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Effect of Different Radiotherapy Techniques on the Left Anterior Descending Coronary Artery Dose in Left-Sided Lung Cancer

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ABSTRACT

Background: This study aims to compare the radiation doses delivered to the heart and left anterior descending artery (LAD) when using Volumetric Modulated Arc Therapy (VMAT) and Intensity Modulated Radiotherapy (IMRT) for the treatment of left-sided lung cancer. ***Materials and Methods:*** We selected 29 stage III lung cancer patients for replanning. Step and shoot IMRT(S&S-IMRT), dynamic IMRT(D-IMRT), full arc VMAT (FA-VMAT) and two partial arc VMAT (2PA-VMAT) techniques were used in plan recreation for each patient. Difference between heart and LAD doses were investigated using dose volume histogram. ***Results:*** FA-VMAT technique resulted in lower LAD mean (Dmean) (1712.43 cGy, $p < 0.001$), LAD maximum (Dmax), LAD 2% (D2%) (3527.33 cGy, $p = 0.003$), LAD 0.1cc (D0.1cc) (3473.12 cGy, $p=0.006$) doses and percentage of LAD that received 15Gy (V15) (43.69%, $p < 0.001$). No statistical difference was observed between the two partial arc VMAT and full arc VMAT techniques in LAD doses. Comparing cardiac V10, V15, and heart mean doses (MHD), the 2PA-VMAT technique showed better organ protection than FA-VMAT, S&S IMRT, and D-IMRT.2PA-VMAT and FA-VMAT showed similar results in cardiac V5, V20, V25, V30, V40 and V45 values. When the median heart volume (567 cc) was used as a threshold, those with heart volume smaller than 567cc had statistically significant differences in LAD and heart doses in favor of 2PA-VMAT ($p < 0.005$). ***Conclusion:*** VMAT technique protects LAD and heart better than IMRT technique in left-sided lung cancer patients.

INTRODUCTION

Thoracic radiotherapy, as the mainstay treatment for locally advanced stage III lung cancer, is also associated with significant side effects, most commonly esophagitis and pneumonitis. However, little is known about the cardiotoxicity of thoracic radiotherapy because of its short overall survival. Long-term cardiotoxicity as a radiation therapy-associated cardiovascular heart disease is well established, primarily based on findings in patients with breast cancer and lymphoma [1,2]. Radiotherapy-induced chronic inflammation in the coronary arteries of these patients is thought to cause accelerated atherosclerosis and the development of cardiac events many years later [3]. The clinical relevance of acute and subacute cardiac disease in stage III non-small cell lung cancer (NSCLC) patients following radiotherapy is unclearbecause lung cancer patients generally already have cardiac comorbidities or predisposing factors, and their overall survival is short. Therefore, during radiotherapy planning optimization, we usually ignore the heart and prioritize the spinal cord, lungs, and esophagus due to acute toxicity. Until the publication of the pivotal RTOG-0617 trial, the relationship between heart dose and mortality had not been adequately studied [4]. Surprisingly, secondary analyses of this study suggested that higher cardiac doses (V5 and V30 values) were associated with inferior survival [5].

Minimizing damage to vital organs while treating intrathoracic tumors is challenging. Advances in radiation treatment technology have helped deliver curative doses to patients with locally advanced disease while keeping critical organ doses within tolerance which has been associated with better quality of life and longer overall survival (OS) [6-8] Today, VMAT and IMRT techniques are more commonly used in lung cancer [9]. The advantage of IMRT over 3-D conformal planning is the reduction in critical organ doses while improving target doses [10]. It was also shown that VMAT had better target volume coverage and shorter treatment durations than IMRT [11,12]. Tumor location, left versus right, is also an important consideration for decreasing heart and LAD doses and toxicity [13,14]. According to our knowledge, there is no literature comparing LAD doses between different IMRT and VMAT techniques

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for locally advanced left-sided lung cancer. So, this study aimed to compare different radiotherapy techniques in locally advanced left-sided lung cancer, where cardiac dose is a much bigger concern, to assess the impact of cardiac dose, LAD dose, and cardiac volume on the planning process.

MATERIALS AND METHODS

The study was approved by the Kocaeli University Non-Interventional Clinical Research Ethics Committee (Approval No: GOKAEK-2022/03.01).

Patient Selection and Contouring

This retrospective study was conducted on 29 patients treated for left lung cancer who were treated with the Varian Trilogy linear accelerator device at Kocaeli University Hospital Radiation Oncology Clinic between 2017 and 2022. Patient characteristics are listed in table 1.

