Volume 21, No 4 | International Journal of Radiation Research, October 2023

Dosimetric evaluation of adding left ventricle and left anterior descending coronary artery cardiac substructures to plan optimization in left lung cancer radiotherapy

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► ***Original article***

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Received: August 2022
Final revised: May 2023
Accepted: June 2023

Int. J. Radiat. Res., October 2023; 21(4): 627-632

DOI: 10.52547/ijrr.21.4.4

Keywords: *Left Lung Cancer, intensity-modulated radiotherapy, volumetric modulated arc therapy, left ventricle and left anterior descending artery, heart-protecting radiotherapy.*

ABSTRACT

***Background*:** The impact of doses on the left ventricle (LV) and left anterior descending artery (LAD) in relation to major adverse cardiac events is well documented. Studies performed on breast cancer have shown that LV doses are correlated with cardiac toxicity. ***Materials and Methods*:** Thirty-two patients with left lung cancer who received radiotherapy at our center were evaluated retrospectively. The left ventricle (LV) and left anterior descending artery (LAD) were contoured as organs at risk on CT simulation images. Seven fields were used in intensity-modulated radiation therapy (IMRT) plans, while two partial arcs were used to create volumetric modulated arc therapy (VMAT) plans. Conventional plans were compared with LV and LAD sparing plans dosimetrically. ***Results*:** When comparing conventional plans to sparing plans, no statistically significant differences were found in target volume parameters and values related to critical structures ($p>0.05$). However, when evaluating the heart (Dmean and V25) and its substructures (LADmean, V15, V30, and LV V5, V10, V15, V30, V40), the plan with LV and LAD sparing demonstrated significantly better outcomes ($p<0.05$). ***Conclusion*:** Therefore, it is essential to contour the substructures of the heart as organs at risk, particularly including LAD and LV in the optimization algorithm during radiotherapy planning for central lung tumors located near the heart.

INTRODUCTION

Lung cancer ranks among the leading causes of cancer-related fatalities worldwide [1]. Radiotherapy in lung cancer patients can result in major adverse cardiac effects (MACE). Individuals diagnosed with locally advanced non-small cell lung cancer face a heightened risk [2]. In RTOG 0617, it was shown that patient survival is linked to the volume receiving 5 Gy (V5) and the volume receiving 30 Gy (V30) of the heart. A higher percentage, therefore, an increased volume is associated with increased mortality. The findings of the RTOG 0617 study also demonstrated a significant correlation between an elevated mean heart dose and an increased incidence of cardiac events [3]. For dosimetric calculation purposes, the heart is often considered as a single structure. The lack of detail for the identification of cardiac substructures based on CT-simulation images limits the ability of cardiac substructure contouring.

A report by Darby *et al.* has shown that a 1 Gy mean dose delivered to the heart equals a MACE increase of 7.4% [4]. Common late MACEs are coronary artery disease, cardiovascular disease, and cardiomyopathy. On the other hand, these diseases originate from substructures of the heart rather than the heart as a whole. This is further supported by a previous study conducted by Hahn *et al.*, which pointed out that ischemic cardiac toxicity is affected by the Left Anterior Descending Artery (LAD) dose rather than the whole heart dose [5]. Important factors in predicting MACE after radiotherapy are pre-existing hypertension, coronary heart disease and LAD V15. The CHyLL study can calculate personalized LAD V15 constraints based on MACE threshold and cardiac risk factors [6].

Serial post-radiotherapy imaging studies have shown that left ventricle (LV) volume in the radiation field is strongly correlated to the incidence of perfusion defects [4, 7]. When the high mean LV dose group was compared to the low mean LV dose group by Hatakenaka *et al.*, the researchers found a significant difference in stroke volume index, wall motion, and a decrease in LV end-diastolic volume index. In addition, the study reported a significant elevation in heart rate [8].

