







ORIGINAL ARTICLE

Nivolumab-induced radiation recall pneumonitis in non-small-cell lung cancer patients with thoracic radiation therapy

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Abstract

The role of previous thoracic radiation therapy as a risk factor of immune-related pneumonitis is unclear. Furthermore, some patients develop radiation recall pneumonitis, which is characterized by a radiation pneumonitis-like imaging pattern with consolidation progressing within a previous radiation field. In this multicenter retrospective study, we analyzed the relationship of previous thoracic radiation therapy with immune-related pneumonitis and the characteristics of radiation recall pneumonitis. The medical records of patients with non-small-cell lung cancer who had received nivolumab between December 2015 and March 2017 at five institutions were retrospectively reviewed. Incidence, imaging patterns, clinical course, and risk factors of immune-related pneumonitis and radiation recall pneumonitis were evaluated. A total of 669 patients were evaluated, and the incidences of all-grade and grade 3 or higher immune-related pneumonitis were 8.8% and 2.6%, respectively. The incidences of immune-related pneumonitis were 13.2% (34/257) and 6.1% (25/412) in patients with and those without previous thoracic radiation therapy, respectively. A history of previous thoracic radiation therapy was associated with immune-related pneumonitis (odds ratio, 2.11; 95% confidence interval, 1.21–3.69 in multivariate analysis). Among the patients with previous thoracic radiation therapy, 6.2% (16/257) showed radiation recall pattern. This study found an increased risk of nivolumab-induced immune-related pneumonitis associated with a history of thoracic radiation therapy. Radiation recall pattern was one of the major patterns of immune-related pneumonitis among the patients with previous thoracic radiation therapy. Incidence, risk factors, and clinical outcome of radiation recall pneumonitis were elucidated.

KEYWORDS

antineoplastic agent, carcinoma, immune checkpoint inhibitor, immunological, nivolumab, non-small-cell lung, radiation pneumonitis

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1 | INTRODUCTION

Immune-checkpoint inhibitors (ICIs) have improved the prognosis of cancer patients, especially for patients with non-small-cell lung cancer (NSCLC). Nivolumab was first approved in Japan as a second-line treatment for metastatic or recurrent NSCLC in 2015.^{1,2} At present, pembrolizumab and atezolizumab are used in combination with a platinum agent as a first-line treatment, and durvalumab is also used for maintenance therapy after chemoradiation treatment for locally advanced NSCLC.³⁻⁵ In the next decade, most NSCLC patients will likely receive ICIs at some point in their treatment.

Immune-related adverse events (irAEs) are sometimes difficult to control and can be fatal in some cases. Immune-related pneumonitis (IRP) is one of the most important irAEs and is reported more frequently among lung cancer patients than among melanoma patients.⁶ Five clinical trials of NSCLC reported incidences of IRP of 1%–5% among patients receiving ICI treatment.^{1,2,7-9} Recently, retrospective studies have reported a higher incidence of 13%–19% in routine clinical practice.¹⁰⁻¹³ Patients with IRP often require the discontinuation of their anticancer treatment and sometimes die from pneumonitis despite the use of corticosteroid treatment.

The risk factors for IRP have attracted interest but remain unclear. Clinical studies have suggested a relationship between a history of thoracic radiation therapy (TRT) and IRP,¹⁴ but the details are not fully understood. Each retrospective study analyzing ICI treatment among NSCLC patients reported different risk factors, including complications from interstitial lung disease, a nonadenocarcinoma histology, combination therapy with other ICIs (such as CTL antigen-4 inhibitors), the use of pembrolizumab, and a low serum albumin level, but none of these studies could clearly point out the relation with previous TRT.¹⁰⁻¹² Although the relation between previous TRT and IRP has not been revealed, a few patients with previous TRT have been reported to show a characteristic imaging pattern, with consolidation progressing within the previous radiation field after ICI treatment. This type of pneumonitis was first reported by Shibaki et al. in 2017¹⁵ and was called radiation recall pneumonitis. Although the mechanism of this pneumonitis is unknown, radiation recall pneumonitis is thought to be affected by both previous TRT and ICI treatment. Thus, we decided to focus on previous TRT as a risk factor for IRP, especially radiation recall pneumonitis.

In this multicenter study, we investigated a large series of 669 patients to analyze the incidence and risk factors of IRP by performing a central radiological analysis. We especially focused on the relation between IRP and a history of TRT and revealed that patients with previous TRT had a different IRP imaging pattern compared with patients who had not received TRT; this difference might have contributed to the higher incidence of IRP among the patients with previous TRT.

