Timing of thoracic radiotherapy combined with immunotherapy influences pulmonary injury

JING YUAN[1], QITENG LIU[1], XUAN LIU[1], XIANBIN ZHENG[1], XIANXIU NAN[1], XINJUE SHI[1], SIYAO ZHONG[1], BIN SUN[1], PAN HAO[2], SEN WANG[3] and YUYAN GAO[1]

[1]Department of Radiation Oncology, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, P.R. China; [2]Department of Radiology, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, P.R. China; [3]Department of Neurosurgery, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, P.R. China

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Abstract. The present study aimed to assess the impact of chest radiotherapy combined with immunotherapy at different time points in lung injury. This retrospective study analyzed 35 patients with thoracic tumors (29 lung cancer cases and 6 esophageal cancer cases) who received radiotherapy combined with immunotherapy between January 2021 and December 2023 at at Capital Medical University, affiliated with Beijing Luhe Hospital (Beijing, China), with a median follow-up time of 21 months. Patients were divided into two groups: Group A (sequential, n=17), who received immunotherapy 2 weeks to 6 months before or after radiotherapy, and group B (synchronous, n=18), who received immunotherapy within 2 weeks before or after radiotherapy. Furthermore, the incidence and severity of lung injury, especially pneumonitis, were also compared. Moreover, risk factors for lung injury, as well as 3-year overall survival (OS) rates for stage III and IV lung cancer, were evaluated. There were no significant differences in tumor location, stage, age, tumor type, Eastern Cooperative Oncology Group score or sex between groups. The proportion of PD-1 in group A was higher, while the proportion of PD-L1 was lower, compared with that in group B. Furthermore, radiotherapy techniques and dosimetric parameters were also similar. Moreover, there were no significant differences in onset time between esophagitis, anemia or pneumonitis between the two groups. However, incidence of grade 3 or higher pneumonitis was 0.0% in the sequential group and 23.5% in the synchronous group, which was significantly different. Univariate analysis identified lung mean dose and the percentage volume receiving ≥30 Gy (V_{30}) as significant risk factors, whereas multivariate analysis revealed that V_{30} was an independent prognostic factor. The 3-year OS rates for stage III and IV lung cancer were 44.8 and 22.5%, respectively. In conclusion, the present study revealed that radiotherapy combined with immunotherapy increases the survival rate; however, it also elevates the risk of grade 3+ pneumonitis, especially within 2 weeks of concurrent therapy. As pneumonia occurs at around 3 months after radiotherapy, a follow-up time of 2-4 months post-treatment is recommended.

Correspondence to: Dr Yuyan Gao, Department of Radiation Oncology, Beijing Luhe Hospital, Capital Medical University, 82 Xinhua South Road, Tongzhou, Beijing 101100, P.R. China
E-mail: yuyan_gao@mail.ccmu.edu.cn

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Introduction

In recent years, with the rapid evolution of tumor treatment technologies, immunotherapy, especially immune checkpoint blockade, such as occurring via used of PD-1/PD-L1 inhibitors, has emerged as a novel and promising therapeutic modality for thoracic tumors (1). This approach offers new hope to countless patients with cancer. One study found that low-dose targeted radionuclide therapy (TRT) combined with immune checkpoint inhibitors (ICIs) could render immunologically cold tumors responsive to ICIs. This combination improves tumor treatment outcomes, reduces metastatic burden, increases the complete response rate and prolongs survival time (2). The PACIFIC (3) study indicated that immunoconsolidation therapy after concurrent chemoradiotherapy increases the 5-year progression-free survival (PFS) and 5-year overall survival (OS) rates in patients with locally advanced non-small cell lung cancer (NSCLC). Therefore, radiotherapy, integrated with immunotherapy such as ICI therapy, has become a standard treatment strategy for patients with NSCLC. (1). However, another study has revealed some concerning issues. The results of the study indicated that both radiotherapy and immunotherapy may disrupt immune homeostasis, thereby triggering systemic immune responses and adverse events, such as pneumonitis, myocarditis and anemia (4). These issues have received significant attention, and corresponding treatment strategies are currently available. Clinicians need to conduct a comprehensive assessment of the adverse reactions caused by immunotherapy (1). After comprehensively considering factors such as the patient's condition, physical status and potential risks, they must carefully weigh the pros and cons and, as appropriate, use immunosuppressive agents for treatment. This is done to minimize the impact of adverse reactions

on patients, and to ensure the safety and effectiveness of the treatment.