In the field of lung cancer treatment, Intensity-Modulated Radiation Therapy (IMRT) has gained significant importance as an advanced radiotherapy technique [9]. IMRT, along with Volumetric-Modulated Arc Therapy (VMAT), offers distinct advantages over conventional Three-Dimensional Conformal Radiation Therapy (3DCRT). These advanced techniques enable the delivery of lower doses to critical organs at risk (OARs) while preserving the surrounding normal tissues [1]. Piroth

[DOI: 10.61186/ijrr.21.4.627]

et al. suggested that in left-sided breast irradiation, heart substructures should be contoured to reduce cardiac toxicity [10]. In locally advanced non-small cell lung cancer (NSCLC) cases, IMRT and VMAT have the capacity to dramatically lower the cardiac dose compared to 3DCRT. RTOG 0617 showed that IMRT should be used routinely instead of 3DCRT because of lower cardiac doses and lower rates of severe pneumonitis [11].

The purpose of this study was to explore the impact of reduced LAD and LV doses through VMAT and IMRT techniques in patients diagnosed with stage 3 left lung cancer.

MATERIAL AND METHODS

Patient selection and contouring

We retrospectively analyzed left lung NSCLC cases treated with VMAT or IMRT at Kocaeli University Faculty of Medicine. Our goal in patient selection was to create patient groups with a similar disease burden. In this analysis, we only included patients with stage IIIA and IIIB lung cancer. These patients are expected to have a relatively heavy burden of disease in the central thorax. Only patients with a mass located 2 cm or closer to the heart and who had undergone conventional treatment with free-breathing computed tomography (CT) scans were included. In total, 32 patients treated from 2017 to 2021 met the inclusion criteria, of whom 29 were male and 3 were female. All 32 patients who met the inclusion criteria were enrolled in this study.

Institutional review board approval was obtained for this study. The study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Kocaeli University. The Ethics Committee convened on 14.02.2022 and assigned the protocol number 2022/02.

In the current standard radiotherapy practice, the heart is contoured as a single organ. However, in this study, the left anterior descending artery (LAD) and left ventricle (LV) were contoured as substructures and included in the optimization algorithms to lower their dosage while maintaining target volume coverage and dose constraints to other critical thoracic organs at risk (OARs).

Preparation for creating LAD and LV sparing plan (LADLVSP)

Free-breathing CT scans were contoured by a radiation oncology specialist according to RTOG contouring atlases [12]. The contoured organs included intrathoracic and intracardiac structures, specifically the left anterior descending artery and left ventricle. An experienced medical physicist created new cardiac-optimized VMAT plans by incorporating the aforementioned structures into the Varian (Palo Alto, CA) Eclipse V13.6 treatment planning system's plan optimizer. The goal was to maximize sparing of the intracardiac substructures while maintaining planning target volume (PTV) coverage and adhering to dose constraints for OARs.

Treatment planning

IMRT and VMAT plans were constructed for all patients. Dynamic IMRT plans utilized 7 fields at gantry angles of 0-40-80-120-160-200-320 in all planes. VMAT planning involved two arcs. The first arc started at 330° with a 30° collimator angle and performed a 210° clockwise arc. The second arc started at 179° with a 330° collimator angle and performed a 210° counterclockwise arc. Subsequently, LADLVSP plans aimed to spare the LAD and LV. The treatment plans were adjusted to ensure that 95% of the Planning Target Volume (PTV) would receive a dose of 60Gy. A total of 128 plans were analyzed.

Evaluation of dose-volume histogram

Dosimetric information of the conventional VMAT and IMRT plans, as well as the LADLVSP VMAT and IMRT plans, was collected using Varian (Palo Alto, CA) Eclipse V13.6 planning software. A comparison was made between IMRT plans and VMAT plans. D2% represents the maximum dose applied to 2% of the PTV. D98% represents the smallest dose applied to 98% of the PTV. D50% represents the median dose received by 50% of the PTV [13]. The dose-volume histogram was used to obtain dosimetric data. Heart mean and V20, lung mean V20, PTV D2, D98, D50, HI, and CI were used to compare OARs. LAD mean, V15, and V30 were used to compare LAD doses. LV V5, V10, V20, V30, V40, V5cc, and V10cc (volume receiving 5Gy and 10Gy) were used to compare LV doses.

