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Pulmonary Artery Invasion, High Dose Radiation, and Overall Survival in Patients with Non-Small Cell Lung Cancer

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Abstract

Purpose—This study aimed to investigate whether high dose radiation to the pulmonary artery (PA) affects overall survival (OS) in patients with non-small cell lung cancer (NSCLC).

Methods and Materials—Patients with medically inoperable/unresectable NSCLC treated with definitive radiotherapy (RT) in prospective studies were eligible for this study. PA involvement was defined on the basis of pre-treatment chest computed tomography (CT) and positron emission tomography CT fusion (PET/CT). PA was contoured according to RTOG 1106 atlas and dose volume histograms were generated.

Results—A total of 100 patients with a minimum follow-up of 1 year for surviving patients were enrolled: 82.0% underwent concurrent chemoradiotherapy. Radiation dose ranged 60–85.5 Gy in 30–37 fractions. Patients with PA invasion of grade 2, 3, 4, and 5 had 1-year overall survival and median survival of 67% and 25.4 months (95% CI, 15.7–35.1), 62% and 22.2 months (95% CI, 5.8–38.6), 90% and 35.8 months (95% CI, 28.4–43.2), and 50% and 7.0 months, respectively ($P = 0.601$). Two of the 4 patients with grade 5 PA invasion died suddenly from massive hemorrhage at 3 and 4.5 months after completion of RT. Maximum and mean doses to PA were not significantly associated with OS. V45, V50, V55, and V60 of PA were correlated significantly with a worse OS

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($P < 0.05$). Patients with $V45 > 70\%$, or $V60 > 37\%$ had significantly worse OS (13.3 vs. 37.9 $P < 0.001$, and 13.8 vs. 37.9 months, $P = 0.04$, respectively).

Conclusions—Grade 5 PA invasion and PA volume receiving more than 45-60 Gy may be associated with inferior OS in patients with advanced NSCLC treated with concurrent chemoradiation.

Keywords

Non-small cell lung cancer; Pulmonary artery; High dose radiation; Survival

INTRODUCTION

Lung cancer is a leading cause of cancer-related death in the world.^[1] Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers, with only 20% of these patients presenting with localized disease at diagnosis.^[2, 3] The standard treatment for stage I/II NSCLC is surgical resection, and 5-year overall survival (OS) ranges from 53% to 82% for stage I and from 29% to 51% for stage II.^[4, 5] In patients with medically inoperable early stage NSCLC, stereotactic body radiotherapy (SBRT) and hypofractionated dose-intensified conventionally fractionated radiotherapy have provided outstanding disease control and are the standard of care.^[6-8] Unfortunately, about one third of NSCLC patients present with locally advanced unresectable disease that cannot be safely treated with SBRT. In patients with good performance status in this group, concurrent chemotherapy and thoracic radiation therapy (RT) are the standard of care.^[8-10] A dose of 60 Gy or slightly higher is considered standard using a conventional schedule of 2.0 Gy daily fractions.^[9, 11, 12] High dose radiotherapy may improve local tumor control, but it is often associated with increased risk of treatment toxicity.^[12, 13] However, preliminary results from the RTOG 0617, a large randomized trial designed to determine whether a high dose of RT (74 Gy) with chemotherapy +/- Cetuximab versus a standard dose of RT (60 Gy) with chemotherapy +/- Cetuximab improved OS in patients with stage III, locally advanced, unresectable NSCLC, reported an inferior median OS (19.5 vs. 28.7 months, $p=0.0007$). RTOG 0617 also noted that 2.3% and 3.9% increase in deaths from treatment-related adverse events at 12 and 18 months, respectively including those from massive hemorrhage in the high dose arm (74 Gy).^[14] The reason for inferior survival from high dose radiation is unclear. One reason may be due to the low local-regional control, and the local failure rates were 25.1% vs. 34.3% at 18 months for 60 Gy and 74 Gy patients, respectively ($p=0.03$). It was also notable that there were 2 more cases with reported massive bleeding in the 74 Gy arm. One would ask whether high dose radiation to blood vessels contributes to such events. Cancer invading large vessels may also cause massive bleeding, which is sometimes not detected. The pulmonary artery (PA) is described as one of the most commonly invaded thoracic vessels in patients with advanced lung cancer, and was reported to be a source of life-threatening massive bleeding from tumor progression.^[15, 16] We hypothesize that high dose radiation applied to tumor-invaded PA may cause perforation or fistula and subsequently life threatening hemoptysis, or unattributable deaths in patients with advanced NSCLC. Our primary aim is to investigate whether high dose radiation to the pulmonary artery is associated with a decrease in 1 year and median overall survival.

