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Effect of Normal Lung Definition on Lung Dosimetry and Lung Toxicity Prediction in Radiation Therapy Treatment Planning

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Abstract

Purpose—This study aimed to compare lung dose–volume histogram (DVH) parameters such as mean lung dose (MLD) and the lung volume receiving 20 Gy (V20) of commonly used definitions of normal lung in terms of tumor/target subtraction and to determine to what extent they differ in predicting radiation pneumonitis (RP).

Methods and Materials—One hundred lung cancer patients treated with definitive radiation therapy were assessed. The gross tumor volume (GTV) and clinical planning target volume (PTV_c) were defined by the treating physician and dosimetrist. For this study, the clinical target volume (CTV) was defined as GTV with 8-mm uniform expansion, and the PTV was defined as CTV with an 8-mm uniform expansion. Lung DVHs were generated with exclusion of targets: (1) GTV (DVH_G); (2) CTV (DVH_C); (3) PTV (DVH_P); and (4) PTV_c (DVH_{Pc}). The lung DVHs, V20s, and MLDs from each of the 4 methods were compared, as was their significance in predicting radiation pneumonitis of grade 2 or greater (RP2).

Results—There are significant differences in dosimetric parameters among the various definition methods (all $P_s < .05$). The mean and maximum differences in V20 are 4.4% and 12.6% (95% confidence interval 3.6%–5.1%), respectively. The mean and maximum differences in MLD are 3.3 Gy and 7.5 Gy (95% confidence interval, 1.7–4.8 Gy), respectively. MLDs of all methods are highly correlated with each other and significantly correlated with clinical RP2, although V20s are not. For RP2 prediction, on the receiver operating characteristic curve, MLD from DVH_G (MLD_G) has a greater area under curve of than MLD from DVH_C (MLD_C) or DVH_P (MLD_P). Limiting RP2 to 30%, the threshold is 22.4, 20.6, and 18.8 Gy, for MLD_G, MLD_C, and MLD_P, respectively.

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Conflict of interest: none.

Conclusions—The differences in MLD and V20 from various lung definitions are significant. MLD from the GTV exclusion method may be more accurate in predicting clinical significant radiation pneumonitis.

Introduction

Radiation therapy plays an important role in the treatment of inoperable non-small cell lung cancer (NSCLC) (1, 2). With current, standard 3-dimensional conformal radiation therapy techniques, radiation-induced lung toxicity remains the most important dose-limiting factor (3, 4). Dose–volume parameters are commonly used tools for treatment plan evaluation. Mean lung dose (MLD) and the lung volume receiving 20 Gy (V20) are the most commonly used in assessment the risk of radiation pneumonitis (RP) (5). These dosimetric limits are based on the dose–volume histograms (DVHs) of bilateral lung (BL) with exclusion of the target volume. However, controversies exist regarding which target volume to exclude: the gross tumor volume (GTV), clinical target volume (CTV), or planning target volume (PTV).

The first lung DVH analysis on RP grade 2 or greater (RP2) was from Graham et al, who subtracted PTV from BL, which was subsequently used for Radiation Therapy Oncology Group (RTOG) 9311/RTOG 0117 (6). In RTOG 0617, however, dose limit of lung DVH was generated from BL excluding the CTV. In more recent studies, such as RTOG 0618/RTOG 0813/RTOG 0915/RTOG 1106, and in the National Comprehensive Cancer Network guidelines, lung DVH was computed as BL minus the GTV. Neither RTOG nor National Comprehensive Cancer Network mention possible differences in safe limits of using different methods.

Adoption of different exclusion methods also results from different clinical considerations. The BL-PTV method is used based on the argument that the PTV is the treatment target and is prescribed the full RT dose. The BL-CTV method considers CTV region as tumor instead of lung. Anatomically, the GTV method makes more sense because it includes all the volume of the BL with exclusion of GTV, which is part of lung already occupied by tumor. QUANTEC (quantitative analysis of normal tissue effects in the clinic) for lung toxicity (7) commented on that PTV subtraction method rather than GTV may increase interinstitutional variations because PTV margins may vary between physicians. However, QUANTEC did not specify which method to use when making recommendations on lung dosimetric limits (7) because there was no evidence regarding the absolute difference in safe limits of these methods and their impacts on clinical decision making.

