6%) patients. According to the hormone receptor status, 8 (67%) patients had luminal A, 3 (25%) patients had luminal B, and 1 (8%) patient had triple negative diseases. Patients and treatment characteristics are detailed in **Table 1**. During radiotherapy, 2 (16%) patients had metastases, of which patients with liver metastasis died at 37 months of follow-up and the other continued to live with disease at 6 months of follow-up. Local control was achieved in the remaining patients (84%). Radiodermatitis in 7 (58%) patients and dysphagia in 5 (42%) patients were reported as acute adverse effects, but none were ≥grade 3 toxicity.

Dosimetric Comparison

When VMAT and HT plans were compared, there was no statistically significant difference in the mean values of the following dosimetric data between the two plans. These are; PTV Dmax, V95%, V105%, whole lung V20, heart Dmean, Dmax and V25, esophagus V35. Statistically significant difference was found only in PTV Dmin and Lung V5 values. Lung V5 (Mean±SD) was 79.78 ± 8.64% for VMAT and 56.48 ± 7.55% for HT (p0.004). PTV Dmin (Mean±SD) was 33.98 ± 5.36 Gy for VMAT and 24.62 ± 4.76 Gy for HT (p0.007). Lung V5 was found statistically better in favor of HT and PTV Dmin in favor of Elekta Versa-VMAT. All dosimetric data are presented in **Table 2** with the values of mean ± SD of PTV and OARs.

Table 2. Dosimetric parameters for each plan (mean±SD, n=12)

	VMAT (n=5)	HT(n=7)	P value
PTV			
D_{max} (Gy)	56.66 ±1.50	56.31 ±1.53	p0.935
D_{min} (Gy)	33.98 ±5.36	24.62 ±4.76	p0.007
V_{95} (%)	94.98 ±1.08	93.53 ±6.62	p0.464
V_{105} (%)	16.52 ±16.41	15.71 ±19.63	p0.935
Whole Lung			
V_{20} (%)	27.34 ±2.56	24.23 ±3.32	p0.088
V_5 (%)	79.78 ±8.64	56.48 ±7.55	p0.004
Heart			
D_{mean} (Gy)	8.72 ±2.95	10.83 ±4.76	p0.570
D_{max} (Gy)	42.04 ±15.99	46.71±5.53	p0.935
V_{25} (%)	5.13 ±5.39	12.65 ±12.79	p0.122
Esophagus			
V_{35} (%)	9.99±11.37	9.64±9.28	p0.935

Abbreviations: SD: standard deviation, PTV: planning target volume, Dmax: maximum dose, Dmin: minimum dose, Dmean:mean dose, V95%: volume covered by 95% of the prescribed dose, V105%: volume covered by 105% of the prescribed dose, V20:volume of the received dose of 20 Gy, V5: volume of the received dose of 5 Gy, V25:volume of the received dose of 25 Gy, V35:volume of the received dose of 35 Gy

Table 1. Patients and treatment characteristics (12 patients, 24 lesions)

	N =24	%
Age (median 45 and range, 29-72 years)	12	100
Surgery		
Lumpectomy	4	16.7
Mastectomy	18	75
No surgery	2	8.3
Axillary Surgery		
Axillary dissection	19	79
Sentinel ln dissection	3	12.7
No surgery	2	8.3
Histology		
Ductal invasive	17	70.8
Lobuler invasive	4	16.7
Other	2	8.3
DCIS	1	4.2
Clinic T stage		
T0	1	4.2
T1	5	20.8
T2	10	41.5
T3	3	12.7
T4	5	20.8
Clinic N stage		
N0	7	29.2
N1	9	37.5
N2	6	25
N3	2	8.3
Pathological T stage		
T0	5	20.8
T1	8	33
T2	3	12.7
T3	3	12.7
T4	3	12.7
Unknown	2	8.3
Pathological N stage		
N0	6	25
N1	7	29.2
N2	6	25
N3	3	12.7
Unknown	2	8.3
Hormone receptor status		
ER (+)	20/24	83.3
PR (+)	18/24	75
HER 2 (3+)	6/24	25
Systemic chemotherapy		
Neoadjuvant	5 patient	41.6
Adjuvant	4 patient	33.3
Unknown	3 patient	25
Treatment volume		
Chest wall+ lymphnodes	18	75
Breast+ lymphnodes+boost	5	20.8
Breast+boost	1	4.2
Radiotherapy Dose		
50 Gy for Chest wall	18	75
50 Gy+10 Gy (boost) for breast	6	25