METHODS AND MATERIALS

Eligibility

Patients with medically inoperable or unresectable NSCLC, enrolled in institutional review board-approved prospective clinical trials at XXX and the XXX hospitals, were eligible for this study. All patients had a cytological or histological diagnosis of stage I-III NSCLC and Karnofsky Performance Status (KPS) score ≥ 60 . All patients were treated with definitive fractionated radiotherapy with or without concurrent chemotherapy. Patients with malignant pleural effusion were excluded.

Radiotherapy was given by using 3D conformal technique. A total dose of 60-85.5 Gy was delivered with 2-3.8 Gy daily fractions over 6-7 weeks using 6-16 MV photons. Patients underwent contouring of gross tumor volume, edited in the best judgment of the radiation oncologist. In general, the prescribed dose covered 95% planning target volume (PTV), and was limited by tolerance limits of normal tissue. In principle, dose to the total lung was limited to less than 35% of lung volume receiving ≥ 20 Gy (V_{20}), spinal cord 50 Gy, brachial plexus 66 Gy, 1/3 heart volume receiving ≥ 60 Gy, 2/3 ≥ 45 Gy, and 3/3 ≥ 40 Gy. Lung volumes were defined as bilateral lungs per an atlas,^[17] with subtraction of gross tumor volume (GTV).^[18] Respiratory motion was assessed by 4DCT simulation when it was available. Active breathing control was applied when the tumor motion was greater than 1 cm. When 4DCT was used, average scan was used for RT planning; lungs were contoured from the average scan.

PA was contoured according to RTOG 1106 atlas (Figure 1), and a dose-volume histogram was generated. The pulmonary artery was contoured separately from the heart, using a mediastinal window to include the vascular wall and all muscular layers and the fatty adventitia. The mean and maximum doses to PA as well as the percentage of volume receiving a specific dose (from V_{10} to V_{95}) were obtained from an in-house image analysis system-FIAT.

Assessment of pulmonary artery invasion

Tumor involvement of the PA was scored based on pretreatment CT scan and PET/CT as 0, 1, 2, 3, 4 and 5 for none, adjacent, abutting, encasement, invasion, and massive invasion, respectively. The grading details are summarized in Table 1 and Figure 2A-H.

Follow-up and post-treatment evaluation

All patients underwent follow up clinically and with chest CT at 3, 6, 9, 12, 18, and 24 months, and yearly thereafter. Additional CT and PET-CT scans were performed as clinically indicated. Toxicity was assessed prospectively using the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical analysis

Overall survival was estimated using the Kaplan-Meier method from start of radiotherapy, and differences were compared with log-rank test. Both univariate and multivariate analyses were performed to test for the statistical significances. Multivariate analysis was conducted

using Cox proportional hazards models containing all significant variables identified by univariate analysis. Pearson correlation was used to evaluate the correlation between two variables, such as PA volume percentage receiving a specific dose and target volume including GTV, CTV and PTV as well as stage, and correlation between RT dose and target volume (GTV, CTV and PTV). If two variables had a correlation co-efficient greater than 0.7, then simultaneous inclusion in the same multiple variable regression models was considered inappropriate. These variables were thus entered separately one by one with other independent variables for multivariable analysis. The optimal cutoff points of PA volume for specific doses were determined by Youden index in receiver operating characteristic (ROC) analysis. Area under the curve (AUC) determined by ROC analysis was used to estimate the predictive ability of covariates for survival status; cutoff values were evaluated and confirmed by repeated Kaplan-Meier and multivariate Cox analyses.

RESULTS

Patient's characteristics

One hundred patients with pathological stage I-III NSCLC with at least 1 year follow-up for surviving patients were eligible for this study. Patient characteristics are summarized in Table 2. Median patient age was 66 years (range: 43 to 85 years). Eighty-two patients (82%) were male, and eighty (80%) had stage III disease. Concurrent chemotherapy was administered in 82 (82%) patients. The median radiation dose was 70 Gy (range: 60 to 85.5 Gy). As shown in Table 3A, 53, 19, 5, 9, 10, and 4 patients had 0, 1, 2, 3, 4, and 5 grade tumor involvement of PA, respectively.

