



Dosimetric and Radiobiological Evaluation of Radiation-induced Pulmonary Toxicity in the Esophageal Malignancy Using VMAT

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OBJECTIVE

The incidence of radiation-induced pneumonitis after radiotherapy treatment of esophageal malignancy is of great concern. The study aims to evaluate the feasibility, assessing the risk of radiation pneumonitis (RP) with dosimetric and radiobiological outcomes treated with volumetric modulated arc therapy (VMAT) in esophageal cancer patients.

METHODS

Twenty patients of esophageal cancer that had received radiotherapy using VMAT in our department were retrospectively analyzed. Each of the patient's treatment plan was analyzed with conformity index (CI_{RTOG}), volume covering 95% isodose line ($V_{95\%}$), isodose line covering 95% of the target ($ID_{95\%}$), dose homogeneity index (DHI), low-dose volume of the organs-at-risks (OARs), normal tissue complication probability (NTCP), and risk factor (RF) of the OARs.

RESULTS

The prescription dose ranged from 45 to 54 Gy. The mean value of CI_{RTOG} , $V_{95\%}$, $ID_{95\%}$, DHI, total MU, and the intensity-modulated radiation therapy ratio was 1.12 ± 0.07 , $96.58 \pm 2.43\%$, $95.57 \pm 2.48\%$, 0.92 ± 0.03 , 741.50 ± 135.50 , and 4.01 ± 0.72 , respectively. The median value of NTCP was 0.17. The observed value of RF in the lung and heart was 0.61 ± 0.13 and 0.86 ± 0.43 , respectively.

CONCLUSION

The VMAT technique reduces the toxicity rate of the patient and the dosimetric as well as the radiobiological parameters with the quantitative analysis of dose-volume parameters such as D_{mean} , V_{20Gy} , RF, and NTCP may be used to assess the probability of post-radiotherapy RP.

Keywords: Esophageal cancer; radiation pneumonitis; radiotherapy; VMAT.

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Introduction

The probability of developing radiation pneumonitis (RP) after treatment with high-dose radiotherapy is becoming one of the main limiting factors when escalating radiation dose for esophageal cancer.[1] The

development of pulmonary complications such as pneumonitis and lung fibrosis is due to excessive radiation dose to the normal lungs in close proximity to the target region, causing life-threatening events or deaths. [2-4] Furthermore, the studies from the past have indicated the correlation between radiation-induced lung

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toxicities to the pre-existing cardiac morbidity or concomitant radiation to the heart.[5,6]

Esophageal carcinoma is the eighth most commonly diagnosed malignancy with an annual incidence of 456,000 new cases (3~4% of all cancers) and the sixth leading cause of cancer-related death globally.[7] In Asian countries, squamous cell carcinoma is the most common type of esophageal malignancy, associated with significant tobacco and alcohol use.[8] Neoadjuvant chemoradiotherapy (CRT) followed by surgical resection is one of the standard treatments of esophageal cancer, if operable in the absence of medical contraindications. Definitive CRT is another treatment modality with curative intent for unresectable tumors.[9] Radiotherapy has been the mainstay of treatment in the management of this diverse spectrum of esophageal malignancies, particularly diagnosed at an advanced stage with a higher risk of failure at the local site.[10,11] Radiotherapy aims to maximize the dose to the target with adequate margins while potentially decreasing dose to the nearby normal healthy tissues in the tumor vicinity, improving local control and survival. In the radical scheme of treatment of esophageal carcinoma, volumetric modulated arc therapy (VMAT), a special variant of intensity-modulated radiation therapy (IMRT), was found to provide similar conformity, homogeneity, and avoiding excess dose to the organ-at-risk (OAR) when compared to fixed field IMRT or 3-dimensional conformal radiation therapy (3D-CRT), with a corresponding improvement in delivery efficiency.[4,12-14]

With this background, we undertook a retrospective analysis of the patients of esophageal malignancy treated in our center to evaluate the feasibility of treatment using VMAT and assessing the probability of radiation-induced lung toxicity with dosimetric parameters and radiobiological outcomes by calculating normal tissue complication probability (NTCP).