2 | MATERIALS AND METHODS

2.1 | Patients

We designed this retrospective study to analyze the incidence and risk factors of IRP and radiation recall pneumonitis. We used

electronic medical records to analyze consecutive patients treated at five institutions in Japan who received nivolumab for metastatic or recurrent NSCLC between December 2015 and March 2017. We reviewed the patients' electronic medical records, and the following clinical data were collected: age, sex, smoking history, ECOG performance status (PS), corticosteroid use at the time of the start of nivolumab therapy, and tumor characteristics including histology, driver mutation status, and TNM staging at the time of diagnosis. Data on the treatment history including surgery, TRT, and systemic chemotherapy were also obtained. We defined TRT as radiation therapy that included a lung field and included not only curative radiation therapy for stage III cancers but also palliative radiation therapy for metastatic or recurrent cancers and stereotactic body radiotherapy for stage I/II cancers. Palliative radiation therapy for spine metastasis or liver metastasis was also included in TRT if the radiation field included lung.

We defined IRP as pneumonitis occurring during or after nivolumab treatment, excluding other causes such as infection and the use of agents other than nivolumab. To exclude non-nivolumab drug-induced pneumonitis, only pneumonitis that occurred after the start of nivolumab treatment and before the next chemotherapy started was considered as nivolumab-induced pneumonitis. Each diagnosis was made clinically by the investigator at each institution based on regular follow-up examinations that included X-ray and computed tomography (CT) imaging throughout the course of treatment; the diagnoses were then confirmed radiologically by board-certified diagnostic radiologists. For patients who were diagnosed as having IRP, grading according to the Common Terminology Criteria for Adverse Events version 4.0 was carried out, and information on the dose and duration of corticosteroid use, the use of other immunosuppressive agents, and the outcome of the pneumonitis were collected. The patients whose respiratory condition and CT images fully recovered, partly recovered, and were exacerbated after the recovery were defined as "cure", "remission", and "exacerbation", respectively, and patients who died because of pneumonitis as "death". We also obtained detailed clinical data on previous TRT, including a history of radiation pneumonitis, elapsed time since the last TRT, and radiation parameters such as the total dose, volumes receiving more than 20 Gy (V_{20}) or 30 Gy (V_{30}), and the mean lung dose.

2.2 | Independent review of imaging patterns

The imaging analysis was undertaken by the consensus of two board-certified diagnostic radiologists. The radiologists reviewed the CT images that had been obtained before the start of nivolumab treatment, those obtained at the onset of pneumonitis, and also any subsequent images, if available. Images obtained for TRT planning were used to evaluate the relation between the previous TRT and IRP. The analysis focused on whether the pneumonitis imaging pattern did or did not support a diagnosis of radiation recall pneumonitis based on a comparison of the pneumonitis field and the radiation field. The diagnostic radiologists were blinded to all other clinical information.

As no clear definition of radiation recall pneumonitis exists, including criteria regarding the total dose of TRT and the elapsed time since the last TRT, we reviewed the cases of IRP based on the imaging patterns only and classified the findings into two patterns. The “radiation recall pattern,” or so-called radiation recall pneumonitis, was defined as a consolidation progressing inside the previous radiation field. Immune-related pneumonitis occurring only outside the radiation field in patients with a history of previous TRT and occurring in patients without TRT were defined as a “radiation-independent pattern,” which included all imaging patterns other than radiation recall pattern.

2.3 | Statistical analysis

We analyzed the risk factors for IRP and radiation recall pattern by undertaking univariate and multivariate logistic regression analyses. The analysis for the risk factors for radiation recall pattern compared the patients who developed radiation recall pattern and those with a history of TRT who developed a radiation-independent pattern. To compare the incidence of specific imaging patterns between the patients with and without a history of previous TRT, we used Pearson's χ^2 -test. To determine the difference in onset time since the initiation of nivolumab treatment and the last TRT between the imaging patterns, comparisons of the cumulative incidence curves between the imaging patterns were carried out using a log-rank test, and the Cox proportional hazards method was used to estimate the hazard ratio. All statistical analyses were undertaken using the JMP Pro version 16.2.0 (SAS Institute, Inc.) software package.

2.4 | Ethical considerations

This research was approved by the institutional review boards of the five participating institutions (National Cancer Center Hospital and National Cancer Center Hospital East, 2018-060; Shizuoka Cancer Center, T30-46; Kanagawa Cancer Center, 2018-155; and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 2189). The need for informed consent was waived as this study was a retrospective analysis.

3 | RESULTS

3.1 | Patient characteristics

In this study, 669 patients who received nivolumab for metastatic or recurrent NSCLC were analyzed. The patient characteristics are shown in Table 1. The median age was 66 years (range, 30–87 years), and 68.3% (457/669) of patients were men. Overall, 68.0% (455/669) and 22.7% (152/669) of the patients were pathologically diagnosed as having adenocarcinoma and squamous cell carcinoma,

respectively; 78.2% (523/669) were current or former smokers, and 38.4% (257/669) had a history of TRT.

