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Purpose
Patients with non–small-cell lung cancer (NSCLC) in the Radiation Therapy Oncology Group (RTOG) 93-11 trial received radiation doses of 70.9, 77.4, 83.8, or 90.3 Gy. The locoregional control and survival rates were similar among the various dose levels. We investigated the effect of the gross tumor volume (GTV) on the outcome.

Methods and Materials
The GTV was defined as the sum of the volumes of the primary tumor and involved lymph nodes. The tumor response, median survival time (MST), and progression-free survival (PFS) were analyzed separately for smaller (≤45 cm³) vs. larger (>45 cm³) tumors.

Results
The distribution of the GTV was as follows: ≤45 cm³ in 79 (49%) and >45 cm³ in 82 (51%) of 161 patients. The median GTV was 47.3 cm³. N0 status and female gender were associated with better tumor responses. Patients with smaller (≤45 cm³) tumors achieved a longer MST and better PFS than did patients with larger (>45 cm³) tumors (29.7 vs. 13.3 months, p < 0.0001, and 15.8 vs. 8.3 months, p = 0.0001, respectively). Increasing the radiation dose had no effect on the MST or PFS. On multivariate analysis, only a smaller GTV was a significant prognostic factor for improved MST and PFS. Increasing the radiation dose had no effect on the MST or PFS. The GTV as a continuous variable was also significantly associated with the MST and PFS (HR, 1.59, p < 0.0001; and HR, 1.39, p = 0.0001, respectively).

Conclusions
Radiation dose escalation up to 90.3 Gy did not result in improved MST or PFS. The tumor responses were greater in node-negative patients and women. An increasing GTV was strongly associated with decreased MST and PFS. Future radiotherapy trials patients might need to use stratification by tumor volume. ©2008 Elsevier Inc.

Key Words: Tumor volume, Lung cancer, Radiotherapy dose escalation.

Introduction
The current American Joint Committee on Cancer staging system for the primary tumor in lung cancer is based mostly on the tumor extent and involvement of the neighboring structures (e.g., pleura, chest wall, mediastinum, bone, esophagus, and proximal airways) rather than on tumor size or volume. A notable exception is Stage T1, in which a tumor surrounded completely by lung parenchyma cannot exceed 3 cm in the largest dimension. However, a Stage T2 tumor can measure 1.5 cm or 8 cm, as long as it invades the visceral pleura only, with sparing of the other structures.

Evidence has been accumulating that an increasing tumor volume has a significant effect on patient outcome, possibly even overriding the T-stage assignment. Other factors influencing the American Joint Committee on Cancer stage assignment are nodal involvement and the presence of distant metastases.

In a recently published Radiation Therapy Oncology Group (RTOG) Phase I-II study of radiation dose escalation for patients with inoperable non–small-cell lung cancer (NSCLC), the observed locoregional control rates and survival rates were similar between treatment groups, receiving escalated radiation doses (from 70.9 Gy to 90.3 Gy), depending on the volume of lung receiving ≥20 Gy (V20). A reasonable initial hypothesis would be, however, to expect that smaller tumors should demonstrate improved locoregional control with greater radiation doses compared with larger tumors.

To investigate this hypothesis, we undertook a retrospective analysis of data from the RTOG 93-11 clinical trial in an attempt to demonstrate any benefit of radiation dose escalation for patients with smaller tumors and to determine any relationship between the initial tumor volume and patient outcome.

Methods And Materials

Patient population
The RTOG 93-11 study was a Phase I-II radiation dose-escalation trial for patients with inoperable Stage I-II NSCLC treated with three-dimensional (3D) radiotherapy alone, without concurrent chemotherapy, although induction chemotherapy was allowed. The primary objective of the study was to determine the treatment-related morbidity and to determine the maximal tolerated radiation dose. The secondary objectives were to determine the local control and overall survival (OS) rates. The patient population consisted of subjects with NSCLC (inoperable Stage I-II, and IIIA and IIIB, supraclavicular node involvement was not allowed; Table 1). Patients were treated according to the volumetric treatment planning computed tomography