Materials and Methods

Patient Demographics

From 2018 to 2019, 20 patients of histologically confirmed esophageal cancer, received radiotherapy in our department were retrospectively analyzed. Only patients with no distant metastases and treated with VMAT planning were included in this study. All of them received radical, adjuvant, or neoadjuvant radiation therapy with curative intent up to a median dose of 50 Gy, ranging from 45 to 54 Gy at 1.8 to 2 Gy dose per fraction, delivered based on their clinical stage, over

4-5 weeks (five fractions per week) by a clinical linear accelerator (LINAC), following International Commission on Radiation Units and Measurements (ICRU) recommendations, either alone or in combination with concomitant chemotherapy (chemoradiation).

All patients were scanned on a 16-slice computed tomography (CT) simulator (Optima 580, GE Healthcare, Waukesha, USA) with a helical acquisition of 2.5 mm slice thickness, positioned supine and arms above their heads while breathing freely for volume delineation and dose computation. Following the ICRU guidelines, the gross tumor volume defined based on primary tumor and clinically positive lymph nodal extensions based on endoscopic, CT, or PET-CT findings. The clinical target volumes (CTVs) were contoured giving 1 cm radial margin and 4 cm craniocaudal margin adjusting to the natural anatomic barriers with no microscopic expansion of the disease. The planning target volumes (PTVs) of each of the patients included the CTV with a 5 mm margin uniformly in all directions.[15] All the organs were contoured according to the Radiation Therapy Oncology Group (RTOG) atlas for normal tissue contouring.[16] The contoured critical organs retrospectively analyzed were bilateral lungs, heart, and spinal cord for this study. Patient characteristics and dose prescriptions are described in Table 1.

Patient Treatment Planning

Clinical plans were generated using VMAT based on Monte Carlo dose calculation algorithm with a grid size of 0.3 cm and 2% calculation uncertainty on Monaco[®] (V5.11.02) (Elekta CMS, Sunnyvale, CA) treatment planning system (TPS) using 6 MV flat photon beam with the maximum dose rate of 600 cGy/min at Dmax. Each of the patients was planned using three coplanar beam orientations, associated with achievable gantry-couch-patient clearance using an optimized number of treatment arcs, gantry angles, and fluences. The 1st arc was starting from 180° to 130°, 2nd one from 50° to 310°, and last 3rd arc from 230° to 180° with a double arc plan (clockwise and anti-clockwise direction). The typical beam arrangements for an example case are illustrated in Figure 1. All clinical plans were optimized based on the clinical objectives to achieve optimum target coverage with dose sparing to the nearby OARs. All treatment plans were delivered on Elekta Versa HD (Elekta, Crawley, UK) equipped with 160 leaves Agility MLC of 5 mm leaf thickness at the isocenter and qualitatively evaluated for each patient assessing the dose-volume histogram (DVH) parameters for all critical organs and target volume.

Table 1 Patient and tumor characteristics and radiation dose (n=20)

Variables	n	%
Age (year)		
Median	57	
Range	32-76	
Sex		
Male	10	50
Female	10	50
Residence		
Urban	15	75
Rural	5	25
Histology		
Squamous cell carcinoma	19	95
Adenocarcinoma	1	5
Stage		
II	1	5
III	12	60
IVA	7	35
GTV length (cm)		
<8	13	65
≥8	7	35
Tumor location		
Upper thoracic	2	10
Middle thoracic	7	35
Lower thoracic	11	55
Radiation dose (Gy)		
45	8	40
>45 and ≤50.4	11	55
>50.4	1	5