Abbreviations: ln: lymph node, ER: estrogen receptor,PR: progesterone receptor,HER 2: Human epidermal growth factor receptor 2

DISCUSSION

It is not simple to implement the optimum RT technique, in order to protect the critical organs such as heart and lung, and to obtain the prescribed dose homogenously without overlapping in RT of rarely seen SBBC. In this study, we aimed to present our clinical experience in SBBC radiotherapy and to compare two separate RT techniques in terms of dosimetric aspects. One of 12 SBBC patients died due to systemic progression. Local control was achieved in 84% of the patients. Acute grade 1-2 dysphagia was observed in 5 (42%) and acute grade 1-2 radiodermatitis in 7 cases (58%). When comparing VMAT and HT plans, statistically significant difference was revealed only in PTV Dmin and Lung V5 values. Lung V5 was found statistically better in favor of HT and PTV Dmin in favor of Elekta Versa-VMAT.

A similar study was conducted with 10 SBBC patients and they compared 4 different RT techniques (HT-VMAT- IMRT- Tangential field in field technique (FIF)) dosimetrically (13). They found the mean lung dose statistically lower in HT plan ($p < 0.01$). FIF plans showed a worse conformity (CI) and homogeneity index (HI) than the other plans, while shorter beam on time (BOT) was reported in VMAT plans. They concluded that the HT plan is uncomfortable for the patient in terms of being longer BOT, while VMAT is acceptable as an optimal technique because of better OAR doses, CI and HI and shorter BOT (13). In their dosimetric studies with SBBC, Dağ et al. (14) compared four different RT planning techniques (HT-VMAT-FIF-inverse IMRT) in 2 early breast cancer patients. In the HT plans, PTV dose coverage and dose homogeneity were found better than the other plans, but had the highest total monitor unit (MU). Mean whole lung dose was similar and better in HT and FIF plans, but worse in VMAT and IMRT plans. Heart volume at high dose (V25 and V35) was lower in HT and VMAT plans than FIF. As the other aforementioned study, the authors reported that HT was a favorable RT technique because it improved lung and heart doses and provided better dose coverage and homogeneity (14). We believe that our study is a valuable in terms of studying with the actual plan data that we applied as a treatment, not with dosimetric data. We found that the values of lung V20, V5 were better in HT plan than VMAT. While PTV Dmax and the volume covered by 95% of the prescribed dose (V95) values were not significantly different in both RT techniques, PTV Dmin was significantly worse in HT plans.

In an another similar dosimetric study with 11 SBBC patients, IMRT, VMAT, HT and intensity-modulated proton therapy (IMPT) techniques were compared with respect to heart protection (15). IMPT plan was also found to be significantly better in terms of dose coverage of PTV. Significantly higher dose homogeneity was achieved in the IMPT and HT plans. The IMPT plan reduced the mean and low doses of the heart (such as V5-V10). The IMPT plan afford maximal protection in lung and normal tissue, other than it led to a higher skin dose than IMRT and VMAT plans. Researchers have stated the IMPT plans as the optimal technique for SBBC radiotherapy, both in respect of target coverage and OARs protection, especially the heart (15).

Valli et al. (16) investigated acute and late skin toxicity in 25 patients with SBBC who underwent RT with VMAT technique. In most of the patients (96%), acute grade 1-2 skin toxicity was observed and in the late period (6 months after RT) grade 1 and 2 skin toxicity was recorded in 4 and 1 patient, respectively (16). The most common acute adverse effect in our patients was grade 1-2 radiodermatitis.

The fact that SBBC is rare, technically the probability of RT field overlapping, the risk of both lungs being organ-at-risk pushes radiation oncologists to try different RT variations. As mentioned above, there is an uncertainty for the best and suitable RT technique in the literature. The optimal RT technique may not be clear due to patient-specific anatomic structure differences.

A limitation of our study is the retrospective design. Due to the rarity of patients with SBBC, the number of patients is low. Moreover, the follow-up is short.

CONCLUSION

Various RT techniques as VMAT and HT can be approached in the management of rare cancers such as SBBC, and the patient-specific optimal plan should be selected..

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of Ankara City Hospital (Decision no: E1-20-1434).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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