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# Interstitial lung disease in patients with recurrent and metastatic head and neck cancer treated with immune checkpoint inhibitors and cetuximab and/or paclitaxel

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## Abstract

# Background

In recurrent and metastatic head and neck cancer (R/M HNC), all of cetuximab (Cmab), paclitaxel (PTX), and immune checkpoint inhibitors (ICI) can cause interstitial lung disease (ILD). This study aimed to clarify the clinical outcome of ILD and risk factors for ILD.

# Methods

We retrospectively analyzed 400 patients with R/M HNC who initiated chemotherapy at our institution with any of ICI, Cmab, and PTX. The incidence of ILD induced by each drug, risk factors for ILD, and survival after ILD were evaluated. ILD was diagnosed by diagnostic radiologists.

# Results

The median follow-up period was 17.7 months. The incidence of ILD was 11.0% (20/182) in patients treated with both ICI and Cmab/PTX. Similarly, those of ILD were 8.8% (8/91) in the patients with ICI alone without Cmab/PTX, and 2.4% (3/127) in those of non-ICI. Multivariable analysis identified a history of heavy smoking (Brinkman index ≥ 600) (odds ratio [OR] 3.49, 95% confidence interval [CI] 1.21–10.1) and history of stroke (OR 4.08, 95% CI 1.01–16.5) as the independent risk factors for ILD. 16 patients of ILD needed to change their regimen or withdraw chemotherapy. Nevertheless, the 5-year overall survival was higher in the ILD group than in the non-ILD group (25.1% vs. 5.7%, p = 0.0106).

# Conclusions

The incidence of ILD was higher in patients with R/M HNC who received ICI than in those who didn't. The history of heavy smoking and stroke were independent risk factors for ILD regardless of sequence of ICI, Cmab and PTX.

## Introduction

Cisplatin (CDDP) remains one of the key drugs in chemotherapy for recurrent and metastatic head and neck cancer (R/M HNC), and the advent of cetuximab (Cmab), a chimeric human-murine IgG1 monoclonal antibody that targets the epidermal growth factor receptor, and immune checkpoint inhibitors (ICI) has improved survival [1]. For the first-line treatment of recurrent and metastatic head and neck squamous cell carcinoma (R/M HNSCC), combination regimens of cetuximab plus platinum-based chemotherapy [2] and pembrolizumab monotherapy or pembrolizumab plus chemotherapy [3], as well as nivolumab for platinum-refractory R/M HNSCC, have shown improved survival [4]. In recent years, several

reports have indicated the efficacy of a combination of Cmab and paclitaxel (PTX) as a second-line treatment after ICI [5–8].

Although sequential therapy using these key drugs provides significant benefits to patients with R/M HNSCC [1], it often induces adverse events (AE). Interstitial lung disease (ILD) is one of the most serious AEs because the treatment of ILD is sometimes challenging. Furthermore, it is often difficult to determine the agents responsible for the development of ILD and whether chemotherapy should be resumed. However, information on the incidence and risk factors for ILD is limited in the paradigm of cytotoxic agents, anti-EGFR antibodies, and ICI.

In this study, we investigated the clinical outcomes and risk factors of ILD in patients with R/M HNC who were treated with these key drugs.

## Patients and methods

# Patients

Patients with R/M HNC, regardless of histology, who were treated with ICI (nivolumab or pembrolizumab), Cmab, or PTX at Shizuoka Cancer Center between April 2010 and March 2025 were included in this study. Patients who met any of the following criteria were excluded: those who received investigational drugs outside of the standard regimen suspected to have contributed to ILD, and those with obvious infectious pneumonia that was manageable by antibiotic treatment. Furthermore, patients who had chest imaging findings consistent with ILD before the start of chemotherapy were excluded because the presence of ILD before ICI treatment is an independent risk factor for ILD [9]. This study was approved by the Institutional Review Board of Shizuoka Cancer Center (J2026-9-2026-1) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants included in the study in the form of an opt-out on the website of our hospital.

## Treatment regimens of chemotherapy

All patients were treated with ICI or Cmab- and/or PTX-containing chemotherapy. The administration of these drugs was continued until disease progression or unacceptable toxicity. The treatment regimens were as follows:

1. ICI:

1) Nivolumab was administered at a dose of 240 mg/body every two weeks or 480 mg/body every four weeks.