GTV: Gross tumor volume; Gy: Gray

Dosimetric and Radiobiological Parameters

According to the ICRU 83 report, 95% of PTV volume should receive 95% of the prescribed dose. The conformity index (CI_{RTOG}), [17] volume receiving 95% isodose line, isodose line covering 95% volume of the target, and dose homogeneity index [18] for target volume were analyzed. Total monitor units (MUs) per fraction and IMRT ratio, that is, total MU per cGy prescription dose for each clinically accepted plan were noted. For OARs, D_{max}, D_{mean}, and dose covering a percentage of the structure's volume (D_%), for example, D_{10%} and D_{35%}, and similarly, the percentage volume of the structure receiving a certain dose (V_{Gy}), for example, V_{5Gy}, V_{10Gy}, V_{13Gy}, V_{20Gy}, V_{25Gy}, V_{30Gy}, and V_{40Gy} were recorded for dosimetric evaluation and planning purposes and verified with quantitative analyses of normal tissue effects in the clinic (QUANTEC) guidelines. [19]

A comprehensive evaluation tool risk factor conformity index (RFC), enclosing clinical, dosimetric parameters, isodose line, and OARs tolerance doses

Table 2 Summary of the quantitative analysis of physical treatment planning parameters and dose-volume histogram (DVH) of the target volumes and organ-at-risk in the patients

Parameter	Mean±SD
PTV	
Volume (cc)	636.69±281.41
CI _{RTOG}	1.12±0.07
V _{95%} (%)	96.58±2.43
ID _{95%} (%)	95.57±2.48
DHI	0.92±0.03
Treatment plan	
MU	741.50±135.50
IMRT ratio	4.01±0.72
Organ-at-risk	
Combined lung	
V _{5Gy} (%)	62.92±13.39
V _{10Gy} (%)	47.80±9.51
V _{13Gy} (%)	39.78±6.90
V _{20Gy} (%)	25.24±4.72
V _{25Gy} (%)	18.02±4.78
V _{30Gy} (%)	12.58±4.22
V _{40Gy} (%)	4.98±2.02
D _{max} (Gy)	52.51±2.93
D _{mean} (Gy)	13.23±2.35
Heart	
V _{25Gy} (%)	47.99±21.14
V _{30Gy} (%)	35.82±16.32
D _{10%} (Gy)	41.88±10.42
D _{mean} (Gy)	24.44±8.51
Spinal cord	
D _{max} (Gy)	39.48±3.98
NTCP	
Combined: Lung and heart	0.16±0.04

PTV: Planning target volume; SD: Standard deviation; CI_{RTOG}: Conformity index (according to RTOG); V_{95%}: Volume receiving 95% isodose line; ID_{95%}: Isodose line covering 95% volume of the target; DHI: Dose homogeneity index; MU: Monitor unit; IMRT ratio: Intensity-modulated radiation therapy ratio; D_%: The dose covering a particular percentage of the structure's volume; D_{max} and D_{mean}: The maximum point dose and mean dose for a volume; V_{Gy}: The volume of the structure receiving a certain dose; NTCP: Normal tissue complication probability; Gy: Gray

was used for the assessment of possible damage in a particular organ which includes CI of the target and risk factor (RF) for a particular organ. [20] The formula used for the evaluation of the RFC was

$$CI = V_{RI} / V_T$$

$$RF = D_p \times \{ (V_{VOI} / (V_{TVO} \times D_{TDO})) \}$$

$$RFC = [(V_{RI} / V_T) + D_p \times \{ (V_{VOI} / (V_{TVO} \times D_{TDO})) \}];$$

that is, RFC=CI+RF, where, V_{RI} is the volume of the reference isodose line, V_T is the target volume, D_p is the prescribed dose to the PTV, V_{VOI} is the irradiated volume of the organ (organ's volume - reference iso-