Overall survival and PA invasion

The relationships between 1-year and median overall survival and PA tumor invasion are listed in Table 3a. There was no significant difference in overall survival among the subgroups according to PA invasion grading ($P = 0.601$, Figure 3A). However, it was of note that 2 of 4 patients with grade 5 PA invasion died suddenly from massive hemorrhage at 3 and 4.5 months after radiotherapy (Figure 2I, J). Univariate analysis demonstrated that radiation dose was an independent significant factor for OS. Age, gender, histology, tumor location, chemotherapy, and higher maximum PA radiation dose were not significantly associated with risk of death in this group of patients (Table 3B). Multivariate analysis confirmed the effect of radiotherapy dose, and higher RT dose was associated with better OS ($P < 0.05$). Median survival was 42.6 months (95% CI 17.3-67.8 months) and 18.2 months (95% CI 10.3-26.0 months) for patients treated to prescription dose > 70 Gy and < 70 Gy, respectively (Figure 3B).

PA dosimetry and overall survival

Maximum and mean PA doses were not significantly associated with OS; however, multivariate analysis showed PA volumes that received 45-60 Gy were significantly correlated with OS independent of GTV, CTV and PTV ($P < 0.05$; Table 3C). RT dose was not correlated with GTV (Pearson correlation coefficient -0.187 , $P = 0.072$), however it did weakly correlate with CTV and PTV (Pearson correlation coefficient -0.284 , $P = 0.007$; -0.458 , $P < 0.001$, respectively). Additionally, weak correlations were noted between the

PA V45-65 and GTV, CTV and PTV, or stage (Pearson correlation coefficient range: 0.254-0.352, $P < 0.05$). According to the ROC curve, the best cutoff value for OS prediction for PA V₄₅ was 70% and for PA V₆₀ it was 37%. Patients with PA V₄₅ > 70% or PA V₆₀ > 37% had significantly worse survival (median survival 13.3 (95% CI 11.3-15.3) vs. 37.9 (95% CI 30.3-45.4) months, $P < 0.001$, and 13.8 (95% CI 10.9-16.7) vs. 37.9 (95% CI 28.2-47.6) months, $P = 0.04$, respectively; Figure 3C). Furthermore, patients with PA V₄₅ > 70% had a significantly worse overall survival or 1-year survival irrespective of total radiation dose (Figure 3D).

DISCUSSION

This study demonstrates that 1-year overall survival and median survival time were not significantly associated with the grade of PA invasion; however, a high percentage of our small sample size of grade 5 PA invasion cases died early from massive hemorrhage, suggesting that grade 5 PA invasion may carry a relatively higher risk of massive bleeding. Maximum and mean PA doses were not significantly associated with OS or 1-year OS, though PA volumes of 45-60 Gy were significantly correlated with OS. Specifically, patients with PA V₄₅ > 70%, or V₆₀ > 37% had a significantly worse OS, suggesting that PA V₄₅ ~70% and PA V₆₀ ~37% are cut-off values predictive of inferior 1-year OS in patients with advanced NSCLC treated with definitive RT.

High dose radiation may cause PA damage and massive bleeding and thus, poorer survival at 1 year. This study, however, did not reach such a correlation. Consistent with our own previous findings and other studies [19-21], high prescription dose was the most significant factor for increasing survival. This, however, differs from the findings of RTOG 617, which showed a decrease in local-regional control and median OS with high dose of 74 Gy compared with standard dose of 60 Gy, and an increase in massive bleeding associated death at high doses.^[14] The reason for this discrepancy is not clear. However, there is a major difference in the methods of dose prescription between this and RTOG studies: we prescribed the tumor dose with a fixed rate of lung normal tissue complication probability thus strictly limiting the risk to other organs, whereas RTOG 617 prescribed a fixed high dose of 74 Gy to the tumor target with simple dose-volume limits. Additionally, 1-year survival may not reflect the true effect of dose on long-term tumor control. Longer follow-up is needed. Nevertheless, it is encouraging that our isototoxicity prescription was not associated with poor survival. Further tests on whether such an approach will improve local regional tumor without increasing toxicity-related death are expected.

The relationship between PA invasion and survival has not been studied previously. The literature on grading PA invasion is also limited. Herein, we attempted to classify the invasion according to tumor involvement of the PA assessed by pretreatment CT or PET/CT scan. It has been reported that the pulmonary artery is the most commonly tumor-involved thoracic vessel.^[22, 23] The present study, consistent with RTOG 617, notes massive bleeding as a cause of death. Such bleeding occurred in 2 out of 4 patients with grade 5 PA invasion, suggesting that massive invasion may be a risk factor for massive bleeding, though the number of cases is small. It is not clear whether the deaths from massive bleeding in RTOG 617 were associated with PA invasion. We also assume that some patients may die from