Statistical analysis and ethical approval

Dosimetric data were compared between the standard and LADLVSP groups using a paired t-test. Significance was assessed at $\alpha = .05$ level. Statistical analyses were conducted using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULT

The demographic and clinical characteristics of the patients are shown in table 1. The reoptimized plans met the prescribed treatment dose, while critical organ doses remained within safety limits in accordance with guidelines [14]. Table 2 summarizes the mean changes in LAD, LV, PTV, and other OARs in the IMRT plans. There was no statistically significant difference in all IMRT plans regarding PTV D2, D98, D95, lung mean, V20, CI (conformity index), and HI (homogeneity index) ($p>0.05$). However, a significant decrease was observed in the heart V25 and heart mean values. The heart mean value, which was

[DOI: 10.61186/ijrr.21.4.627]

9.86±1.55 in the conventional plan, decreased to 8.57±1.37 in the LADLV sparing plan (p<0.001). Similarly, the V25 value, which was 12.43±2.77, decreased to 10.01±2.45 (p<0.001). Moreover, significant reductions were measured in all LAD and LV parameters after reoptimization. Additionally, LV doses were also reduced, with a more pronounced difference observed at high LV doses, but there was a significant reduction at all doses.

Table 1. Demographic characteristics of patients.

	N=32	%
GENDER		
MALE	29	87,5
FEMALE	3	12,5
AGE MEDİAN	63 (44-84)	
TNM		
T3N1	10	31,3
T3N2	9	28,1
T4N0	4	12,5
T4N1	3	9,4
T4N2	6	18,8
STAGE		
3A	17	53,1
3B	15	46,9
LOBE		
LEFT LOWER	17	53,1
LEFT UPPER	15	46,9
PTV VOLUME MEAN (cc)	472 (87-1558)	
LEFT VENTRICLE VOLUME MEAN (cc)	131 (94-285)	
LAD VOLUME MEAN (cc)	1.575 (0,9-3,15)	

Table 2. Dosimetric Comparison of IMRT Plans.

	IMRT-SP	IMRT-LADLVSP	DIFFERENCE	P VALUE
PTV D1cm^3 (Gy)	65.19±0.25	65.20±0.23	-0.01±0.08	0.887
PTV D2 (Gy)	64.28±0.22	64.35±0.21	-0.07±0.05	0.183
PTV D98 (Gy)	58.63±0.08	58.63±0.08	0.00±0.03	0.922
PTV D50 (Gy)	62.85±0.17	62.91±0.17	-0.06±0.03	0.091
PTV D95 (Gy)	60.01±0.01	59.99±0.01	0.02±0.01	0.174
LUNG MEAN (Gy)	12.61±0.69	12.60±0.70	0.00±0.02	0.913
LUNG V20 (%)	21.80±1.37	21.74±1.37	0.05±0.13	0.653
CI	0.995±0.005	0.998±0.004	-0.002±0.002	0.174
HI	0.089±0.004	0.090±0.004	-0.001±0.001	0.346
HEART MEAN (Gy)	9.86±1.55	8.57±1.37	1.29±0.26	0.000
HEART V25 (%)	12.43±2.77	10.01±2.45	2.41±0.56	0.000
LAD MEAN (Gy)	18.23±1.93	9.48±1.22	8.74±1.00	0.000
LAD V15 (%)	48.73±5.20	21.52±4.05	27.21±3.65	0.000
LAD V30 (%)	28.61±4.23	6.31±2.11	22.29±3.55	0.000
LV MEAN (Gy)	10.48±1.83	7.12±1.28	3.35±0.66	0.000
LV V5 (%)	39.67±6.85	35.38±6.66	4.28±1.31	0.003
LV V10 (%)	34.59±6.71	24.40±5.39	10.18±2.79	0.001
LV V15 (%)	29.14±5.99	15.87±3.82	13.27±3.06	0.000
LV V30 (%)	11.61±2.94	4.69±1.56	6.92±1.62	0.000
LV V40 (%)	3.96±1.31	1.88±0.76	2.07±0.60	0.002
LV V5 (cc)	54.2±9.3	48.8±9.2	5.4±1.3	0.000
LV V10 (cc)	46.9±9.1	33.8±7.5	13.1±3	0.000

When evaluating the VMAT plans, the results were consistent with the IMRT plans, showing a decrease in both LAD and LV values (table 3). There were no significant differences in PTV and OAR doses (p > 0.05). Furthermore, statistically significant reductions in all LV doses were achieved with the sparing plan (p < 0.05).