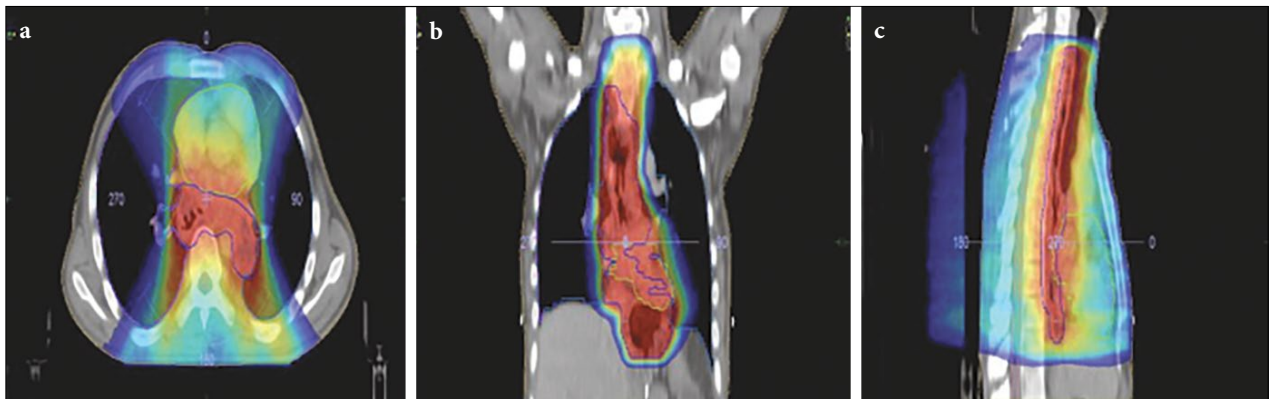


Fig. 1. The typical beam arrangements with (a) axial, (b) coronal, and (c) sagittal plane for an example case with a dose color wash display ranging from 10 Gy to 50 Gy, respectively.

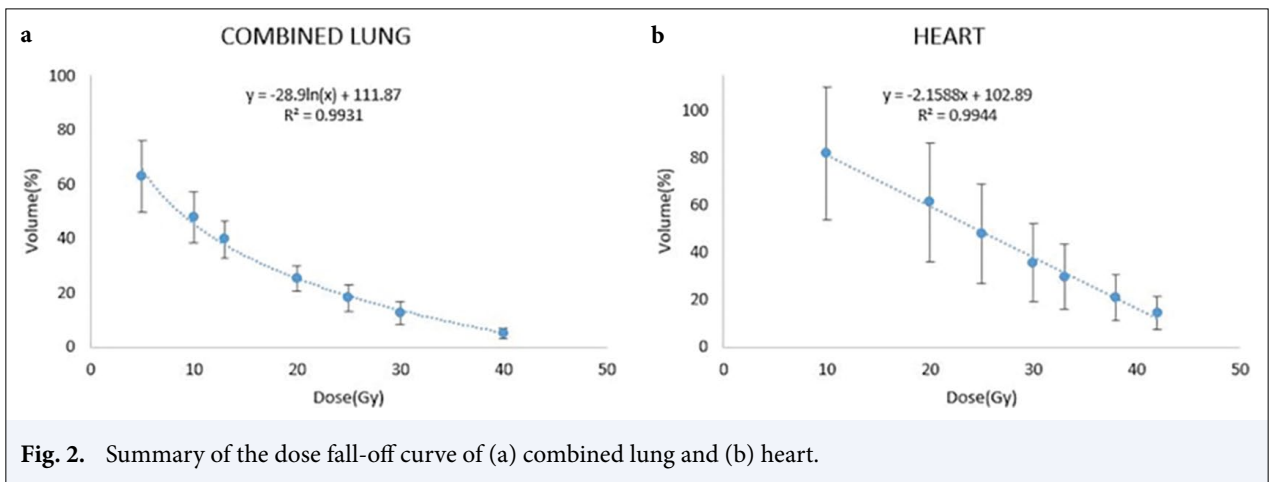


Fig. 2. Summary of the dose fall-off curve of (a) combined lung and (b) heart.

dose volume), V_{TVO} is the total volume of the organ, and D_{TDO} is the tolerance dose of that vital organ.

In addition, to calculate the predicted risk of RP in these patients, we used a combined heart and lung irradiation model and evaluated the NTCP depending on $D_{10\%}$ of the heart (D_{10-H}) and D_{mean} of combined lung volume (MLD)[6] as,

$$NTCP = \frac{1}{1 + \exp(-x)}$$

where, $x = 0.0234 \times D_{10-H} + 0.0649 \times MLD - 3.5$.

