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The relationship between lung doses, dosimetric factors, survival, and radiation pneumonitis in lung cancer treated with volumetric-modulated arch therapy and helical tomotherapy

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► ***Original article***

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ABSTRACT

Background: We aimed to evaluate dosimetric, clinical parameters, and survival factors contributing to the risk of radiation pneumonia in lung cancer patients treated with volumetric-modulated arch therapy (VMAT) and helical tomotherapy (HT). ***Materials and Methods:*** Retrospective analysis of 79 lung cancer patients treated between January 2018-2020, with 54 eligible patients. Radiotherapy using HT and VMAT at a total dose of 60Gy. Lung volumes receiving >5, 10, 20 Gy, mean lung dose, and organ doses were recorded. The associations among clinical factors, dose-volume parameters, grade >3 RP, and survival outcomes (OS, LRFS, DMFS) were analyzed. ***Results:*** Median follow-up: 18.9 months (range 10.1-34.4). Median OS: 17 months, with 1- and 2-year OS rates of 71.8% and 45.2%, respectively. Univariate analysis showed significant associations with OS for mean lung dose, lung V5Gy, V10 Gy, V20Gy, mean esophagus dose, esophagus V20Gy, V60Gy, heart V40Gy, and grade >3 RP (all $p<0.05$). For LRFS, significant factors included PTV% 95 coverage >59Gy, PTV volume <55cm3, esophagus V20Gy, and grade>3 RP (all $p<0.05$). In multivariate analysis, lung V5 Gy, V10 Gy, mean esophagus dose, esophagus V20 Gy, V60 Gy, heart V40 Gy, and grade >3 RP remained significant for OS, while PTV volume was significant for LRFS. Lung volumes of V5, V10, and V20 strongly associated with grade>3 RP. ***Conclusion:*** In this study we found that low-dose lung volumes and doses to organs at risk (esophagus, heart) are not only significant for radiation pneumonitis (RP) but also play a crucial role in overall survival in arch treatments.

INTRODUCTION

Radiation-induced pneumonitis (RP) stands out as the predominant dose-limiting toxicity following chemo-radiotherapy and/or radiotherapy in lung cancer. The impact of radiation-induced lung injury on the patient's quality of life persists, occasionally resulting in fatal outcomes [1]. Volume-modulated arc therapy (VMAT), which aims to protect surrounding tissues against lung cancer, and the ability to increase radiation doses due to highly usable dose distribution have recently yielded better treatment outcomes compared to 3D conformal radiotherapy. Nevertheless, the possibility of radiation-induced lung damage cannot be discounted [2]. Some studies have reported significant associations between the relative volume of low-dose radiation (Vx) in normal lung tissue and the mean lung doses (MLD) with the development of radiation-induced lung injury [3]. To improve both survival and local control, radiation doses are frequently administered, yet this practice is often linked to the risk of toxicity, particularly in concurrent chemotherapy settings [4]. As a result, radiation doses should be restricted to spare normal organs, including the esophagus, lungs, spinal cord, and heart.

Radiation pneumonitis is a critical concern, and minimizing the applied radiation dose to the lung volume as much as possible poses a significant challenge. The normal lung volume receiving 20 Gy or higher (V20) has been widely used as a significant indicator for estimating the risk of symptomatic radiation-induced pneumonia [5]. Arc-based intensity-modulated radiation therapy (IMRT) is designed to improve dose distribution. Two such arc-based approaches, Volumetric Modulated Arc Therapy (VMAT), and Helical Tomotherapy (HT), utilize megavoltage CT (MVCT) for image-guided radiation

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therapy (IGRT) [6]. IMRT, has the potential to decrease the MLD while concurrently reducing the incidence of radiation pneumonitis by 10% [7]. However, while it is well-established that IMRT can deliver higher doses to the tumor within the lung, the volume receiving low doses, particularly V5 and V10, has been proven to be closely associated with radiation-induced pneumonitis. There is a reported close correlation between severe radiation lung injury and a lower radiation dose to the lung. Larger volumes exposed to lower radiation doses may be more prone to eliciting a significant inflammatory response compared to smaller volumes exposed to higher radiation doses [8,9]. Recently, the V5 dose has emerged as a significant indicator; a few studies recommend keeping the V5 dose below 60-65% in concomitant chemo-radiotherapy [3,10]. In VMAT and HT treatments, V5% and V10% reflected in the lungs may raise more concern about low doses. Furthermore, a higher theoretical risk involves the development of secondary malignancies [11]. When comparing 3D-RT and VMAT treatments, there might be a higher incidence of radiological pneumonia [12]. Nevertheless, conflicting results have been reported regarding the emergence of pulmonary complications after VMAT or IMRT [13].