Given the widespread clinical use of radiotherapy combined with immunotherapy for thoracic tumors and the uncertainty regarding the impact of treatment timing on pneumonia, the present retrospective study examined the data of patients with thoracic tumors who received this combined treatment. The study focused on analyzing the influence of different scheduling of chest radiotherapy and immunotherapy on the incidence of pneumonia. Additionally, it identified relevant risk factors to provide data and theoretical support for optimizing clinical treatment protocols and enhancing patient quality of life.

Patients and methods

Patient selection. The present retrospective analysis included 35 patients with thoracic tumors (29 cases of lung cancer and 6 cases of esophageal cancer), aged 30-78 years old, consisting of 32 males and 2 females, who underwent radiotherapy combined with immunotherapy between January 2021 and December 2023 at Capital Medical University, affiliated with Beijing Luhe Hospital (Beijing, China). The median follow-up time was 21 months (range, 6-52 months). The total radiotherapy dose received by the lungs was converted to the 2 Gy per fraction equivalent dose according to the biologically effective dose formula, with a 50-62 Gy dose range. The patients were divided into 2 cohorts: Group A, or the sequential group, which comprised 17 patients who received immunotherapy either 2 weeks before radiotherapy or from 2 weeks to 6 months before and after radiotherapy, and Group B, or the concurrent group, which included 18 patients who received immunotherapy within 2 weeks before or after radiotherapy. Grouping was based firstly on clinical experience and secondly on a retrospective study referenced in the literature (5). In that study, mouse experiments showed that lung damage may occur around day 10 after the start of combined radiotherapy and immunotherapy. None of the patients had chronic obstructive pulmonary disease or interstitial lung disease. Fig. 1 presents the details of the treatment course and endpoints.

Adverse events were graded based on the Common Terminology Criteria for Adverse Events 5.0 (6). The incidence and severity of pneumonia, esophagitis, myocarditis and anemia between the two groups were compared. Furthermore, the risk factors for lung injury and the time of chest radiotherapy in combination with immunotherapy were assessed. Moreover, the median and 3-year survival rates of patients with lung cancer (stage III and IV) under combined treatment were also evaluated.

Statistical analysis. This study employed SPSS 20.0 (IBM Corp.) and SAS9.4 (SAS Institute, Inc.) for all the statistical analyses. Dose information was assessed for clinical baseline characteristics using unpaired Student's t-test when data conformed with a normal distribution (assessed by Shapiro-Wilk test) and by Wilcoxon rank-sum test when data did not conform with a normal distribution. Categorical variables were analyzed using the χ^2 test. If the expected count in any cell was <5, Fisher's exact test was applied as an alternative, and these results were marked with an asterisk. For categorical variables with multiple categories, Fisher's exact test was directly used. In the overall patient cohort, univariate and multivariate logistic regression analyses were performed to elucidate factors influencing pneumonia incidence. In univariate analysis, the variables with $P \leq 0.10$ were selected for the multivariate logistic regression analysis, where lung volume receiving ≥20 Gy (V_{20}) was the influencing factor for pneumonia, which was also included in the analysis. For multivariate analyses, the forward stepwise method was employed. All the statistical assessments were two-tailed, with $P<0.05$ used to indicate a statistically significant difference. Furthermore, swim plots indicating treatment processes and each patient's disease status were presented using R software (7). Furthermore, Kaplan-Meier curves were generated with log-rank test used to assess the survival outcomes in the patients with advanced lung cancer undergoing co-treatment with radiotherapy and immunotherapy.

Results

General and therapeutic characteristics of the patients. The median follow-up time for the 35 patients (stage III and IV) was 21 months (range, 6-52 months). No statistical difference was observed in terms of tumor location, stage (8), age, tumor type, Eastern Cooperative Oncology Group (ECOG) score (9), TNM stage, coronary heart disease and sex between the two cohorts (Table I). However, in the selection of immunotherapeutic drugs, the sequential group used more PD-1 drugs than the concurrent group (P=0.018; Table I).