Statistical Analysis

Statistical comparison of planning parameters and dose to the OARs in the VMAT plans was performed using SPSS, a data analysis software. As all the variables are quantitative, each of them was denoted by their respective means with standard deviation or with their ranges and analyzed statistically using the one-sample t-test. Evaluation of the level of significance of the ob-

served difference between the dosimetric parameters had been performed and $p < 0.05$ was considered as statistically significant.

Results

From the analyzed data of the 20 patients with a median age of 57 years, the mean volume of the PTV was 636.69 ± 281.41 cc (range; 368.15-1434.35 cc). In Table 2, the DVH parameters for the PTV and OARs were mentioned with mean value and standard deviation for all the cases. Analyzing all the VMAT plans, the mean value of total MU and the IMRT ratio was 741.50 ± 135.50 and 4.01 ± 0.72 , respectively.

Figure 1 depicts the typical dose distribution of the beam arrangements in VMAT treatment plans with a color wash display ranging from 10 Gy to 50 Gy for an example case. The analysis of the volume of the OARs such as lungs and heart receiving low doses of the tune of 5 Gy, 10 Gy, 20 Gy, and 30 Gy, etc., revealed that

Table 3 Summary of the quantitative analysis

Dosimetric parameters		Scoring guideline organ-at-risk (QUANTEC)	Radiation-induced toxicity		Our study result				
Type	Value		Toxicity rate (%)	Endpoint	Mean value	Number of patients exceeding; n (%)	Mean difference	p	
D _{mean} (Gy)	7	Lung	5	Symptomatic pneumonitis	13.23±2.35	20 (100)	6.23	0.000	
	13		10			10 (50)	0.23	0.666	
	20		20			0	-		
	24		30			0	-		
	27		40			0	-		
V _{20Gy} (%)	30	Heart	<20	Long-term cardiac mortality	25.24±4.72	3 (15)	-4.76	0.000	
V _{25Gy} (%)	10		<1			47.99±21.14	19 (95)	37.99	0.000
V _{30Gy} (%)	46		<15				4 (20)	-10.18	0.012
D _{mean} (Gy)	26		<15				12 (60)	-1.56	0.422
			<15						

QUANTEC: Quantitative analyses of normal tissue effects in the clinic; D_{mean}: Mean dose; V_{Gy}: The volume of the structure receiving a certain dose; Gy: Gray

there was a risk of complications after the radiotherapy treatment regimen according to the QUANTEC constraints. From the quantitative analysis of Figure 2, it was noted that the dose fall-off beyond the target region for the case of the combined lung was following a logarithmic pattern for the decrease in the average value of total volume (V) encompassed with the increase in the dose (D) value and the dose fall-off in case of heart was following a linear curve; as $D \propto 1/V$.

On analysis of DVH parameters of the main OARs from Table 3 based on QUANTEC, it was noted that D_{mean} of the combined bilateral lung was 13.23±2.35 Gy. According to the scoring guidelines based on lung dose for symptomatic pneumonitis, for all the cases, the value of D_{mean} was significantly higher than 7 Gy with a 5% toxicity rate but the difference with 13 Gy was not significant and 50% of patients were exceeding the 10% toxicity rate in the VMAT plans. Similarly, for V_{20Gy}, 85% of patients were below the value of 30% (<20% toxicity rate) with a significant difference.

At the same time in DVH parameters of heart, 95% and 20% of the patients had exceeded the quoted value of V_{25Gy} and V_{30Gy} with a significant difference and the difference in the D_{mean} (24.44±8.51 Gy) of the heart was not significantly different from 26 Gy with 60% patients exceeding the quoted mean dose in the VMAT plans.

The mean value of the combined NTCP from the dosimetric parameters of lungs and heart was 0.16±0.04 and the median value was 0.17 ranging from 0.05 to 0.20. Figure 3 depicts the NTCP values of each patient graphically. The NTCP value of 0.17 is consistent with the risk observed with the QUANTEC criteria where none of our patients crossed the 20% pulmonary morbidity risk (Table 3).