Although the aim of the study was not to compare both techniques, the results were worse in the non-sparing IMRT plans compared to the non-sparing VMAT plans. After substructure contouring and converting the plans to sparing plans, the improvement in protection rate in the IMRT plans was significantly superior to the VMAT plans (p<0.05). This apparent increase in protection rate in IMRT plans can be attributed to the poorer results of IMRT in the non-sparing plans. Figure 1 shows a schematic representation of the LAD and LV doses in each of the four plans.

When the patients were evaluated individually, 10 patients with an initial LAD V15 dose greater than 10% had a dose reduction of less than 10% after IMRT plan reoptimization, with more than a 50% reduction in dose observed in 18 patients. Similarly, 15 patients with an initial LAD V30 dose greater than 10% were successfully transferred to the group with a dose reduction of less than 10% after IMRT plan reoptimization, with more than a 50% reduction in LAD V15 dose observed in 12 patients. These dose reductions became more pronounced, especially as the distance between the LV and PTV increased.

In VMAT plans, LAD V15 in 5 patients, LAD V30 in 10 patients, and LV V30 in 5 patients decreased by more than 50%. The IMRT and VMAT plan sections, as well as the sparing plans, of a patient with a dose reduction of more than 50%, are shown in figure 2.

Table 3. Dosimetric Comparison of VMAT Plans.

	VMAT-SP	VMAT-LADLVSP	DIFFERENCE	P VALUE
PTV D1cm3 (Gy)	66.71±0.25	66.62±0.28	0.08±0.12	0.479
PTV D2 (Gy)	65.53±0.22	65.54±0.23	-0.01±0.03	0.779
PTV D98 (Gy)	58.81±0.03	58.79±0.03	0.01±0.01	0.125
PTV D50 (Gy)	63.01±0.17	63.03±0.18	-0.02±0.02	0.392
PTV D95 (Gy)	60.01±0.01	59.99±0.01	0.025±0.018	0.174
LUNG MEAN (Gy)	12.83±0.72	12.84±0.72	-0.01±0.01	0.587
LUNG V20 (%)	21.01±0.14	20.93±0.14	0.06±0.06	0.336
CI	0.987±0.003	0.987±0.003	0.000±0.001	1.000
HI	0.106±0.003	0.106±0.003	-0.000±0.001	0.466
HEART MEAN (Gy)	8.57±1.27	8.22±1.23	0.35±0.08	0.000
HEART V25 (%)	8.63±2.01	7.82±1.87	0.80±0.22	0.001
LAD MEAN (Gy)	17.22±1.85	13.27±1.54	3.95±0.50	0.000
LAD V15 (%)	45.31±4.72	33.98±4.61	11.33±2.12	0.000
LAD V30 (%)	23.17±4.11	12.68±3.02	10.48±2.05	0.000
LV MEAN (Gy)	8.88±1.54	7.80±1.37	1.07±0.24	0.000
LV V5 (%)	40.06±6.96	38.63±6.71	1.42±0.67	0.043
LV V10 (%)	30.41±6.07	26.49±5.42	3.92±1.53	0.016
LV V15 (%)	22.76±4.87	17.48±4.17	5.28±1.51	0.001
LV V30 (%)	7.48±2.24	5.55±1.81	1.93±0.51	0.001
LV V40 (%)	3.14±1.09	2.50±0.93	0.64±0.18	0.002
LV V5 (cc)	53.80±9.02	52.56±8.96	1.23±0.42	0.007
LV 10 (cc)	41.18±8.16	36.60±7.69	4.58±1.61	0.008

[DOI: 10.61186/ijrr.21.4.627]