Table 1. Demographic and clinical characteristics of patients.

Characteristics	N=29	%
GENDER		
Male	26	89,65
Female	3	10,35
AGE (MEDIAN) (Range)	63 (44-84)	
TNM		
T3N1	9	31,1
T3N2	8	27,6
T4N0	3	10,3
T4N1	3	10,3
T4N2	6	20,7
STAGE		
3A	15	51,7
3B	14	48,3
LOBE		
Left Lower	16	55,1
Left Upper	13	44,9
PTV VOLUME MEAN (cc) (Range)	472 (87-1558)	
TOTAL LUNG VOLUME MEAN (cc) (Range)	3445 (1426-6646)	
LAD VOLUME MEAN (cc) (Range)	1,575 (0,9-3,15)	
HEART VOLUME MEAN (cc) (Range)	563 (374-934)	

Patients were stabilized with lung boards and computerized tomography (CT) images were obtained with a 3 mm slice thickness and fused with positron emission tomography (PET) images. Gross tumor volume (GTV) was defined as the macroscopic tumor, including lymph nodes, as detected on PET/CT and simulation CT. The CTV encompassed the GTV with an 8mm margin and the affected lymph nodes with a 5 mm margin. For the planning target volume (PTV), a 10 or 15-mm margin was isotropically added to the CTV. The spinal cord, heart, LAD, aorta, lungs, and esophagus were contoured as organs at risk (OAR). Planned risk volume (PRV) for the spinal cord was calculated with a 3 mm safety margin. LAD and Heart volumes were recontoured by a physician using non-contrast-enhanced CT imaging according to the contouring atlas designed by Feng *et al.* [15].

Treatment Planning

Four different plans (D-IMRT, S-IMRT, FA-VMAT, and 2PA-VMAT) were generated for each patient. The prescribed dose was 60 Gy in 30 fractions. Treatment plans with IMRT and VMAT were optimized to achieve 95% coverage of the PTV. All plans were calculated with the Varian (Palo Alto, CA) Eclipse V13.9 treatment planning system using the anisotropic analytical algorithm (AAA). 6MV FF photon energy was used in all plans. Intensity-modulated radiation therapy (IMRT) plans were created using two techniques - Dynamic-IMRT (D-IMRT) and Step-and-Shoot IMRT (S&S-IMRT). Depending on the tumor location, seven gantry angles (0°-40°-80°-120°-160°-200°-320°) were used. All plans were first made using the dynamic IMRT technique, and MLC movement was recalculated for the step-and-shoot technique without changing the dynamic IMRT optimization.

The FA-VMAT and 2PA-VMAT techniques were used for VMAT planning. 2PA-VMAT plan was generated using 2 partial arcs. The first arc began at 330° with a 30° collimator angle and a 210° clockwise rotation. The second arc began at 179° with a 330° collimator angle and a 210° counterclockwise arc. Two full arcs were used for the FA-VMAT planning. The first arc started at 181° with a 30° collimator angle and 360° clockwise arc. The second arc started at 179° with a 330°collimator angle and 360° counterclockwise arc. An example of a patient treatment plan showing the dose distribution and field arrangements of four different treatment techniques is shown in figure 1.

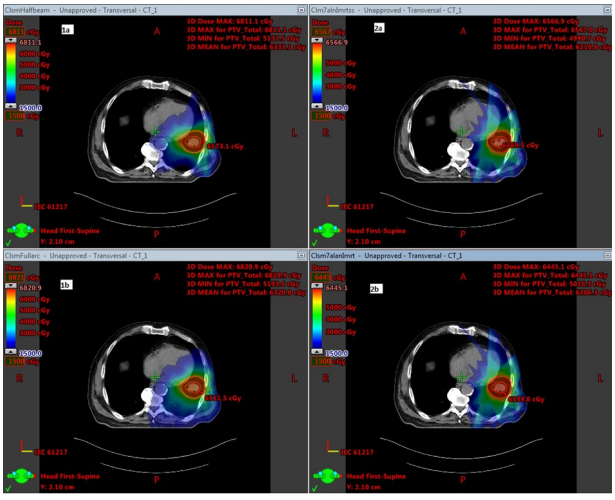

Figure 1. A patient treatment plan showing the dose distribution of four different treatment techniques;1a- two partial arc VMAT (2PA-VMAT), 1b- full arc VMAT (FA-VMAT), 2a- Step and shoot IMRT (S&S-IMRT) techniques, 2b- dynamic IMRT (D-IMRT).

