

Radiation Pneumonitis following Thoracic Radiotherapy for Lung Cancer

Does Technique Matter?

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ABSTRACT

Background: Radiation pneumonitis (RP) is a common and potentially serious toxicity following thoracic radiotherapy, with symptomatic (Grade ≥ 2) RP occurring in approximately 20% of patients. While modern techniques such as IMRT and VMAT improve dose conformity compared with 3D-CRT, concerns remain regarding increased low-dose lung irradiation and the potential risk of RP. Concurrent chemotherapy, immunotherapy, and lung dose-volume parameters have also been associated with RP.

Aim: To compare the incidence of radiation pneumonitis among patients treated with 3D-CRT, IMRT, and VMAT for primary lung malignancies and identify the clinical and dosimetric predictors associated with its development.

Methods: A single-institution retrospective cohort study was conducted including adults (≥ 18 years) with primary lung malignancies treated with definitive or palliative thoracic radiotherapy (≥ 36 Gy) from January 2013 to December 2024. Clinical, treatment, and dosimetric data were obtained through chart and treatment plan review. The primary endpoint was radiation pneumonitis. RP incidence was compared across radiotherapy techniques, and univariate and multivariate logistic regression analyses were performed to determine clinical and dosimetric predictors.

DOSIMETRIC AND SYSTEMIC PARAMETERS