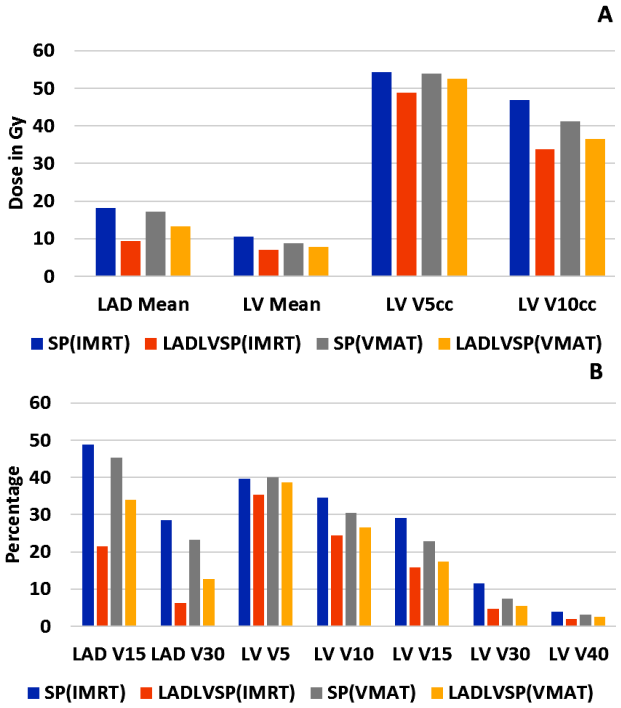

Figure 1. Schematic Illustration of LAD and LV Doses. **(A)** dose in Gy; **(B)** percentage. SP: Standard plan, LADLVSP: Left anterior descending coronary artery and left ventricle–sparing plan.

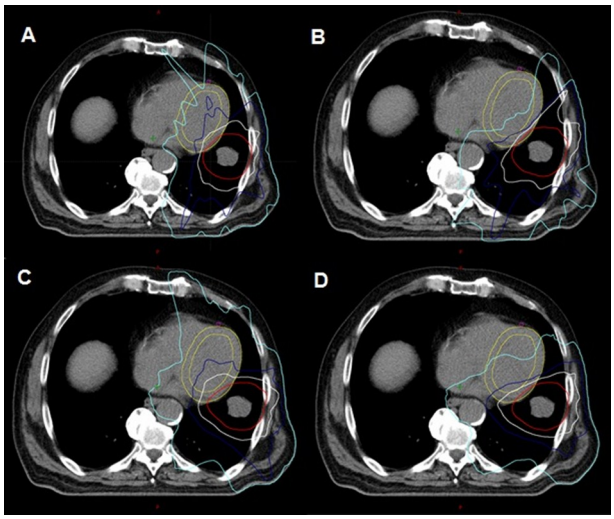

Figure 2. Axial Section Images of an Exemplary Patient's Dose. Distribution. IMRT Plan **(A)**; LADLVSP IMRT Plan **(B)**; VMAT Plan **(C)**; LADLVSP VMAT Plan **(D)**. Left ventricle(yellow), LAD (purple), 15Gy dose distribution (cyan), 30Gy dose distribution (dark blue), 40Gy dose distribution (white), 57Gy dose distribution(red).

DISCUSSION

The aim of this study was to minimize LAD and LV doses by retrospectively reoptimizing IMRT and VMAT treatment plans based on heart substructures. In recent years, studies investigating the effects of LAD and LV doses on major adverse cardiac events (MACE) and mortality have been published. Wang *et al.* demonstrated that LAD V30≥10% is associated with a higher incidence of MACE compared to the LAD V30 < 10% group [15]. The CHyLL study can estimate individualized LADV15 constraints based on risk factors and an acceptable MACE threshold [6]. It has been shown that LV V5<42 cc and LV V10<38 cc can lower the risk of radiation-related late cardiac events to <5% over baseline at 10 years [16]. In our study, after heart substructure contouring and LV sparing, we significantly reduced the volumes of LV V5 (cc) and LV V10 (cc). We believe it is important to focus on these doses in treatment planning and when designing similar studies.

In a study conducted by Tanaka *et al.* on esophageal cancer patients, anatomical plans and sparing plans were created using the VMAT technique to lower the LV dose. In the sparing plan, V30 and V40 doses were significantly smaller [17]. It has been shown that evaluating the mean heart dose (MHD) is not an appropriate parameter for LV and LAD. In our study, LADLVSP in VMAT significantly reduced LV V5, V10, V15, V30, and V40 doses. These findings correlate with previous findings of Tanaka *et al.* [17]. Therefore, it is important to evaluate heart substructures to better estimate the risk of cardiac adverse effects [18].