2) Pembrolizumab: As monotherapy, pembrolizumab was administered at a dose of 200 mg/body every three weeks or 400 mg/body every six weeks. Following combination therapy with CDDP at a dose of 80–100 mg/m$^2$ on day 1 or carboplatin (CBDCA) targeting an area under the blood concentration–time

curve (AUC) of 4–5 mg/mL × min on day 1 plus 5-fluorouracil (5-FU) at a dose of 800–1000 mg/$m^2$ on days 1–4 every 3 weeks for up to six cycles, pembrolizumab-monotherapy was repeated for maintenance.

2. Cmab and PTX:

The initial dose of Cmab was 400 mg/$m^2$ and the dose from the second administration onward was 250 mg/$m^2$ once weekly. PTX was administered at a dose of 60–100 mg/$m^2$, once per week. The administration method and regimen details of drugs other than Cmab and PTX were as follows:

1) 5-FU/CDDP/Cmab: CDDP was administered at a dose of 80–100 mg/$m^2$ on day 1, and continuous infusion of 5-FU was administered at a dose of 800–1000 mg/$m^2$ for four consecutive days every three weeks.

2) 5-FU/CBDCA/Cmab: CBDCA targeting an AUC of 4–5 mg/mL × min was administered on day 1, and 5-FU was administered as described above.

3) PTX/CBDCA/Cmab: CBDCA was administered targeting an AUC of 1.5–2.5 mg/mL × min on day 1 and 8. PTX was administered on days 1 and 8. The Cmab was administered weekly.

4) PTX/Cmab: Both PTX and Cmab were administered weekly.

The 5-FU/CDDP/Cmab, 5-FU/CBDCA/Cmab, and PTX/CBDCA/Cmab regimens were repeated every three weeks for up to six cycles, followed by Cmab-monotherapy.

## Assessment of interstitial lung disease

Chest CT was performed before and after chemotherapy every 8–12 weeks, along with abdominal, head, and neck CT scans. Board-certified diagnostic radiologists reviewed the chest CT scans. ILD was comprehensively diagnosed using chest CT findings, β-D-glucan levels, and fibrosis markers. ILD severity was assessed according to the National Cancer Institute Common Terminology Criteria for AEs, version 5.0.

## Data collection and Statistical analysis

All clinical data, including treatment delivery, survival outcomes, and adverse events of ILD, were retrospectively collected from medical records. The data cutoff date was December 31, 2025. The Mann–Whitney U test was used to identify differences in continuous variables between patients with and without ILD. Fisher's exact test was used to compare categorical data. To estimate the association between the clinical characteristics and ILD, univariable analysis was performed for all covariables, including age, sex, ECOG-PS, Brinkman index, metastasis to the lung or liver, irradiation history to the chest, past history, sequence of chemotherapy, type of ICI, and platinum sensitivity. "Irradiation history to

chest" included not only cases where the target lesion of radiation was in the lung or mediastinum, but also cases where the lung field was part of the irradiation area, even if the target lesion was not in the thoracic cavity. Covariables with $p < 0.10$ in the univariable analysis were further analyzed using a multivariable logistic regression model. Overall survival (OS) was defined as the time from the initiation of palliative chemotherapy to death from any cause or the date of last confirmed survival. Survival curves for OS were estimated using the Kaplan–Meier method. Statistical significance was set at $p < 0.05$. All the statistical analyses were performed using R for Mac (version 4.4.2; GUI 1.81; Big Sur ARM Build 8462).

## Results

# Patient selection and the frequency of ILD

427 patients with R/M HNC were treated with ICI, Cmab, or PTX. Among them, four patients with ILD occurring prior to Cmab/PTX, one patient with ILD occurring prior to ICI, and 22 patients treated with investigational drugs were excluded from the study. The details of the administration of each anticancer drug are as follows (Fig. 1): 91 patients received ICI alone without Cmab or PTX (A in **Supplementary Fig. 1**), 74 patients received PTX and Cmab without ICI (F in **Supplementary Fig. 1**), 33 patients received PTX alone without ICI or Cmab (C in **Supplementary Fig. 1**), 20 patients received Cmab alone without ICI or PTX (B in **Supplementary Fig. 1**), and 182 patients received ICI and Cmab and/or PTX (D + E+G in **Supplementary Fig. 1**).