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findings and the gross tumor volume (GTV) included the primary tumor and any enlarged regional lymph nodes (>1 cm) with a minimal 3D margin of 1 cm. Noninvolved nodal areas were not irradiated, and no special effort was made to account for the respiratory motion, apart for assessing motion with fluoroscopy. Patients were placed into dose-escalation groups according to the V_{20} value in their radiotherapy (RT) plan, predicting the likelihood of treatment-related pneumonitis\(^{13}\). Patients with a V_{20} of <22% were assigned to Group 1 and received an escalated dose to 70.9, 77.4, or 83.8 Gy. Patients with a V_{20} of 26–35% were assigned to Group 2 and received an escalated dose to 70.9, 77.4, or 83.8 Gy. Patients with a V_{20} of >35% were assigned to Group 3 and received an escalating dose to 64.5, 70.9, or 77.4 Gy. All fraction sizes were 2.15 Gy. The study accrued patients only to Groups 1 and 2. Group 3 enrollment was stopped because of poor accrual.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 127)</th>
<th>Group 2 (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;60)</td>
<td>18 (14)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>(≥60)</td>
<td>109 (86)</td>
<td>43 (90)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72 (57)</td>
<td>22 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (43)</td>
<td>26 (54)</td>
</tr>
<tr>
<td>KPS (≥70)</td>
<td>85 (67)</td>
<td>30 (63)</td>
</tr>
<tr>
<td>(50–69)</td>
<td>43 (34)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma</td>
<td>71 (56)</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>42 (33)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Other</td>
<td>34 (27)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Stage (T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>83 (65)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Stage II</td>
<td>18 (14)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Stage III</td>
<td>32 (25)</td>
<td>22 (46)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2 (1)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Abbreviation: KPS = Karnofsky performance status. Data in parentheses are percentages.

### Results

#### Patient characteristics

A total of 176 patients were included in the original report of the study\(^{12}\). Of the 176 patients, 161 had available data on GTV and tumor response and were the subject of this secondary analysis. The patient characteristics are presented in Table 1. Overall, most patients were older (>60 years) with a Karnofsky performance status between 70 and 80. The patients in this analysis were approximately equally split between men and women and those in Group 1 were more likely to have node-negative disease than were those in Group 2. The distribution of the American Joint Committee on Cancer stage was Stage I in 67, Stage II in 12, and Stage III in 48 patients in Group 1 and Stage I in 10, Stage II in 3, and Stage III in 35 patients in Group 2.

#### Tumor response, OS, and PFS

The GTV was ≤45 cm\(^3\) in 79 (49%) and >45 cm\(^3\), 82 (51%) of 161 patients (median, 47.3; range, 1.0–1,039.9 cm\(^3\)), 14 patients had an unknown GTV. The tumor response rate (CR/PR) was better for smaller tumors (≤45 cm\(^3\)) than for larger tumors (>45 cm\(^3\); 87% vs. 76%, respectively), as was stable/progressive disease (13% vs. 24%, respectively; \(p = 0.0691\)), Female patients more often had stable/progressive disease than using a cutoff point of 45 cm\(^3\) (\(p = 0.0462\)). A cutoff point of 60 cm\(^3\) did not discriminate between the two groups (\(p = 0.4199\)). When the GTV was analyzed as a continuous variable, on univariate analysis, it was borderline statistically significantly associated with tumor response (\(p = 0.0551\)), however, on multivariate analysis, N stage (N0 vs. N1–N3) and female gender were the only significant variables (\(p = 0.025\) and \(p = 0.02\), respectively). This can be explained by the greater rate of responses (70%) in patients with N0 disease vs. N1–N3 (30%).

Patients with smaller tumors (≤45 cm\(^3\)) achieved a longer median survival than did patients with larger tumors (>45 cm\(^3\); 29.7 vs. 13.3 months, \(p < 0.0001\), Fisher's exact test). Results using a cutoff point of 30 cm\(^3\) did not better distinguish between those patients with a tumor response and those with stable or progressive disease than using a cutoff point of 45 cm\(^3\) (\(p = 0.0642\)). A cutoff point of 60 cm\(^3\) did not discriminate between the two groups (\(p = 0.4199\)). When the GTV was analyzed as a continuous variable, on univariate analysis, it was borderline statistically significantly associated with tumor response (\(p = 0.0551\)); however, on multivariate analysis, N stage (N0 vs. N1–N3) and female gender were the only significant variables (\(p = 0.025\) and \(p = 0.02\), respectively). This can be explained by the greater rate of responses (70%) in patients with N0 disease vs. N1–N3 (30%).