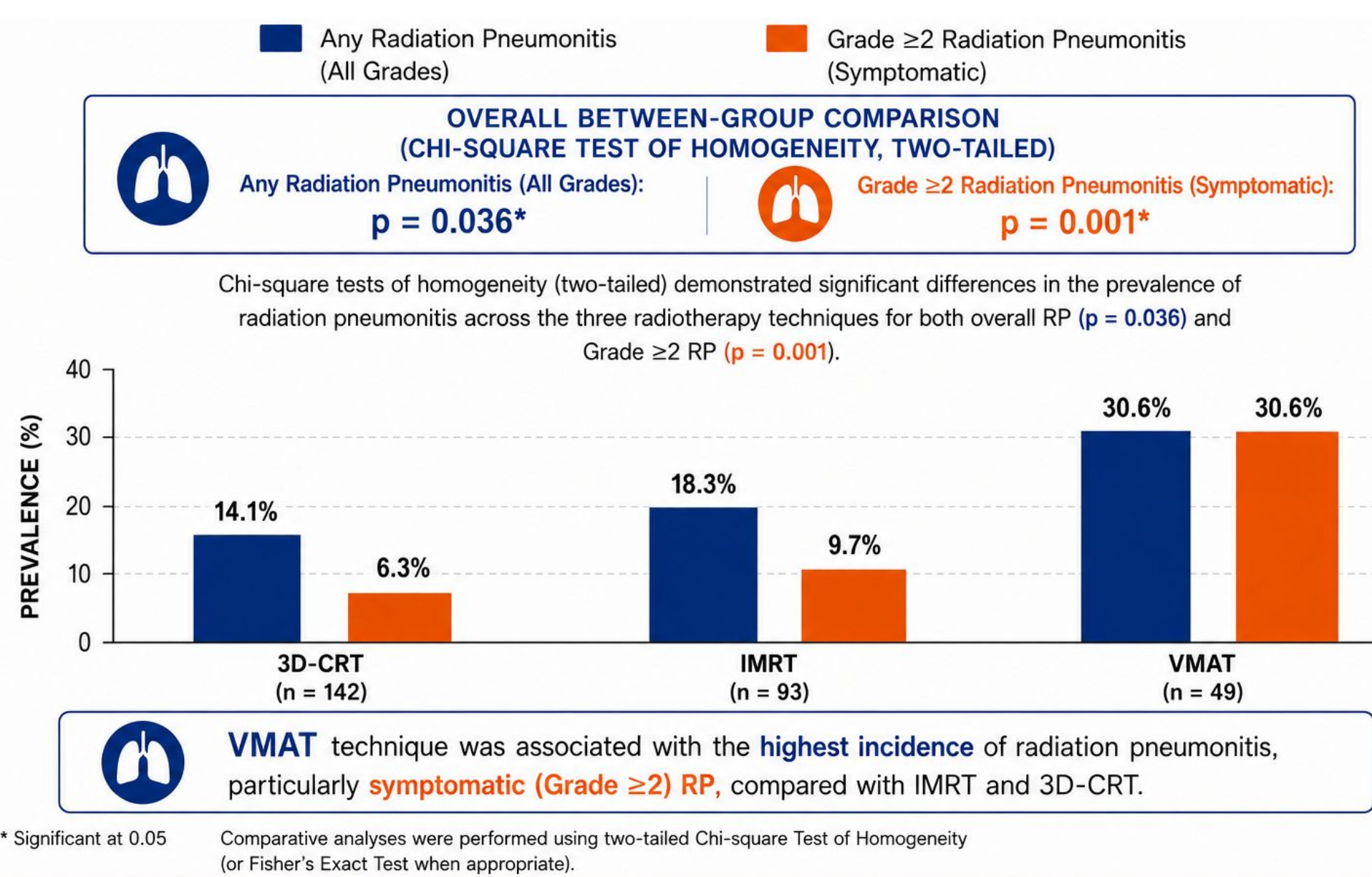
Characteristics	Radiotherapy Technique (N = 284)				p-value (Two-Tailed)
	Total (N=284)	3DCRT (n=142)	VMAT (n=49)	IMRT (n=93)	
Prescribed Dose per Fraction (Gy; $\bar{x}$, SD)	2.09 (0.21)	2.09 (0.22)	2.10 (0.24)	2.07 (0.18)	0.737 ^d
1.50Gy to 2.00 Gy	228 (80.28%)	111 (78.17%)	41 (83.67%)	76 (81.72%)	0.687 ^a
>2.00Gy	56 (19.72%)	31 (21.83%)	8 (16.33%)	17 (18.28%)	
PTV Total Dose (Gy; $\bar{x}$, SD)	59.29 (5.76)	59.05 (6.66)	59.06 (5.39)	59.77 (4.29)	0.617 ^d
PTV Volume (mL; Md, IQR)	385.00 (256.20–561.60)	464.35 (313.60–594.50)	342.50 (222.10–508.10)	309.70 (214.50–449.20)	0.001 ^{c*}
Mean Lung Dose (Gy; Md, IQR)	15.10 (12.35 – 17.05)	16.05 (13.50 – 17.70)	14.00 (11.60 – 16.30)	14.40 (12.50 – 16.60)	0.002 ^{c*}
Bilateral Lung (%; Md, IQR)					
V5 Gy	56.50 (49.10 – 61.80)	56.60 (48.50 – 61.70)	56.50 (48.50 – 61.40)	56.50 (50.20 – 62.20)	0.794 ^c
V10 Gy	40.20 (34.05 – 45.80)	39.70 (34.40 – 44.50)	41.10 (30.50 – 46.20)	41.00 (34.60 – 47.10)	0.622 ^c
V20 Gy	26.15 (22.05 – 29.60)	26.90 (22.70 – 30.10)	24.90 (19.40 – 28.90)	25.70 (22.30 – 29.50)	0.086 ^c
V30 Gy	19.20 (14.65 – 22.20)	21.00 (17.30 – 23.90)	15.70 (12.60 – 19.70)	18.50 (13.90 – 20.60)	0.001 ^{c*}
Receipt of Any Chemotherapy (f, %)	232 (81.69%)	113 (79.58%)	43 (87.76%)	76 (81.72%)	0.443 ^a
Concurrent Chemotherapy (f, %)	196 (69.01%)	89 (62.68%)	41 (83.67%)	66 (70.97%)	0.021 ^{a*}
Consolidation Immunotherapy (f, %)	89 (31.34%)	13 (9.15%)	27 (55.10%)	49 (52.69%)	0.001 ^{a*}