undetected massive bleeding, thus contributing to the poorer 1-year survival. However, there was no significant difference in 1-year overall survival among the subgroups classified by the degree of PA invasion in this study. It is challenging to treat patients with PA invasion. Some studies have reported that the pulmonary artery may be reconstructed after surgical resection,^[22, 24] which unfortunately is associated with life-threatening postoperative complications.^[22, 24] It is interesting and encouraging that the maximum PA dose was not significantly associated with overall survival. Furthermore, patients given higher-dose radiation exhibited better overall survival compared to those receiving radiation doses 70 Gy, suggesting that the survival benefit may be due to the high dose radiation to the tumor of NSCLC. Interestingly, PA volume receiving more than 45-60 Gy was predictive of inferior 1-year overall survival in patients with NSCLC regardless of the prescription dose. Although the reason for these results is not clear, this might suggest a negative impact of tumor location as well as the target volume in proximity to PA. This is the first report of such a result; studies with a larger group size are needed for further validation.

CONCLUSIONS

Overall grade of PA invasion was not associated with overall survival in patients with inoperable NSCLC, although massive PA invasion may result in a high risk for severe hemoptysis and early mortality. Moderate-to-high PA dose volume was predictive of worse survival for patients with PA-involved NSCLC. Future prospective studies with larger numbers of patients are needed to validate these findings.

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SUMMARY

This study investigates whether high dose radiation to pulmonary artery (PA) decreases OS in patients with NSCLC. PA involvement was defined on the pre-treatment chest CT according to a defined grading system. Our study shows the maximum and mean PA doses and grade of PA invasion were not significantly associated with OS or 1-year OS, however, PA volume receiving more than 45-60 Gy may be predictive of inferior OS.

Figure 1.

Pulmonary artery (PA) contouring according to RTOG 1106 atlas A: PA contour starts at this level, B: Left PA trunk, C: Right PA trunk, D: Left PA ends at this level, E: PA trunk and right PA, F: Right PA ends at this level.

Figure 2.

CT Grading system of PA invasion. A, B, C, D, E, F, G and H are grade -2, -1, 0, 1, 2, 3, 4 and 5 respectively. White arrow indicates PA invasion.

A: Grade -2, >20mm from the closest vessel wall;

B: Grade -1, 5-20mm from the closest vessel wall;

C: Grade 0, no evidence of vessel invasion, 1-5mm from the closest vessel wall;

D: Grade 1, <50% circumferential involvement without presence of narrowing or truncation of vessels;

E: Grade 2, >50% circumferential involvement without presence of narrowing or truncation of vessels;

F: Grade 3, smooth narrowing without truncation;

G: Grade 4, presence of truncation of left PA;

H: Grade 5, tumor encasing, narrowing, and invading left PA extensively, with presence of irregularity, and invading 2 great vessels (left PA and descending aorta)

I,J: Example CT scans of two patients with grade 5 PA invasion died from massive hemorrhage at 3 and 4.5 months respectively after radiotherapy.

Figure 3.

Pulmonary Artery (PA) invasion, radiation dose, dose volume of PA and overall survival.

A: PA invasion and overall survival. MS= median survival B: Radiation dose and overall survival.

C: Dose volume of PA and overall survival.

D: RT dose and PA V45 (70%). There was no linear correlation between RT dose and PA V45. However, overall survivals were significantly different between PA V45 ≤ 70% vs. PA V45 > 70%, MS 23.0 (95% CI 2.0-44.1) months vs. 13.3 (95% CI 11.4-15.2) months

($P=0.016$) in patients received RT 70 Gy. In patients with PA 45–70%, patients received RT >70 Gy survived significant better, with MS of 42.6 (95% CI 35.9–49.3) months in RT >70 Gy vs 23.0 (95% CI 2.0–44.1) months of RT 70 Gy ($P=0.015$).

Table 1
Grading criteria of pulmonary artery invasion

Grade*	Descriptions
Grade -2	>20mm from the closest vessel wall
Grade -1	5-20mm from the closest vessel wall
Grade 0	No evidence of vessel invasion, 1-5mm from the closest vessel wall (presence of a fat plane between tumor and vessel wall)
Grade 1	50% circumferential involvement (0 mm to the closest vessel wall, no fat plane) without presence of narrowing or truncation of vessels, nor signs of vessel wall damage (irregularity, discontinuity or intra-luminal mass formation)
Grade 2	>50% circumferential involvement without presence of narrowing or truncation of vessels, and without signs of vessel wall damage (irregular, discontinuity or intra-luminal mass formation)
Grade 3	Any circumferential involvement with smooth narrowing without truncation nor signs of vessel wall damage.
Grade 4	Presence of slit-like narrowing, or truncation of vessel, without signs of vessel wall damage (irregular, discontinuity or intra-luminal mass formation).
Grade 5	Tumor encasing, narrowing, and invading vessel extensively , with presence of at least one of invading features of luminal irregularity, discontinuity, intra-luminal mass formation or truncation, or invading at least 2 great vessels.