3.2 | Incidence of IRP

The incidences of all grade and grade 3 or higher IRP were 8.8% (59/669) and 2.6% (18/669), respectively (Table 2). The incidences of IRP in patients with and those without a history of previous TRT were 13.2% (34/257) and 6.1% (25/412), respectively; this difference was statistically significant ($p = 0.0015$). Three (0.4%) patients without a history of TRT died because of pneumonitis.

The imaging analysis undertaken by board-certified diagnostic radiologists divided the patients who developed IRP into three groups: those with a radiation recall pattern, those with a radiation-independent pattern and a history of previous TRT, and those without TRT. Representative images are shown in Figure 1. The incidence of a radiation recall pattern was 6.2% (16/257) among the patients with a history of previous TRT, and the incidences of radiation-independent patterns were 7.0% (18/257) and 6.1% (25/412) among patients with and those without previous TRT, respectively (Table 2, Figure 2). Previous TRT was associated with the incidence of IRP but was not associated with the radiation-independent pattern.

3.3 | Risk factors of IRP

We undertook univariate and multivariate analyses to evaluate possible risk factors of IRP including age (≥ 65 years old or not), sex, smoking history, histology (adenocarcinoma or not), history of previous TRT, and ECOG PS (Table 3). A smoking history and a history of TRT were statistically significant risk factors in univariate analyses (smoking history: odds ratio [OR], 2.64; 95% confidence interval [CI], 1.11–6.26; previous TRT: OR, 2.36; 95% CI, 1.37–4.06), and a history of previous TRT was an independent risk factor in a multivariate analysis (OR, 2.11; 95% CI, 1.21–3.69).

3.4 | Radiation recall pattern

Focusing on the radiation recall pattern, the incidences of all grade and grade 3 and higher pneumonitis were 6.2% (16/257) and 1.6% (4/257), respectively, and none of these patients died because of pneumonitis (Table 2). The patient characteristics are shown in Table 4. A periradiation field pattern tended to occur within 24 months after the last TRT, whereas a radiation-independent pattern tended to appear more gradually within a period of up to 60 months after the last TRT (Figure 3C).

Although the number of patients was restricted in the analysis, a shorter time (≤ 24 months) after the last TRT was a potential risk factor (OR, 5.60; 95% CI, 0.97–32.20; Table S1), and the same tendency was preserved when adjustments according to age,

TABLE 1 Characteristics of patients with non-small-cell lung cancer treated with nivolumab

	IRP (N = 59)	Non-IRP (N = 610)	All (N = 669)
Age, years			
Median (range)	68 (45–83)	66 (30–87)	66 (30–87)
Sex			
Male	45 (76.3)	412 (67.5)	457 (68.3)
Female	14 (23.7)	198 (32.5)	212 (31.7)
Histology			
Ad	34 (57.6)	421 (69.0)	455 (68.0)
Sq	21 (35.6)	131 (21.5)	152 (22.7)
NSCLC	2 (3.4)	35 (5.7)	37 (5.5)
NEC/LCC	2 (3.4)	13 (2.1)	15 (2.2)
Spindle/ pleomorphic	0 (0.0)	4 (0.7)	4 (0.6)
Other	0 (0.0)	6 (1.0)	6 (0.9)
Stage			
IV	29 (49.2)	358 (58.7)	387 (57.9)
III	15 (25.4)	127 (20.8)	142 (21.2)
I and II	2 (3.4)	5 (0.8)	7 (1.0)
Postoperative recurrence	13 (22.0)	120 (19.7)	133 (19.9)
Biomarker mutation			
EGFR	5 (8.5)	102 (16.7)	107 (16.0)
ALK	0 (0.0)	10 (1.6)	10 (1.5)
ROS1	0 (0.0)	8 (1.3)	8 (1.2)
Smoking history			
Nonsmoker	6 (10.2)	140 (23.0)	146 (21.8)
Smoker	53 (89.8)	470 (77.0)	523 (78.2)
Median pack-years	43	41	41
Previous chemotherapy line			
Median (range)	1 (0–6)	2 (0–12)	2 (0–12)
Previous TRT			
–	26 (44.1)	387 (63.4)	412 (61.6)
+	33 (55.9)	223 (36.6)	257 (38.4)
ECOG PS			
0	18 (30.5)	119 (19.5)	137 (20.4)
1	34 (57.6)	399 (65.4)	433 (64.7)
2	6 (10.2)	75 (12.3)	81 (12.1)
3	1 (1.7)	17 (2.8)	18 (2.7)
Corticosteroid use at initiation of Nivo			
+	2 (3.4)	30 (4.9)	32 (4.8)
Treatment duration of Nivo, months			
Median (range)	3.3 (0.0–39.0)	1.9 (0.0–42.6)	2.3 (0.0–42.6)