We hypothesized that DVHs of the various normal lung definitions would have an impact on the accuracy of RP prediction. In this study, we compare and analyze numeric differences and the significances and areas under curve for RP prediction in dosimetric parameters such as V20 and MLD generated from lung DVHs of different normal lung definitions.

Methods and Materials

Patient selection

This study included patients with stage I–III NSCLC enrolled on prospective studies approved by an institutional review board (IRB). Written informed consent was obtained from all patients. Patients received definitive thoracic radiation therapy (60 Gy) and had treatment planning computed tomography (CT) scans, volumes of interest, and dose distributions available for this analysis.

Treatment planning

Treatment-planning CT scans were performed with patients in the treatment position, (immobilized in the supine position with their arms above their head) with scans including the entire thorax, at a minimum of 3-mm slice thickness. Intravenous contrast was applied in most patients for target delineation.

GTV, defined as disease visible on CT, was contoured on each CT slice on contrast-enhanced scans whenever available. When lymph nodes were involved, GTVs of lymph nodes were contoured separately. All of the GTVs were combined into a composite GTV for this analysis. The clinical planning target volume (PTV_c) was defined by the treating physician and had nonconsistent margins based on specific clinical considerations.

Lung volume definition and lung DVH

BL was contoured in CT data sets using pulmonary windows via threshold autosegmentation followed by manual edits per the thoracic atlas published by Kong et al (8). All inflated, collapsed, fibrotic, and emphysematic lung tissues were contoured with inclusion of small vessels in the lung parenchyma. Great vessels, trachea, and proximal bronchial tree were excluded. UPlan was used for treatment planning. Radiation was delivered using a 3-dimensional conformal radiation therapy technique and normal tissue dose constraints, as previously described (5). Total normal-lung volumes were calculated by subtracting the overlapping GTV.

The GTV was contoured by the treating physician using lung window/level for tumor-lung interfaces and using mediastinal window/level for tumor-soft tissue interfaces. The CTV was defined as the GTV with an 8-mm uniform expansion. The PTVs were defined as the CTV with an 8-mm uniform expansion. Normal lung DVHs were generated with exclusion of targets: (1) GTV (DVH_G); (2) CTV (DVH_C); (3) PTV (DVH_P); and (4) PTV_c (DVH_{Pc}). Target exclusion was performed by overlapping rules (ie, only the intrapulmonary parts of targets were subtracted). From each lung DVH, 2 dosimetric factors were extracted: MLD and V_{dose}. The V_{dose} (from V5 to V75) was defined as the percentage of total normal lung volume receiving equal to or greater than the designated dose (Gy) of radiation.

Evaluation of radiation pneumonitis

RP was diagnosed and graded as previously defined (5), based on clinical and radiographic presentations, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. In brief, diagnosis of RP required the presence of

radiographic pneumonitis not attributable to other causes such as infection or tumor recurrence. Grade 1 pneumonitis was radiographic RP with no or minimal symptoms that did not require medical intervention; grade 2 was symptomatic but did not interfere with daily activities; grade 3 was symptomatic and interfered with daily activities or required administration of oxygen to the patient; grade 4 required assisted ventilation for the patient; and grade 5 pneumonitis was fatal. An RP event for analysis was defined as RP2.

Statistical analysis

MLD and Vdose for all 4 normal lung definitions were calculated in all patients. Dose parameters from the 4 methods were compared using repeated analysis of variance (ANOVA) (equivalent to paired *t* test for 2 groups). Spearman rank correlation was used to test the correlation between the differences of MLDs or V20s and GTV/BL ratio. Bonferroni correction for multiple testing was performed in ANOVA means comparison of paired groups. Logistic regression analysis was performed to assess the relationship between clinical factors and RP2. The areas under the curve (AUC) of receiver operating characteristic (ROC) curves were calculated to quantify the ability of the various MLDs to discriminate between patients who did and did not develop RP. SPSS, version 19.0 (IBM, Armonk, NY), was used. Differences were considered significant if $P < .05$ (2-sided). Data are presented as mean (95% confidence interval [CI]) unless otherwise specified.

