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**CLINICAL INVESTIGATION** **Lung**

# IMPACT OF FRACTION SIZE ON LUNG RADIATION TOXICITY: HYPOFRACTIONATION MAY BE BENEFICIAL IN DOSE ESCALATION OF RADIOTHERAPY FOR LUNG CANCERS

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**Purpose:** To assess how fraction size impacts lung radiation toxicity and therapeutic ratio in treatment of lung cancers.

**Methods and Materials:** The relative damaged volume (RDV) of lung was used as the endpoint in the comparison of various fractionation schemes with the same normalized total dose (NTD) to the tumor. The RDV was computed from the biologically corrected lung dose–volume histogram (DVH), with an $\alpha/\beta$ ratio of 3 and 10 for lung and tumor, respectively. Two different (linear and S-shaped) local dose-effect models that incorporated the concept of a threshold dose effect with a single parameter $D_{L50}$ (dose at 50% local dose effect) were used to convert the DVH into the RDV. The comparison was conducted using four representative DVHs at different NTD and $D_{L50}$ values.

**Results:** The RDV decreased with increasing dose/fraction when the NTD was larger than a critical dose ($D_{CR}$) and increased when the NTD was less than $D_{CR}$. The $D_{CR}$ was 32–50 Gy and 58–87 Gy for a small tumor (11 $cm^3$) for the linear and S-shaped local dose-effect models, respectively, when $D_{L50}$ was 20–30 Gy. The $D_{CR}$ was 66–97 Gy and 66–99 Gy, respectively, for a large tumor (266 $cm^3$). Hypofractionation was preferred for small tumors and higher NTDs, and conventional fractionation was better for large tumors and lower NTDs. Hypofractionation might be beneficial for intermediate-sized tumors when NTD = 80–90 Gy, especially if the $D_{L50}$ is small (20 Gy).

**Conclusion:** This computational study demonstrated that hypofractionated stereotactic body radiotherapy is a better regimen than conventional fractionation in lung cancer patients with small tumors and high doses, because it generates lower RDV when the tumor NTD is kept unchanged. 

**Hypofraction, Stereotactic body radiotherapy, Non–small-cell lung cancer, Radiobiology, Normal tissue complication probability.**

## INTRODUCTION

Because normal lung tissue usually has a relatively lower $\alpha/\beta$ ratio than does tumor tissue, traditionally, hypofractionation is not considered beneficial in terms of normal tissue sparing. However, the newly emerging technique of hypofractionated stereotactic body radiotherapy (SBRT) has achieved improved tumor control with minimal lung toxicity for the treatment of inoperable Stage I non–small-cell lung cancers (NSCLC) (1–8). Stereotactic body radiotherapy has also been used in the treatment of tumors in many other body sites (9–11). Do the successful clinical results in SBRT contradict the conventional wisdom that hypofractionation is not beneficial for normal tissue sparing? In other words, is there an underlying principle supporting that hypofractionated SBRT is superior to conventional fractionated treatment? In addition, is there an optimal fractionation scheme for maximizing the therapeutic ratio? Can hypofractionation be applied to lung cancer patients with larger tumors? And in which situations is hypofractionation preferred?

This study aimed to answer these questions by evaluating the impact of fraction size on lung radiation toxicity and therapeutic ratio. The combination of a linear-quadratic model in radiobiology and a dose–volume histogram (DVH)-based lung toxicity model was used in the study. In particular, considering that the lung is a parallel organ consisting of many individual lung function units, new local dose-effect functions that incorporated the concepts of a threshold dose effect and a partial damage effect were used to calculate lung toxicity.

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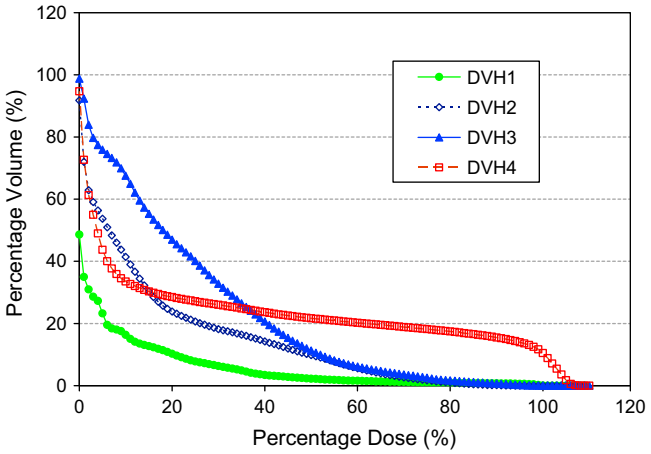


Fig. 1. Four representative dose–volume histograms (DVHs) used for the analysis. DVH1 was from a stereotactic body radiotherapy plan of a small gross tumor volume (GTV) (11 $cm^3$). DVH2 was from a similar hypothetical seven-field intensity-modulated radiotherapy plan of a relatively large peripheral tumor (GTV = 224 $cm^3$). DVH3 was from a seven-field plan of a large central lesion (GTV = 266 $cm^3$). DVH4 was from an anteroposterior/posteroanterior plan of the same large central lesion.