Note: Data are shown as *n* (%) unless otherwise indicated. Abbreviations: Ad, adenocarcinoma; IRP, immune-related pneumonitis; LCC, large cell carcinoma; NEC, neuroendocrine carcinoma; Nivo, nivolumab; NSCLC, non-small-cell lung cancer; PS, performance status; Sq, squamous cell carcinoma; TRT, thoracic radiation therapy.

sex, PS, and V_{20} were performed. Focusing on the time course of nivolumab treatment after the last TRT, we also compared the cumulative incidence since the last TRT as well as since the initiation of nivolumab treatment (Figure 3). Although patients with a history of previous TRT tended to develop IRP earlier than those without a history of TRT, we could not find a statistical difference between these groups. Considering the confounding of time after the last TRT and after the initiation of nivolumab treatment, a shorter time (≤ 24 months) after the last TRT was a potential risk factor for a radiation recall pattern.

Patients with a radiation recall pattern had a relatively good outcome, and all 16 patients were cured or experienced remission and none of them were refractory to corticosteroid therapy (Table 2). Four of these patients were cured without requiring any drug treatment, including corticosteroid use (Table S2).

4 | DISCUSSION

The current study was the first report to identify a history of previous TRT as a risk factor for IRP in a relatively large cohort of 669 patients who had been treated with nivolumab. We also undertook a central radiological analysis to distinguish the imaging patterns of IRP, and we examined the incidence and risk factors of a radiation recall pattern, which have not been previously reported.

Two clinical trials reported the incidences of IRP after nivolumab monotherapy as 3%–5%,^{1,2} while four retrospective analyses reported incidences of 13%–19%.^{10–13} The incidence of 8.8% in the present study was thus relatively low. This difference might be because our study only included patients who had received nivolumab, while the previous reports included all ICI treatments, including pembrolizumab, and even combination therapies, which have been reported as risk factors for IRP.^{10,12} Only one previous study focused on the details of previous TRT,¹³ and they reported in a subset analysis that IRP was more common among patients who had received curative-intent TRT, compared with those who had received palliative-intent TRT. However, this study only determined the different incidences of IRP between patients receiving radiotherapy with different intents, and TRT itself was not a risk factor for IRP. Our study is the first report to date to show that TRT might serve as an independent risk factor of IRP. In addition, our study was the only one to include a central imaging analysis to distinguish the imaging pattern of radiation recall pneumonitis, and this analysis revealed that the additive incidence of IRP among patients with previous TRT might be caused by this characteristic imaging pattern (Figure 2). This suggests that radiation recall pneumonitis is a subset of IRP that likely develops through a different mechanism.

The present study was the first to report the incidence and clinical characteristics of radiation recall pneumonitis. Our study showed that a radiation recall pattern occurred in 6.2% of patients with a history of previous TRT and that most of these cases occurred within 24 months after the last TRT. This result could be an indicator

TABLE 2 Grading and outcome of immune-related pneumonitis in patients with non-small-cell lung cancer treated with nivolumab

Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All (%)
All	10	31	14	1	3	59/669 (8.8)
TRT+						
Radiation recall pattern	4	8	4	0	0	16/257 (6.2)
Radiation-independent pattern	3	11	4	0	0	18/257 (7.0)
TRT-						
Radiation-independent pattern	3	12	6	1	3	25/412 (6.1)
Outcome	Cure	Remission	Exacerbation	Death	All	
All	21	34	1	3	59	
TRT+						
Radiation recall pattern	9	7	0	0	16	
Radiation-independent pattern	5	13	0	0	18	
TRT-						
Radiation-independent pattern	7	14	1	3	25	

Abbreviations: TRT, thoracic radiation therapy.