Limited studies showing that low-dose baths in helical tomotherapy cause an increase in radiation pneumonia. It aimed to investigate the clinical significance of the effect of two different devices and planning systems on lung cancer patients receiving simultaneous chemoradiotherapy. In this retrospective study, we aim to explore the relationship between dose-volume parameters (such as V5, V10, V20) and normal organ doses, the incidence of radiation pneumonitis (RP), dosimetric factors, and survival outcomes in lung cancer patients treated with VMAT and HT.

MATERIALS AND METHODS

Patients and clinic-pathological features

We conducted a retrospective analysis of the medical records of 79 lung cancer patients treated between January 2018 and 2020. The inclusion criteria were as follows: (i) confirmation of lung cancer through pathology, (ii) undergoing first chest radiotherapy, (iii) no treatment interruptions exceeding 7 days during radiotherapy, and (iv) survival for at least 6 months after the confirmation of lung cancer. Patients with a follow-up duration of less than 6 months or those who received a second round of radiotherapy due to recurrence or metastasis within 6 months were excluded from the study. For each patient, we conducted a comprehensive set of laboratory studies, including chest radiography, chest computed tomography (CT), brain magnetic resonance imaging (MRI), liver function tests, and positron emission tomography (PET-CT). A retrospective analysis was performed on laboratory and imaging results retrieved from the hospital records, and dose-volume histograms (DVH) from treatment planning records for all patients. The diagnosis of lung cancer was confirmed through bronchoscopy or percutaneous needle aspiration. In cases with suspicious lymph nodes, biopsies were guided by endoscopic ultrasound when necessary for N2 and N3 treatment decisions. This research adheres to the principles of the Declaration of Helsinki and received approval from the institutional review board of the hospital (2020/514/182/16).

Simulation and target delineation

To obtain images of patients for contouring and treatment planning systems, a simulation based on computerized tomography (CT, General Electric Bright Speed, USA) was used. All patients were positioned in a supine position with a T-lung bar to immobilize for CT simulation. To define target volumes, and OARs and to design treatment plans properly and more precisely the scanning thickness chosen as 2.5 mm including the whole chest area for each patient. The simulation CT images were transferred to Eclipse (Varian Medical Systems, Palo Alto, CA, USA, Siemens Healthineers AG (Frankfurt: SHL)) treatment planning system (TPS). The target volumes: gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and organ at risk (OARs) were delineated by the same radiation oncologist for each patient. Gross tumor volume is depicted relative to all tumors that can be detected, and respective lymph nodes are determined based on the PET and chest CT information. Afterwards, CTV was established by adding 6-8 mm margin and PTV was generated by adding 8-15 mm margin to the CTV, considering target movement through respiration. Elective regional node irradiation was not done. The OARs are also contoured. The definition of OARs includes not only the total lung but also the right and left lungs separately, the esophagus, the heart, and the spinal cord. Lungs are defined individually, to restrict the radiation dose to the opposite lung during the planning optimization.

Treatment planning

All patients' volume delineation was performed using the Eclipse TPS. Computerized tomography images, including OARs and delineated targets, were transferred to the Precision version 3.3.1.3 (Accuray Inc., Sunnyvale, CA, USA) TPS for the HT treatment plan design. Eclipse TPS version 13.7.20 was used for the VMAT treatment plan design. Planning data were collected from two different treatment system plans, and these plans were designed to deliver radiation to lung cancer patients through the delineated target volumes and OARs.

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One of the treatment systems utilized ARC therapy, administered via the Varian Trilogy (RapidArc, Varian Medical Systems, Siemens Healthineers AG (Frankfurt: SHL)) treatment device. Treatments were created using unicentered coplanar double full arcs with a 30-degree collimator rotation, and 6 MV photon beams were employed for the ARCs. The primary reference center volume of the beam was selected as the PTV. Treatment plan optimization was calculated with the anisotropic analytical algorithm (AAA), and isodose normalization was set at %100 of the target means. The PTV coverage was defined to ensure 95 % of the prescribed dose (figure 1).