Results

Patient characteristics

From 2004 to 2011, 126 patients who enrolled in prospective trials with lung toxicity data recorded prospectively were evaluated. Twenty-six patients were excluded either with palliative dose (<60 Gy) or <6 months follow-up. All patients were treated with 3-dimensional conformal radiation therapy. Until November 2011, 17 patients (17%) developed RP2 at a minimum follow-up of 6 months. Table 1 details patient characteristics. Seventy-seven patients (77%) were stage III, 76 patients (98.7%) received concurrent chemo radiation therapy with the Carbo-Taxol regimen; and only 1 stage II patient received concurrent chemo-radiation therapy. None of the baseline clinical factors, including age, gender, smoking history, clinical stage, tumor location, tumor volume, forced expiratory volume in 1 second, Karnofsky performance status, chronic obstructive pulmonary disease, radiation dose and chemotherapy, were significantly correlated with the risk of RP2.

Differences of lung DVHs and Vdoses

Differences in the average DVH of lung from the 4 contouring methods are shown in Figure 1a. There are significant differences between V5 and V70 for all 4 methods (all P s $< .05$). The differences in Vdose among the 4 lung DVHs of all patients are shown in Figure 1b. Greater differences in Vdose are located in middose region (V20–V60). As expected, the differences in Vdose between DVH_G and DVH_P methods are significantly greater than for any other 2 methods in all dose regions (V5–V75). The mean difference is 3.5% (2.6%–4.3%). The maximal difference of mean Vdose was 4.9% (4.0%–5.7%) in V40 between DVH_G and DVH_P methods.

Differences of MLDs and V20s

The differences of MLDs and V20s among the 4 methods are shown in Table 2. The individual differences of MLDs and V20s among the 4 methods are shown in Figure 2. The largest individual differences are 7.5 Gy for MLD and 12.6% for V20, which are both between DVH_G and DVH_P methods. Repeated ANOVA test shows that the means of MLD or V20 are significantly different between any 2-paired methods (all P s<.01). The mean difference between the DVH_G and DVH_P method is 3.3 Gy (1.7–4.8 Gy) for MLD and 4.4% (3.6%–5.1%) for V20. As expected, these differences are significantly greater than for any other 2 methods.

Correlation between tumor volume and MLD or V20 differences

Spearman rank test shows a significant correlation between the difference observed in MLD or V20 and GTV volume or GTV/BL ratio (both P s<.05). Figure 3 shows an increasing trend in the differences of MLD or V20 among the 4 normal lung tissue definitions as GTV/BL ratio increases (especially when comparing the DVH_G and DVH_P methods). The correlation between the differences of MLD and V20 among the 4 methods and the GTV has a similar trend compared with the GTV/BL ratio. However, the R^2 value from GTV is lower than that of the GTV/BL ratio (GTV data not shown).

Correlation between RP2 and MLD or V20

All MLDs are significantly correlated with RP2 (all P s<.05); the significance is greater (P value smaller) for MLD from DVH_G (MLD_G) which has the numerically largest AUC for predicting RP2 risk compared to MLDs from DVH_C (MLD_C) or DVH_P (MLD_P) (Fig. 4a). To limit the incidence of RP2 to <30% (9), the threshold is 22.4, 20.6, and 18.8 Gy for MLD_G, MLD_C, and MLD_P, respectively (Fig. 4b).

None of the 4 V20s significantly predict RP2. The AUC results for the ROC plots of each V20 are not shown. Limiting RP2 to 30%, the thresholds are 41.5%, 38.5%, 34.8%, for V20 from DVH_G (V20_G), DVH_C (V20_C), and DVH_P (V20_P), respectively (Fig. 4c).

Discussion

This study demonstrates that methods of normal lung definition have a significant impact on dosimetric parameters obtained from lung DVHs, such as V20 and MLD, and for RP prediction. Such differences vary from patient to patient, ranking the greatest in patients with large tumor to normal lung ratios. The maximum difference is 12.6% and 7.5 Gy for V20 and MLD, respectively. More important, these differences also have an impact on RP2 prediction; MLD from DVH_G had a greater AUC for RP2 than that of CTV and PTV.