Among patients treated with ICI, Cmab, and/or PTX (D + E+G), the frequency of ILD was 11.0% (20/182 cases). Similarly, the incidence of ILD was 8.8% (8/91 cases) in patients treated with ICI alone without Cmab or PTX (A) and 2.4% (3/127 cases) in patients who were never treated with ICI (B + C+F in **Supplementary Fig. 1**).

## Patient characteristics

The characteristics of the patients treated with Cmab and/or PTX in addition to ICI for R/M HNC (D + E+G) are presented in Table 1. The patients were divided into two groups: those with ILD (ILD group) and those without ILD (non-ILD group). There were no significant differences between the ILD and non-ILD groups in sex, age, ECOG-PS, primary site of cancer, histological subtype, irradiation history, disease location, liver metastasis, and platinum sensitivity. However, the Brinkman index was significantly higher in the ILD group (median 760, interquartile range [IQR] 530–945) than in the non-ILD group (median, 450, IQR 75–740) ($p = 0.0136$).

Table 1
Patient characteristics

| **Age** | **Characteristic** | **Total** | **ILD** | **non ILD** | ***p*** |
|---|---|---|---|---|---|
| | | **[N = 182]** | **[N = 20]** | **[N = 162]** | |
| | **Median** | **66** | **69.5** | **65.5** | **0.125** |
| | (range [IQR]) | (57–71) | (64-73.25) | (56.25-71) | |
| Sex | Male | 148 | 17 | 131 | 1 |
| | Female | 34 | 3 | 31 | |
| ECOG PS | 0 | 42 | 8 | 34 | 0.204 |
| | 1 | 98 | 9 | 89 | |
| | 2 | 42 | 3 | 39 | |
| Brinkman Index | Median | 485 | 760 | 450 | **0.0136** |
| | (range [IQR]) | (86-768.75) | (530–945) | (75–740) | |
| Primary site | Oral cavity | 59 | 7 | 52 | 0.859 |
| | Hypopharynx | 38 | 4 | 34 | |
| | Oropharynx | 23 | 4 | 19 | |
| | Larynx | 17 | 3 | 14 | |
| | Salivary glands | 14 | 0 | 14 | |
| | Nasal cavity and Paranasal sinuses | 14 | 1 | 13 | |
| | Nasopharynx | 12 | 1 | 11 | |
| | Unknown primary | 3 | 0 | 3 | |
| | External auditory canal | 2 | 0 | 2 | |
| Histological subtype | Squamous cell carcinoma | 162 | 19 | 143 | 0.486 |
| | Salivary duct carcinoma | 7 | 0 | 7 | |
| | Adenoid cystic carcinoma | 2 | 0 | 2 | |
| | Mucoepidermoid carcinoma | 2 | 0 | 2 | |

ILD, interstitial lung disease; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status

| Age | Characteristic | Total [N = 182] | ILD [N = 20] | non ILD [N = 162] | *p* |
|---|---|---|---|---|---|
| | **Median** | **66** | **69.5** | **65.5** | **0.125** |
| | Olfactory neuroblastoma | 1 | 0 | 1 | |
| | Undifferentiated carcinoma | 1 | 0 | 1 | |
| | Nonintestinal type adenocarcinoma | 1 | 0 | 1 | |
| | Adenosquamous carcinoma | 1 | 1 | 0 | |
| | Others | 5 | 0 | 5 | |
| Irradiation history | Yes | 169 | 17 | 152 | 0.158 |
| | No | 13 | 3 | 10 | |
| Disease status | Locoregional | 70 | 6 | 64 | 0.657 |
| | Distant | 67 | 9 | 58 | |
| | Locoregional and distant | 45 | 5 | 40 | |
| Liver | Metastasis | 23 | 2 | 21 | 1 |
| | Non-metastasis | 159 | 18 | 141 | |
| Platinum sensitivity | Sensitive | 56 | 4 | 52 | 0.316 |
| | Refractory | 126 | 16 | 110 | |