When a different GTV was chosen as a cutoff point (30 cm\(^3\) or 60 cm\(^3\)), patients with smaller tumors (<30 cm\(^3\) or ≤60 cm\(^3\)) still achieved better OS (12.9 vs. 14.6 months for 30 cm\(^3\); \(p = 0.0002\); and 26.8 vs. 13.3 months for 60 cm\(^3\); \(p = 0.0004\)), and more patients for 30 cm\(^3\); \(p = 0.0031\); and 14.7 vs. 8.7 months for 60 cm\(^3\); \(p = 0.0023\)).

### Evaluation of local control, OS, and progression-free survival

A chest X-ray was obtained 4 weeks after RT completion. Computed tomography scans of the chest were obtained at 6 and 12 months and repeated yearly thereafter. Local control (complete response [CR] or partial response [PR] vs. stable or progressive disease) was reported by the enrolling institutions. No central review of the follow-up computed tomography scans was performed. OS and progression-free survival (PFS) were reported as measured from the date of registration in the study.

### Statistical analysis

The GTV was defined as the sum of the volumes of the primary tumor and involved lymph nodes. In the 3D plans, the primary tumor volume and the involved nodal volume were outlined as one structure; no data are available in the RTOG electronic database to allow for separation of the two volumes. Therefore, in an attempt to at least partially correct this deficiency, nodal status (N0 vs. N1 or N2 or N3) was analyzed as one of the variables. This allowed for the separation of the effect of this deficiency, nodal status (N0 vs. N1 or N2 or N3) was analyzed as a continuous variable, on univariate analysis, it was borderline statistically significantly associated with tumor response (\(p = 0.0551\)); however, on multivariate analysis, N stage (N0 vs. N1–N3) and female gender were the only significant variables (\(p = 0.025\) and \(p = 0.02\), respectively). This can be explained by the greater rate of responses (70%) in patients with N0 disease vs. N1–N3 (30%).

Patients with smaller tumors (<45 cm\(^3\)) achieved a longer median survival than did patients with larger tumors (>45 cm\(^3\); 29.7 vs. 13.3 months, \(p < 0.0001\), Fisher's exact test). Results using a cutoff point of 30 cm\(^3\) did not better distinguish between those patients with a tumor response and those with stable or progressive disease than using a cutoff point of 45 cm\(^3\) (\(p = 0.0642\)). A cutoff point of 60 cm\(^3\) did not discriminate between the two groups (\(p = 0.4199\)). When the GTV was analyzed as a continuous variable, on univariate analysis, it was borderline statistically significantly associated with tumor response (\(p = 0.0551\)); however, on multivariate analysis, N stage (N0 vs. N1–N3) and female gender were the only significant variables (\(p = 0.025\) and \(p = 0.02\), respectively). This can be explained by the greater rate of responses (70%) in patients with N0 disease vs. N1–N3 (30%).

When a different GTV was chosen as a cutoff point (30 cm\(^3\) or 60 cm\(^3\)), patients with smaller tumors (<30 cm\(^3\) or ≤60 cm\(^3\)) still achieved better OS (12.9 vs. 14.6 months for 30 cm\(^3\); \(p = 0.0002\); and 26.8 vs. 13.3 months for 60 cm\(^3\); \(p = 0.0004\)), and more patients for 30 cm\(^3\); \(p = 0.0031\); and 14.7 vs. 8.7 months for 60 cm\(^3\); \(p = 0.0023\)).
When the effect of GTV was analyzed on univariate analysis, a smaller GTV was associated with improved OS, with significant hazard ratios (HRs) for cutoff points of 30 cm³ (HR, 2.13; p = 0.0002), 45 cm³ (HR, 2.14; p < 0.0001), and 60 cm³ (HR, 1.91; p = 0.0008), as well as for GTV analyzed as a continuous variable (HR, 1.59; p < 0.0001). The other variables associated with improved OS on univariate analysis were female gender (p = 0.0407) and nodal status (p = 0.087, borderline significance).

The same factors were significant for PFS on univariate analysis (data not shown).