The dose-volume constraints for OAR were set as follows: For the lung; V5 ≤ 65%, V10 ≤ 50%, V20 ≤ 30%, V30 ≤20%, and mean lung dose ≤ 18 Gy. For the heart, V50≤ 25% and mean heart dose ≤ 20 Gy. Esophageal mean dose ≤34 Gy. In this study, the LAD

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and heart doses were kept as low as possible.

Evaluation of Dose Volume Histogram

A dose-volume histogram (DVH) was used for PTV and OAR dose comparisons. The PTV D98%, PTV D2%, PTV D50%, HI {(PTV D2% - PTV D98%) /PTV D50%}, and CI (PTVvol/IRvol 95%) were evaluated for target coverage. For organs at risk, whole lung V5, V10, V20 (the percentages of volumes receiving 5,10,20 Gy respectively) and Dmean, contralateral lung V5 and Dmean, for spinal cord Dmax, for esophagus Dmean and V35 values, for heart V5, V10, V15, V20, V25, V30, V40, V45, V60, Dmax and Dmean values, LAD V15, Dmax, Dmean, D0.1cc and D2% values were obtained.

Dosimetric Evaluation Strafied by Heart Volume

To investigate the effect of heart volume on the selection of the optimal technique, we separated the 29 patients into two groups: Fifteen patients with heart volumes smaller and 14 patients with volumes larger than the median volume of the heart (567 cm3). Heart V5, V10, V15, V20, V25, V30, V40, V45, V50, V60, Dmax, and Dmean values for IMRT (D-IMRT, S&S-IMRT) and VMAT (FA-VMAT and 2PA-VMAT) were compared separately for the four groups.

Statistical analysis

Groups were analyzed for normal distribution using the Shapiro-Wilk test. For parametric data, Repeated Measures ANOVA and the Friedman test for nonparametric data were used for analysis. When the Friedman analysis reported a significant difference, the Wilcoxon test with Bonferroni correction was used to compare each pair. Statistical significance was set at $p < 0.05$. All data were analyzed using SPSS v25.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Target Coverage

The PTV coverage data for the IMRT and VMAT plans are summarized in table 2. Both the D-IMRT and FA-VMAT techniques had better HI than S&S-IMRT and 2PA-VMAT. The VMAT techniques (FA -VMAT and 2PA-VMAT) had better CI than IMRT (S&S -IMRT and D-IMRT). Statistical data are presented in table 2.

Table 2. Evaluation of non-cardiac critical organ doses in IMRT and VMAT plans by DVH.

	S&S-IMRT (mean±SD)	D-IMRT (mean±SD)	2PA-VMAT (mean±SD)	FA-VMAT (mean±SD)	S&S-IMRT versus D-IMRT(p)	S&S-IMRT versus 2PA-VMAT (p)	S&S-IMRT versus FA-VMAT (p)	D-IMRT versus 2PA -VMAT(p)	D-IMRT versus FA-VMAT(p)	2PA-VMAT versus FA-VMAT(p)	P
WHOLE LUNG											
V5 (%)	51.94 ± 3.15	52.49 ± 3.20	56.55 ± 3.56	58.43 ± 3.19	0.000	0.000	0.000	0.000	0.000	0.006	<0.001*
V10 (%)	32.46 ±2.11	32.86 ±2.15	34.52 ± 2.49	39.95 ±2.71	0.000	0.007	0.000	0.023	0.000	0.000	<0.001*
V20 (%)	21.61 ±1.39	21.79 ±1.40	20.88 ± 1.33	21.73 ± 1.39	0.000	0.007	0.854	0.003	0.754	0.005	<0.004*
MLD (cGY)	1247.42 ± 68.75	1256.59 ± 69.16	1286.51 ± 69.70	1332.76 ± 70.51	0.000	0.002	0.000	0.005	0.000	0.000	<0.001*
CONTRA-LATERAL LUNG											
V5 (%)	43.32 ± 3.77	43.98 ± 3.82	50.23 ± 3.91	52.61 ± 6.64	0.000	0.000	0.000	0.000	0.000	0.045	<0.001*
MLD (cGy)	559.22 ± 45.47	566.09 ± 46.06	614.55 ± 48.55	704.52 ± 52.28	0.000	0.000	0.000	0.000	0.000	0.000	<0.001*
MEDULLA SPINALIS											
D_{MAX}	3329.11 ± 159.62	3340.38 ± 158.38	2878.61 ± 174.05	2920.93 ± 164.79	0.086	0.000	0.000	0.000	0.000	0.265	<0.001*
ESOPHAGUS											
D_{MEAN} (cGy)	1193.90 (907.90-1915.55)	1193.40 (923.30-1935.40)	1403.7 (977.70-1931.2)	1458.70(1005.35-1878.10)	0.000	0.020	0.082	0.056	0.206	0.247	<0.001*
V35 (%)	11.16(0.04-24.88)	11.42(0.02-25.22)	13.96(0.02-20.87)	11.19(0.03-20.83)	0.001	0.77	0.853	0.635	0.727	0.889	0.250**
AORTA											
D_{MAX} (cGy)	6464.86 ± 95.91	6415.69 ± 93.39	6602.76 ± 110.40	6493.23 ± 118.56	0.000	0.001	0.191	0.000	0.028	0.000	<0.001*
D_{MEAN} (cGy)	3473.57 ± 210.66	3486.09 ± 209.42	3449.61 ± 212.53	3478.95 ± 204.34							0.474*
HI(Mean-Range)	0.10(0.09-0.11)	0.09(0.08-0.10)	0.10(0.09-0.11)	0.09(0.08-0.10)	0.000	0.112	0.721	0.008	0.122	0.000	<0.001*
CI(Mean-Range)	0.99(0.98-1.00)	0.99(0.98-1.00)	0.98(0.97-1.00)	0.97(0.97-0.99)	0.102	0.361	0.000	0.655	0.001	0.000	<0.001*
MU(Mean-Range)	678(575-738)	944(782-1046)	520(200-1046)	596(538-634)	0.000	0.000	0.008	0.000	0.000	0.000	<0.001*