ILD, interstitial lung disease; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status

## Risk factors for ILD

The univariable and multivariable logistic regression analyses of ILD are presented in Table 2. In univariable logistic regression analysis, the history of heavy smoking (Brinkman index ≥ 600) [odds ratio (OR): 3.53, 95% confidence interval (CI): 1.37–9.08, p = 0.0132], chest irradiation (OR: 2.71, 95% CI: 1.02–7.18, p = 0.0451), and stroke (OR: 4.25, 95% CI: 1.18–15.4, p = 0.0274) were associated with ILD. Multivariable logistic regression analysis identified Brinkman index ≥ 600 (OR: 3.49, 95% CI: 1.21–10.1, p = 0.0208) and a history of stroke (OR: 4.08, 95% CI: 1.01–16.5, p = 0.0483) as the independent risk factors for ILD development. However, chest irradiation was not significantly associated with ILD in multivariable logistic regression analysis (OR: 2.20, 95% CI: 0.72–6.75, p = 0.166).

Table 2
Uni- and multivariable logistic regression analysis

| Age | Variables | Univariable OR (95%CI) | *p* | Multivariable OR (95%CI) | *p* |
|---|---|---|---|---|---|
| | **≥ 67 vs. <67** | **2.10 (0.797–5.54)** | **0.133** | **-** | **-** |
| Sex | Male vs. Female | 1.34 (0.370–4.86) | 0.655 | - | - |
| ECOG PS | ≥ 1 vs. 0 | 0.398 (0.151–1.05) | 0.0633 | 0.491 (0.170–1.42) | 0.189 |
| Brinkman index | ≥ 600 vs. <600 | 3.53 (1.37–9.08) | **0.0132** | 3.49 (1.21–10.1) | **0.0208** |
| Lung metastasis | + vs. - | 2.38 (0.902–6.28) | 0.0797 | 1.98 (0.682–5.72) | 0.209 |
| Liver metastasis | + vs. - | 0.746 (0.161–3.45) | 0.708 | - | - |
| Radiation to chest | + vs. - | 2.71 (1.02–7.18) | **0.0451** | 2.20 (0.72–6.75) | 0.166 |
| Past history | None: Yes vs. No | 0.867 (0.298–2.52) | 0.793 | - | - |
| | Other cancer: Yes vs. No | 1.01 (0.215–4.77) | 0.986 | - | - |
| | Hypertension: Yes vs. No | 1.95 (0.764–4.96) | 0.163 | - | - |
| | Diabetes mellitus: Yes vs. No | 1.92 (0.637–5.76) | 0.247 | - | - |
| | Dyslipidemia: Yes vs. No | 0.353 (0.0449-2.78) | 0.323 | - | - |
| | Hyperuricemia: Yes vs. No | 1.25 (0.337–4.66) | 0.737 | - | - |
| | Ischemic heart disease: Yes vs. No | < 0.0001 (0-inf) | 0.991 | - | - |
| | Non-ischemic heart disease: Yes vs. No | 2.89 (0.542–15.4) | 0.214 | - | - |
| | Stroke: Yes vs. No | 4.25 (1.18–15.4) | **0.0274** | 4.08 (1.01–16.5) | **0.0483** |

OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GU, gastric ulcer; ICI, immune checkpoint inhibitor; Cmab, cetuximab; PTX, paclitaxel.

| | | | | | |
|---|---|---|---|---|---|
| **Age** | **Variables** | **Univariable OR (95%CI)** | ***p*** | **Multivariable OR (95%CI)** | ***p*** |
| | **≥ 67 vs. <67** | **2.10 (0.797–5.54)** | **0.133** | **-** | **-** |
| | Chronic kidney disease: Yes vs. No | 0.722 (0.0884-5.91) | 0.762 | - | - |
| | Liver disorder: Yes vs. No | < 0.0001 (0-inf) | 0.992 | - | - |
| | Ashtma: Yes vs. No | < 0.0001 (0-inf) | 0.99 | - | - |
| | COPD: Yes vs. No | < 0.0001 (0-inf) | 0.992 | - | - |
| | GERD / GU: Yes vs. No | < 0.0001 (0-inf) | 0.989 | - | - |
| | Mental disorder: Yes vs. No | < 0.0001 (0-inf) | 0.991 | - | - |
| | Autoimmune disease: Yes vs. No | < 0.0001 (0-inf) | 0.992 | - | - |
| Sequence | ICI prior to Cmab / PTX: Yes vs. No | 1.45 (0.528–3.96) | 0.473 | - | - |
| ICI | Nivolumab vs. Pembrolizumab | 0.675 (0.256–1.78) | 0.426 | - | - |
| Platinum sensitivity | Sensitive vs. Resistant | 0.529 (0.168–1.66) | 0.275 | - | - |

OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; GU, gastric ulcer; ICI, immune checkpoint inhibitor; Cmab, cetuximab; PTX, paclitaxel.

# Characteristics of drug-induced ILD

The characteristics of drug-induced ILD are summarized in Table 3. In terms of treatment sequence of chemotherapy, the number of patients who received the ICI followed by Cmab/PTX (ICI-first group) and that of Cmab/PTX followed by ICI (Cmab/PTX-first group) were 14 and 6 cases, respectively. Organizing pneumonia was the most frequent imaging pattern of ILD (10/20 cases). A nonspecific interstitial pneumonia pattern was observed in five cases in the ICI-first treatment group, but not in any cases in the Cmab/PTX-first treatment group, although the difference was not significant. There was no significant difference in the severity of ILD between groups. Grade 1 ILD was most frequently observed in both groups (9/14 cases in the ICI-first group and 3/6 cases in the Cmab-first group), and all cases resolved without steroid administration. In patients with grade 2–3 ILD, chemotherapy was suspended or withdrawn, and steroids were administered to both groups.

Table 3
Characteristics of drug-induced ILD

| ILD type | Characteristic | Total [N = 20] | ICI → Cmab/PTX [N = 14] | Cmab/PTX → ICI [N = 6] | *p* |
|---|---|---|---|---|---|
| | **OP** | **10** | **6** | **4** | **0.323** |
| | HP | 5 | 3 | 2 | |
| | NSIP | 5 | 5 | 0 | |
| ILD grade | 1 | 12 | 9 | 3 | 0.408 |
| | 2 | 5 | 4 | 1 | |
| | 3 | 3 | 1 | 2 | |
| Suspected drug of ILD* | Cetuximab | 11 | 11 | 0 | **0.000371** |
| | Resume (G1/G2/G3) | 4/0/0 | 4/0/0 | 0/0/0 | |
| | Withdrawal (G1/G2/G3) | 3/3/1 | 3/3/1 | 0/0/0 | |
| | Paclitaxel | 7 | 6 | 1 | |
| | Resume (G1/G2/G3) | 2/0/0 | 2/0/0 | 0/0/0 | |
| | Withdrawal (G1/G2/G3) | 2/1/2 | 2/1/1 | 0/0/1 | |
| | ICI | 6 | 1 | 5 | |
| | Resume (G1/G2/G3) | 0/0/0 | 0/0/0 | 0/0/0 | |
| | Withdrawal (G1/G2/G3) | 3/3/0 | 0/1/0 | 3/2/0 | |
| ILD medication | None | 12 | 9 | 3 | 0.586 |
| | PSL (0.5-1mg/kg/day) | 4 | 3 | 1 | |
| | mPSL (125-1000mg/day) | 3 | 1 | 2 | |

ILD, interstitial lung disease; ICI, immune checkpoint inhibitor; Cmab, cetuximab; PTX, paclitaxel; OP, organizing pneumonia; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia; PSL, prednisolone; mPSL, methylprednisolone; DEX, dexamethasone

