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ORIGINAL ARTICLE

Investigation of the Effect of Hybrid Techniques Created with Intensity Modulated Radiotherapy on the Plan Quality in Breast Cancer Radiotherapy

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OBJECTIVE

The aim of the study is to investigate the best radiotherapy modality in breast cancer patients regarding obtaining more conformal dose distribution while sparing the surrounding healthy tissues around the tumor using hybrid planning techniques.

METHODS

The study was conducted retrospectively using computed tomography images of 20 breast cancer patients, 10 right and 10 left received radiotherapy. After preparing three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT) plans, IMRT based hybrid plans, named as 3DCRT+IMRT, IMRT+VMAT, and created with 50–50% dose weighted combinations for each patient using 3DCRT and VMAT. Dose volume histogram data were used to evaluate the plan quality. The comparison parameters are critical organ (OAR) doses, homogeneity index (HI), conformity index (CI), and monitor unit (MU) number.

RESULTS

Among the hybrid plans created with IMRT, the CI and HI values for the right and left breast irradiation were found to be the best in IMRT+VMAT hybrid plans and the doses to critical organs could be reduced using the 3DCRT+IMRT hybrid plans. At the same time, the quality of the plan increased by reducing the contralateral breast dose, irradiated breast volume, and heart dose. IMRT+3DCRT hybrid application should be considered as an option to reduce critical organ doses.

CONCLUSION

In cases that critical organ doses need to be reduced, IMRT+3DCRT hybrid technique should be considered as an alternative option.

Keywords: Breast cancer; hybrid plan; radiotherapy; treatment plan comparison.

INTRODUCTION

Cancer is a group of diseases that consists of uncontrolled proliferation of cells and differs in cell behavior, clinical appearance, and treatment approach. It is important to determine the appropriate treatment to control the disease locally. When the cancer map of Turkey is examined, approximately 150,000 new

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cancer cases are diagnosed every year. Breast cancer is most common in women.[1] Breast cancer, which is the most common type of cancer in women in the United States (USA) and England, also has the highest mortality rate among cancer types in women.[2] Breast cancer is a hormone dependent disease. The proliferative effect of estrogens in the mammary epithelium may lead to mutations by increasing the possibility of DNA misreplication. Many known risk factors are associated with the duration and level of endogenous or estrogen stimulation. Early menarche, regular ovulation, and late menopause in premenopausal women, obesity, and hormone treatments in postmenopausal women are factors that increase estrogen exposure.[3] In addition, the incidence of breast cancer increases with age, especially after the age of 45–50.[4] Surgery, radiotherapy, chemotherapy, and hormone therapy are used in the treatment of breast cancer. Among these treatment modalities, radiotherapy has an important role as primary and adjuvant treatment.[5] Studies on breast cancer treatment have shown that radiotherapy reduces the 10-year risk of any local or distant recurrence from 35% to 19%, and the 15-year risk of breast cancer death from 25% to 21%.[6]

The aim of radiotherapy is to accurately deliver high radiation dose to the target volume without exceeding the tolerance doses of critical organs.[7] Different radiotherapy techniques are needed because of the anatomical structure of the breast and heart, the contralateral breast received radiotherapy before, the cardiac diseases, the anatomical structure of the heart, the proximity of the heart to the chest wall, and the previous pulmonary disorders.[8] It is difficult to give the desired dose to the tumor without exceeding the reference doses of the critical organs around the target volume with the three dimensional conformal radiotherapy (3DCRT) technique.

In recent years, techniques such as IMRT and VMAT have been widely used, and there has been a perception that conformal techniques are no longer needed. This study shows that critical organ doses can be reduced by using advanced techniques such as IMRT and conformal techniques together.

The dose applied to the tumor can be increased while the doses received by the surrounding tissues can be minimized with innovative planning techniques such as volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT).[9] Thus, a good local control ratio can be achieved.

Each radiotherapy technique has both advantages and disadvantages. With 3DCRT, some of the volume of critical organs adjacent to the tumor is exposed to high doses. In other treatments with IMRT and VMAT, healthy tissues are exposed to a low dose bath. In order to eliminate the disadvantages of the techniques, hybrid treatment methods have been developed by using a combination of different techniques. The hybrid technique created by the combination of 3DCRT and IMRT techniques was first used in the treatment of breast cancer.