On multivariate analysis of the factors associated with improved OS and PFS, only a smaller tumor volume was significantly prognostic for both endpoints (HR, 2.12; p = 0.0002, and HR, 2.50; p = 0.0002, respectively) when GTV was analyzed as a continuous variable. Age, gender, performance status, histologic type, N stage (N0 vs. N1-3), previous chemotherapy, and maximal radiation dose were not significant (Tables 2 and 3). The other GTV cutoff points (≤30 cm³, ≤45 cm³, and ≤60 cm³) retained their statistically significant association with improved OS and PFS on multivariate analysis and again were the only factors in the multivariate models using a stepwise selection method.

Table 4 shows the primary research hypothesis of this study was that higher radiation tumor volume doses would lead to increased efficacy in smaller tumors. The results for the 30-cm³ and 60-cm³ cutoff points were similar (data not shown). The consistently statistically significant increase in the relative risk of death for all doses to a GTV >45 cm³ can be attributed to the strong effect of a larger GTV on OS rather than the radiation dose. However, the analysis was not powered to detect a dose–tumor volume interaction, and it could not be ruled out on the basis of this analysis.

**Table 4.** Multivariate analysis of overall survival for different gross tumor volumes used as cutoff point and as continuous variable

<table>
<thead>
<tr>
<th>Model</th>
<th>Comparison</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV (cm³)</td>
<td>≤30 vs. ≥30</td>
<td>2.18</td>
<td>1.43–3.32</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>GTV (cm³)</td>
<td>≤45 vs. ≥45</td>
<td>2.12</td>
<td>1.43–3.13</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>GTV (cm³)</td>
<td>≤60 vs. ≥60</td>
<td>2.08</td>
<td>1.27–3.35</td>
<td>0.0015</td>
</tr>
<tr>
<td>GTV⁡</td>
<td>Continuous</td>
<td>1.59</td>
<td>1.33–1.91</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Abbreviation: CI = confidence interval; GTV = gross tumor volume; HR = hazard ratio; N = number of patients.*

†Dose-effect analysis done post hoc, analysis for any multivariate model: age (<60 vs. ≥60 y), gender (female vs. male), KPS (90–100 vs. 70–80), histologic type (nonsquamous vs. squamous), N stage (N0 vs. N1-3), previous chemotherapy (no vs. yes), or minimal dose to lung (continuous).

‡Nonparametric tests were used.

§The dose-effect model considered the interaction with age, gender, performance status, histologic type, histologic type (nonsquamous vs. squamous), N stage (N0 vs. N1-3), previous chemotherapy (yes vs. no), or minimal dose to lung (continuous).

**Discussion**

The aim of RTOG 93-11 was to determine the dose-limiting toxicity of 3D RT. The radiation dose was safely escalated to 83.8 Gy for patients with V₂5 <25% and to 77.4 Gy for patients with a V₂5 of 25–36%. The 90.3-Gy dose level was too toxic. The observed locoregional control was similar among the study arms, without evidence that the higher doses eliminated or at least lowered the recurrence rates. Our initial hypothesis was that patients with volumetrically smaller tumors would have improved survival with radiation dose escalation but not patients with larger tumors. However, we were not able to demonstrate that in this secondary analysis of the RTOG 93-11 trial, at least not with
the small patient numbers that were available at each radiation dose level tested. It could be that doses >83.8 Gy in standard fractions are necessary to eliminate local failure. Additionally, the protracted overall treatment time of 7–9 weeks might have facilitated tumor repopulation and therefore attenuated any radiation dose response. Finally, the PTV margins were tight (1–1.5 cm around the GTV), which might have increased the likelihood for a marginal miss in mobile tumors, obliterating any potential benefit of dose escalation.

Such a benefit has been suggested in the Memorial Sloan-Kettering Cancer Center experience, with the observation of improved local control and survival in Stage III NSCLC patients with large (>100 cm³) tumors treated with radiation doses >64 Gy compared with those who received lower radiation doses. A significant interaction between radiation dose and tumor size was shown in the University of Michigan retrospective analysis of 114 patients with medically inoperable Stage I and II NSCLC treated with 3D conformal RT in a dose-escalation study. Patients treated to a biologically equivalent dose of 67.2 Gy more often achieved local control than those whose tumors did not exceed 51.8 cm³ in volume. However, patients treated to a biologically equivalent dose of >79.2 Gy had the same overall survival, irrespective of tumor volume. With all the limitations of the retrospective study, a hypothesis dose of >79.2 Gy had the same overall survival, irrespective of tumor volume. A strong association of increasing tumor volume, defined as the sum of the primary tumor and the volume of the involved lymph nodes, with worse survival and PFS was observed.