* Repeated Measures ANOVA, ** Friedman Test, MHD: Mean Heart Dose, 2PA-VMAT: Two Partial Arc Volumetric Modulated Arc Therapy, FA-VMAT: Full Arc Volumetric Modulated Arc Therapy, S&S-IMRT: Step and Shoot Intensity Modulated Radiotherapy, D-IMRT: Dynamic Intensity Modulated Radiotherapy, MLD: Mean Lung Dose, HI: Homogeneity Index, CI: Conformity Index, MU: Monitor Unit.

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Evaluation of cardiac structures

VMAT techniques resulted in lower LAD Dmean values compared to IMRT. While D-IMRT had the highest LAD Dmax value, FA-VMAT had the lowest. LAD V15 was significantly lower in the VMAT technique compared to IMRT. When comparing the LAD D2% and LAD D0.1cc, VMAT techniques were found to outperform IMRT techniques. Based on the LAD data, the VMAT techniques were found to be superior overall. Comparing cardiac V10, V15, and MHD, the 2PA-VMAT technique showed better organ protection than FA-VMAT, S&S IMRT, or D-IMRT. 2PA -VMAT and FA-VMAT showed similar results for the cardiac V5, V20, V25, V30, V40, and V45 values. The physical parameters and statistical data for the LAD and heart are given in table 3.

Table 3. Evaluation of cardiac doses in IMRT and VMAT plans by DVH.

