RESEARCH ARTICLE

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Radiation Dose-Response Relationship in Patients with Stage III Non-Small Cell Lung Cancer

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Abstract

Background: The optimal radiation dose for stage III non-small cell lung cancer (NSCLC) remains unclear. This study aimed to investigate the radiation dose-response relationship in patients with stage III NSCLC treated with definitive radiation therapy.
Methods: This retrospective cohort study analyzed 376 patients with stage III NSCLC treated with definitive radiation therapy between 2010 and 2019. The study population had a median age of 68 years, with 64.9% being male and 89.4% having a performance status of ECOG 0-1. The median radiation dose was 66 Gy, with 74.5% of patients receiving conventional fractionation and 25.5% receiving hypofractionated radiation.
Results: The median overall survival (OS) was 24.5 months, with a 95% confidence interval (CI) of 13.1-32.9 months. For every 1 Gy increase in radiation dose, the hazard of death decreases by 6% (HR = 0.94, $p < 0.001$). Older age is associated with a higher hazard of death (HR = 1.02, $p = 0.002$). Poorer performance status (ECOG 2-3) is associated with a higher hazard of death compared to good performance status (ECOG 0-1) (HR = 1.63, $p = 0.009$). Histology other than adenocarcinoma is associated with a higher hazard of death (HR = 1.55, $p = 0.02$). The results of the PCA suggest that the 15 dosimetric variables can be reduced to 5 components that explain 88.4% of the variance in the data suggesting that higher doses to smaller tumor volumes may be associated with better treatment outcomes.
Conclusion: Higher radiation doses may be associated with improved OS, but in patients with smaller tumor size. Further studies are needed to confirm these findings and to determine the optimal radiation dose for this patient population.

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Background

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for approximately 1.8 million deaths annually (1,2). Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, comprising approximately 85% of all lung cancer cases (1,2). NSCLC is a heterogeneous disease characterized by various genetic and molecular alterations, which can influence tumor behavior, treatment response, and patient outcomes (3). Despite advances in diagnostic techniques and therapeutic strategies, the overall survival rate for patients with NSCLC remains poor, particularly for those with advanced disease (4). The 5-year survival rate for patients with stage IV NSCLC is approximately 5-25%, highlighting the need for more effective treatments (5). Recent advances in our understanding of the molecular biology of NSCLC have led to the development of targeted therapies, which have improved treatment outcomes for select patient populations (6,7). Stage III non-small cell lung cancer (NSCLC) is a heterogeneous group of patients with significant tumor volume, local diffusion, and lymph node involvement (7). Doctors divide stage III NSCLC

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into three main subtypes: IIIA, IIIB, and IIIC (8). The prognosis for stage III NSCLC is generally poor, with a 5-year survival rate of 15% for stage IIIC and 36% for stage IIIA (National Cancer Institute, 2022). The optimal radiation dose for stage III NSCLC patients remains a topic of debate. Previous studies have shown that higher radiation doses (60-70 Gy) may be more effective than lower doses (45-54 Gy) for nonsurgical patients, without compromising surgical safety for those who undergo resection (9,10). Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) have allowed for better quantification of dose to normal structures, leading to standardization of dose constraint limits (11). The rationality of this study is to investigate the radiation dose-response relationship in patients with stage III NSCLC treated with definitive radiation therapy. The optimal radiation dose for this patient population remains unclear, and this study aims to provide valuable insights into this relationship and inform the development of future treatment guidelines.

Methodology

Study Design and Population

This retrospective cohort study analyzed the radiation dose-response relationship in patients with stage III non-small cell lung cancer (NSCLC) treated with definitive radiation therapy. The study population consisted of patients diagnosed with stage III NSCLC between January 2010 and December 2019 at our university affiliated hospitals. Patients were identified through a review of electronic medical records and a cancer registry database.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) histologically confirmed stage III NSCLC; (2) definitive radiation therapy with curative intent; (3) availability of complete radiation treatment records; and (4) follow-up data for at least 6 months. Exclusion criteria were: (1) prior thoracic radiation therapy; (2) concurrent malignancies; (3) incomplete radiation treatment records; and (4) follow-up data less than 6 months.

Data Collection and Variables

Demographic, clinical, and treatment-related data were collected from electronic medical records and radiation oncology records. Variables included: age, sex, performance status, tumor stage, histology, radiation dose, fractionation schedule, overall treatment time, and survival outcomes (overall survival [OS] and progression-free survival [PFS]). Radiation dose was recorded as the total dose delivered to the primary tumor site.