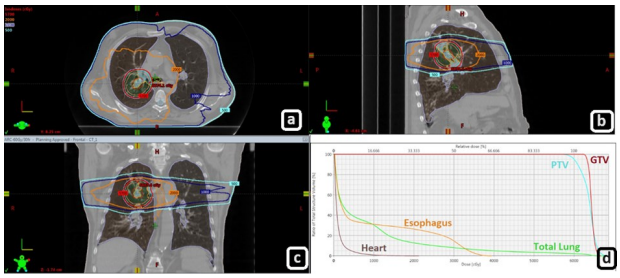

Figure 1. VMAT treatment plan image of a case. Isodose lines of 5Gy, 10Gy, 20Gy, and 57Gy of the plan on axial **(a)**, sagittal **(b)**, and coronal **(c)** sections and dose-volume histogram of the plan **(d)** are displayed. (PTV: planning target volume, GTV: gross tumor volume).

The other system utilized for helical-arc therapy in our clinic was administered via the TomoTheraphy (Accuray, USA) treatment device. Helical treatment plans are calculated on Precision TPS, with the Convolution / Superposition algorithm. Plans designed with 6 FFF MV photons, pitch value applied between 0.300-0.400, modulatii factor from 1.8 up to 3.1, dynamic jaw technique with 5.0 cm jaw width chosen. The PTV coverage was defined to ensure 95 % of the prescribed dose. (figure 2).

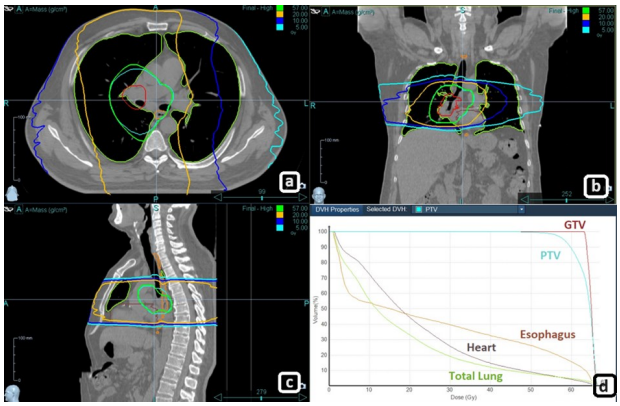

Figure 2. HT treatment plan image of a case. Isodose lines of 5Gy, 10Gy, 20Gy, and 57Gy of the plan on axial **(a)**, coronal **(b)**, and sagittal **(c)** sections and dose-volume histogram of the plan **(d)** are displayed. (PTV: planning target volume, GTV: gross tumor volume).

For both plans within these two different systems, the primary objective was to minimize the dose to normal lung tissue (Lung-PTV volume) while delivering the prescribed dose to the PTV as comprehensively as possible, with a minimum of 95% coverage of the isodose line.

Dose prescription

Treatments for all patients were designed to deliver the same prescription dose and fractions, with a prescribed dose of 60 Gy at a conventional 2 Gy per fraction. Senior physicians reviewed and approved all plans.

Dose evaluation

The PTV doses were covered by the 95% isodose curves, with PTV inhomogeneity ranging from 95% to 107%, and OAR doses remained within the specified tolerances. Additionally, we analyzed OARs, including mean lung dose (MLD), volume receiving 5 Gy (V5), 10 Gy (V10), and 20 Gy (V20) for the lungs; mean dose (Dmean), V20, and V60 for the esophagus; V20, V40, and V60 for the heart; and maximum dose (Dmax) for the spinal cord, all of which were collected from the plans' DVHs. To minimize the impact on OARs as much as possible, we generated OARs-PTV volumes by using calculation operators, such as Lung-PTV (Lungs- target volume), heart-PTV, and esophagus-PTV, for all patients. The creation of these volumes is crucial for designing techniques such as volume-modulated arc and helical plans.

Treatment and follow-up

Throughout the treatment, we conducted weekly physical examinations. Chest tomography was performed 6 weeks after treatment completion. Tumor response was assessed using PET-CT scans 3 months post-treatment. In the case of a complete response, chest and abdominal CT scans were conducted every 3 months during the follow-up period. We evaluated toxicities based on their duration and severity. For the first 6 months of treatment, we graded pneumonia diagnosis using clinical symptoms and radiological findings. In cases of suspected bacterial or viral pneumonia, a differential diagnosis was sought through consultation with pulmonologists. We utilized Common Terminology Criteria for Adverse Events (CTCAE) version 4 to assess radiation-induced esophagus and lung toxicities, with the development of grade>3 pneumonitis considered a significant event.