The purpose of current study is to investigate the plan quality of IMRT, and hybrid techniques based on IMRT in breast cancer patients by comparing the doses to critical organs and the conformity and homogeneity indexes.

MATERIALS AND METHODS

Twenty women breast cancer patients, ten of whom were left-sided and ten of whom were right-sided, received radiotherapy the Istanbul University Oncology Institute, were randomly selected for this study. The breast volumes were ranging between 500 and 1500 cm^3 for left-sided and 600–1700 cm^3 for right-sided patients.

Image Data Acquisition

The computed tomography (CT) images of the patients were obtained using Philips Brillance Big Bore computed tomography device. While obtaining CT images, immobilization tools were used to accurately repeat the treatment position and to ensure the stability of the patient. The patients were placed on an inclined plane with the head gantry and supine, and the arm was fixed on the head on the side of the breast to be irradiated with the vacuum bed. CT images were acquired using the varian real-time position management system (RPM). While acquiring the breath-controlled CT of the patient, the amplitude (amplitude) and breath hold (breath holding) options of the RPM system were selected. With this technique, it is aimed to reduce the doses received by the ipsilateral lung and heart. The CT dataset were transferred to the Eclipse (Varian Medical Systems) 15.6 treatment planning system (TPS).

Delineation of Target Volume and OARs

The clinical target volume (CTV), ipsilateral lung, contralateral lung, heart, and contralateral breast tissues were contoured by the radiation oncologist in accordance with the recommendations of the ICRU protocols 50, 62, 83. No margin was given to the contoured CTV, and treatment plans were prepared directly to the breast tissue.

Treatment Planning and Dose Prescription

Five different treatment plans were prepared on CT data of patients by same medical physicist in Eclipse 15.6 TPS. First, the plans were created using 3DCRT, IMRT, and VMAT planning techniques for each patient. Then, IMRT+3DCRT and IMRT+VMAT hybrid plans were generated for each patient by combining the 3DCRT, IMRT, and VMAT plans. Thus, each hybrid plan was consisting of two components. The dose prescription of each component of hybrid plan was made to be 50% of the fraction dose. The isocenters of CTVs in all plans were the same point. In the prepared treatment plans, HD-MLC was used and calculations were performed using the Analytical Anisotropic Algorithm with a dose grid of 0.25 cm. The prescription dose to CTV was 5000 cGy in 25 fractions for all plans. All plans were created with 6 MV photon beams from a Varian Trilogy linac equipped. The dose rate was selected as 600 MU/min. The dose normalization was made so that 95% of the CTV receiving 4500 cGy.

- **Three-dimensional conformal radiotherapy (3DCRT) plan**

3DCRT plans were prepared using the two tangential fields with beam angles ranging from 300°–100° for the left breast and 50°–200° for the right breast. The table angle was 0° and collimator angles were adjusted to be 15°–345° or 30°–330° according to the patient anatomy.

- **Intensity modulated radiotherapy (IMRT) plan**

IMRT plans were created with a total of seven angles obtaining by choosing 2 non-reciprocal tangential angles for all patients and adding 15 degrees to these angles. The defined beam angles for the left-sided and right-sided breast cancer patients were 300°, 315°, 330° –100°, 85°, 70°, 55°, and 50°, 35°, 20°–200°, 215°, 230°, 245°, respectively. The selection of the beam angles may vary depending on the patient anatomy.

Table angle is 0° and collimator angles are adjusted to be 15°–345° or 30°–330° according to the patient anatomy.

- **Volumetric modulated arc therapy (VMAT) plan**

Two partial arc was used in VMAT plans for all patients. In the left-sided breast cancer treatment plans,, the two arcs were set from 300° to 160° (clockwise) and 160° to 300° (counterclockwise), respectively. In right-sided breast cancer treatment plans, the two arcs was set from 200° to 50° (clockwise) and 50°–200° (counterclockwise), respectively. Table angle is 0° and collimator angles are adjusted to be 15°–345° or 30°–330° according to patient anatomy.