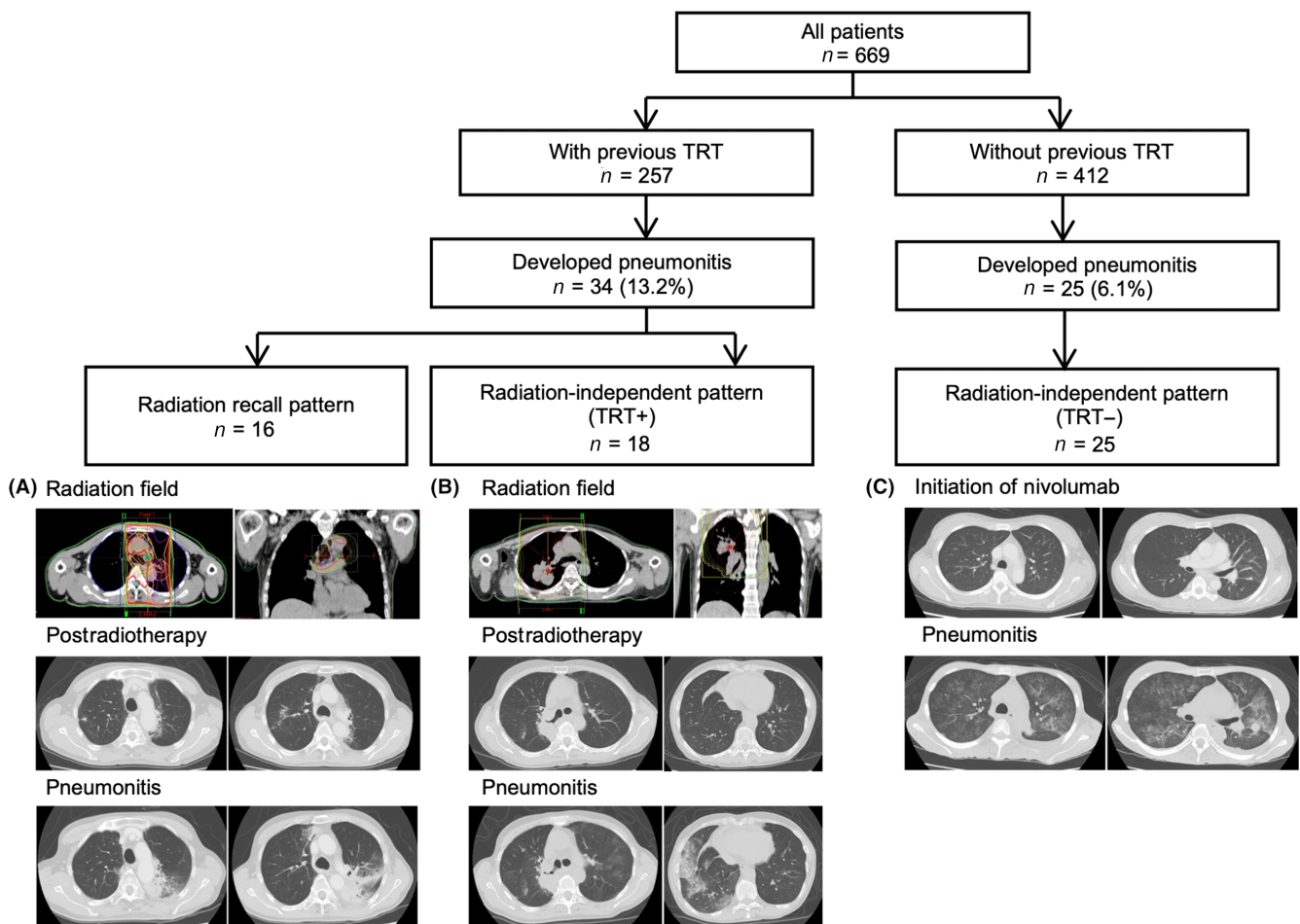
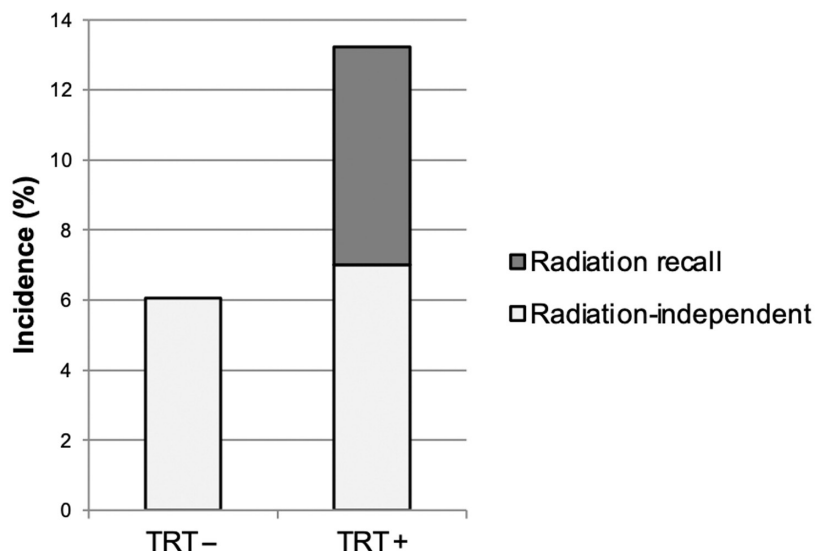