* Grade -2, -1 are considered as grade 0 when statistical analysis was done.

Table 2
Clinicopathological characteristics of patients

Variables	No. of patients
Gender	
Male	82
Female	18
Age	
65	46
>65	54
Median (range)	66 (43-85)
COPD	
No	55
Yes	45
CVD	
No	60
Yes	40
HBP	
No	45
Yes	55
Stage	
I	12
II	8
III	80
Histology	
ade.	16
scc.	31
large CC	2
nos.	51
smoking	
no	11
yes	89
Chemo	
no	18
yes	82
RT Dose (Gy)	
>70	44
70	56
Median (range) (Gy)	70 (60-85.5)
KPS	
Median (range)	90 (60-100)

Abbreviations: COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; HBP: hypertension; ade.: adenocarcinoma; scc.: squamous cell carcinoma; large CC: large cell carcinoma; nos.: not otherwise specified; chemo: chemotherapy; RT: radiotherapy; KPS: Karnofsky performance status.

Table 3
Pulmonary artery involvement and overall survival (OS), and other factors significantly associated with OS by using univariate and multivariate analysis

A: Pulmonary artery involvement and overall survival

Grade	n	1-year survival rate	Median survival (months)*
0	53		
1	19	67%	25.4 (95% CI, 15.7-35.1)
2	5		
3	9	62%	22.2 (95% CI, 5.8-38.6)
4	10	90%	35.8 (95% CI, 28.4-43.2),
5	4	50%	7.0

*
 $P=0.601$ for trend

B: Factors associated with overall survival by using univariate analysis*

Variables		P value	HR	95.0% CI	
				Lower	Upper
Continuous variable	KPS	0.041	0.98	0.95	1.00
	RT_dose	0.000	0.94	0.91	0.97
	PA mean dose	0.030	1.00	1.00	1.00
	GTV_Vol	0.047	1.00	1.00	1.00
	PTV_Vol	0.002	1.00	1.00	1.00
	CTV_Vol	0.005	1.00	1.00	1.00
	PA_V15	0.035	3.27	1.09	9.83
	PA_V20	0.013	4.05	1.35	12.17
	PA_V25	0.006	4.79	1.56	14.65
	PA_V35	0.003	5.34	1.80	16.21
	PA_V40	0.002	5.85	1.93	17.69
	PA_V45	0.001	6.53	2.19	19.52
	PA_V50	0.001	6.49	2.15	19.52
	PA_V55	0.001	6.99	2.24	21.85
	PA_V60	0.001	6.77	2.14	21.39
	PA_V65	0.045	4.00	1.03	15.49
	PA_maximum dose	0.775	1.000	1.000	1.000
Categorical variable	Gender	0.276	0.675	0.333	1.368
	Age	0.072	1.021	0.998	1.043
	Smoking	0.501	1.263	0.640	2.492
	COPD	0.254	0.748	0.454	1.232
	CVD	0.513	0.843	0.506	1.405
	HBP	0.180	1.416	0.852	2.354
	Histology	0.912	1.012	0.825	1.240
	Stage	0.377	1.167	0.828	1.646
	Chemotherapy	0.192	0.688	0.393	1.206
	Grade of PA invasion	0.881	0.948	0.467	1.924
	Tumor location	0.380	0.760	0.413	1.401

Abbreviations: RT, radiation prescribed dose; PA_V15-V65, pulmonary artery volumes that received 15-65Gy.

C: Factors significantly associated with overall survival by using multivariate analysis*

	B	P value	HR	95% CI	
				lower	upper
RT Dose	-0.05	0.003	0.95	0.92	0.98
PA V45	1.22	0.047	3.37	1.02	11.18
PA V50	1.23	0.048	3.41	1.01	11.50
PA V55	1.30	0.042	3.68	1.05	12.95
PA V60	1.37	0.029	3.82	1.14	12.79

* Multivariate analysis variables contain all significant variables according to univariate analysis in table 3B. Dosimetric parameters (PA_V15, V20, V25, V30, V35, V40, V45, V50, V55, V60, and V65) or tumor volume parameters (GTV, CTV, and PTV) were entered into multivariate analysis separately one by one.