Statistical analysis

Distant metastasis free survival (DMFS), overall survival (OS) time and loco-regional recurrence (LRFS) were measured since lung cancer diagnosis. Loco-regional recurrence means progression in the target lesion or the formation of a new lesion within the previously irradiated area. OS was measured since the first day of biopsy to death due to any cause.

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Patients at their last follow-up accepted as alive and included in the analysis. The results of this study were analyzed statistically software package SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The Kaplan -Meier method was used to estimate LRFS and OS and groups were compared using two-sided log-rank test. For all analysis, p≤ 0.05 values were considered statistically significant. The relationship of pre-treatment parameters to LRFS and OS was evaluated by using Cox regression analyzes. Logistic analysis was used to investigate the relationship between RP and dosimetric parameters for lung DVH. The logistic regression analysis was done to subject the important factors in univariate analysis (P≤0.05) to multivariate analysis.

RESULTS

Characteristics of the patients

Out of the initial 79 patients, 3 were excluded due to receiving a second round of radiotherapy for metastasis, 7 were followed up for less than 6 months, and 15 were lost to follow-up. Therefore, this study included a total of 54 eligible subjects. The median age was 65, ranging from 42 to 87, with 46 males and 8 females. Among these 54 patients, 23 were diagnosed with squamous cell carcinoma, 13 with adenocarcinoma, 12 with small cell carcinoma, and 6 with other pathological types of lung cancer. The staging was performed according to the 8th edition of the AJCC staging system (2017), classifying 15 patients as stage IIIA, 24 as stage IIIB, and 10 as having limited-stage SCLC. The primary tumor was located in the upper lobe for 17 patients and in the middle or lower lobe for 37 patients. In terms of smoking history, 53 patients were former or current smokers, while 1 was a non-smoker. Furthermore, 38 patients had underlying lung diseases, such as pulmonary bullae, allergic asthma, chronic bronchitis, emphysema, etc., while 16 patients did not have any underlying lung diseases. (table 1). Thirty-seven patients received concurrent chemo-radiotherapy followed by consolidation chemotherapy, 13 patients admitted sequential chemotherapy first to reduce the tumor volume and 4 patients had radiotherapy alone. Total of 50 patients had concurrent chemo-radiotherapy. The concurrent chemotherapy regimen consisted of carboplatin and paclitaxel (3 weeks/cycle for 2 cycles) or etoposide plus cisplatin (3 weeks /cycle for 2 cycles) during radiotherapy followed by the same regimens (3 weeks/cycle for 3-4 cycles) after radiotherapy.

There was temporary RT interruption in eleven patients due to toxicities related to chemotherapy or RT, and RT interruption had the median duration of 4 days (range 1-7). All 54 patients had the median follow-up period of 18.9 months (range of 10.1 to 34.4) and the surviving patients had the follow-up term of 20.1 months (range 10.1-34.4).

Table 1. Characteristics of the patients (KPS: Karnofsky Performans Status, SCLC: small cell lung cancer, mo: month, HT: Helical Tomotherapy, VMAT: Volumetric Arc-therapy).

Characteristics	n,(range,%)
Median age (y)	65(42-87)
Gender	
Male	46(85)
Female	8(15)
KPS	
≤ 90	33 (61)
100	21 (39)
Family history	
Absent	36 (67)
Present	18 (33)
Smoking Status	
>30 pack-year	42 (78)
≤ 30 pack-year	11(20)
Absent	1 (2)
Symptoms	
Cough	27 (50)
Dyspnea	11 (21)
Chest pain	3(6)
Haemoptysis	4(7)
Weight loss	5(9)
Others (hoarseness, fatigue, fever)	4(7)
Histology	
Squamous cell	23(43)
Adenocarcinoma	13(24)
SCLC	12(22)
Other	6(11)
Stage	
I-IIA	3 (5)
IIIA	15(28)
IIIB	24(44)
Limited stage	10(19)
Extensive stage	2(4)
Chemotherapy	
Concomitant	37(69)
Sequential	13(25)
none	4(6)
RT technique	
VMAT	20(37)
HT	34(63)
Overall Survival	
Median (mo)	17
1 year	71.8%
2 years	45.2%
Loco-regional recurrence free survival	
Median (mo)	16
1 year	67.2%
2 years	25.4%
Distant-free Survival	
Median (mo)	15
1 year	79.8%
2 years	39%