Table 1 Critical organ dose limits for OARs

Lung	V20 <20%
	V10 <45%
	V5 <65%
Contralateral Breast	Maximum <20 Gy
	Mean <3 Gy
Heart	Mean <5 Gy
	V30 <10%

- **Hybrid plan**

IMRT+3DCRT and IMRT+VMAT hybrid plans, which are separate combinations of IMRT and VMAT plans, were prepared with equal dose weights (50%–50%). The prepared IMRT and their hybrids, 3DCRT+IMRT, were normalized so that 95% of the target volume received 4500 cGy in the IMRT+VMAT plans.

The critical organ dose limits are given in Table 1.[10,11]

The 4500 cGy dose distributions and beam angles for IMRT, IMRT+3DCRT, and IMRT+VMAT are shown in Figures 1-3, respectively.

Figure 1 shows IMRT, Figure 2 shows 3 DCRT+IMRT hybrid plans, and Figure 3 shows IMRT+VMAT hybrid plans.

Comparison of Treatment Plans

The comparisons of treatment plans were performed based on dose volume histogram (DVH) data. The comparisons were made considering the PTV, OAR doses of each patient, and CI, HI, MU data. The statistical analyses were conducted using the IBM SPSS (version 26.0) software package homogeneity index (HI) and conformity index (CI) values were calculated in five plans for comparisons to be made in terms of plan quality. The HI values were calculated by considering the equation recommended in the ICRU 83 report.

$$HI=\frac{D2\%-D98\%}{D50\%}$$

In the equation [12] the doses represent the following explanation;

D2%=Dose received by 2% of target volume (minimum dose received by target)

D98%=Dose received by 98% of target volume (maximum dose received by target)

D50%=Defined as the dose received by 50% of the target volume.

The HI value approaching “0” indicates that a more homogeneous treatment plan is obtained.

In this study, the formulation defined by RTOG was used for the CI value. CI formula;[13]

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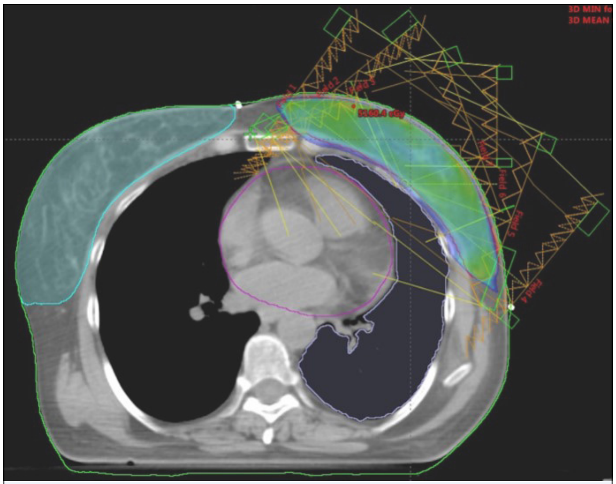

Fig. 1. The dose distributions of intensity modulated radiotherapy plan.

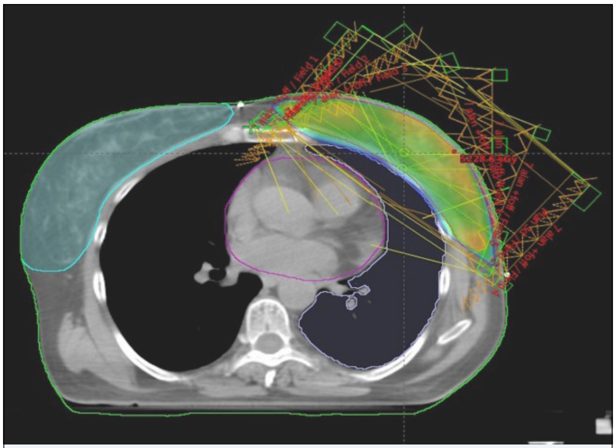

Fig. 2. The dose distributions of intensity modulated radiotherapy+three dimensional conformal radiotherapy, plan.

$$Conformity\ index_{RTOG} = \frac{V_{RI}}{TV}$$

VRI=Reference isodose volume

TV=Defined as the target volume.