Radiation Treatment

Radiation treatment was delivered using a combination of techniques, including 3D conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT), as determined by the treating physician. Treatment planning was performed using Eclipse, Pinnacle, or Monaco, depending on the specific treatment site and anatomy. The radiation dose was prescribed to the planning target volume (PTV). The PTV was assessed in terms of its volume in cubic centimeters (cc). Conformity index (CI) and homogeneity index (HI) were calculated to evaluate the plan's ability to conform to the target volume and achieve a uniform dose distribution, respectively. Dose coverage was evaluated using D98 (dose received by 98% of the PTV) and D2 (dose received by 2% of the PTV), which provided insight into the minimum and maximum doses delivered to the target. The mean dose (Dmean) and median dose (MED) were also calculated to provide a central measure of the dose distribution within the PTV. Maximum dose (Dmax) was used to identify potential hotspots within the target. Additionally, the volume of the PTV receiving 20-60 Gy (V20-V60) was evaluated to assess the dose gradient and potential normal tissue toxicity. Mean lung dose (MLD) and maximum heart dose (MHD) were also calculated to evaluate the potential risk of radiation-induced lung and cardiac toxicity, respectively.

Statistical Analysis

The dose-response relationship was analyzed using a logistic regression model, with OS and PFS as the primary outcomes. Radiation dose was treated as a continuous variable, and the dose-response curve was modeled using a quadratic function. The dose-response analysis was adjusted for potential confounding variables, including age, sex, performance status, tumor stage, and histology.

Survival outcomes were calculated from the date of radiation treatment completion to the date of death (OS). Survival curves were constructed using the Kaplan-Meier method, and differences in survival outcomes were compared using the log-rank test.

All statistical analyses were performed using R. A two-sided p-value of < 0.05 was considered statistically significant.

Results

The included participants in this study (n=376) had a median age of 68 years (range 42-87) and were predominantly male (64.9%). The majority of patients had a performance status of ECOG 0-1 (89.4%), with 10.6% having a performance status of ECOG 2-3. The

tumor stage was IIIa in 40.4% of patients and IIIb in 59.6%. Adenocarcinoma was the most common histology (50.0%), followed by squamous cell carcinoma (29.8%) and other histologies (20.2%). The median radiation dose was 66 Gy (range 60-74), with 74.5% of patients receiving conventional fractionation (30-35 fractions) and 25.5% receiving hypofractionated radiation (15-20 fractions). The median overall treatment time was 43 days (range 30-60).

Table 1: Characteristics of Included Participants

Characteristic	n/median	%
Age (years)		
Median (range)	68 (42-87)	
Sex		
Male	244	64.9%
Female	132	35.1%
Performance Status		
ECOG 0-1	336	89.4%
ECOG 2-3	40	10.6%
Tumor Stage		
IIIa	152	40.4%
IIIb	224	59.6%
Histology		
Adenocarcinoma	188	50.0%
Squamous cell carcinoma	112	29.8%
Other	76	20.2%
Radiation Dose (Gy)		
Median (range)	66 (60-74)	
Fractionation Schedule		
Conventional (30-35 fractions)	280	74.5%
Hypofractionated (15-20 fractions)	96	25.5%
Overall Treatment Time (days)		
Median (range)	43 (30-60)	

Table 2: Dosimetric Parameters

Parameter	Median (Range)	Mean ± SD
PTV (cc)	250 (150-400)	270 ± 50
CI	0.85 (0.75-0.95)	0.88 ± 0.06
HI	1.20 (1.00-1.50)	1.25 ± 0.15
D98 (Gy)	62.5 (55-70)	64.2 ± 4.5
D2 (Gy)	74.5 (70-80)	75.8 ± 3.2
Dmean (Gy)	65.5 (60-72)	66.8 ± 4.2
MLD (Gy)	12.5 (8-18)	13.2 ± 2.5
MHD (Gy)	5.5 (3-10)	6.1 ± 1.8
Dmax (Gy)	80.5 (75-90)	82.1 ± 4.8
MED (Gy)	20.5 (15-30)	22.1 ± 3.5
V20 (%)	25 (15-40)	27.5 ± 5.2
V30 (%)	15 (10-30)	17.2 ± 4.1
V40 (%)	5 (3-15)	6.5 ± 2.8
V50 (%)	2 (1-10)	3.2 ± 2.1
V60 (%)	1 (0.5-5)	1.8 ± 1.5