Survival analyzes

Thirty-one patients (57.4%) survived during the follow-up period. The median overall survival time was 17 months, 71.8% and 45.2% had 1- and 2-year overall survival rates, respectively. Loco-regional recurrence developed in 27 patients (50%). The median LRFS 16 months, 1- and 2-year rates were 67.2% and 25.4%, respectively. 15 of the 27 patients developing loco-regional recurrence, experienced recurrence based on the high dose radiation therapy

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volume. 18 (33.3%) patients had developed distant metastasis. The most common distant metastatic sites were brain in 5 patients, bone in 6 patients, and adrenal gland in 5 patients. The median DMFS was for overall 15 months,1- and 2-year DMFS were 79.8 % and 39%, respectively (table 1). We did not find any statistical difference between the dose-volume profiles of HT and VMAT radiotherapy techniques (table 2).

Table 2. Statistical analysis of dose-volume profiles according to radiotherapy techniques. (DVH: Dose-volume histogram, HT: Helical Tomotherapy, VMAT: Volumetric Arc-therapy, PTV: planning target volume, CTV: clinical target volume, GTV: gross tumor volume, MLD: Mean Lung Dose, vol: volume, max: maximum, min: minimum, HR: hazard ratio).

DVH parameters	Whole group Med. (min-max)	HT Med. (min-max)	VMAT Med. (min-max)	p
PTV max	65 (62-70)	65 (63-68)	66 (62-70)	0.25 HR 0.39 (%95CI 0.08-1.94)
PTV min	46 (39-59)	43 (40-59)	51 (39-58)	0.08 HR 0.33 (%95CI 0.01-1.12)
PTV %95	59 (47-64)	60 (47-62)	59 (57-64)	0.23 HR 0.48 (%95CI 0.14-1.62)
GTV vol cm^3	13.4 (11-74.4)	11.1 (21-74.4)	15.3 (11-74)	0.40 HR 0.62 (%95CI 0.20-1.89)
PTV vol cm^3	49.3 (14.3-201.4)	49.1 (14.3-201.4)	50 (17.2-86)	0.63 HR 0.76 (%95CI 0.25-2.32)
Lung-CTV cm^3	336.7 (132.6-660.7)	309 (132.6-616.9)	383 (226.7-660.7)	0.051 HR 0.32 (%95CI 0.10-1.00)
MLD Gy	16 (5-26)	15 (8-21)	17 (5-26)	0.16 HR 0.45 (%95CI 0.15-1.38)
Lung V5 Gy	57 (28-88)	58 (28-81)	57 (32-88)	0.40 HR 1.62 (%95CI 0.53-4.93)
Lung V10 Gy	41 (14-66)	42 (19-66)	39 (14-66)	0.43 HR 0.65 (%95CI 0.20-1.99)
Lung V20 Gy	27 (11-47)	27 (11-40)	26 (13-47)	0.81 HR 1.13 (%95CI 0.33-3.02)
Mean Esophagus Dose	26 (8-41)	27 (8-35)	26 (8-41)	0.40 HR 1.62 (%95CI 0.53-4.93)
Esophagus V20 Gy	50 (12-72)	49 (12-70)	52 (16-72)	0.44 HR 0.65 (%95CI 0.21-1.96)
Esophagus V60 Gy	9 (0-59)	9 (0-42)	8 (0-59)	0.98 HR 1.01 (%95CI 0.32-3.22)
Heart V20 Gy	13 (0-45)	13 (0-45)	12 (0-45)	0.39 HR 1.65 (%95CI 0.53-5.16)
Heart V40 Gy	3 (0-29)	3 (0-29)	3 (0-28)	0.81 HR 1.15 (%95CI 0.36-3.63)
Heart V60 Gy	2 (0-13)	2 (0-11)	2 (0-13)	0.93 HR 1.63 (%95CI 0.48-5.61)