According to this formulation, the ideal value for a conformal plan is “1”. A CI value between “1” and “2” indicates that the treatment is suitable for RT. As the conformity index value gets to “1” closer, the quality of the plan increases, and as it gets farther away, it decreases.

The comparison of the data obtained in the prepared treatment plans was made with the Wilcoxon Signed Ranks test belonging to the SPSS statistical program. As a result of the comparisons, the statistical $p<0.05$ condition obtained from the SPSS program was accepted as a significant difference. The obtained mean, standard deviation, and p values were used in the plan quality assessment.

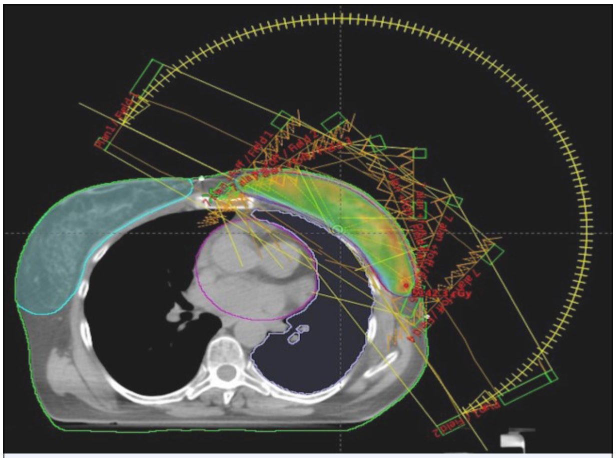

Fig. 3. The dose distributions of intensity modulated radiotherapy+volumetric modulated arc therapy plan.

RESULTS

The calculated CI and HI values for IMRT, IMRT+3DCRT, and IMRT+VMAT plans are shown in Tables 2 and 3, respectively.

The ipsilateral lung V20, V10, V5, mean dose, contralateral lung V10, V5, mean dose, heart V30, V5, mean dose, contralateral breast V5, mean dose, max dose, and 5 Gy dose volume values are shown in Table 4 for the right breast irradiations and in Table 5 for the left breast irradiations.

The MU values of IMRT, IMRT+3D, and IMRT+VMAT hybrid plans for the right and left breast irradiations are shown in Table 6.

DISCUSSION

The present study was prepared using computed tomography images of 20 breast cancer patients (10 left-sided and 10 right-sided). First, IMRT, 3DCRT, and VMAT plans were generated for all patients. Then, IMRT based hybrid plans, as named 3DCRT+IMRT and IMRT+VMAT were composed. The comparisons of treatment plans in terms of target coverage and homogeneity and normal tissues doses were performed using DVH data.

There were no statistically significant differences among IMRT, IMRT+3DCRT, and IMRT+VMAT

Table 2 CI values for IMRT and IMRT based hybrid plans in the right and the left breast patients

Planning technique	Right breast CI (p)	Left breast CI (p)
IMRT/3D+IMRT	0.85±0.033/0.79±0.037 (0.008)	0.83±0.039/0.77±0.036 (0.005)
IMRT/IMRT+VMAT	0.85±0.033/0.89±0.019 (0.008)	0.83±0.039/0.88±0.025 (0.005)
IMRT+VMAT/3D+IMRT	0.89±0.019/0.79±0.037 (0.008)	0.88±0.025/0.77±0.036 (0.005)

CI: Conformity index; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy

Table 3 HI values for IMRT and IMRT based hybrid plans in the right and the left breast patients

Planning technique	Right breast HI (p)	Left breast HI (p)
IMRT/3D+IMRT	0.13±0.042/0.13±0.014 (0.441)	0.10±0.020/0.13±0.021 (0.007)
IMRT/IMRT+VMAT	0.13±0.042/0.11±0.021 (0.110)	0.10±0.020/0.10±0.022 (0.386)
IMRT+VMAT/3D+IMRT	0.11±0.021/0.13±0.013 (0.011)	0.10±0.022/0.13±0.022 (0.005)

