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Increasing Tumor Volume Is Predictive of Poor Overall and Progression-Free Survival: Secondary Analysis of the Radiation Therapy Oncology Group 93-11 Phase I-II Radiation Dose-Escalation Study In Patients With Inoperable Non-Small-Cell Lung Cancer

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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 cm^3) vs. larger (>45 cm^3) tumors.

Results

The distribution of the GTV was as follows: ≤45 cm^3 in 79 (49%) and >45 cm^3 in 82 (51%) of 161 patients. The median GTV was 47.3 cm^3. N0 status and female gender were associated with better tumor responses. Patients with smaller (≤45 cm^3) tumors achieved a longer MST and better PFS than did patients with larger (>45 cm^3) 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 (hazard ratio [HR], 2.12, $p = 0.0002$; and HR, 2.0, $p = 0.0002$, respectively). 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[1–11] 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[12] 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 [V_{20}]). A reasonable initial hypothesis would be, however, to expect that smaller tumors should demonstrate improved local 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-III 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 Stage IIIB; supraclavicular nodes involvement was not allowed; Table 1). Patients were treated according to the volumetric treatment planning computed tomography

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 <25% were assigned to Group 1 and received an escalated dose to 70.9, 77.4, 83.8, or 90.3 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

Characteristic	Group 1 (*n* = 127)	Group 2 (*n* = 48)
Age (y)		
<60	18 (14)	5 (10)
≥60	109 (86)	43 (90)
Gender (*n*)		
Male	72 (57)	22 (46)
Female	55 (43)	26 (54)
KPS (*n*)		
70–80	85 (67)	30 (63)
90–100	42 (28)	18 (37)
Histologic type (*n*)		
Squamous cell carcinoma	51 (40)	21 (44)
Adenocarcinoma	42 (33)	17 (35)
Other	34 (21)	10 (21)
N stage (*n*)		
N0	83 (65)	17 (35)
N1	10 (8)	6 (13)
N2	32 (25)	22 (46)
N3	2 (1)	3 (6)

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

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 those 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 the tumor GTV vs. nodal GTV (at least for Stage I, or N0, patients). OS was defined as death from any cause; an event for PFS was local or regional progression, distant metastases, or death from any cause. For the purpose of this investigation, tumor response, OS, and PFS were analyzed separately for the smaller tumors (≤45 cm^3) vs. larger tumors (>45 cm^3), first among all patients and, later, within each radiation dose level. GTV was also analyzed as a continuous variable. The association of response (CR/PR vs. stable/progressive disease) and the GTV categorized by cutpoint was tested by Fisher's exact test. OS and PFS were estimated by the Kaplan-Meier method and tested using the log–rank test statistic. Univariate and multivariate analyses of OS and PFS with the GTV and other prognostic factors (age [<60 vs. ≥60], gender, Karnofsky performance status [90–100 vs. 70–80], histologic type [nonsquamous vs. squamous], stage [I-II vs. IIIA-IIIB], previous chemotherapy [yes vs. no], and maximal radiation dose to the lung) were done using the Cox proportional hazards model. Multivariate modeling used the stepwise selection method. When analyzed as a continuous variable, GTV was transformed using a $\log_{10}$ transformation to ensure normality. Patients with unknown tumor volumes were excluded from this analysis.

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, 1.9–1,039.9 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, 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 = 0.4139). 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; Fig. 1), as well as better median PFS (15.8 vs. 8.3 months; p < 0.0001; Fig. 2).

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 (32.9 vs. 14.6 months for 30 cm^3, p = 0.0002; and 26.8 vs. 13.3 months for 60 cm^3, p = 0.0006), as well as better PFS (15.5 vs. 9.0 months 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 cm^3 (HR, 2.15; $p = 0.0002$); 45 cm^3 (HR, 2.14; $p < 0.0001$); and 60 cm^3 (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 ($p = 0.067$, 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, 2.0; $p = 0.0002$, respectively) when GTV was analyzed as a continuous variable. Age, gender, performance status, histologic type, N stage (N0 vs. N1-N3), previous chemotherapy, and maximal radiation dose were not significant (Tables 2 and 3). The other GTV cutoff points (≤30 cm^3, ≤45 cm^3, and ≤60 cm^3) 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.