FIGURE 1 Flowchart of imaging analysis and representative images of each imaging pattern from patients with non-small-cell lung cancer treated with nivolumab. The flowchart shows the imaging patterns that were confirmed during an independent review by board-certified diagnostic radiologists. Representative images of each imaging pattern are shown in the lower part of the figure. Images obtained for thoracic radiation therapy (TRT) planning and computed tomography images obtained at the onset of immune-related pneumonitis (IRP) are shown. (A) A radiation recall pattern showing consolidation within the previous radiation field. This patient developed IRP within the radiation field. (B) A radiation-independent pattern showing IRP outside the radiation field. This patient only developed pneumonitis in the bottom lung field, although the radiation field was in the right upper lobe. (C) IRP in a patient without a history of TRT. This patient developed a hypersensitive pneumonitis pattern in the whole lung field

FIGURE 2 Incidence of immune-related pneumonitis according to history of previous thoracic radiation therapy (TRT) and imaging patterns. N/A, not applicable



Previous TRT	Radiation recall pattern	Radiation-independent pattern	All
TRT-	0 (0.0%)	25 (6.1%)	25/412 (6.1%)
TRT+	16 (6.2%)	18 (7.0%)	34/257 (13.2%)
<i>p</i> value	N/A	0.4213	0.0015

TABLE 3 Risk factors for immune-related pneumonitis in patients with non-small-cell lung cancer treated with nivolumab

Factors	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value	Odds ratio	95% CI	<i>p</i> value
Age, years						
<65	Reference			Reference		
≥65	1.66	0.92–2.98	0.0881	1.59	0.87–2.88	0.1266
Sex						
Female	Reference			Reference		
Male	1.54	0.83–2.88	0.1687	0.99	0.48–2.03	0.9795
Histology						
Ad	Reference			Reference		
Non-Ad	1.64	0.95–2.82	0.0733	1.20	0.68–2.13	0.5293
Smoking history						
Nonsmoker	Reference			Reference		
Smoker	2.64	1.11–6.26	0.0229	2.25	0.83–6.11	0.1110
Previous TRT						
-	Reference			Reference		
+	2.36	1.37–4.06	0.0015	2.11	1.21–3.69	0.0089
ECOG PS						
0–1	Reference			Reference		
≥2	0.76	0.33–1.72	0.5063	0.73	0.32–1.68	0.4580

Abbreviations: Ad, adenocarcinoma; CI, confidence interval; PS, performance status; TRT, thoracic radiation therapy.

TABLE 4 Characteristics of patients with non-small-cell lung cancer treated with nivolumab, according to radiological pattern

	Radiation recall (N = 16)	Radiation-independent (TRT+) (N = 18)	Radiation-independent (TRT-) (N = 25)
Age, years			
Median (range)	69 (61–80)	69 (59–79)	68 (45–85)
Sex			
Male	13 (81.3)	14 (77.8)	18 (72.0)
Female	3 (17.7)	4 (22.2)	7 (28.0)
Smoking history			
Nonsmoker	1 (6.2)	2 (11.1)	3 (12.0)
Smoker	15 (93.8)	16 (88.9)	22 (88.0)
Median pack-years	50	46	39
ECOG PS			
0	9 (56.3)	2 (11.1)	7 (28.0)
1	5 (31.2)	15 (83.3)	14 (56.0)
2	2 (12.5)	1 (5.6)	3 (12.0)
3	0 (0.0)	0 (0.0)	1 (4.0)
Background lung disease			
COPD	5 (31.3)	10 (55.6)	8 (32.0)
ILD	0 (0.0)	0 (0.0)	2 (8.0)
Purpose of radiation therapy			
Curative	11 (68.8)	14 (77.8)	-
Palliative	5 (31.2)	4 (22.2)	-
Previous radiation pneumonitis			
+	8 (50.0)	9 (50.0)	-
Total dose, Gy			
<40	2 (12.5)	5 (27.8)	-
40–60	3 (18.8)	1 (5.5)	-
≥60	10 (62.5)	12 (66.7)	-
Unknown	1 (6.2)	0 (0.0)	-
V ₂₀ (%)			
≤20	7 (43.8)	7 (38.9)	-
20–30	6 (37.5)	3 (16.7)	-
>30	1 (6.2)	1 (5.5)	-
Unknown	2 (12.5)	7 (38.9)	-
V ₃₀ (%)			
≤20	11 (68.8)	8 (44.4)	-
>20	3 (18.7)	3 (16.7)	-
Unknown	2 (12.5)	7 (38.9)	-
MLD, Gy			
≤10	8 (50.0)	7 (38.9)	-
>10	6 (37.5)	4 (22.2)	-
Unknown	2 (12.5)	7 (38.9)	-
Last TRT to Nivo, months			
<12	9 (56.3)	7 (38.9)	-
12–24	5 (31.2)	6 (33.3)	-
24–36	2 (12.5)	1 (5.6)	-
36–48	0 (0.0)	3 (16.6)	-
≥48	0 (0.0)	1 (5.6)	-

Note: Data are shown as n (%) unless otherwise indicated.