Although LAD V15≥10% is an independent estimator of the probability of MACE and mortality in patients without chronic heart disease, LV V15 ≥ 1% was associated with an increased risk of MACE in patients with chronic heart disease [19]. Wennstig *et al.* suggested that LAD dose should be kept as low as possible to lower the risk of radiation-induced stenosis [20]. The results of our study showed that LAD V15 and LV V15 doses were significantly reduced after heart substructure sparing in both techniques. While previous studies have primarily used volumetric measurements based on MHD doses alone [21-23], incorporating LAD and LV substructure contouring into radiation therapy planning can help better examine and identify radiation-induced cardiac damage. Several studies have aimed to investigate the dosimetric effect of radiotherapy on LAD and LV sparing.

In a study by Ferris *et al.* on patients diagnosed with stage 3 non-small cell lung cancer in 2019, VMAT plans were created by adding cardiac structures to the optimization process. The results showed significant improvements in non-cardiac and cardiac organs-at-risk (OAR) dose distribution without compromising the prescribed PTV dose [24]. In a study conducted by Zhao et al. in 2015, dosimetric data of 11 patients with left breast cancer were analyzed using different treatment plans. Significant superiority of the IMRT technique in terms of cardiac mean dose was observed, similar to our results [25]. In our study, we did not alter the number of arcs used, eliminating another variable. Our results demonstrated that significant reductions in Heart Dmean and LAD Dmean were achieved after only

[DOI: 10.61186/ijrr.21.4.627]

adding cardiac substructures.

Welsh *et al.* compared standard plans with LAD sparing plans in 49 left breast cancer patients in 2017. Doses to organs at risk were significantly reduced after LAD shielding. Mean LAD dose was reduced by 7.0 Gy, maximum LAD dose by 12 Gy, and MHD by 0.73 Gy. Target volume coverage was clinically acceptable for 96% of patients. Differences were observed between the standard plan and LAD sparing plan in forty patients (82%) [26]. Our results showed similar reductions in both VMAT and IMRT techniques. Mean LAD and MHD were reduced by 3.95 Gy and 0.35 Gy in VMAT plans, respectively. Mean LAD and MHD were reduced by 8.74 Gy and 1.29 Gy in IMRT plans, respectively. In a study conducted by Arslan *et al.* in 2021 with 22 left breast cancer patients, using the IMRT technique to reduce the dose of LAD and LV, they obtained significant results in cardiac substructures after reoptimization [27]. In a 2020 study conducted by Lorris *et al.*, cardiac protection plans reduced mean heart dose, LAD mean, and LAD 0.03cc. LV 0.03cc was reduced by >1.5 Gy for 10 patients, while 6 cases had reductions greater than 7% in LV-V5 [28].

The limitation of this study is that substructure contouring was conducted with computed tomography. Substructure contouring with magnetic resonance imaging (MRI) might offer more detail for better substructure contouring. Further studies should incorporate MRI.

CONCLUSION

In conclusion, the effects of LV and LAD sparing in the optimization of treatment planning for left lung radiotherapy were shown in this study. LV and LAD doses can be reduced by contouring these substructures. We recommend that in lung tumors, especially centrally located lung tumors, heart substructures should be contoured. Prospective studies with a larger patient group are needed to further examine the major radiation-related cardiac side effects.

***Funding*:** This research did not receive any specific grant from funding agencies in the public, commercial, no - profit sectors.

Disclosures: The authors of this manuscript declare that they have no relevant conflicts of interest.

***Ethical consideration*:** Institutional review board approval was obtained for this study. The study was conducted with the approval of the Non-Interventional Clinical Research Ethics Committee of Kocaeli University. The Ethics Committee convened on 14.02.2022 and assigned the protocol number 2022/02.

***Authors' contribution*:** All authors had full access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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[DOI: 10.61186/ijrr.21.4.627]

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[DOI: 10.61186/ijrr.21.4.627]