From Table 4, the observed value of RF in the lung was 0.61±0.13 with a maximum and minimum value of 0.84 and 0.37, respectively, which showed a mod-

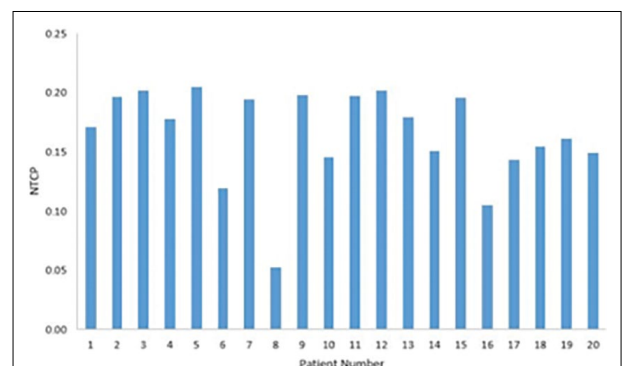


Fig. 3. Summary of the combined normal tissue complication probability value due to bilateral lungs and heart for all the cases.
NTCP: Normal tissue complication probability.

Table 4 Summary of the risk factor analysis in VMAT technique for esophageal cancer

Organ-at-risk	Tolerance dose (Gy) (Mean dose)	Endpoint	RF	RFC
Lung	20 Gy	Radiation pneumonitis	0.61±0.13	1.12+0.61
Heart	26 Gy	Pericarditis	0.86±0.43	1.12+0.86

VMAT: Volumetric modulated arc therapy; RF: Risk factor; RFC: Risk factor conformity index

erate risk of complication as per the RFC method of evaluation. Similarly, in the case of the heart, the observed value of RF was 0.86±0.43 with a maximum and minimum value of 1.46 and 0, respectively, and the probability of risk for the particular organ was at high risk and the chances of complications were at higher side. With the observed value of CI as 1.12±0.07, the value of RFC was 1.12+0.61 and 1.12+0.86 for lung and heart, respectively.

Discussion

Radiation-induced lung injury in the latent period is often asymptomatic. Subsequently, acute RP, due to appreciable endothelial cell loss in vascular tissues resulting in disrupted homeostasis in the pulmonary microenvironment, became most often clinically apparent after 2-6 months of the radiotherapy treatment. Second, radiation-induced lung fibrosis evolves between 6 and 24 months of post-treatment, which may occur permanent deterioration of lung function after a few years.[21] Radiation-induced lung toxicities are volume dependent. Reduced volume of exposed lung tissues with a smaller dose fractionation will reduce the probability of lung toxicity.[22]

Current treatment modalities introduced new radiotherapy techniques which improved the quality of treatment. VMAT is a widely used technique for esophageal malignancy delivering a non-uniform dose from multiple angles generating dose fluences throughout the gantry rotation with the aid of variable speed of gantry, MLC movements, and dose rate to create a very conformal dose to targets with minimal complication to surrounding OARs.[12,23-25]

In our study, the dosimetric parameters in the treatment of esophageal cancer patients were investigated and assessed by comparing our results to the QUANTEC guidelines, a summarized available published data for risk and toxicity assessment. We found that the VMAT plan is robust for both target and normal tissues with increasing target coverage and conformity. In esophageal malignancy, the critical OARs are the lungs, heart, and spinal cord. From the previous study,

dosimetric parameters such as D_{mean} , V_{20Gy} , and V_{30Gy} seemed to be the closely associated important RFs for RP due to the significant damage of the lung subvolumes. The probability of RP was increased with the increase in the value of the dosimetric parameters.[26] In our study result (Table 3), the dosimetric parameters, for example, D_{mean} , V_{20Gy} of the lung, and heart were quite less according to the QUANTEC guidelines.