Abbreviations: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; MLD, median lung dose; Nivo, nivolumab; PS, performance status; TRT, thoracic radiation therapy; V₂₀, volume receiving more than 20 Gy; V₃₀, volume receiving more than 30 Gy.

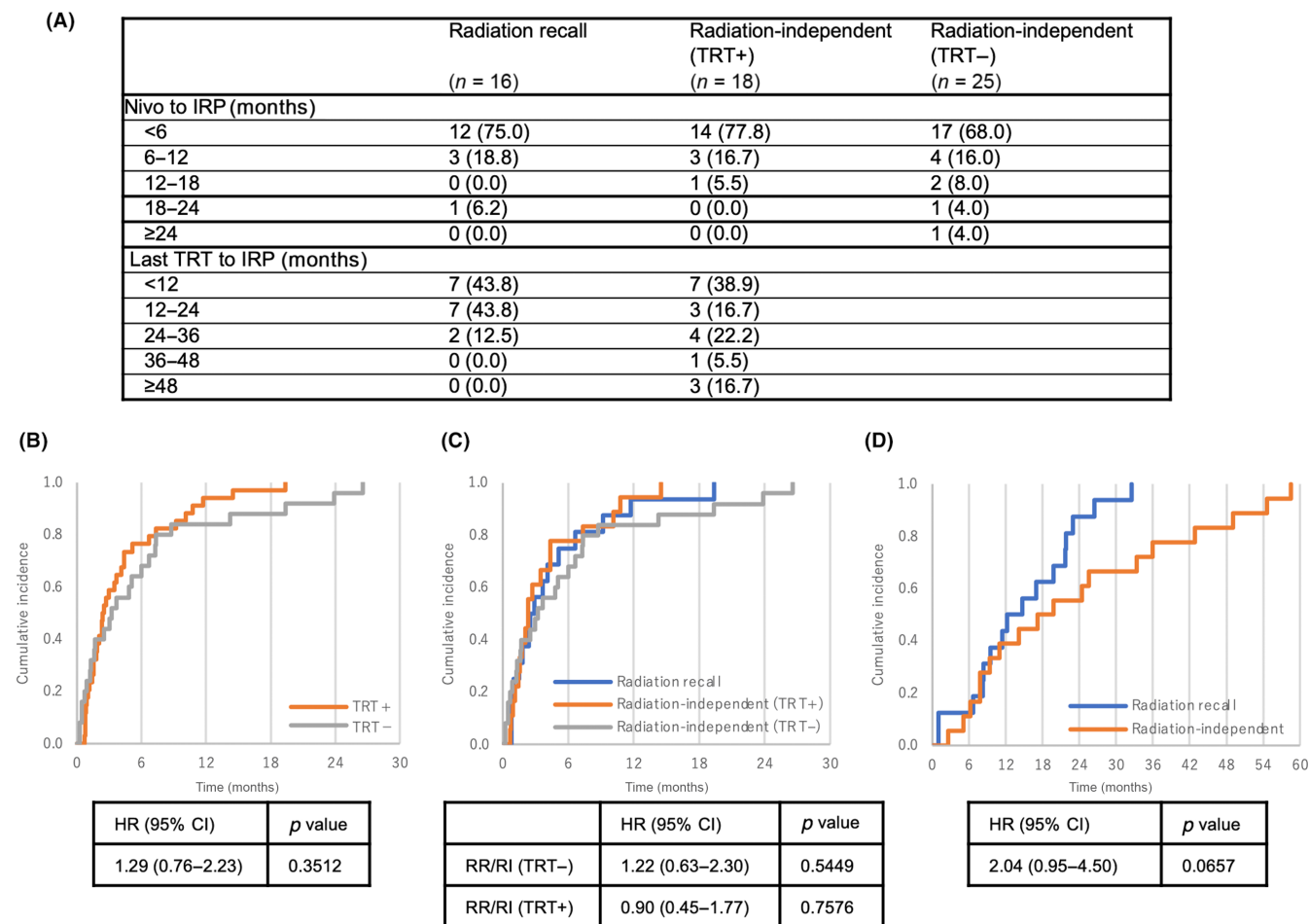


FIGURE 3 Cumulative incidences of immune-related pneumonitis (IRP) in patients with non-small-cell lung cancer treated with nivolumab. (A) Duration since the initiation of nivolumab treatment or the last thoracic radiation therapy (TRT) to the occurrence of IRP. (B) Cumulative incidences of IRP showing the time since the initiation of nivolumab treatment according to the history of previous TRT. (C) Cumulative incidences of IRP showing the time since the initiation of nivolumab treatment according to imaging pattern. (D) Cumulative incidences of IRP showing the time since the last TRT according to imaging pattern. CI, confidence interval; HR, hazard ratio; RI, radiation-independent pattern; RR, radiation recall pattern

suggesting the need for careful observation in patients receiving ICI treatment who have a history of previous TRT. In the present study, the patients with a radiation recall pattern were responsive to corticosteroid therapy and had a relatively good outcome. Although the sample size of this study is still limited, it suggests the possibility that patients with a history of previous TRT could successfully undergo ICI treatment with careful monitoring, similar to patients without TRT.

Although the mechanism underlying IRP has not yet been fully revealed, CTLs induced by ICIs recruit lymphoid infiltration of the lung and other organs and are thought to contribute to irAEs, including IRP.¹⁶ The synergetic effect of radiation therapy and ICIs is now attracting interest, and radiation-induced inflammatory cytokine signaling and immune cell recruitment, as well as tumor antigens and the generation of damage-associated molecular patterns resulting from tumor cell death, are known to stimulate the immune response in the irradiated lung field.^{17,18} The mechanism of radiation recall pneumonitis is yet to be elucidated, but ICI-induced radiation recall

pneumonitis might involve the persistence of immune reactive products caused by previous TRT that enhance the immune response within the radiation field.

This study has some limitations. The first is that our study was evaluated only in Japanese patients. Japanese patients reportedly to have a relatively higher incidence of IRP and higher toxicity,^{19,20} therefore evaluating the risk factors of IRP in this population is reasonable. Second, our study was retrospective, and methods of follow-up monitoring were not standardized. However, the institutions that participated in our study were high-volume centers, and follow-up examinations did not differ so much by each