In the sequential group, 66.7 and 33.3% of patients received intensity-modulated radiation therapy (IMRT) and volumetric arc therapy (VMAT), respectively. In the synchronized group, 58.8 and 41.2% of patients received VMAT and IMRT, respectively (P=0.181). The V_{20} for the bilateral lungs was 15±7.3 and 15.2±8.0% in the sequential and synchronized cohorts, respectively (P=0.947). Furthermore, the mean lung dose (D_{mean}) value for the bilateral lungs was 9±3.2 and 11±3.7 Gy in the sequential and synchronized groups, respectively (P=0.99). Overall, no statistically essential differences between groups were observed for radiotherapy technique or dose (Table II).

Treatment-related adverse reactions. The results indicated no grade 4 or higher adverse reactions in both groups. The incidence of grade 0, 1, 2 and 3 pneumonia in the sequential group was 38.9, 38.9, 22.2 and 0.0%, respectively, while in the synchronous group it was 11.8, 52.9, 11.8 and 23.5%, respectively (P=0.061). Moreover, the incidence of grade 0, 1, 2, and 3 esophagitis in the sequential group was 6.3, 37.5, 37.5 and 18.8%, respectively, while it was 13.3, 60.0, 13.3 and 13.3% in the synchronous group (P=0.441), respectively. Similarly, the grade 0, 1 and 2 incidence of anemia was 93.8, 0.0 and 6.3%, respectively, in the sequential group, and 73.3, 26.7 and 0.0%, respectively, in the synchronous group (P=0.069). There were no statistically essential differences observed for adverse reactions between the cohorts (Table III).

Symptoms, incidence and duration of different levels of pneumonia. The analysis of pneumonia-related symptoms in the sequential and synchronized groups (Table IV) revealed

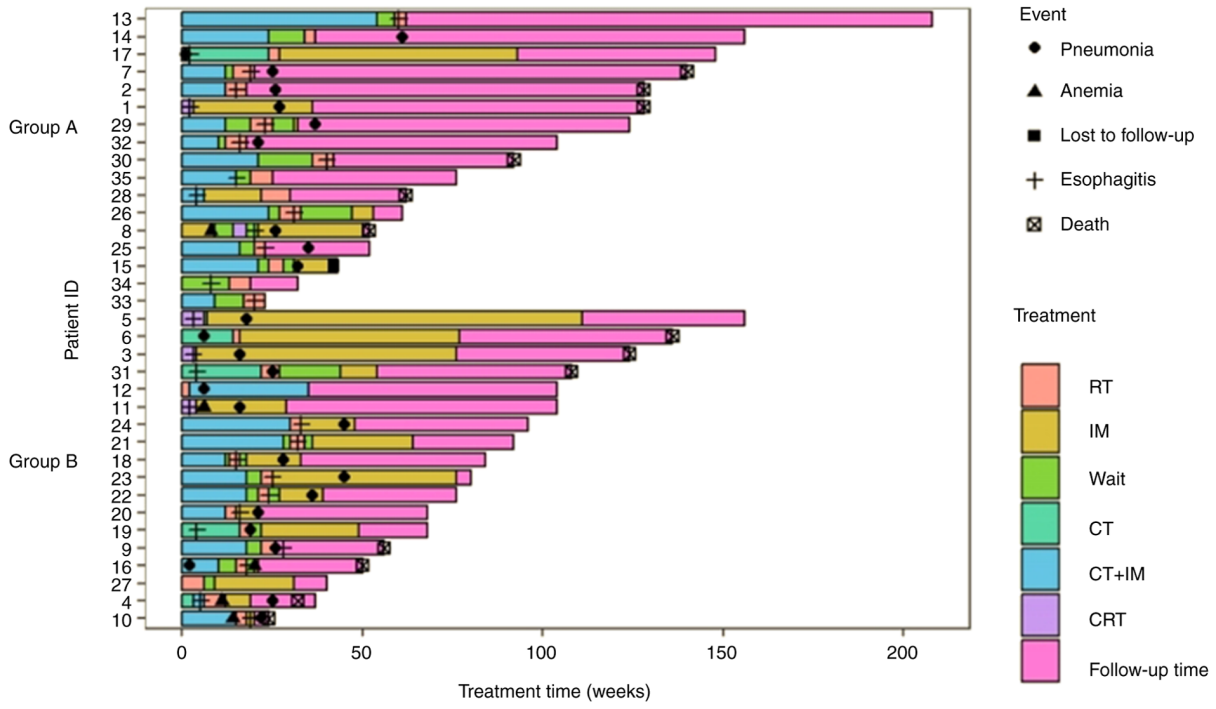

Figure 1. Treatment regimens, timing and outcomes for each patient. RT, radiotherapy; IM, immunotherapy; CT, chemotherapy; CRT, chemoradiotherapy.