Prognostic factors

Prognostic factors for loco-regional- recurrence-free survival, overall survival, and distant metastasis-free survival were analyzed. In univariate analysis, the mean lung dose (16Gy<)(p=0.05), lung receiving V5Gy (55%<) (p=0.02) ,V10Gy (40%<) (p=0,008), V20Gy (27%<) (p=0.002), mean esophagus dose (25Gy<) (p=0.002), esophagus receiving V20Gy (50% <) (p=0.02),V60Gy (10%<) (p=0.001), heart receiving V40Gy (7%<) (p=0.02) and grade >3 RP (p=0.009) were significantly associated with overall survival. PTV 95% coverage (≥ 59Gy) (p=0.012), PTV volume (≥ 55cm^3) (p=0.001), esophagus receiving V20Gy (50%<)(p=0.04) and grade 3 RP (p=0.001) had significant association with LRFS (Table 3).We also analyzed that lung receiving V5Gy (55%<) (p=0.03),V10Gy(< 40%) (p=0.02) and V20 Gy (< 27%) (p=0.01) were statistically significance different between grade>3 radiation pneumonitis (table 4)

In univariate analysis, important factors were evaluated by multivariate analysis. In multivariate analysis, lung receiving V5Gy, V10Gy, mean esophagus dose, esophagus receiving V20Gy, V60Gy, heart receiving V40Gy, and grade 3 RP remained to significantly predict overall survival and only PTV volume was prognostic factor for LRFS (table 5, figure 3).

Side effect analysis

In table 6, the esophageal and radiation-related lung toxicities are summarized. Grade 4 toxicity was not observed, and radiation-related toxicity did not lead to death of the patients. The median duration since the RT start to the toxicity's development was 1.5 months (range, 0.6-1.5) for esophagitis, 9.5 months (range of 5-16.2) for pulmonary fibrosis, and 3.4 months (range 2.1-3.7) for pneumonitis (table 4). At the post-treatment follow-up, grade >3 RP was observed in 7 patients within 6 months after treatment. Five of these 7 patients were died, 2 from bacterial pneumonia, 2 from loco-regional recurrence and 1 from congestive heart failure. In addition, 46 patients experienced acute radiation esophagitis. In total, 14patients (25.9%) were grade 1, 25 (46.9%) grade 2 and 7 (13%) were grade>3.

Table 3. Univariate analysis of dose–volume histogram of all patients (OS: Overall Survival, LRFS: Loco-regional-Free Survival, MLD: Mean Lung Dose).

Variables	OS (p)	LRFS (p)
PTV95 59Gy<& 59Gy≥	0.8	**0.012**
PTV volume cm^3 55 cm^3< & 55cm^3 ≥	0.6	**0.001**
MLD 16Gy<&16Gy≥	**0.05**	0.7
Lung V5 Gy 55 <& 55≥	**0.02**	0.3
Lung V10 Gy 40<& 40≥	**0.008**	0.9
Lung V20 Gy 27 <&27 ≥	**0.002**	0.4
Mean Esophagus Dose 25Gy<&25Gy≥	**0.002**	0.5
Esophagus V20 Gy 50<& 50≥	**0.02**	**0.04**
Esophagus V60 Gy 10<&10 ≥	**0.001**	0.9
Heart V40 Gy 3<&3≥	**0.02**	0.7
Radiation Pneumonitis Grade≥3 Yes& No	**0.009**	**0.001**

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Table 4. Analysis of Grade>3 radiation pneumonitis (RP) according to the doses received by the lungs.

Variables	n (%)		p
	RP≥3 Median (range)	RP<3 Median (range)	
Lung V5 Gy			
55 <	2 (3.7%)	20 (37.1%)	
55≥	5 (9.2%)	27(50%)	**0.03**
Lung V10 Gy			
40<	2 (3.7%)	33(61.2%)	
40≥	5 (9.2%)	14(25.9%)	**0.02**
Lung V20 Gy			
27 <	1(1.8%)	13 (24.1%)	
27 ≥	6 (11.1%)	34(63%)	**0.01**

Table 5. Multivariate analysis of dose–volume histogram of all patients (OS: Overall Survival, LRFS: Loco-regional-Free Survival, PTV: planning target volume, HR: hazard ratio)