To the best of our knowledge, this is the first study to systematically investigate the effect of normal lung definition on lung DVH and lung toxicity prediction, although the effect of lung definition on lung DVH has been noted previously. Graces et al questioned the V20 definition when making comments on differing research results reported by Seppenwoolde et al and Tsujino et al in 2003 (10). Schallenkamp et al reported that subtracting GTV from BL may weaken the ability of dosimetric parameters to predict RP (11). In their study,

however, only “BL without exclusion of any target” and BL-GTV methods were compared, and differences in dosimetrics were not investigated. Kong et al adopted the BL-GTV method, consistent with QUANTEC recommendations, because there was no evidence supporting one method versus another (7, 8). The effect of lung definition on lung dosimetry and the impact on RP prediction have not been reported previously. In this study, we simulated CTV and PTV with uniform margin (8 mm) expansions commonly used in clinical practice. We demonstrated a significant difference in the absolute values. MLD_G had a slightly greater AUC than that of CTV and PTV, supporting the superiority of the BL-GTV method. The differences in MLD and V20 between the different methods of normal lung definition are greater in patients with larger GTVs or GTV/BL ratios. This is likely because larger tumors have a larger expanded volume even with the same circumferential margin, thus causing a greater difference in the relative normal lung volume and DVH. This result differs from that of Graham et al, who reported little correlation between the tumor size (measured by GTV in cubic centimeters) and the V20 (6). In our study, both the GTV and GTV/BL ratio significantly affected V20 and MLD representations. GTV/BL ratio (ie, tumor size relative to BL) may be more accurate than GTV alone.

The magnitudes of the differences in V20 and MLD have a significant clinical impact, although the difference in V20 and/or MLD from various DVH computing methods is somewhat expected. Using RTOG study, for example, a patient may have a safe V20 (30%–35%) and MLD (20 Gy) (12) under DVH_P as defined for RTOG 9311 but would be far beyond the limit of RTO G0617 (DVH_C) or of RTOG 1106 (DVH_G). For RTOG 1106, where the dose prescription is individualized to a MLD of 20 Gy, using the incorrect method of defining normal lung would have an impact on the dose prescription to the tumor and the potential safety of the plan. For daily clinical practice, the mean difference in V20 or MLD from various methods is enough to change planning decisions and/or final toxicity. Thus, different methods may produce under- or overestimated metrics, which may lead to treatment decisions that would affect treatment outcome in tumor control or treatment toxicity (2 totally opposite decisions of treatment plan selection). When MLD is underestimated, a plan judged safe may actually pose a risk for lung toxicity. When MLD is overestimated, the tumor prescription may be decreased due to the exaggerated MLD. In this study, 24 patients (24%) with acceptable treatment plans using the DVH_P method would be unacceptable when switching to the DVH_G method when using a MLD 20 Gy criterion. For clinical trials, such as RTOG 1106, adaptive phase dose escalation is mainly limited by a maximal composite MLD of 20 Gy. Per the protocol adaptive table, if a patient's MLD was 13.5 Gy using the DVH_G method in the initial phase, a 37.05 Gy (2.85 Gy/fraction) boost dose can be delivered in the adaptive phase. If the DVH_P method is used, the MLD may be as high as 20 Gy, and 34.0 Gy (4.85 Gy/fraction) should be prescribed in the adaptive phase. Such a difference in prescription could have a significant impact on the treatment outcome both in tumor control and lung toxicity.

It is worth mentioning that this study has confirmed previous reports that MLD is a significant predictor for RP, regardless of the calculation method (6, 13, 14), although some lung DVH studies neglected to mention the method of DVH computation (11, 15–18). In the studies that clearly specified lung volume definition, more researchers used the BL-GTV method recently; however, methods vary from study to study (5, 6, 19, 20). It is also