## METHODS AND MATERIALS

We first set the normalized total dose (NTD) (12) to the same value for the various fractionation schemes. Thus, the lung toxicity reflected the therapeutic ratio, because the tumor control was the same for the same NTD to the target. The relative damaged volume (RDV) (13) or fraction of damaged subfunction units ($f_{dam}$) (14) was then calculated from the lung DVH and the local dose-effect functions to represent the lung toxicity. Therefore, the optimal fractionation scheme can be determined by comparing the RDVs of different fractionation sizes. To determine the optimal fractionation scheme in various situations, such comparisons were performed for different NTD values, various parameters used in the lung toxicity models, and four representative lung DVHs with different tumor sizes, locations, and planning techniques.

### *Representative DVHs for analysis*

Four representative lung DVHs (Fig. 1) were used for the analysis. DVH1 was from an SBRT plan for a patient with a relatively small gross tumor volume (GTV) (11 $cm^3$). Intensity-modulated radiotherapy (IMRT) planning with seven coplanar fields was used for the SBRT treatment plan (15). DVH2 was from a similar seven-field IMRT plan for a patient with a larger peripheral tumor (GTV = 224 $cm^3$); DVH3 was from a seven-field IMRT plan for a patient with a large central lesion (GTV = 266 $cm^3$); and DVH4 was from an opposing anterior-to-posterior (AP) and posterior-to-anterior (PA) plan of the same large central lesion (GTV = 266 $cm^3$).

### *Converting physical DVHs into normalized biologic equivalent DVHs*

Each lung DVH was converted to the normalized biologic equivalent (NBE) DVH for various fractionation schemes, assuming that the target received the same NTD for each fractionation scheme. Alpha/beta ratios of 10 and 3 were used for tumor and normal lung tissue, respectively. Table 1 lists the doses per fraction for some selected fractionation schemes with the same NTD of 60, 80, 100, and 120 Gy. For a particular fractionation scheme, NTD was calculated using the following equation:

$$NTD = D_F \bullet n \bullet \frac{(1 + D_F/10Gy)}{(1 + 2Gy/10Gy)} = BED/1.2 \qquad (1)$$

where $D_F$ is the dose per fraction, $n$ is the number of fractions, $10Gy$ is the $\alpha/\beta$ ratio of the tumor, $2Gy$ is the dose per fraction for conventional fractionation, and BED is the biologic equivalent dose. We assumed that the original lung DVH was expressed as the volume vs. the percentage dose, with the percentage dose divided into many percentage dose bins (Di%). Thus, the lung NBE-DVH was computed by converting each Di% into the NBE dose bin (NBEDi) using the following equation:

$$NBED_i = D_F \bullet D_i\% \bullet n \bullet \frac{(1 + D_F \bullet D_i\%/3Gy)}{(1 + 2Gy \bullet D_i\%/3Gy)} \qquad (2)$$

where $3Gy$ is the $\alpha/\beta$ ratio for the lung tissue.

### *Lung complication models*

There are many DVH-based normal tissue toxicity models in the literature (13, 14, 16–21), and these can be grouped into two categories according to how the DVH is reduced into a single parameter (16): (1) the equivalent dose model, in which a lung DVH is converted into an equivalent dose to the whole lung with specific conversion functions, and (2) the effective volume model, in which the lung DVH is converted into an equivalent RDV using a local effective dose function, E(D). The effective volume model can also be called the "parallel functional subunit model," and the RDV is the fraction of damaged functional subunits ($f_{dam}$) (14).

Because the lung is considered a parallel organ consisting of many individual lung function units, the effective volume model should better reflect the lung toxicity mechanism than the equivalent dose model. Mathematically, this model can be expressed as:

$$RDV = \sum_i E(D_i) \bullet V_i \qquad (3)$$

where $V_i$ is the percentage of lung volume receiving a dose ($D_i$) from the lung DVH. The simple threshold model such as the V20 model is

Table 1. Dose per fraction for different numbers of fractions to achieve the same NTD of 60, 80, 100 and 120 Gy at 2-Gy fractions

| | | Dose per fraction for hypofractionation with different number of fractions (Gy) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NTD (Gy) | Conventional fractionation | 1 F | 2 F | 3 F | 4 F | 5 F | 6 F | 10 F | 20 F |
| 60 | 2 Gy × 30 F | 22.30 | 14.62 | 11.28 | 9.32 | 8 | 7.04 | 4.85 | 2.81 |
| 80 | 2 Gy × 40 F | 26.39 | 17.47 | 13.57 | 11.28 | 9.73 | 8.60 | 6 | 3.54 |
| 100 | 2 Gy × 50 F | 30 | 20 | 15.62 | 13.03 | 11.28 | 10 | 7.04 | 4.22 |
| 120 | 2 Gy × 60 F | 33.28 | 22.29 | 17.47 | 14.62 | 12.69 | 11.28 | 8 | 4.85 |

*Abbreviations:* NTD = normalized tumor dose; F = fraction(s).