* Multiple possible selections

| ILD type | Characteristic | Total [N = 20] | ICI → Cmab/PTX [N = 14] | Cmab/PTX → ICI [N = 6] | *p* |
|---|---|---|---|---|---|
| | **OP** | **10** | **6** | **4** | **0.323** |
| | DEX (3.3mg/day) | 1 | 1 | 0 | |
| Chemotherapy after ILD | Resume | 4 | 4 | 0 | 0.402 |
| | Change the regimen to | 13 | (8) | (5) | |
| | Paclitaxel | | 5 | 3 | |
| | S-1 | | 2 | 2 | |
| | Nedaplatin | | 1 | 0 | |
| | Withdraw chemotherapy | 3 | 2 | 1 | |
| ILD, interstitial lung disease; ICI, immune checkpoint inhibitor; Cmab, cetuximab; PTX, paclitaxel; OP, organizing pneumonia; HP, hypersensitivity pneumonitis; NSIP, nonspecific interstitial pneumonia; PSL, prednisolone; mPSL, methylprednisolone; DEX, dexamethasone | | | | | |
| * Multiple possible selections | | | | | |

Moreover, there was no significant difference in cancer treatment after ILD between the two groups (p = 0.402). Except for four patients who resumed the same regimen, 13 patients required a change in their treatment regimen, and three patients needed to withdraw from chemotherapy.

Figure 2 shows a swimmer plot of ILD events and chemotherapy. The onset of ILD varied widely, with a median of 10.3 months (IQR, 6.6–16.7 months). Notably, there was only one case of ILD recurrence among the 20 patients who experienced ILD. In Case 14 (Fig. 2), first-line chemotherapy with Cmab, CDDP, and 5-FU was initiated for postoperative recurrence, followed by nivolumab after disease progression. After S-1 was initiated as third-line therapy, the patient was diagnosed with ILD, which improved with prednisolone. Because disease progression was observed during S-1, PTX treatment was initiated. However, ILD recurred one week after the first PTX dose, requiring hospitalization and treatment with methylprednisolone. The interval between the initial onset of ILD and recurrence was approximately four months. After the resolution of ILD, PTX was carefully resumed, and ILD did not recur; however, chemotherapy was discontinued because of progression. The patient died six months after the final PTX treatment.

# Survival

The median follow-up period was 17.7 months (IQR, 10.9–26.5 months). The 5-year OS rate for all patients was 8.4% and the median survival time (MST) was 18.2 months (Fig. 3A). When distinguished

by the presence or absence of ILD, the 5-year OS in the non-ILD group was 5.7% (MST: 17.4 months), while that in the ILD group was 25.1% (MST: 32.6 months), indicating a significantly longer survival in the ILD group (p = 0.0106, Fig. 3B).

## Discussion

In our study cohort of patients with R/M HNC, the incidence of ILD was 8.8% and 11.0% in the group treated with ICI alone and in those treated with ICI plus Cmab or PTX, respectively, whereas the incidence in the group that was never treated with ICI was 2.4%. The history of heavy smoking (Brinkman index ≥ 600) and stroke were the independent risk factors for ILD development. The 5-year OS rate was higher in the ILD group than in the non-ILD group.

Upon the initial introduction of Cmab and ICI for HNC treatment, the incidence of ILD was evaluated, mainly focusing on a single agent or regimen. The incidence of ILD associated with Cmab or ICI in patients with R/M HNSCC has been reported to be approximately 4–5% [10–13]. For instance, a retrospective study revealed that two patients (3.4%) developed interstitial pneumonia among 59 R/M HNSCC patients who received a combination of Cmab and PTX [13]. Because combination and sequential chemotherapy using multiple agents involved in ILD are available in real-world practice, information on adverse events related to these agents is required. Our study targeted patients with R/M HNC who received multiple treatment combinations and sequences in clinical practice. Notably, the incidence of ILD in patients treated with ICI, Cmab, and/or PTX was 11.0%, regardless of the treatment order. This result is consistent with those of previous studies, in which the incidence of ILD in R/M HNSCC treated with Cmab and PTX after ICI was approximately 10% [7, 8]. Although there are some differences in patient characteristics, history of chemotherapy and irradiation, and definition of ILD among the studies, these findings suggest that sequential treatment with ICI and Cmab and/or PTX may result in a higher frequency of ILD occurrence than Cmab and/or PTX without ICI.

Drug-induced pulmonary toxicity has been well recognized since classical chemotherapy [14]. In particular, the risk factors for ICI-related ILD have been widely reported in lung cancer. For instance, a smoking history of ≥ 50 pack-years [15] and a history of radiotherapy [16] have been indicated as risk factors for ILD. However, this finding does not necessarily apply to other cancer types. In a cross-cancer evaluation of patients with various malignancies treated with anti-PD-1 antibodies [17], a history of chest irradiation was identified as a risk factor for the development of pneumonitis, whereas smoking history was not.