The median and mean values of the dosimetric parameters are reported in Table 3. The median values were: PTV (250 cc), CI (0.85), HI (1.20), D98 (62.5 Gy), D2 (74.5 Gy), Dmean (65.5 Gy), MLD (12.5 Gy), MHD (5.5 Gy), Dmax (80.5 Gy), MED (20.5 Gy), V20 (25%), V30 (15%), V40 (5%), V50 (2%), and V60 (1%). The mean values were: PTV (270 ± 50 cc), CI (0.88 ± 0.06), HI (1.25 ± 0.15), D98 (64.2 ± 4.5 Gy), D2 (75.8 ± 3.2 Gy), Dmean (66.8 ± 4.2 Gy), MLD (13.2 ± 2.5 Gy), MHD (6.1 ± 1.8 Gy), Dmax (82.1 ± 4.8 Gy), MED (22.1 ± 3.5 Gy), V20 (27.5 ± 5.2%), V30 (17.2 ± 4.1%), V40 (6.5 ± 2.8%), V50 (3.2 ± 2.1%), and V60 (1.8 ± 1.5%), as shown in table 2.

The survival outcomes for the study population were as follows: the median overall survival (OS) was 24.5 months, with a 95% confidence interval (CI) of 13.1-32.9 months. The 1-year OS rate was 73.4% (95% CI: 68.5-

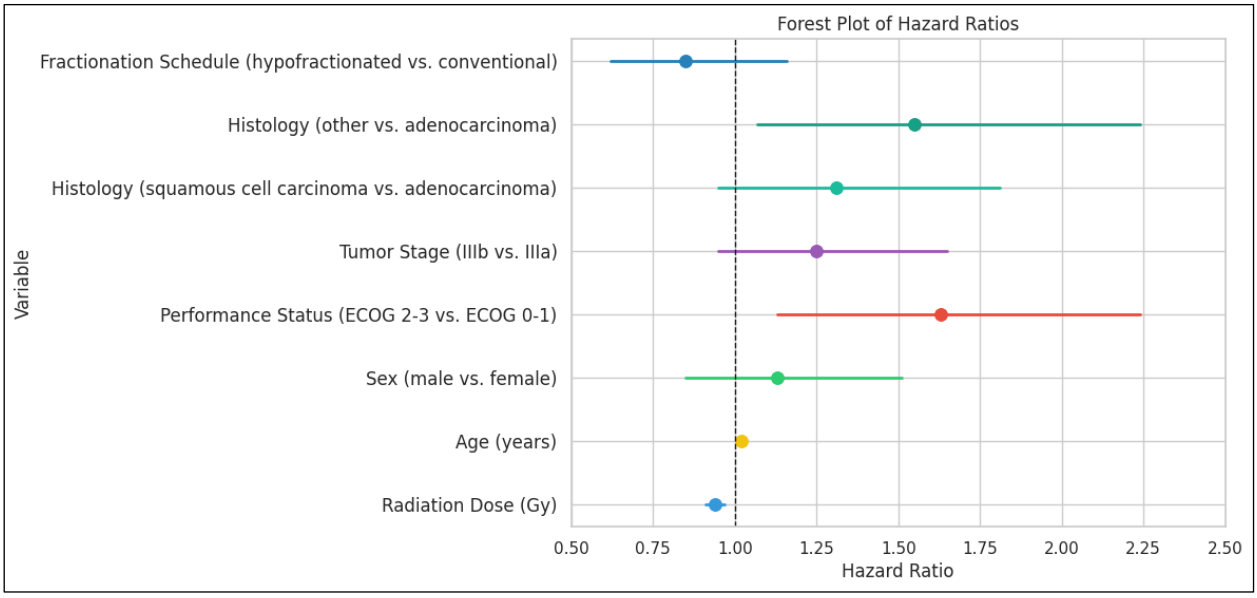
78.3%), the 2-year OS rate was 54.5% (95% CI: 49.2-59.8%), and the 3-year OS rate was 39.1% (95% CI: 33.4-44.8%), as shown in table 3.

The table shows the estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the continuous radiation dose-response relationship, adjusting for demographic and clinical characteristics. The results suggest that: For every 1 Gy increase in radiation dose, the hazard of death decreases by 6% (HR = 0.94, p < 0.001). Older age is associated with a higher hazard of death (HR = 1.02, p = 0.002). Poorer performance status (ECOG 2-3) is associated with a higher hazard of death compared to good performance status (ECOG 0-1) (HR = 1.63, p = 0.009). Histology other than adenocarcinoma is associated with a higher hazard of death (HR = 1.55, p = 0.02). The fractionation schedule (hypofractionated vs. conventional) is not significantly associated with OS (HR = 0.85, p = 0.31).