interesting to note that the MLDs of all DVHs in this study had a significant correlation with RP2, but V20s did not. This is not surprising because V20 is a point dosimetric factor, which varies with the shape of DVH and beam arrangement, and may not represent the DVH as well as MLD. It should be noted that the predictive accuracy of even the MLD of GTV method is suboptimal. In addition to the difference of target exclusion addressed in this study, many other factors will make a difference in the lung DVH. As mentioned in QUANTEC (7), such factors include (but are not limited to): (1) dose computation algorithms (Monte Carlo, convolution/superposition) for tissue heterogeneity correction; (2) respiratory phases (inhale vs exhale, vs free breathing, vs average scan); (3) radiation field arrangement and techniques that alter the shape of DVH (a little to a lot vs a lot to a little); (4) location and function of lung being radiated; (5) hot spot and location of the hot spot; (6) fractionation and treatment duration of radiation; (7) changes of lung volumes (from tumor shrinkage) during the course of fractionated radiation therapy; and (8) chemotherapy regimens. Of course, there are also other factors associated with RP such as those related to biological, patient, and tumor factors. These were not directly investigated in this study.

We recognize that this study is limited in several aspects. First, a sample size of 100 is small and may have been underpowered for significant testing. This is particularly true of the chemotherapy effect on RP (ie, this study is not powered to detect a small difference related to chemotherapy because there were only 77 and 23 patients with and without chemotherapy, respectively). The stage heterogeneity (stage III with chemotherapy vs stage I–II without chemotherapy) may also have an impact on the RP incidence and prediction. Nevertheless, these were not the primary objectives of this study.

In summary, our findings suggest that variations in normal lung volume definition had a significant effect on the dosimetrics of lung DVHs and their value in predicting radiation pneumonitis. These differences cannot be neglected because they have a direct impact on clinical treatment decision making.

Conclusions

Our study demonstrated that the differences in V20 and MLD among various methods of defining normal lung were significant, and the GTV method seems to provide more accurate prediction for lung toxicity. When integrating DVH parameters from published guidelines or institutional studies into clinical practice, normal lung definition should take this into consideration cautiously. We recommend that lung DVH be computed by the bilateral lung excluding GTV method. This conclusion should be prospectively validated in a larger cohort study.

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Summary

This study suggests that variations in normal lung volume definition have a significant effect on the dosimetric metrics of lung dose–volume histograms and their value in predicting radiation pneumonitis. These differences cannot be neglected because they have a direct impact on clinical treatment decision making. Although all mean lung doses are significant, the gross tumor volume exclusion method may be more accurate in predicting clinically significant radiation pneumonitis

Fig. 1. (a) Differences of lung dose–volume histogram (DVHs). (b) Differences of V_{dose} among 4 lung DVHs (averaged over all $n=100$ patients based on 4 lung definitions). DVHG, DVHC, DVHP, and DVHPc were generated from GTV, CTV, PTV and PTVc exclusion methods, respectively.

Fig. 2.

(a) Differences of V20 (d_V20) in 100 patients (d_V20_x : normalized by $V20_G$, $d_V20_G = 0$). (b) Difference of mean lung dose (MLD) in 100 patients (d_MLD_x : normalized by MLD_G , $d_MLD_G = 0$).

Fig. 3.

(a) Scatterplot with linear trend of difference of V20 (d_V20) versus GTV/BL ratio. (d_V20_x: normalized by V20_G, d_V20_G = 0) (b) Scatterplot with linear trend of difference of V20 (d_V20) versus GTV/BL ratio. (d_MLD_x: normalized by MLD_G, d_MLD_G = 0). BL = bilateral lung; GTV = gross tumor volume; MLD = mean lung dose.

Fig. 4.

(a) Receiver operator characteristic curve analysis using mean lung dose (MLDs) and clinical significant radiation pneumonitis (grade 2, RP2). (b) MLD cutoffs for limiting 30% RP2 using different lung definitions. (c) V20 cutoffs for limiting 30% RP2 using different lung definitions. AUC = area under the curve.

MLD_G=MLD computed from lung DVH with exclusion of GTV;

MLD_C=MLD computed from lung DVH with exclusion of CTV;

MLD_P=MLD computed from lung DVH with exclusion of PTV.