HI: Homogeneity index; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy

Table 4 Critical organ doses in the right breast patients

Right breast OAR	IMRT	IMRT+3D (p=IMRT and IMRT+3D)	IMRT+VMAT (p=IMRT and IMRT+VMAT)
Ipsilateral lung V20 (%)	11.6±2.7	14.3±2.4 (0.011)	11.9±1.9 (0.139)
Ipsilateral lung V10 (%)	23.7±2.9	21.9±2.8 (0.008)	29.7±3.8 (0.008)
Ipsilateral lung V5 (%)	51.6±7.3	38.9±4.0 (0.008)	64.9±5.5 (0.008)
Ipsilateral lung mean dose (cGy)	883±99.8	868.3±106 (0.374)	952±86.8 (0.008)
Contralateral lung V10 (%)	<1	<1	<1
Contralateral lung V5 (%)	0.53±1.59	0 (0.18)	6.24±3.56 (0.008)
Contralateral lung mean dose (cGy)	102.8±51.9	56.5±25.4 (0.008)	215±37.6 (0.008)
Heart V30 (%)	0	0	0
Heart V5 (%)	4.8±4.34	1.80±2.70 (0.008)	7.86±4.27 (0.008)
Heart mean dose (cGy)	204.9±47.8	131±28.37 (0.008)	261.7±49.6 (0.008)
Contralateral breast V5 (%)	0.34±0.74	0.74±1.14 (0.008)	7.5±2.9 (0.008)
Contralateral breast mean dose (cGy)	172.8±44.2	98.1±25.4 (0.008)	230.3±44.7 (0.008)
Contralateral breast max dose (cGy	1282±268.6	1101±466.4 (0.139)	1354±180.1 (0.139)
5Gy volume (cc)	4802±1218	4076±1025 (0.008)	5823±1257 (0.008)

OAR: Critical organ; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy

plans in CI and HI for all patients. The CI values calculated for the IMRT+VMAT hybrid plans created with the VMAT plan contribution were closer to the ideal value than that of the 3DCRT+IMRT hybrid plans created with the 3DCRT contribution.

The 3DCRT+IMRT and IMRT+VMAT hybrid plans did not contribute to the improvement of the HI value. The ipsilateral lung V10, V5, mean dose, contralateral lung V10, V5, mean dose, heart mean dose, contralateral breast V5, mean and max dose, and the body volume receiving a dose of 5 Gy were lowest in 3DCRT+IMRT hybrid plans for the right and left breast irradiations.

When similar studies in the literature are evaluated; In the study conducted by Mayo et al.[14] with 5 patients from each right breast and left breast, the convergence prepared tangent plan (3DCRT), IMRT plan, hybrid plans of these plans were compared. Compared to the IMRT plan alone, they reported lower doses given to healthy tissues such as lungs and heart in hybrid plans. Ramasubramanian et al.[15] conducted a study with 26 left breast patients and evaluated hybrid VMAT (H-VMAT) plans, which are a combination of 3DCRT and VMAT plans. They stressed the importance of hybrid plans for PTV coverage, CI, HI improvement, and reduction of critical organ doses.

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Table 5 Critical organ doses in the left breast patients

Left breast OAR	IMRT	IMRT+3D (p=IMRT and IMRT+3DCRT)	IMRT+VMAT (p=IMRT and IMRT+VMAT)
Ipsilateral lung V20 (%)	12.6±1.7	15.4±2.5 (0.009)	11.9±1.7 (0.047)
Ipsilateral lung V10 (%)	24.5±4.3	22.4±3.0 (0.037)	24.1±4.2 (0.959)
Ipsilateral lung V5 (%)	50.5±4.3	39.5±5.9 (0.003)	50.7±7.9 (0.646)
Ipsilateral lung mean D (cGy)	884±119	901.5±103 (0.241)	853±95.6 (0.093)
Contralateral lung V10 (%)	<1	<1	<1
Contralateral lung V5 (%)	2.72±4.32	0.43±0.88 (0.008)	6.7±3.99 (0.005)
Contralateral lung mean dose (cGy)	105±56.1	83±29 (0.005)	226.2±44 (0.005)
Heart V30 (%)	0.74±1.16	1.18±1.52 (0.012)	0.41±0.67 (0.018)
Heart V5 (%)	13.6±4.7	8.4±3.6 (0.005)	13.8±5.16 (0.878)
Heart mean Dose (cGy)	332.4±86.4	281.9±96.6 (0.005)	349.6±83.9 (0.022)
Contralateral breast V5 (%)	4.27±2.33	0.56±0.92 (0.005)	5.24±1.62 (0.059)
Contralateral breast mean dose (cGy)	193.7±50.8	108.5±26.09 (0.005)	219.6±33.3 (0.013)
Contralateral breast max dose (cGy)	1424.1±421.3	1424.1±421.3 (0.005)	1348.8±339.1 (0.386)
5Gy volum (cc)	4057.7±929.7	3569.5±877.8 (0.007)	4554.1±1187.6 (0.007)