Variables	OS			LRFS		
	p	95% HR	Confidence Interval	p	95% HR	Confidence Interval
Lung V5 Gy	0.03	0.998	(1.096-6.707)	0.6		
Lung V10 Gy	0.01	1.06	(1.265-6.579)	0.7		
Mean Esophagus Dose	0.004	0.256	(0.100-0.655)	0.9		
Esophagus V20 Gy	0.02	1.016	(1.119-6.819)	0.6		
Esophagus V60 Gy	0.001	1.479	(1.884-10.222)	0.4		
Heart V40 Gy	0.01	0.928	(1.275-9.163)	0.3		
Grade ≥3 Radiation Pneumonitis	0.01	1.229	(1.275-9.163)	0.2		
PTV volume cm^3	0.5			0.001	1.651	(2.002-13.573)

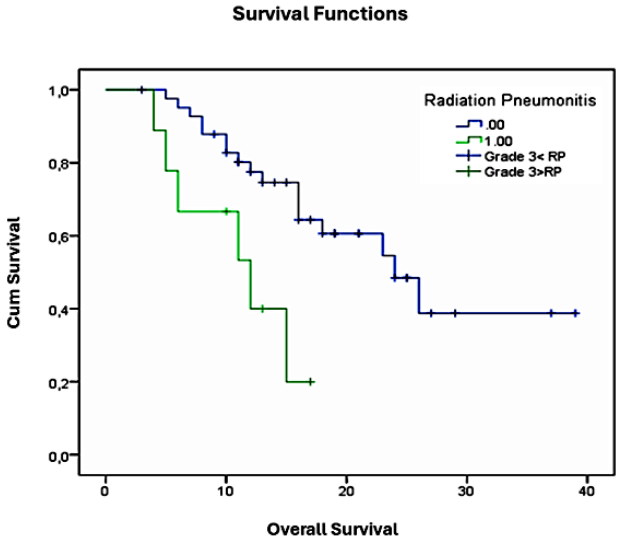

Figure 3. Overall survival for Grade >3 & <3 Radiation Pneumonitis.

Table 6. Incidence of radiation-related pulmonary and esophageal toxicities in all patients.

Toxicity	Acute Pulmonary Toxicity (Pneumonitis) n (%)	Acute Esophageal Toxicity (Esophagitis) n (%)	Late Pulmonary Toxicity (Pulmonary Fibrosis) n (%)	Late Esophageal Toxicity (Esophageal Stricture) n (%)
Grede 0	11 (20.4%)	8 (14.8%)	18 (33.3%)	11 (20.3%)
Grade 1	19 (35.3%)	14 (25.9%)	24 (44.4%)	35 (72.3%)
Grade 2	17 (31.4%)	25 (46.3%)	8 (14.8%)	4 (7.4%)
Grade ≥3	7 (12.9%)	7 (13%)	4 (7.4%)	0 (0%)

DISCUSSION

One of the most common side effects after thoracic radiation is radiation pneumonitis, despite the widespread use of modern radiotherapy techniques [14]. Among the dosimetric parameters, V20 and MLD are widely recognized as associated with an increased risk of developing RP. However, there have been few studies reporting the incidence of RP in lung cancer patients treated with VMAT or HT. Studies have shown that lung V20 is a predictive factor for grade >2 RP in both multivariate and univariate analyses. [5, 10, 15]. Similarly, other studies have found a strong correlation between RP and MLD [16, 17].

In this study, we aimed to evaluate whether low-dose lung volumes differ in terms of survival and RP among lung cancer patients treated with VMAT or HT. Our findings indicate that there was a significant relationship between the V5, V10, and V20 doses received by the lung and the development of grade ≥3 RP in univariate analysis. This is consistent with previous studies that have reported lung V20 as a predictive factor for grade >2 RP in both multivariate and univariate analyses. Similarly, other studies have found a strong correlation between RP and MLD. However, our study did not find any patient who died of severe pneumonia, and only 12.9% of patients experienced severe RP.