In the reports of highly hypofractionated ("radioablative") RT using precise localization techniques to account for tumor motion, very high local control rates have been achieved in medically inoperable patients with Stage I NSCLC receiving 60 Gy in three fractions of 20 Gy each or other hypofractionated regimens. Such doses have not yet been tested in Stage III NSCLC and might be too dangerous for large and central tumors.

We found that the increasing tumor volume, defined as the sum of the primary tumor volume and the volume of the involved lymph nodes, was associated with a greater risk of local failure, with significantly better control achieved with tumors <45 cm³ than with the larger tumors. The 45-cm³ volume corresponds roughly to a spherical tumor diameter of 4.4 cm. It must be remembered that the "tumor volume" in our analysis denoted a sum of the volume of the primary tumor and the involved lymph nodes, if any. However, in the multivariate analysis of the tumor volume studied as a continuous variable, it was only the earlier nodal stage and female gender, not the tumor volume, that was associated with better local control. In reality, those two variables (volume and nodal stage) overlap to a large degree, because Stage I NSCLC is defined as a tumor stage (and the GTV (and pathologic findings) were predictive for survival on multivariate analysis, but overall stage and nodal stage were not. Those patients with tumor volumes not exceeding 33 cm³ appeared to have the best outcome.

Local response was evaluated volumetrically on 107 followup thoracic computed tomography scans of 22 patients (19 with Stage III NSCLC).
treated with definitive thoracic RT. A volume of ≤6 cm³ and a diameter of ≤4 cm were significantly associated with improved local control compared with larger volumes or diameters. In a large series from Wuerepeng, 784 scans of 136 patients were evaluated volumetrically; and a cutoffpoint of 100 cm³ for tumor volume was a discriminating factor for local control, but not survival. In that study, the primary tumor volume and nodal volume were measured separately. The total tumor volume (tumor plus nodes), as well as primary tumor volume alone, was a significant prognostic factor for survival in a Japanese group experience.

Because most of the studies cited in our report included a significant proportion of patients with nodal involvement (N1-N3), the relative prognostic value of the "T" tumor volume vs. the "N" nodal volume needs to be elucidated. One would expect that worse survival and possibly lower local control would be associated with an increasing nodal volume rather than the primary tumor volume. However, contradictory data have been published on this issue. On univariate analysis of the factors associated with overall survival and failure-free survival in a Phase I-II radiation dose escalation trial, only the increasing GTV (defined as tumor plus nodes), but not the nodal stage or the overall stage, were predictive. Similarly, in the Japanese experience of 71 patients with Stage III NSCLC, on univariate analysis, the total tumor volume, the primary tumor volume and the nodal tumor volume were significant and the nodal volume was not.

On multivariate analysis, the total tumor volume and primary tumor volume were both significant prognostic factors.

Investigators from Shanghai Medical University created a prognostic index model predicting for local control in patients with NSCLC treated with RT. Patients with a smaller tumor volume (primary plus nodal), earlier clinical stage, and treated with higher total irradiation dose with a shortened overall treatment time had better local control.

In a Classification and Regression Tree analysis of the Thomas Jefferson University’s 107 patients with Stage III NSCLC (9), an aggregate nodal volume ≤12.5 cm³ (sum of volumes of the abnormal hilar and mediastinal lymph nodes), as well as central tumor location, but not the primary tumor volume, were associated with a greater risk of nodal recurrence and shorter median survival time than a nodal volume of ≤12.5 cm³ (MST 13.9 months vs. 17.1 months, respectively). We are not aware of other reports that have focused on the prognostic value of the involved nodal volume.

Conclusions

Our study is one of several publications demonstrating the importance of tumor volume in patients receiving thoracic RT for NSCLC. It is not fully clear whether patients with smaller tumors have better outcomes simply because of the lower number of clonogenic cells or whether smaller tumors are inherently more biologically favorable, however; the tumor volume may need to be considered in the staging system for lung cancer, once user-friendly volume assessment becomes commonplace in diagnostic studies.

References