that chest tightness (16.7 and 47.1%; P=0.075), cough (50.0 and 52.9%; P>0.999) and fever (5.6 and 17.6%; P=0.338) symptoms were not statistically different between groups. The pneumonia incidence in the sequential and synchronized groups was 61.1 and 88.2%, respectively (P=0.073; Table V). The subgroup analysis of the 26 patients who developed pneumonia revealed that the mean time to pneumonia development in the sequential and synchronized groups was 3.18±1.83 and 3.27±1.98 months, respectively (P=0.912). The incidence of grade 2 and higher pneumonia in the sequential and synchronized groups was 22.2 and 35.3%, respectively (P=0.471), whereas the incidence of grade 3 and higher pneumonia was 0.0 and 23.5%, respectively (P=0.045). The incidence of grade 3 and higher pneumonia exhibited the only statistically significant difference between the groups (Table V).

Influencing factors of pneumonia. The univariate analysis revealed that lung D_{mean} and V_{30} were the factors influencing pneumonia incidence rate. Following multivariate analysis, only V_{30} retained statistical significance as an independent prognostic factor (Table VI).

Overall survival rates in stage III/IV lung cancer. The survival analysis was performed on 29 patients with lung cancer, with a median follow-up time of 21 months (range, 6-52 months). The 3-year OS rates were 44.8 and 22.5% for stage III and IV patients, respectively (Fig. 2). There was no significant difference in the survival curves between the two groups (Log-rank test, P>0.05).

Discussion

Co-treatment with radiotherapy and immunotherapy has become a new modality for cancer treatment. The KEYNOTE-001 (10) study indicated that patients with stage IV NSCLC who underwent radiotherapy before immunotherapy had longer 5-year OS and 5-year progression-free survival (PFS) rates than those who did not undergo radiotherapy. Furthermore, the PACIFIC study revealed that patients with unresectable stage III lung cancer who underwent simultaneous radiotherapy and chemotherapy, and then continued with sequential divalizumab consolidation therapy, had 5- and 3-year survival rates of 42.9 and 56.7%, respectively (3). The present study showed 3-year OS rates of 44.8 and 22.5% after radiotherapy combined with immunotherapy for stage III and IV lung cancer, respectively. This may be due to the fact that SCLC, which has a poorer prognosis, was also included in the present research. Overall, it was validated that immunotherapy combined with radiotherapy has a survival benefit over any mono-treatment (3,10). However, clinical applications require careful monitoring, as both radiotherapy and immunotherapy can promote the development of pneumonia.

Radiotherapy predominantly kills tumor cells by ionizing radiation-induced DNA damage (11). Radiotherapy also affects the immune system in various ways, such as tumor immune microenvironment remodeling, cytokine and chemokine release, immune cell infiltration and increasing tumor cell sensitivity to immunogenic cell death (12). Furthermore, it can be employed to generate 'immunovaccines' to promote antitumor T cell immune responses (13). Radiotherapy is also employed for immunomodulation and reconstructing the immune microenvironment of the tumor. Immunopharmaceuticals block pathways that inhibit the immune response to maintain and restore the cancer cell recognition and immune system response (14). Radiotherapy-induced antitumor immune response and its synergy with immunotherapy has evolved as a potential therapeutic modality (15).

Table I. Characteristics of patients.