Many studies on lung cancer have shown a high correlation between various dosimetric parameters in radiotherapy treatment with RP [18-20]. It is still unknown which dose parameter is important in radiotherapy treatment and which value should be prioritized at the expense of increasing it. However, with HT and VMAT treatment, a higher dose can be given to the tumor, while a significant volume is irradiated with a low-dose bath. Several studies have debated whether one should administer a low dose to a larger volume or a high dose to a lower volume to decrease the likelihood of symptomatic RP. Studies by Willner *et al.* suggested that a small dose over a high volume is preferred over a high dose to a lower

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lung volume [21]. Numerous studies, on the other hand, have emphasized the significance of V5 or other small dose predictors. Wang *et al*. found that low-dose lung volume was associated with severe RP, with a cutoff point of 42% in lung V5 dose [19]. According to Yorke *et al*., the lower dose in total and ipsilateral lung volume V5 to V13 had a stronger association with more severe RP than V20 and larger doses [20]. According to Mehta *et al*., "more than a little" might be worse than "more than a lot", since there is carbon monoxide diffusion capacity loss at 13 Gy [22]. However, as demonstrated in most studies, during the IMRT treatment period, lung V5 was not preferred over other dose measures for the prevention of lung toxicity [3, 23]. Tucker *et al*. assessed the risks of RP for patients with different DVHs but the same MLD. They suggested that the region receiving the high dose is more effective than the median lung dose in the severe RP risk. They concluded that "a lot to little" has an association with a higher risk of severe RP than "a little to a lot". Later, their subsequent control studies also detected these findings [24, 25]. A definite dose limitation for lung toxicity in arch treatments has not yet been established. Our results align with these findings, showing that low-dose bath V5, V10, and V20 are important in the development of severe RP with HT and VMAT.

For most lung cancer patients related to previous smoking cardiac comorbidities, including coronary damage, are more common. Over the years, cardiac dose restrictions have been poorly explained, and RT related cardiotoxicity has been often analyzed. In the secondary analysis of RTOG 0617 which was reported, IMRT is advantageous over 3D CRT because the dose delivered to the heart could decrease [26, 27]. RTOG 0617 study showed a higher heart dose in the high-dose arm. Multivariate analysis of survival data showed an association between higher heart V5Gy and V30Gy and worse survival. There have been recent studies based on evidence with cardiac doses, showing a correlation between cardiac events and the association between cardiac doses and overall survival. Univariate and multivariate analyzes indicate that larger tumor volume is significantly associated with worse survival [28]. Larger tumors also result in higher cardiac and mediastinal doses. However, our multivariate survival analysis shows that PTV >55cm3 had worse LFRS but did not affect OS. Speirs *et al*. also demonstrated that heart V50 is associated with OS, especially for the chemo-radiation arm but they concluded that their follow-up period was slightly lower for that purpose [27]. Our study found that a heart receiving 40 Gy is a prognostic factor for OS our follow-up period is approximately 19 months. It is not appropriate to attribute the toxicities of OAR to a single factor because it highlights the complex interplay between multi-organ dosimetric assessment and treatment toxicity in patients suffering from lung cancer.

Most of the patients in our study received chemotherapy together with radiotherapy, therefore, cardiac radiotherapy doses gained more importance in accordance with the literature. A limitation of our analysis is that, although smoking-related chronic heart and respiratory diseases are more common in patients with lung cancer, the data on cardiac comorbidities in our analysis are lacking and the actual causes of cardiac death of the patients cannot be correlated. Further research with longer follow-up and more homogeneous patient groups is needed to validate our findings.

The potential survival benefit of increasing the dose should be balanced with the risks of treatment-related toxicity. The RTOG 0617 phase III study found that survival was worse in the high-dose arm, suggesting no dose escalation using traditionally fractionated RT [26]. In our study, radiotherapy was administered as 60 Gy in 2 Gy fractions concurrently with chemotherapy, consistent with the standard therapy for patients with stage III non-small cell lung cancer (NSCLC) as established by the RTOG 0617 study.

In addition to the disadvantages of retrospective studies, our study has some other limitations. First, as well as patients treated with VMAT or HT, there is no control group who is treated with 3D-RT. Second, the current study is heterogeneous in terms of concurrent chemotherapy modality and histology. Third, the short follow-up period makes interpreting late toxicity rates complicated. When using VMAT and HT techniques to assess respiratory parameters, ideally using pulmonary function tests before and after treatment and evaluation of clinical results with this analysis gives much better results.

CONCLUSION

Grade >3 pulmonary and esophageal toxicity rates were consistent with the literature and low-dose bath is an important parameter in our patient group and should be kept as low as possible. We have shown that the doses received by organs at risk also play an important role in terms of both radiation pneumonia and overall survival. Use of arc therapy with VMAT and HT in lung cancer has been observed as a safe technique for irradiation. Further prospective studies necessary for the radiological semiology of pneumonia immunotherapy-induced and/or VMAT and HT-induced more work needs to be further studies.

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