Table 1

Demographic and baseline clinical characteristics of patients

Clinical factors	No. of patients (%)	No. of RP (%)	OR	95% CI	P value *
Age (y), n (%)					
66.1 (median)	47 (47)	7 (14.9)	1.00		
>66.1 (median)	53 (53)	10 (18.9)	1.33	0.46–3.83	.598
Gender, n (%)					
Male	82 (82)	12 (14.6)	1.00		
Female	18 (18)	5 (27.8)	2.24	0.68–7.45	.187
Smoking, n (%)					
No	10 (10)	1 (10.0)	1.00		
Yes	90 (90)	16 (17.8)	1.97	0.23–16.69	.533
Clinical stage, n (%)					
I	10 (10)	1 (10.0)	1.00		
II	13 (13)	2 (15.4)	3.00	0.23–38.88	.401
III	77 (77)	14 (18.2)	2.67	0.32–22.23	.365
Tumor location, n (%)					
RUL	39 (39)	5 (12.8)	1.00		
RML	2 (2)	1 (50.0)	6.80	0.36–126.89	.199
RLl	17 (17)	2 (11.8)	0.91	0.16–5.21	.913
LUL	27 (27)	6 (22.2)	1.94	0.53–7.17	.319
LLl	15 (15)	3 (20.0)	2.04	0.41–10.06	.381
FEV1					
1.82 (median)	50 (50)	6 (12.0)	1.00		
>1.82 (median)	50 (50)	11 (22.0)	2.07	0.70–6.12	.189
Tumor volume (cc), n (%)					
126.2 (median)	49 (49)	6 (12.2)	1.00		
>126.2 (median)	51 (51)	11 (21.6)	1.97	0.67–5.83	.220
KPS, n (%)					
80	38 (38)	4 (10.5)	1.00		
>80	62 (62)	13 (21.0)	2.30	0.69–7.67	.175

Clinical factors	No. of patients (%)	No. of RP (%)	OR	95% CI	P value*
COPD					
No	53 (53)	10 (18.9)	1.00		
Yes	47 (47)	7 (14.9)	0.735	0.26–2.12	.569
Radiation dose (Gy)					
70 (median)	60 (60)	7 (11.7)	1.00		
>70 (median)	40 (40)	10 (25.0)	2.48	0.85–7.19	.095
Chemotherapy, n (%)					
No	23 (23)	3 (13.0)	1.00		
Yes	77 (77)	14 (18.2)	1.48	0.39–5.68	.567

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in 1 second; KPS = Karnofsky performance status; LLL = left lower lobe; LUL = left upper lobe; OR = odds ratio; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

* By logistic regression analysis.

Table 2

Differences of mean lung doses (MLDs) and V20s among the 4 methods

Methods	MLD				V20			
	Max difference*	Mean (Gy)	95% CI	P value [†]	Max difference*	Mean (%)	95% CI	P value*
BL-GTV	-	16.0	14.9–17.1	-	-	25.8	23.8–27.8	-
BL-CTV	-	14.6	13.5–15.6	-	-	24.2	22.3–26.0	-
BL-PTV	-	12.7	11.7–13.7	-	-	21.5	19.7–23.2	-
BL-PTVc	-	14.0	13.0–15.0	-	-	23.5	21.6–25.3	-
BL-GTV vs BL-CTV	3.7	1.4	1.2–1.6	<.01	5.6	1.7	1.3–2.0	<.01
BL-GTV vs BL-PTV	7.5	3.3	1.7–4.8	<.01	12.6	4.4	3.6–5.1	<.01
BL-GTV vs BL-PTVc	6.5	1.9	1.6–2.3	<.01	7.1	2.4	1.8–2.9	<.01
BL-CTV vs BL-PTV	3.9	1.9	1.6–2.1	<.01	7.0	2.7	2.3–3.1	<.01
BL-CTV vs BL-PTVc	3.6	0.5	0.3–0.7	<.01	3.2	0.7	0.3–1.1	<.01
BL-PTV vs BL-PTVc	4.3	1.3	1.1–1.6	<.01	7.1	2.0	1.5–2.6	<.01

Abbreviations: BL = bilateral lung; CI = confidence interval; CTV = clinical target volume; PTV = planning target volume; GTV = gross tumor volume; PTVc = clinical planning target volume; MLD = mean lung dose; V20 = the lung volume receiving 20 Gy.

* Maximum individual difference.

[†] By repeated analysis of variance test.