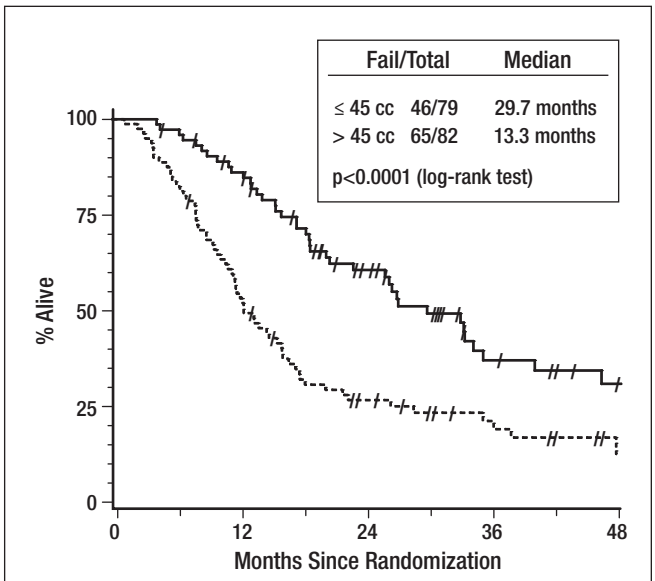

Figure 1. Five-year overall survival rate for patients with gross tumor volume ≤45 cm3 (solid curve) vs. those with gross tumor volume >45 cm^3 (dotted curve).

Effect of radiation dose escalation on tumor response, OS, and PFS by tumor volume

The primary research hypothesis of this study was that higher radiation doses would lead to increased efficacy in smaller tumors. Table 4 shows the frequencies and percentages of patients with a CR/PR and stable or progressive disease for each radiation dose and GTV combination using the 45 cm^3 cutoff point. No evidence was found in these data that the CR/PR rates increased as the radiation dose increases for the two categories of GTV ($p = 0.2213$). Increasing the radiation dose had no effect on OS or PFS (data not shown for PFS) when examined separately for smaller vs. larger tumors when the 45-cm^3 GTV cutoff point was used (Table 5). The results for the 30-cm^3 and 60-cm^3 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 cm^3 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.

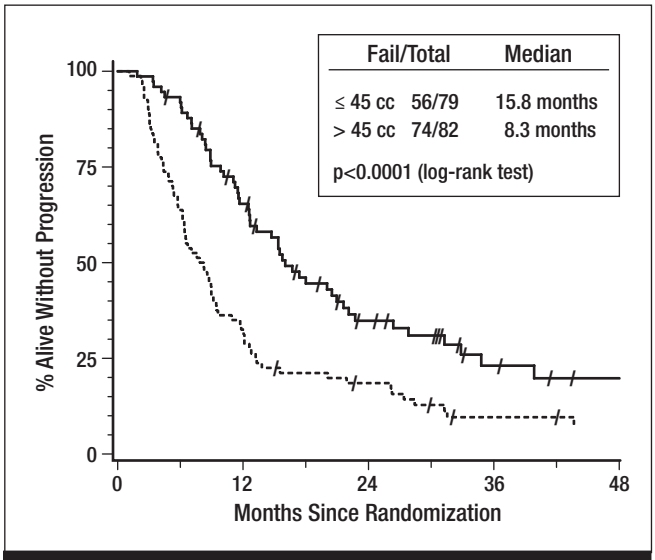

Figure 2. Five-year progression-free survival rate for patients with gross tumor volume ≤45 cm^3 (solid curve) vs. those with gross tumor volume >45 cm^3 (dotted curve).

Table 2. Multivariate analysis of overall survival for different gross tumor volumes used as cutoff point and as continuous variable

Model*	Comparison	Hazard ratio	95% CI	$p^{\dagger}$
GTV (cm^3)	<30 vs. ≥30	2.18	1.43–3.32	0.0003
GTV (cm^3)	≤45 vs. >45	2.12	1.43–3.13	0.0002
GTV (cm^3)	≤60 vs. >60	1.87	1.27–2.75	0.0015
GTV‡	Continuous	1.59	1.33–1.91	<0.0001

Abbreviation: CI = confidence interval; GTV = gross tumor volume; KPS = Karnofsky performance status.
*Following covariates did not meet entry criteria 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-N3), previous chemotherapy (no vs. yes), or maximal dose to lung (continuous).
†Chi-square test using Cox proportional hazards model; stepwise selection, with entry level of 0.05 and exit level of 0.10.
‡GTV transformed using log10 to ensure normalcy.