Characteristic	Group A (n=18)	Group B (n=17)	P-value
Sex, n (%)			0.603[a]
Male	17 (94.4)	15 (88.2)	
Female	1 (5.6)	2 (11.8)	
Median age, years	63	61.8	0.105
Tumor type, n (%)			0.141[a]
Small cell carcinoma of the lungs	4 (22.2)	7 (41.2)	
Squamous lung cancer	5 (27.8)	6 (35.3)	
Adenocarcinoma of the lungs	2 (11.1)	3 (17.6)	
Esophageal cancer	7 (38.9)	1 (5.9)	
ECOG PS, n (%)			0.603[a]
1	17 (94.4)	15 (88.2)	
2	1 (5.6)	2 (11.8)	
Tumor location, n (%)			0.267[a]
Lung (upper left)	5 (27.8)	3 (17.6)	
Lung (lower left)	1 (5.6)	1 (5.9)	
Lung (upper right)	3 (16.7)	6 (35.3)	
Lung (middle right)	1 (5.6)	1 (5.9)	
Lung (lower right)	1 (5.6)	4 (23.5)	
Esophagus	7 (38.9)	2 (11.8)	
TNM staging, n (%)			
T			0.256[a]
T2	3 (16.7)	6 (35.3)	
T3	0 (0.0)	2 (11.8)	
T4	9 (50.0)	5 (29.4)	
Tx	6 (33.3)	4 (23.5)	
N			0.480[a]
N0	2 (11.1)	0 (0.0)	
N1	1 (5.6)	0 (0.0)	
N2	6 (33.3)	8 (47.1)	
N3	3 (16.7)	5 (29.4)	
Nx	6 (33.3)	4 (23.5)	
M			0.738
M1	9 (50.0)	10 (58.8)	
M2	9 (50.0)	7 (41.2)	
Tumor staging, n (%)			0.401[a]
II	1 (5.6)	0 (0.0)	
III	7 (38.9)	10 (58.8)	
IV	10 (55.6)	7 (41.2)	
Coronary heart disease, n (%)			0.603
No	15 (83.3)	16 (94.1)	
Yes	3 (16.7)	1 (5.9)	
Immunization, n (%)			0.018
PD-1	14 (77.8)	6 (35.3)	
PD-L1	4 (22.2)	11 (64.7)	

[a]Fisher's exact test. ECOG, Eastern Cooperative Oncology Group; TNM, Tumor-Node-Metastasis; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

A meta-analysis by Nishino *et al* (16) indicated that patients who underwent combination therapy were significantly more prone to pneumonia than those who received monotherapy for all grades of pneumonia [odds ratio (OR), 2.04] and grade 3 or

Table II. Radiotherapy techniques.

Parameter	Group A (n=18)	Group B (n=17)	P-value
Radiotherapy techniques, n (%)			0.181
VMAT	6 (33.3)	10 (58.8)	
IMRT	12 (66.7)	7 (41.2)	
Lung dose			
D_{mean}, Gy	9.0±3.2	11.0±3.7	0.990
V_5, %	34.0±11.8	36.4±13.1	0.604
V_{10}, %	23.4±9.6	25.0±10.0	0.629
V_{20}, %	15.0±7.3	15.2±8.0	0.947
V_{30}, %	8.2±5.2	9.6±6.1	0.487

VMAT, volumetric arc therapy; IMRT, intensity-modulated radiation therapy; D_{mean}, mean dose; V_5, volume receiving ≥5 Gy.

Table III. Adverse reactions.

Adverse reaction	Group A (n=18)	Group B (n=17)	P-value
Pneumonia, n (%)			0.061[a]
0	7 (38.9)	2 (11.8)	
1	7 (38.9)	9 (52.9)	
2	4 (22.2)	2 (11.8)	
3	0 (0.0)	4 (23.5)	
Esophagitis, n (%)			0.226[a]
0	2 (11.1)	2 (11.8)	
1	6 (33.3)	11 (64.7)	
2	7 (38.9)	2 (11.8)	
3	3 (16.7)	2 (11.8)	
Anemia, n (%)			0.128[a]
0	16 (88.8)	12 (70.6)	
1	1 (5.6)	5 (29.4)	
2	1 (5.6)	0 (0.0)	

[a]Fisher's exact test

Table IV. Symptoms of pneumonia.

Symptom	Group A (n=18)	Group B (n=17)	P-value
Chest distress, n (%)			0.075
No	15 (83.3)	9 (52.9)	
Yes	3 (16.7)	8 (47.1)	
Cough, n (%)			>0.999
No	9 (50.0)	8 (47.1)	
Yes	9 (50.0)	9 (52.9)	
Fever, n (%)			0.338[a]
No	17 (94.4)	14 (82.4)	
Yes	1 (5.6)	3 (17.6)	

[a]Fisher's exact test.