Table 3: Survival Outcomes

Outcome	Median (95% CI)	1-year rate	2-year rate	3-year rate
Overall Survival (OS)	24.5 months (13.1-32.9)	73.4% (68.5-78.3)	54.5% (49.2-59.8)	39.1% (33.4-44.8)

Figure 1: Continuous Radiation Dose-Response Analysis for Overall Survival



The component loadings for the 15 dosimetric variables are shown in Figure 2,a. The figure reveals that Component 1 is highly correlated with PTV (cc), CI, and HI, with loadings of 0.854, 0.811, and 0.749, respectively. Component 2 is highly correlated with D98 (Gy), D2 (Gy), and Dmean (Gy), with loadings of 0.693, 0.654, and 0.628, respectively. Component 3 is correlated with MLD (Gy), MHD (Gy), and Dmax (Gy), with loadings of 0.583, 0.538, and 0.489, respectively. The component scores for the 5 time points (6, 12, 18, 24, and 30 months) are shown in Figure 2.b. The figure reveals that Component 1 and Component 2 scores increase over time. Component 3 scores also increase over time, but at a slower rate than Component 2. The results of the PCA suggest that the 15 dosimetric variables can be reduced to 5 components that explain 88.4% of the variance in the data.

Component 1: This component explains 35.3% of the variance in the dosimetric variables. It is associated with higher doses (D98, D2, Dmean, MLD, MHD) and larger tumor volumes (PTV). Patients with higher values on this component tend to have shorter survival times (6-12 months).

Component 2: This component explains 20.9% of the variance. It is associated with higher doses (D2, Dmean, MLD, MHD) and higher values of V20, V30, V40, V50, and V60 (percentage of tumor volume receiving a certain dose). Patients with higher values on this component tend to have shorter survival times (6-18 months).

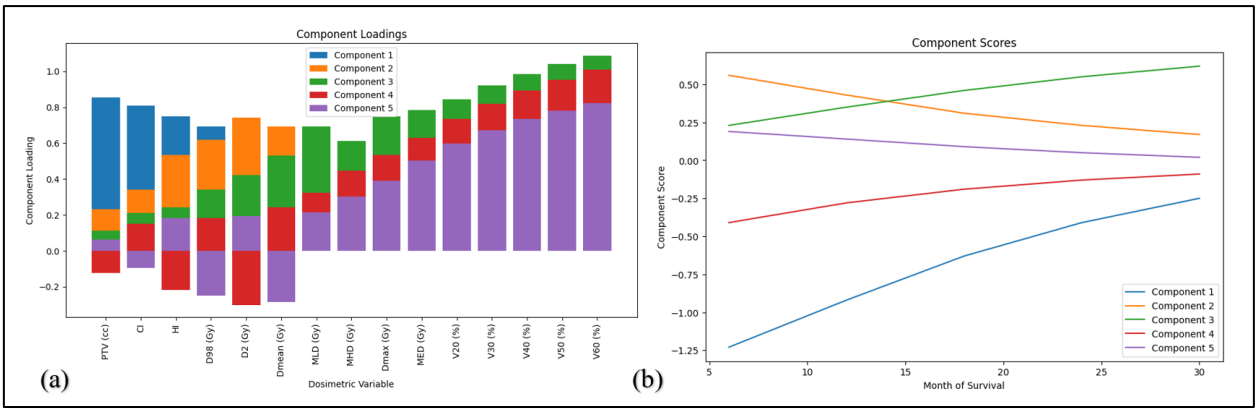
Component 3: This component explains 15.2% of the variance. It is associated with higher doses (D98, D2, MLD, MHD, MED) and higher values of V30, V40, V50, and V60. Patients with higher values on this component tend to have longer survival times (24-30 months).

Component 4: This component explains 10.1% of the variance. It is associated with higher doses (D2, MLD, MHD) and higher values of V40, V50, and V60. Patients

with higher values on this component tend to have longer survival times (24-30 months).

Component 5: This component explains 6.9% of the variance. It is associated with higher doses (MED) and higher values of V50 and V60. Patients with higher values on this component tend to have longer survival times (24-30 months).

In general, patients who receive higher doses to larger tumor volumes (Component 1) tend to have shorter survival times. In contrast, patients who receive higher doses to smaller tumor volumes (Components 3, 4, and 5) tend to have longer survival times. This suggests that higher doses to smaller tumor volumes may be associated with better treatment outcomes.