	S&S-IMRT (mean±SD)	D-IMRT (mean±SD)	2PA-VMAT (mean±SD)	FA-VMAT (mean±SD)	S&S-IMRT versus D-IMRT(p)	S&S-IMRT versus 2PA -VMAT(p)	S&S-IMRT versus FA-VMAT(p)	D-IMRT versus 2PA -VMAT(p)	D-IMRT versus FA-VMAT(p)	2PA-VMAT versus FA-VMAT(p)	P
LAD											
V15 (%)	48.69 ±5.62	49.08 ±5.60	43.69 ± 5.06	43.79 ±5.21	0.001	0.001	0.005	0.001	0.002	0.878	<0.001*
D_{MEAN} (cGy)	1823.48 ±209.70	1840.20 ±211.38	1716.83 ±201.27	1712.43 ±205.38	0.000	0.012	0.021	0.004	0.009	0.381	<0.001*
$D_{2\%}$ (cGy)	3711.01 ±354.29	3726.51 ±354.19	3589.99 ±360.20	3527.33 ±359.96	0.033	0.239	0.030	0.206	0.020	0.127	0.003*
$D_{0.1cc}$ (cGy)	3635.34 ±351.45	3652 ±351.53	3517.14 ±358.51	3473.12 ±358.59	0.024	0.352	0.048	0.184	0.025	0.122	0.006*
HEART											
V5 (%)	43.31 ± 7.00	42.52 ± 7.12	41.99 ±6.74	43.49 ± 6.94	0.467	0.358	0.885	0.618	0.213	0.055	0.477*
V10 (%)	32.58 ± 6.24	33.06 ± 6.42	28.00 ±5.36	31.91 ± 6.21	0.000	0.033	0.879	0.036	0.584	0.033	0.002*
V15 (%)	24.29 ± 5.20	24.74 ± 5.30	17.80 ± 3.70	20.08 ± 4.08	0.000	0.010	0.048	0.009	0.031	0.011	<0.001*
V20 (%)	17.68 ±4.11	17.95 ±4.15	11.39 ± 2.56	12.29 ± 2.63	0.000	0.002	0.002	0.002	0.003	0.127	<0.001*
V25 (%)	11.78 ± 2.96	12.02 ± 2.98	7.52 ± 1.83	7.73 ± 1.79	0.002	0.002	0.001	0.002	0.001	0.794	<0.001*
V30 (%)	7.93 ± 2.14	8.14 ± 2.18	5.15 ± 1.35	5.09 ± 1.30	0.000	0.007	0.003	0.005	0.003	0.695	<0.001*
V40 (%)	3.36 ± 1.06	3.40 ± 1.06	2.66 ±0.85	2.60 ± 0.81	0.011	0.011	0.008	0.008	0.006	0.266	<0.001*
V45 (%)	2.38 ± 0.83	2.40 ±0.83	2.03 ± 0.72	1.97 ± 0.69	0.026	0.157	0.030	0.127	0.021	0.231	<0.001*
V50 (%)	1.74 ± 3.61	1.75 ± 3.6	1.61 ± 3.34	1.53 ± 3.23	0.566	0.185	0.035	0.183	0.036	0.162	0.445*
D_{MAX} (cGy)	4600.56 ±470.01	4580.85 ±465.93	4672.30 ±475.45	4641.35 ±472.40	0.074	0.333	0.536	0.244	0.384	0.278	0.415*
MHD (cGy)	944.93 ± 164.46	956.38 ±166.37	814.19 ±129.20	859.24 ±134.78	0.000	0.071	0.417	0.078	0.198	0.01	<0.001*

* Repeated Measures ANOVA, ** Friedman Test, MHD: Mean Heart Dose, 2PA-VMAT: Two Partial Arc Volumetric Modulated Arc Therapy, FA-VMAT: Full Arc Volumetric Modulated Arc Therapy, S&S-IMRT: Step and Shoot Intensity Modulated Radiotherapy, D-IMRT: Dynamic Intensity Modulated Radiotherapy, MLD: Mean Lung Dose, HI: Homogeneity Index, CI: Conformity Index, MU: Monitor Unit.

Subgroup analysis based on heart volume

The patients were divided into two groups to examine the effect of heart volume on LAD and heart dose. In the subgroup analysis, those with heart volumes smaller than 567cc had statistically significant differences in LAD and heart doses between VMAT and IMRT, except for heart V5. In addition, 2PA-VMAT was better than FA-VMAT for LAD V15, Heart V5, V10, V20 and MHD. The 2PA-VMAT provided better organ protection. The S&S-IMRT technique was better than the D-IMRT technique for all the parameters. In patients with heart volumes bigger than 567cc, VMAT techniques were statistically superior to IMRT only for LADV15, but no other difference was observed for the others between VMAT and IMRT. Statistical data are presented in table 4.

Evaluation of critical organs and physical parameters

S&S IMRT resulted in the lowest values for total lung V5, V10, and MLD, 51.94%, 32.46% and 1247.42 cGy, respectively. In contrast, V20 was the lowest in the 2PA-VMAT plans. When the contralateral lung data were analyzed, S&S-IMRT had the lowest V5 and MLD doses, resulting in 43.32% and 559.22 cGy, respectively. The 2PA-VMAT technique had the lowest Dmax in the medulla spinalis. The lowest mean esophageal dose was observed with S&S-IMRT. The Dmax of the aorta received the lowest dose of 6415.69 cGy with D-IMRT. The 2PA-VMAT technique had the shortest treatment duration. The critical organ doses and physical parameters are summarized in table 2.

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Table 4. Subgroup analysis based on heart volume.