The probability of RP will increase with the coexistence of pulmonary complications. The dosimetric parameters obtained from the DVH analysis had been shown to influence and predict the occurrence of RP. Compared to 3D-CRT or IMRT, the incidence of late toxicities was quite lesser in the VMAT technique and using advanced radiotherapy techniques, we can achieve better outcomes and alleviate toxicities. Yang et al.[27] reported on 22 patients of esophageal malignancy treated with VMAT technique with an overall 2-year overall survival and failure-free survival rates of 56.0% with a concurrent CRT and the incidence of RP was much lower in VMAT group from 3D-CRT and IMRT groups because of the significantly lower dose bath in the lungs, comparing mean dose and V_{20Gy} of the lung. Münch et al.[4] reported a study on 17 patients of esophageal cancer with VMAT technique showing D_{mean} , V_{5Gy} , and V_{20Gy} were lower than 3D-CRT planning and 13% of patients of that group had post-operative pneumonia. From a previous study, it was shown that there was no such evidence of RP with a $V_{5Gy} > 71\%$ developed Grade 2 or higher lung toxicity. [11] Analyzing the Milano data for lung toxicity, it was reported that the value of D_{mean} and V_{30Gy} should be in between 10-20 Gy and 10-15%; if the V_{20Gy} is <25-30%, the chances of late Grade 3 toxicity will be <5-10% and if V_{13Gy} is <40%, the probability of late Grade 2 toxicity will be <10-20%, respectively.[19] In our study, dosimetric parameters for the lung were within the limits prescribed by the Milano data for toxicity assessment.

Radiobiological analysis of a treatment plan serves as an important adjunct to a dosimetric evaluation in determining the overall quality of the treatment plan as well as complication rate to the OARs due to radiotherapy. Evaluation of the radiobiological parameters of a

treatment plan with the help of dosimetric parameters is more comprehensive and rational. From the previous studies, it was demonstrated that radiobiological analysis supported that VMAT was a better choice because of more superior tumor control probability (TCP) and lower NTCP of lungs and heart compared with IMRT and other types of modalities.[3,25] Radiation-induced heart toxicities enhanced the probability of early radiation-induced lung function loss and using the combined heart and lung irradiation model for predicting the occurrence of RP, the risks of RP were greater than for the lung only model with a median NTCP value 14.2% in 50 Gy and 15.5% in 62.5 Gy dose prescription, respectively.[6] In our study, the median NTCP value was 17.43%, slightly larger than the previous study increases the risk of RP. According to Nalbantov et al.,[5] the value of D_{mean} of heart was the confounding factor for predicting radiation-induced lung injury and 29.3% of patients from all groups where 44% of the cardiac comorbidity patients with D_{mean} of heart developed dyspnea more than Grade 2 after radiotherapy.

CI_{RTOG} interpreted as target covering the reference isodose line with no information about the damage to the nearby critical organs and RF signified the degree of damage to a particular organ with the dosimetric parameters from a radiobiological point of view. The significance of RF value as $RF \approx 0, 0.5$, and ≥ 1 means low, moderate, and high- RFs, respectively. Combining both the parameters, RFC denotes the target coverage as well as a RF for nearby critical organs radiobiologically.[20] In our study, the value of CI_{RTOG} and RF for lung and heart from Table 4 represented that the radiotherapy plans were highly conformal with a moderate risk of lung and heart toxicities.

Conclusion

Modern radiotherapy techniques with better precision such as VMAT technique may reduce the toxicity rate of the patient after radiotherapy but adverse effects are remaining causing the quality of life. Radiation-induced lung toxicity, an inevitable accompaniment to thoracic radiotherapy, depends on many parameters, for example, tumor location, functional status of the organ, total dose to the tumor, the irradiated volume of the critical organ nearby, and other so many factors. Dosimetric as well as radiobiological parameters such as D_{mean} , $V_{20\text{Gy}}$, and NTCP may predict the probability of RP incidence but there is a still lack of evidence of oncological outcomes with a larger patient cohort, long-term follow-up with these predictive parameters

at the same time. Therefore, more research is needed for a better understanding of the dosimetric and radiobiological model for the assessment of the radiation-induced lung injury and how to minimize the toxicity rate with optimum tumor control.

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