above (OR, 2.86). Furthermore, a recent phase I study revealed that 26% of the 23 patients who underwent co-treatment with paborizumab and chemoradiotherapy had grade 2 or higher pneumonia (17). Another study retrospectively analyzed 196 patients who underwent chest radiotherapy with immunotherapy and revealed that the incidence of grade 2 or higher pneumonia was 25.5%, while the incidence of grade 3 or higher pneumonia was 4.1% (18). Moreover, another study revealed that in patients with thoracic tumors, the incidence of treatment-related pneumonia was ~30% after immunotherapy combined with radiotherapy (19). The data of the present study revealed that the incidence of grade 2 or higher pneumonia, which requires drug treatment, for the entire cohort was 28.5% (22.2 and 35.3% in the sequential and synchronous groups, respectively), which was higher than the incidence in the sequential group. However, there was no statistically significant difference between the two cohorts (P=0.471). These results were consistent with previous studies. Moreover, the incidence of grade 3 or higher pneumonia was 11.4% for the whole cohort (0.0% in the sequential group and 23.5% in the synchronous group), and the difference was statistically significant between groups (P=0.045). This shows that the application of immune drugs within 2 weeks before and after radiotherapy may aggravate the incidence of grade 3 or higher pneumonia.

The timing of the pneumonia onset is also important. The mean pneumonia onset time after immunotherapy has been reported as 2.5 months (range, 9 days to 19 months) (20). Delaunay *et al* (21) diagnosed immunopneumonia in 64 out of 1,826 patients, and the median time to checkpoint inhibitor pneumonitis onset was 2.3 months. The majority of patients (42.2%) developed pneumonia within 2 months of receiving immunotherapy. The pneumonia onset time was 2-4 months in 26.6% of the patients, 4-6 months in 17.2% of the patients and >6 months in 14.1% of the patients (21). In another study, the median time between the end of chest radiotherapy and the onset of pneumonia was 88.5 days (22). In an aforementioned retrospective study (19), the median pneumonia onset time after immunotherapy followed by combined radiotherapy was ~65 days (19). The results of the present study showed that the mean pneumonia onset time was 2.45 and 2.88 months in the sequential and synchronized groups, respectively, which is consistent with the aforementioned studies. Therefore, the clinical review and follow-up of patients is recommended after 2-4 months of treatment.

Saito *et al* (23) retrospectively analyzed the data from 275 patients with locally advanced NSCLC who received concurrent radiotherapy followed by consolidation therapy with duvarizumab. The mean V_{20} of the enrolled patients was 19.4% (range, 1.4-37.9%) and the D_{mean} was 10.9 Gy (range, 1.5-31.3 Gy). Furthermore, logistic regression analysis indicated that V_{20} ≥25% was an independent risk factor for grade ≥2 pneumonia (23). In another study, the receiver operating characteristic curve showed that in the V_{20} ≥21% group, the prevalence of grade ≥2 pneumonia was 33.3%, which was

Table V. Grading analysis of pneumonia.

Parameter	Group A (n=18)	Group B (n=17)	P-value
Pneumonia, n (%)			0.073[a]
No	7 (38.9)	2 (11.8)	
Yes	11 (61.1)	15 (88.2)	
Time to pneumonia, months	3.18±1.83	3.27±1.98	0.912
Pneumonia grade, n (%)[a]			0.471[b]
≥2	4 (22.2)	6 (35.3)	
<2	14 (77.8)	11 (64.7)	
Pneumonia grade, n (%)[a]			0.045[a]
≥3	0 (0.0)	4 (23.5)	
<3	18 (100.0)	13 (76.5)	

[a]Pneumonia grades <2 and <3 include grade 0 (no pneumonia). [b]Fisher's exact test.

Table VI. Univariate analysis and multivariate analysis.

	Univariate analysis			Multivariate analysis		
Variable	P-value	OR	95% CI	P-value	OR	95% CI
D_{mean}	0.027	1.412	1.041-1.040	0.731	1.125	0.575-2.198
V_5	0.131	1.055	0.984-1.132			
V_{10}	0.057	1.110	1.132-1.236	0.145	1.581	0.854-2.928
V_{20}	0.223	1.073	0.958-1.201	0.043	0.313	0.102-0.962
V_{30}	0.031	1.308	1.024-1.670	0.027	3.069	1.138-8.277
Radiotherapy timing (sequential/synchronization)	0.081	4.773	0.826-27.562	0.341	0.278	0.020-3.868
Radiotherapy technology (VMAT/IMRT)	0.391	2.010	0.410-9.757			
Immunization	0.160	3.501	0.609-20.13			
Age, years	0.304	0.953	0.87-27.562			
ECOG	0.753	1.502	0.119-18.836			

VMAT, volumetric arc therapy; IMRT, intensity-modulated radiation therapy; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; CI, confidence interval.