HEART VOLUME <567cc	S&S-IMRT (mean±SD)	D-IMRT (mean±SD)	2PA-VMAT (mean±SD)	FA-VMAT (mean±SD)	S&S-IMRT versus D-IMRT (p)	S&S-IMRT versus 2PA-VMAT (p)	S&S-IMRT versus FA-VMAT (p)	D-IMRT versus 2PA-VMAT (p)	D-IMRT versus FA-VMAT (p)	2PA-VMAT versus FA-VMAT (p)
LADV15	59.28 ± 7.87	59.73 ± 7.81	53.54 ± 6.92	55.24 ± 7.01	0.023	0.041	0.136	0.039	0.101	0.041
LAD D_{MEAN} (Gy)	21.41 ± 3.02	21.63 ± 3.05	20.15 ± 2.96	20.46 ± 3.02	0.011	0.027	0.112	0.015	0.069	0.100
HEART V5	59.28 ± 9.78	59.59 ± 9.78	57.75 ± 9.37	60.77 ± 9.58	0.005	0.861	0.169	0.552	0.262	0.050
HEART V10	46.09 ± 9.10	47.22 ± 9.63	38.22 ± 7.6	46.32 ± 9.10	0.001	0.039	0.507	0.028	0.917	0.003
HEART V20	23.66 ± 5.37	24.13 ± 5.44	14.05 ± 3.31	16.34 ± 3.40	0.002	0.005	0.006	0.005	0.006	0.023
HEART V30	10.08 ± 2.39	10.38 ± 2.48	5.99 ± 1.51	6.13 ± 1.34	0.005	0.008	0.012	0.008	0.012	0.695
HEART V40	3.85 ± 0.93	3.91 ± 0.95	2.86 ± 0.72	2.85 ± 0.66	0.019	0.013	0.016	0.013	0.016	0.878
MHD (Gy)	12.34 ± 2.10	12.55 ± 2.13	10.18 ± 1.64	11.17 ± 1.74	0.001	0.023	0.307	0.02	0.061	0.004
HEART VOLUME >567cc										
LADV15	32.94 ± 7.5	33.32 ± 7.06	28.45 ± 6.24	26.54 ± 6.03	0.024	0.058	0.025	0.044	0.021	0.103
LAD DMEAN (Gy)	13.08 ± 2.70	13.19 ± 2.71	12.33 ± 2.50	11.90 ± 2.50	0.005	0.155	0.055	0.106	0.041	0.262
HEART V5	26.24 ± 8.34	23.90 ± 9.31	24.82 ± 8.42	24.78 ± 8.33	0.382	0.596	0.597	0.364	0.428	0.955
HEART V10	18.17 ± 2.50	17.66 ± 8.00	16.76 ± 7.22	16.17 ± 7.32	0.512	0.229	0.140	0.362	0.222	0.325
HEART V20	11.42 ± 6.59	11.43 ± 6.82	8.13 ± 4.28	7.47 ± 4.35	0.222	0.221	0.154	0.221	0.156	0.313
HEART V30	5.64 ± 3.97	5.71 ± 4.10	4.05 ± 2.54	3.76 ± 2.60	0.148	0.334	0.252	0.156	0.238	0.241
HEART V40	2.82 ± 8.11	2.83 ± 8.08	2.39 ± 6.59	2.23 ± 6.37	0.672	0.365	0.269	0.339	0.257	0.107
MHD(Gy)	6.33 ± 2.57	6.32 ± 2.58	5.83 ± 2.07	5.69 ± 2.02	0.945	0.417	0.316	0.416	0.320	0.449

DISCUSSION

In our study, we compared the cardiovascular doses among S&S-IMRT, D-IMRT, 2PA-VMAT, and FA-VMAT techniques, while ensuring that cardiac doses were kept as low as possible and other critical organ doses were within tolerance limits. IMRT is increasingly used to treat lung cancer, although high-level evidence does not support its routine use. It delivers high doses of radiation therapy to targets while protecting surrounding normal tissues [16]. Therefore, it could improve treatment rates for lung cancer while minimizing toxicity. In a prospective phase 1 study, IMRT decreased V20 and mean dose for the lung, V5 for the heart, and all dosimetric endpoints for the esophagus [17]. In our study, although MHD and esophagus (Dmean and V35) showed similar results, the 2PA-VMAT technique resulted in further reduction for V20. A study about acute toxicity results of VMAT proved that VMAT is safe for large non-small cell lung cancer masses [18]. VMAT is a type of IMRT technique in which the dose volume is delivered during a single 360°gantry arc continually delivering radiation. During rotation, MLCs are adjusted to generate hundreds of fields that generates a more conformal dose distribution. In our study, VMAT protected the LAD and heart better than IMRT.