OAR: Critical organ; IMRT: Intensity modulated radiotherapy; 3DCRT: Three-dimensional conformal radiotherapy; VMAT: Volumetric modulated arc therapy

Table 6 MU values in the right and left breast irradiation

Planning tecnique	MU (right breast irradiation)	MU (left breast irradiation)
IMRT/IMRT+3D	1272±118/739±67 (0.008)	1193±148/705±76 (0.005)
IMRT/IMRT+VMAT	1272±118/855±55 (0.008)	1193±148/821±69 (0.005)
IMRT+VMAT/3D+IMRT	855±55/739±67 (0.008)	821±69/705±76 (0.005)

MU: Monitor unit; IMRT: Intensity modulated radiotherapy; VMAT: Volumetric modulated arc therapy

Doi et al.[16] reported that the HI and CI values of H/VMAT plans, which are hybrids of 3DCRT and VMAT plans, were better than 3DCRT for 35 left breast and 35 right breast patients. They also stated that ipsilateral lung, contralateral lung mean and V5 (%) and mean heart dose values were lower in H-VMAT technique than VMAT. The studies have been emphasized that the hybrid technique reduces the doses of critical organs compared to VMAT plans.

Farace et al.[17] prepared 3DCRT and IMRT plans for a total of 78 breast cancer patients, 36 right and 42 left. They observed that the mean dose values of the H/3D-IMRT plans, lung V5 (%), contralateral breast V5 (%), heart V5 (%), heart V2.5 (%), and especially the heart were lower than the IMRT plan alone. They also stressed that the HI and CI values of the H-IMRT plans were better.

In our study, it has seen that the best CI and HI value were obtained in the plans created using IMRT+VMAT hybrid plans for the right and left breast irradiations.

While, the ipsilateral lung volume receiving 20 Gy (V20) were found lowest in IMRT plans for the right breast and in IMRT+VMAT hybrid plans for the left breast. The contralateral and ipsilateral lung volume receiving 10 Gy and 5 Gy were lowest in IMRT+3DCRT for both left-sided and right-sided breast.

The contralateral breast doses had the in the IMRT+3DCRT for all patients. The lowest heart volume receiving 30 Gy was obtained with IMRT+VMAT technique in left breast irradiations. In right and left breast irradiations, the lowest heart Dmean doses and V5 (%) were acquired with IMRT+3DCRT hybrid plans. The lowest values of MU values were obtained in IMRT+3DCRT plans, while the highest values were obtained in IMRT plans. When our study is evaluated together with similar studies in the literature, it shows parallelism.

According to the findings of this study, the IMRT and 3DCRT hybrid plans in left and right breast irradiations were calculated as heart V5 (%), heart Dmean, contralateral breast V5 (%), contralateral breast Dmean, contralateral breast Dmax, ipsilateral and contralateral lung V5 (%), and V10 (%) appears to decrease lung Dmean doses. Hybrid techniques should be considered as an important option in reducing critical organ doses without deteriorating the plan quality in the right and left breast irradiation.

The our study had been concluded that the CI and HI values for right and left breast irradiation were found to be the best in IMRT+VMAT hybrid plans and the doses to critical organs could be reduced with the 3DCRT+IMRT hybrid plans.

IMRT+3DCRT hybrid application should be considered as an option in reducing radiation doses to critical organ for both left- and right-sided breast cancer patients.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the İstanbul University Institute of Health Sciences Ethics Committee (no: 141353, date: 19/03/2021).

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