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 V_{20} <25% and to 77.4 Gy for patients with a V_{20} 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

Table 3. Multivariate analysis of progression-free survival for different gross tumor volumes used as cutoff point and as continuous variable

Model*	Comparison	Hazard ratio	95% CI	$p^{\dagger}$
GTV (cm^3)	<30 vs. ≥30	1.74	1.20–2.53	0.0039
GTV (cm^3)	≤45 vs. >45	2.00	1.40–2.86	0.0002
GTV (cm^3)	≤60 vs. >60	1.65	1.16–2.36	0.0056
GTV‡	Continuous	1.39	1.18–1.64	<0.0001

Abbreviations as in Table 2.
*Following covariates did not meet entry criteria 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-N3), previous chemotherapy (no vs. yes), or maximal dose to lung (continuous).
†Chi-square test using Cox proportional hazards model; stepwise selection, with entry level of 0.05 and exit level of 0.10.
‡GTV was transformed using log10 to ensure normality.

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[4], with the observation of improved local control and survival in Stage III NSCLC patients with large (>100 cm^3) 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[5] 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 ≤79.2 Gy lived longer if their tumors did not exceed 51.8 cm^3 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 has been raised that radiation dose escalation can result in improved outcome in NSCLC, at least in node-negative, early-stage tumors.

Table 4. Frequency of tumor response subdivided by radiation dose level and gross tumor volume cutpoint of 45 cm^3

	Incidence (n)		
GTV ≤45 cm^3	CR/PR	SD/PD	p^{*}
Dose 70.9 Gy	13 (93)	1 (7)	0.2736
Dose 77.4 Gy	14 (82)	3 (18)	
Dose 83.8 Gy	15 (88)	2 (12)	
Dose 90.3 Gy	23 (88)	3 (12)	
Dose 70.9 Gy	21 (70)	9 (3)	
Dose 77.4 Gy	19 (68)	9 (32)	
Dose 83.8 Gy	12 (92)	1 (8)	
Dose 90.3 Gy	8 (89)	1 (11)	

Abbreviation: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; GTV = gross tumor volume.
Data in parentheses are percentages.
*Fisher's exact test.

Table 5. Multivariate analysis of overall survival subdivided by radiation dose level and gross tumor volume cutpoint of 45 cm^3

Model*	n	Hazard ratio	95% CI	$p^{\dagger}$
GTV ≤45 cm^3, dose 83.8 Gy	17	1.60	0.65–3.93	0.3058
GTV ≤45 cm^3, dose 77.4 Gy	17	1.10	0.43–2.82	0.8432
GTV ≤45 cm^3, dose 70.9 Gy	14	1.57	0.63–3.91	0.3301
GTV >45 cm^3, dose 90.3 Gy	9	4.20	1.52–11.64	0.0058
GTV >45 cm^3, dose 83.8 Gy	13	3.83	1.53–9.60	0.0041
GTV >45 cm^3, dose 77.4 Gy	28	2.41	1.06–5.48	0.0361
GTV >45 cm^3, dose 70.9 Gy	30	2.61	1.17–5.84	0.0193

Abbreviations as in Table 4.
Reference level: GTV ≤45 cm^3, dose 90.3 Gy.
*Chi-square test using Cox proportional hazards model.

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[10] or other hypofractionated regimens[11]. 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 cm^3 than with the larger tumors. The 45-cm^3 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 node-negative tumor measuring ≤3 cm in the largest dimension. Separate values for the primary GTV and the nodal GTV were not available in the RTOG 93-11 study; therefore, we were unable to isolate their respective influences on outcomes.

Because a rigorous evaluation of locoregional control was not performed in the RTOG 93-11 trial, local control was not assessed in an actuarial fashion and the radiographic responses might not reflect the true biologic tumor elimination; using survival as an endpoint is a more objective measure of the relevance of tumor volume. A strong association of increasing tumor volume with worsened survival and PFS was observed in our analysis, overriding other known prognostic factors for survival, such as lower disease stage.

Such an association has been previously reported[1–9]. In 207 patients with inoperable NSCLC (Stage I-III) treated at the Washington University with 3D-conformal thoracic RT[1], overall survival, cause-specific survival, and local tumor control were highly correlated with the GTV, 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 cm^3 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[2]. A volumeof ≤63cm^3 and a diameter of ≤4 cm were significantly associated with improved local control compared with larger volumes or diameters. In a large series from Wuerzburg[6], 784 scans of 136 patients were evaluated volumetrically, and a cutoffpoint of 100 cm^3 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[7].

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[3], 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[7] of 71 patients with Stage III NSCLC, on univariate analysis, the total tumor volume and the primary 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[8] 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 cm^3 (sum of volumes of the abnormal hilar and mediastinal lymph nodes), as well as a 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 cm^3 (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.

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