There is limited data in the literature comparing the IMRT and VMAT techniques for lung cancer. A retrospective study was conducted to compare the effectiveness of IMRT and Single Arc (SA)/Partial Arc (PA)-VMAT plans. The SA-VMAT technique provided a highly conformal dose distribution to the target and reduced high lung doses compared to IMRT. However, there was no significant difference between heart doses in both techniques [19]. In our study, V20 was found to be the lowest with VMAT while significantly lower heart doses were observed with VMAT plans than with IMRT.

In most studies, the entire heart was regarded as a single organ at risk and was contoured accordingly. However, studies have shown that the toxic effects of radiation on the heart also depend on the substructures; therefore, dose limits should be adjusted accordingly [4]. In general, studies have investigated the dose to the heart and its substructures in left breast irradiation, and the relationship between survival and toxicity. Only a few studies have compared the doses to the heart and its substructure in patients with lung cancer. Atkins *et al.* studied the effects of cardiac doses and MACE on

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lung cancer [20,21]. They reported a correlation between LAD V15 and the risk of major adverse cardiac events. They also showed that MHD was insufficient to predict LAD V15 with confidence, and when LAD was included in the calculation parameters, the percentage of LAD V15 was reduced to 87.19 % of the original plan. In our study, we reduced the mean LAD V15 dose by 10.9% by changing the planning technique, without adding LAD to the optimization. Another study showed that by including the LAD and LV cardiac substructures in the optimization of IMRT and VMAT plans, the cardiac substructures caused a significant dose reduction [22].

An increased heart dose was also associated with overall survival in patients with lung cancer. A study by Speirs et al. found that an increased dose to the heart is associated with worse overall survival independently and keeping cardiac V50 below 25% improves the 2-year OS by nearly 20% [23]. In our study, V50 mean values were also very low (<5 Gy) for all techniques. Both 2PA-VMAT and FA/VMAT reduced the heart and LAD doses compared with the IMRT technique, indicating that the 2PA-VMAT technique was effective in all patients, especially if the heart volume was less than 567 cc. The studies did not provide the cut-off value associated with the heart.

CONCLUSION

To our knowledge, this is the first study to compare LAD doses between different IMRT and VMAT techniques for locally advanced lung cancer. Because isolated low LAD V15 was also shown to significantly reduce the risk of MACE, LAD should also be added to the optimization process of radiotherapy planning. Combination systemic therapies like targeted and immunotherapy will make cardiotoxicity a greater priority in lung cancer treatment. Prospective studies are needed to evaluate the clinical benefits of VMAT in locally advanced lung cancer.

