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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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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.

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 Ps<.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.

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.

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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. UMPlan 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 was 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 Vdose. The Vdose (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.