Regarding HNC, a history of heavy smoking (≥ 50 pack-years) was reported to be significantly associated with the development of ILD in patients treated with Cmab [10]. Furthermore, in a retrospective study of patients with advanced extrapulmonary cancer treated with ICIs, including HNC, smoking was identified as a risk factor for all-grade immune-mediated pneumonitis [18]. These findings support our results showing that a history of heavy smoking is an independent risk factor for ILD in patients receiving sequential chemotherapy with ICI plus Cmab and/or PTX for R/M HNC.

Our analysis revealed that a history of stroke was significantly associated with the development of ILD. Since no reports have demonstrated a direct association between a history of cerebrovascular disease and ILD [19, 20], it is difficult to clinically interpret why stroke is a risk factor for drug-induced ILD. The occurrence of ILD in patients with a history of stroke may be partially explained by the use of antiplatelet and anticoagulant therapies. It is suggested that antiplatelet drugs may increase the risk of checkpoint inhibitor-related pneumonitis in patients with advanced cancer [21]. Several studies have also demonstrated that direct oral anticoagulants (DOACs) increase the risk of ILD [22, 23]; therefore, antiplatelet and anticoagulant therapies may be potential confounding factors for stroke. Furthermore, antiplatelet and anticoagulant therapies can lead to alveolar hemorrhage. Blood components entering the alveoli subsequently inactivate the surfactant function [24], leading to increased idiopathic pulmonary fibrosis [25]. In our cohort, among the four patients with a history of stroke who developed ILD, one continued low-dose aspirin therapy and one continued DOAC therapy.

However, a history of radiation to the chest was not an independent risk factor for ILD in R/M HNC in the multivariable analysis, unlike in lung cancer. In our cohort, extrapulmonary regions, but not pulmonary regions, such as the pleura, esophagus, thoracic vertebrae, and ribs, were the direct targets in all patients who underwent chest irradiation. Furthermore, while almost half of the lung cancer cases received a dose of 60 Gy or more [16], only one of the 20 ILD cases in this study received a dose of 60 Gy to the chest. Thus, the radiation dose and area in this study differed from those used in lung cancer.

Identifying the causative agent at the time of ILD onset in the sequence of anticancer drugs is challenging. However, this study frequently identified drugs administered later as suspected causative agents; Cmab or PTX was often considered a suspected causative drug for ILD in ICI-first cases, and ICI was in Cmab/PTX-first cases. Furthermore, none of the patients progressed to fatal ILD following these decisions. Even in treatments including ICI, considering the anticancer drugs used closest to the onset of ILD as suspected drugs and discontinuing chemotherapy may be reasonable.

Several studies have suggested that ILD negatively affects patient survival during cancer treatment. A retrospective study of patients with advanced NSCLC treated with ICI showed that the occurrence of ICI-induced pneumonitis independently increased the risk of death [26]. Furthermore, a meta-analysis showed that treatment with epidermal growth factor receptor tyrosine kinase inhibitors significantly increased the risk of fatal ILD-related events in advanced NSCLC [27]. In contrast, our study suggests that survival was longer in the ILD group than in the non-ILD group. One of the primary reasons for maintained survival may be the early detection of ILD, withdrawal or suspension of causative drugs, and immediate initiation of steroids. More than half of the cases (12/20) were grade 1, and there were a few severe cases of ILD. Additionally, favorable survival outcomes may be partially explained by the appropriate management of complications from steroid treatment, such as blood glucose control, prevention of gastric ulcers, and opportunistic infections, which makes it possible to avoid prolonged interruptions in chemotherapy due to complications. Thus, it may be possible to maintain a patient's general condition and performance status even after the onset of ILD and to use all available key drugs. Of the 20 patients, 17 resumed chemotherapy, while three withdrew.