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REFERENCES

1. Cuzick J, Stewart H, Rutqvist L, *et al*. (1994) Cause specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. *J Clin Oncol,* ***12:*** *447-453.*
2. Van Nimwegen FA, Schaapveld M, Cutter DJ, *et al*. (2016) Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *J Clin Oncol,* ***34:*** *235-243.*
3. Banfill K, Giuliani M, Aznar M, Franks K, McWilliam A, Schmitt M, Sun F, Vozenin MC, Faivre Finn C; IASLC Advanced Radiation Technology committee. (2021) Cardiac Toxicity of Thoracic Radiotherapy: Existing Evidence and Future Directions. *J Thorac Oncol,* ***16(2):*** *216-227.*
4. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, *et al*. (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with Stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): A randomised, two-by-two factorial phase 3 study. *The Lancet Oncology,* ***16(2):*** *187-199.*
5. Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, Bogart JA, Forster KM, Magliocco AM, Kavadi VS, Narayan S, Iyengar P, Robinson CG, Wynn RB, Koprowski CD, Olson MR, Meng J, Paulus R, Curran WJ Jr, Choy H (2020) Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy with or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. *J Clin Oncol,* ***38(7):*** *706-714. DOI:10.1200/JCO.19.01162. Epub 2019 Dec 16. PMID: 31841363; PMCID: PMC7048161.*
6. Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, *et al*. (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, Vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *Journal of Clinical Oncology,* ***17(9)****.*
7. Aupérin A, Le Péchoux C, Rolland E, Curran WJ, Furuse K, Fournel P, *et al*. (2010) Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology,* ***28(13):*** *2181-2190.*
8. Machtay M, Paulus R, Moughan J, Komaki R, Bradley J, Choy H, *et al*. (2012) Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *Journal of Thoracic Oncology,* ***7(4):*** *716-722.*
9. Saglam Y, Bolukbasi Y, Alpan V, Topkan E, Selek U, Matthew B, *et al*. (2017) Hybrid arc could combine the benefits of IMRT and VMAT to deliver a fast, conformal, homogeneous treatment in non-small cell lung cancer without limitations of Low Dose Bath: A planning study. *International Journal of Hematology and Oncology,* ***27(3):*** *161-170.*
10. Murshed H, Liu HH, Liao Z, Barker JL, Wang X, Tucker SL, *et al*. (2004) Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer. *International Journal of Radiation OncologyBiologyPhysics,* ***58(4):*** *1258-1267.*
11. Pasler M, Georg D, Bartelt S, Lutterbach J (2013) Node-positive left-sided breast cancer: Does VMAT improve treatment plan quality with respect to IMRT? *Strahlentherapie und Onkologie,* ***189(5):*** *380-386.*
12. Akcay M, Etiz D, Duruer K, Bozdogan O, Ozen A (2021) Dosimetric comparison of single-arc/partial-arc volumetric modulated arc therapy and intensity-modulated radiotherapy for peripheral and central lung cancer. *Journal of Cancer Research and Therapeutics. DOI: 10.4103/jcrt.JCRT_221_19.*
13. Darby SC, McGale P, Taylor CW, Peto R (2005) Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol,* ***6(8):*** *557-565.*
14. Sardar P, Kundu A, Chatterjee S, Nohria A, Nairooz R, Bangalore S, Mukherjee D, Aronow WS, Lavie CJ (2017) Long-term cardiovascular mortality after radiotherapy for breast cancer: a systematic review and meta-analysis. *Clin Cardiol,* ***40(2):*** *73-81.*
15. Feng M, Moran JM, Koelling T (2011) Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. *Int J Radiat Oncol Biol,* ***79:*** *10-18.*
16. Cao D, Holmes TW, Afghan MKN, Shepard DM (2007) Comparison of plan quality provided by intensity-modulated arc therapy and Helical Tomotherapy. *International Journal of Radiation Oncology, Biology, Physics,* ***69(1):*** *240-250.*
17. Boyle J, Ackerson B, Gu L, Kelsey CR (2017) Dosimetric advantages of intensity-modulated radiation therapy in locally advanced lung

[DOI: 10.61186/ijrr.22.3.617]

cancer. *Adv Radiat Oncol,* ***2(1):*** *6-11. DOI: 10.1016/j.adro.2016.12.006.*

18. Scorsetti M, Navarria P, Mancosu P, Alongi F, Castiglioni S, Cavina R, *et al*. (2010) Large volume unresectable locally advanced non-small cell lung cancer: Acute toxicity and initial outcome results with Rapid Arc. *Radiation Oncology,* ***5:*** *94.*
19. Jiang X, Li T, Liu Y, Zhou L, Xu Y, Zhou X, *et al*. (2011) Planning analysis for locally advanced lung cancer: Dosimetric and efficiency comparisons between intensity-modulated radiotherapy (IMRT), single-arc/partial-arc volumetric modulated arc therapy (SA/PA-VMAT). *Radiation Oncology,* ***6:*** *140.*
20. Atkins KM, Bitterman DS, Chaunzwa TL, Kozono DE, Baldini EH, Aerts HJWL, *et al*. (2021) Mean heart dose is an inadequate surrogate for left anterior descending coronary artery dose and the risk of major adverse cardiac events in Lung Cancer Radiation therapy. *International Journal of Radiation Oncology, Biology, Physics,* ***110 (5):*** *1473-1479.*
21. Atkins KM, Chaunzwa TL, Lamba N, *et al*. (2021) Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. *JAMA Oncol,* ***7:*** *206-219.*
22. Suyusal IH, Konuk AO, Diremsizoglu U (2023) Dosimetric evaluation of adding left ventricle and left anterior descending coronary artery cardiac substructures to plan optimization in left lung cancer radiotherapy. *Int. J. Radiat. Res., October 2023;* ***21(4):*** *627-632.*
23. Speirs CK, DeWees TA, Rehman S, Molotievschi A, Velez MA, Mullen D, Fergus S, Trovo M, Bradley JD, Robinson CG (2017) Heart dose is an independent dosimetric predictor of overall survival in locally advanced non-small cell lung cancer. *J Thorac Oncol,* ***12(2):*** *293-301.*

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