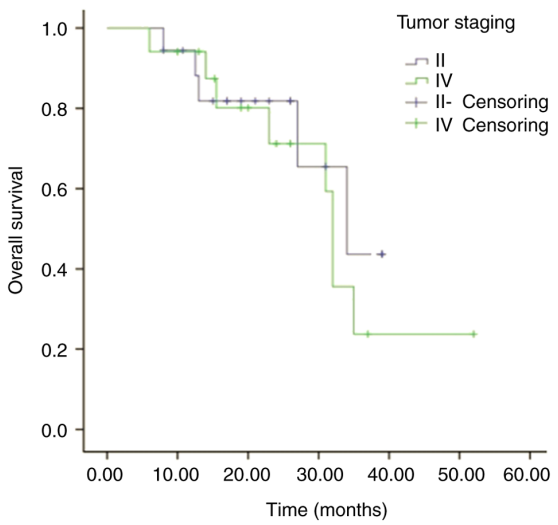

Figure 2. Patient 3-year overall survival data in individuals with stage III-IV lung cancer.

significantly higher than the 4.8% in the V_{20} <21% group (14). Moreover, the incidence of pneumonia was significantly associated with a history of chronic lung disease (P=0.050), D_{mean} (P=0.038), V_5 (P=0.012) and V_{20} (P=0.030) (22). Emphysema, lung V_{20}, V_{30}, D_{mean} and V_5 are risk factors for symptomatic pneumonia (18,24). In line with the results of previous studies, in the present study, the lung D_{mean} and V_{30} were observed as the influential factors of pneumonia.

Radiotherapy combined with immunotherapy has survival benefits for patients with advanced NSCLC (14); however, the treatment can increase the incidence of pneumonia. The appropriate combination modality, suitable radiotherapy dose and precise timing of the combination are therefore particularly important. The PACIFIC study (3) investigated the effect of consolidation therapy with immunomedicine 1-42 days after standard radiotherapy treatment for stage III unresectable lung cancer. The immunized and placebo groups indicated grade 3 or higher radiation pneumonitis rates of 3.4 and 2.6%, respectively (3), but no further time stratification was performed.

Furthermore, another study performed multifactorial analysis and suggested that an interval of <3 months between chest radiotherapy and immunotherapy was independently associated with grade 2 or higher pneumonia (P=0.004). However, in clinical practice, a number of patients cannot wait for 1 or 3 months before starting systemic therapy due to the disease severity. Therefore, immunotherapy should be started within 1 month before or after radiotherapy; however, the precise time remains elusive. A recent *in vivo* study (5) found that when radiotherapy is combined with immunotherapy, lung injury may progress faster from days 15 to 20 after the start of treatment. In the study (25), 40 patients were studied retrospectively, and the radiotherapy and immunotherapy intervals of <3 weeks and 3 weeks to 6 months were also compared. There was no difference in the incidence of pneumonia, which might due to the small sample size. Therefore, a large sample is required to validate these analyses.

In summary, the present study revealed that radiotherapy combined with immunotherapy has a survival benefit for patients with advanced thoracic tumors; however, it also increases the risk of pneumonia, with an increase in the incidence of grade 3 or higher pneumonia within a 2-week interval between radiotherapy and immunotherapy. Furthermore, the identified factors that influenced the incidence of pneumonia included lung D_{mean}, V_{30} and the interval between radiation therapy combined with immunotherapy. Moreover, pneumonia typically develops 2-4 months after radiotherapy; therefore, the clinical review and follow-up of patients 2-4 months after treatment is recommended.

The number of cases included in this study is relatively small, which may introduce some bias. Additionally, the chest tumors in this study included both lung cancer and esophageal cancer, which differ in terms of radiation field and dose, potentially impacting the occurrence of pneumonia. Data collecrion will continue and further studies will investigate the specifics of each individual cancer type.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JY contributed to the preparation, creation and description of the work for publication, in particular writing a first draft (including substantial translations). JY and YYG contributed to presentation of research ideas and the development and formation of overall research objectives. QTL and XL contributed to the application of statistical, mathematical, computer and other analyses to assess and integrate the research data. XJS, XXN and XBZ contributed to implementing the research and data/evidence collection. YYG performed the review and revision (both pre- and post-publication phases). SYZ and BS helped with data collection. PH and SW helped with the analysis and design of the article. JY and YYG confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study obtained ethical approval from the Ethics Office of Beijing Luhe Hospital, Capital Medical University (approval no. 2024-LHKY-070-02).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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