Note: Comparative analyses were conducted using (a) Chi-Square Test of Homogeneity, (b) Fisher's Exact Test, (c) Kruskal-Wallis H Test, or (d) Analysis of Variance (ANOVA)
*Significant at 0.05

DEMOGRAPHIC DATA

Characteristics	Radiotherapy Technique (N = 284)				p-value (Two-Tailed)
	Total (N=284)	3DCRT (n=142)	VMAT (n=49)	IMRT (n=93)	
Age (Years; $\bar{x}$, SD)	67.38 (10.37)	66.49 (10.54)	69.37 (10.01)	67.70 (10.23)	0.231 ^d
Sex (f, %)					0.701 ^a
Male	177 (62.32%)	88 (61.97%)	33 (67.35%)	56 (60.22%)	
Female	107 (37.68%)	54 (38.03%)	16 (32.65%)	37 (39.78%)	
Histology (f, %)					0.124 ^a
Adenocarcinoma	133 (46.83%)	58 (40.85%)	22 (44.90%)	53 (56.99%)	
Small Cell Carcinoma	49 (17.25%)	32 (22.54%)	5 (10.20%)	12 (12.90%)	
Squamous Cell Carcinoma	72 (25.35%)	36 (25.35%)	16 (32.65%)	20 (21.51%)	
Other	30 (10.56%)	16 (11.27%)	6 (12.24%)	8 (8.60%)	
TNM Staging: Tumor (f, %; N = 265)					0.539 ^b
Tx	6 (2.26%)	4 (2.99%)	1 (2.33%)	1 (1.14%)	
T1	60 (22.64%)	27 (20.15%)	7 (16.28%)	26 (29.55%)	
T2	82 (30.95%)	43 (32.09%)	13 (30.23%)	26 (29.55%)	
T3	53 (20.00%)	28 (20.89%)	7 (16.28%)	18 (20.45%)	
T4	64 (24.15%)	32 (23.88%)	15 (34.88%)	17 (19.31%)	
TNM Staging: Node Involvement (f, %; N = 265)					0.312 ^a
N0	42 (15.85%)	22 (16.42%)	6 (13.95%)	14 (15.91%)	
N1	36 (13.58%)	18 (13.43%)	10 (23.26%)	8 (9.09%)	
N2	146 (55.09%)	72 (53.73%)	19 (44.19%)	55 (62.50%)	
N3	41 (15.47%)	22 (16.42%)	8 (18.60%)	11 (12.50%)	
TNM Staging: Metastasis (f, %; N = 265)					0.047 ^b
M0	254 (95.85%)	130 (97.01%)	38 (88.37%)	86 (97.73%)	
M1	11 (4.15%)	4 (2.99%)	5 (11.63%)	2 (2.27%)	
Recurrence	19 (6.69%)	8 (5.63%)	6 (12.24%)	5 (5.38%)	0.236 ^b
Lung Function ($\bar{x}$, SD)					
FEV1 (L; N = 144)	1.90 (0.64)	1.84 (0.72)	1.84 (0.58)	2.00 (0.58)	0.361 ^d
FEV1 (%; N = 132)	73.13 (21.45)	69.49 (25.88)	72.01 (23.48)	76.37 (16.06)	0.256 ^d
FVC (L; N = 139)	3.08 (0.88)	3.10 (0.84)	3.03 (0.81)	3.08 (0.97)	0.947 ^d
FVC (%; N = 130)	91.48 (17.69)	93.76 (16.11)	90.84 (20.90)	90.03 (17.45)	0.559 ^d
FEV1/FVC (N = 139)	64.04 (15.51)	60.62 (14.46)	63.64 (15.30)	67.34 (16.07)	0.069 ^d
Post-Pneumonectomy (f, %)	63 (22.18%)	31 (21.83%)	8 (16.33%)	24 (25.81%)	0.447 ^a

INCIDENCE OF RP ACCORDING TO TECHNIQUE



PREDICTORS OF RP

Univariate and Multivariate Binary Logistic Regression Analyses of the Predictors of $\geq$ Grade 2 Radiation Pneumonitis among the Participants (N = 284)

	Crude Odds Ratio (cOR)	95% CI	p-value (Two-Tailed)	Adjusted Odds Ratio (aOR)	95% CI	p-value (Two-Tailed)
Radiation Therapy Technique						
3DCRT	Referent	–	–	Referent	–	–
VMAT	6.52	2.63 to 16.17	0.001	5.64*	2.34 to 13.60	0.001
IMRT	1.58	0.60 to 4.15	0.350	–	–	–
Bilateral Lung Dosimetry						
Lung Mean Dose	1.18	1.04 to 1.35	0.013	1.28*	1.08 to 1.51	0.004
V5 Gy	1.02	0.99 to 1.06	0.178	0.96	0.90 to 1.02	0.166
V10 Gy	1.05	1.01 to 1.10	0.015	1.08	0.98 to 1.19	0.134
V20 Gy	1.06	0.99 to 1.13	0.058	0.96	0.80 to 1.16	0.691
V30 Gy	1.03	0.97 to 1.10	0.375	–	–	–
Clinical Factors						
Post-Pneumonectomy (With)	0.94	0.39 to 2.27	0.886	–	–	–
Receipt of Any Chemotherapy (With)	3.86	0.89 to 16.65	0.071	3.10	0.45 to 21.29	0.250
Concurrent Chemotherapy (With)	2.77	1.03 to 7.43	0.043	0.64	0.19 to 2.13	0.464
Consolidation Immunotherapy (With)	4.06	1.91 to 8.60	0.001	2.86*	1.27 to 6.46	0.011

*Note: Baseline outcome for grade of radiation pneumonitis was Grade 0 to 1 radiation pneumonitis.
Final Multivariate Model [Included Variables: VMAT Radiotherapy Technique, Lung Mean Dose, Consolidation Immunotherapy]: $\chi^2=35.15$, $p=0.001$, $R^2=17.23\%$
*Significant at 0.05

CONCLUSION

- Treatment with VMAT was associated with significantly increased odds of RP when compared to 3DCRT
- VMAT technique, lung mean dose, and consolidation immunotherapy were independently associated with the development of clinically significant RP on multivariate analysis
- Consolidation immunotherapy increases the likelihood of RP development for the VMAT cohort
- In the current era of thoracic cancer treatment, use of VMAT and immunotherapy with its possible synergistic effects and toxicity should be studied further

REFERENCES



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