institution. Third, despite a large cohort of 669 patients, the number of patients with previous TRT who developed IRP was relatively small to evaluate the difference of characteristics between radiation recall pattern and the other pattern. Our analysis indicated that radiation recall pneumonitis occurred within a relatively short time after the last TRT and that this pneumonitis had a relatively better outcome; however, this should be further verified in larger sample sizes. Despite

these limitations, our study has significant value as this was the first report to clarify the relationship between previous TRT and risk of IRP along with imaging analysis to characterize radiation recall pneumonitis.

Our study showed that previous TRT was an independent risk factor of IRP after nivolumab treatment and that a specific IRP imaging pattern, which was previously reported as radiation recall pneumonitis, was one of the main patterns among the patients with previous TRT. Although the mechanism of radiation recall pneumonitis has not been fully investigated, our study revealed this specific type of IRP contributed to the higher risk of IRP in NSCLC patients with a history of previous TRT. The clinical characteristics of radiation recall pattern shown in this study, which tends to occur earlier after the last TRT and to have a better outcome than a radiation-independent pattern, should be further verified in larger sample size. Further investigation to explore the mechanism of radiation recall pneumonitis in preclinical fields is warranted.

AUTHOR CONTRIBUTIONS

Hidehito Horinouchi, Yuichiro Ohe, and Shoko Noda-Narita conceived and designed the study. Tomoyuki Naito, Hibiki Udagawa, Koichi Goto, Taichi Miyawaki, Nobuaki Mamesaya, Kazuhisa Nakashima, Hirotsugu Kenmotsu, Tadasuke Shimokawaji, Terufumi Kato, Taiki Hakozaki, Yusuke Okuma, Hidehito Horinouchi, and Shoko Noda-Narita participated in the data collection. Masaki Nakamura and Yuko Nakayama participated in the data collection for the previous radiation therapy. Hirokazu Watanabe and Masahiko Kusumoto performed the imaging analysis. Hidehito Horinouchi and Shoko Noda-Narita performed the overall analysis and interpreted the data. Shoko Noda-Narita wrote the manuscript. All the authors read and approved the final article.

DISCLOSURES

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ETHICS STATEMENT

Approval of the research protocol by and institutional review board: The study was approved by the institutional review boards of the five participating institutions (National Cancer Center Hospital and National Cancer Center Hospital East, 2018-060; Shizuoka Cancer Center, T30-46; Kanagawa Cancer Center, 2018-155; and Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 2189).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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