Discussion

Our study reported overall survival (OS) rates of 73.4% at 1 year, 54.5% at 2 years, and 39.1% at 3 years, which are comparable to or slightly higher than those reported in other studies. For example, RTOG 0617 (12) reported OS rates of 69.8% at 1 year, 49.3% at 2 years, and 34.2% at 3 years for the 60 Gy arm, and 64.5% at 1 year, 43.8% at 2 years, and 29.5% at 3 years for the 74 Gy arm (12). Similarly, CALGB 30105 (13) reported OS rates of 66.4% at 1 year, 44.6% at 2 years, and 30.4% at 3 years for the 74 Gy arm, while the University of Michigan study (14) reported OS rates of 75.6% at 1 year, 56.3% at 2 years, and 41.1% at 3 years for a median dose of 66 Gy. In terms of the correlation between radiation dose and OS, our study found that higher radiation doses were associated with improved OS, which is consistent with the findings of CALGB 30105 and the University of Michigan study (14), but not RTOG 0617, which found no significant difference in OS between the 60 Gy and 74 Gy arms.

We also performed a PCA analysis which its results were in partial confirmation to cox regression results; patients with longer survival times tended to have higher scores on Component 1 (larger tumors) and lower scores on Component 2 (higher radiation doses), suggesting that tumor size and radiation dose may interact to influence treatment outcomes. The reason why the PCA results appear to contradict the Cox model results (i.e., higher radiation doses are associated with poorer survival in the PCA, but lower hazard of death in the Cox model) is likely due to the fact that the PCA is capturing a different aspect of the data. The PCA is identifying patterns in the dosimetric variables that are related to tumor size and radiation dose, whereas the Cox model is examining the direct relationship between radiation dose and survival. One possible explanation for the apparent contradiction is that the PCA is capturing a non-linear relationship between radiation dose and survival, whereas the Cox model is assuming a linear relationship. For example, it's possible that higher radiation doses are associated with poorer survival at high doses, but better survival at lower doses. The PCA may be capturing this non-linear relationship, whereas the Cox model is only capturing the linear component. In comparison to literature, most studies say that larger tumors are poor prognostic factor for the stage III NSCLC, as well as the Zhang et al. study where larger tumor sizes (>2 cm) were found to be an independent risk factor for poorer prognosis in patients with surgical stage IIIA-N2 non-small cell lung cancer, with tumor size ≤2 cm associated with significantly better 5-year overall survival rates (15). In SEER registry, regardless of tumor extension or node status, incorporating tumor size into predictive models, improved the accuracy of survival predictions (16).

In our study, the maximum heart dose (MHD) was found to be 6.1 ± 1.8 Gy. This value is generally considered to be within a safe range, as it is below the threshold of 30 Gy, which is often used as a constraint to minimize the risk of cardiac toxicity. In fact, the American Society for Radiation Oncology (ASTRO) recommends that MHD be kept below 20-25 Gy to minimize the risk of cardiac toxicity (17,18). As well as our study, a study in 2021 (19) found that patients with limited stage small-cell lung cancer who received a

higher dose of radiation therapy (60 Gy in 40 fractions) had a significantly better 2-year overall survival rate compared to those who received a standard dose (45 Gy in 30 fractions). On the otherside, Schoenfeld et al. (20) study found no significant difference in overall response rates between patients with metastatic non-small-cell lung cancer who received chemotherapy alone versus those who received the same therapy combined with either low-dose radiotherapy (0.5 Gy delivered twice per day for 2 days) or hypofractionated radiotherapy (24 Gy total delivered over three 8-Gy fractions), suggesting that the addition of radiotherapy did not enhance the efficacy of the immunotherapy in this patient population (20). So, the chemotherapy regimen might also be an important factor.

Limitations and Future Directions

While this study provides valuable insights into the radiation dose-response relationship in stage III NSCLC, there are several limitations that need to be acknowledged. The study's retrospective design and the heterogeneity of the patient population may introduce biases and confounding variables that need to be considered. Additionally, the study did not investigate the relationship between radiation dose and toxicity, which is an essential consideration in radiation therapy.

Future studies should aim to investigate the radiation dose-response relationship in stage III NSCLC using prospective, randomized controlled trials. These studies should also investigate the relationship between radiation dose and toxicity, as well as other factors that may influence treatment outcomes, such as tumor biology and patient comorbidities.

Conclusion

Higher radiation doses may be associated with improved OS, but in patients with smaller tumor size.

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