This study has some limitations. First, it was a retrospective study conducted at a single institution. Second, although ILD was defined by diagnostic radiologists, high-resolution CT, bronchoalveolar lavage, and pulmonary fibrosis laboratory markers were not evaluated in all ILD cases. Third, the causative drugs were identified at the discretion of the attending physicians. Therefore, the involvement of other anticancer drugs, such as platinum agents and S-1, in ILD cannot be completely ruled out.

In conclusion, the incidence of ILD was higher in patients with R/M HNC who received ICI than in those who did not. The history of heavy smoking and stroke were independent risk factors for ILD, regardless of the treatment sequence of ICI, Cmab, and PTX.

# Declarations

Acknowledgments

The authors declare no conflict of interest.

Data availability

Data supporting the findings of this study are available from the author upon request.

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# Figures

## Figure 1

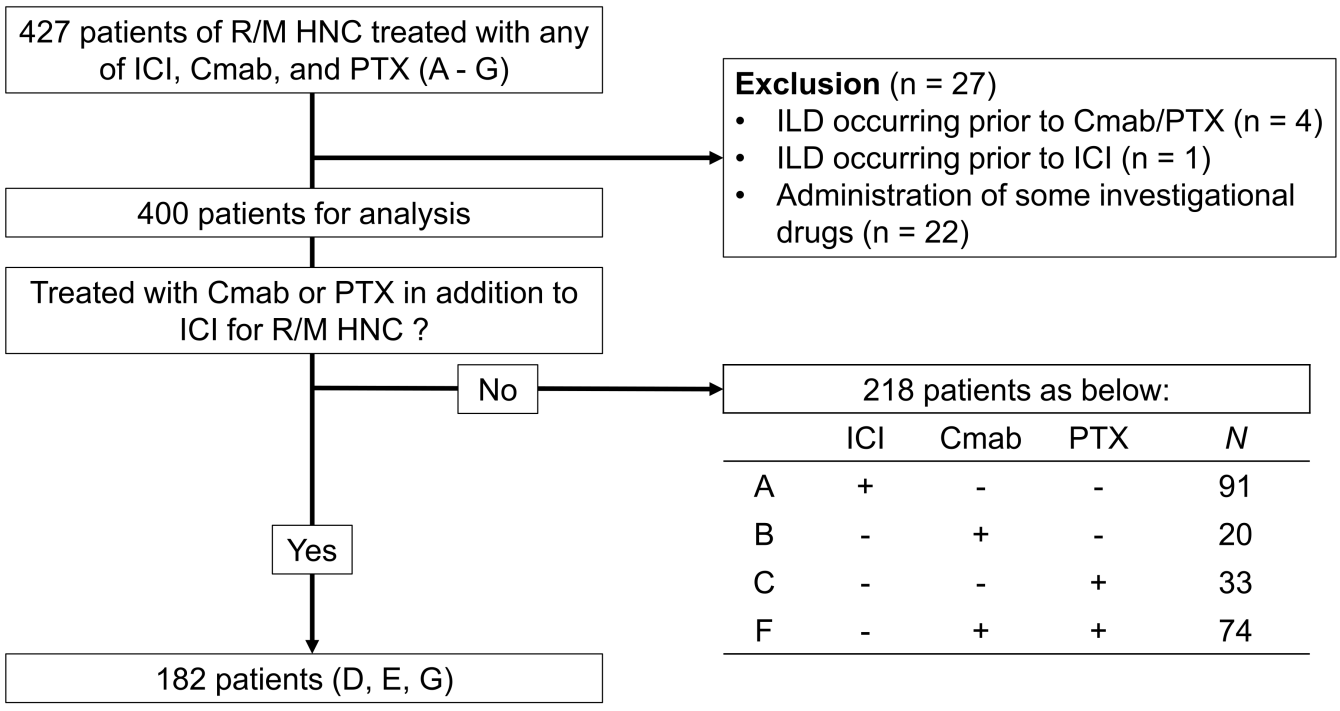



**Figure 1**

**Patient selection criteria**

Flowchart illustrating the composition of the study cohort (N = 400). A-G are shown in Supplementary Figure 1.

R/M, recurrent and/or metastatic; HNC, head and neck cancer; ICI, immune checkpoint inhibitor; Cmab, cetuximab; PTX, paclitaxel

Figure 2

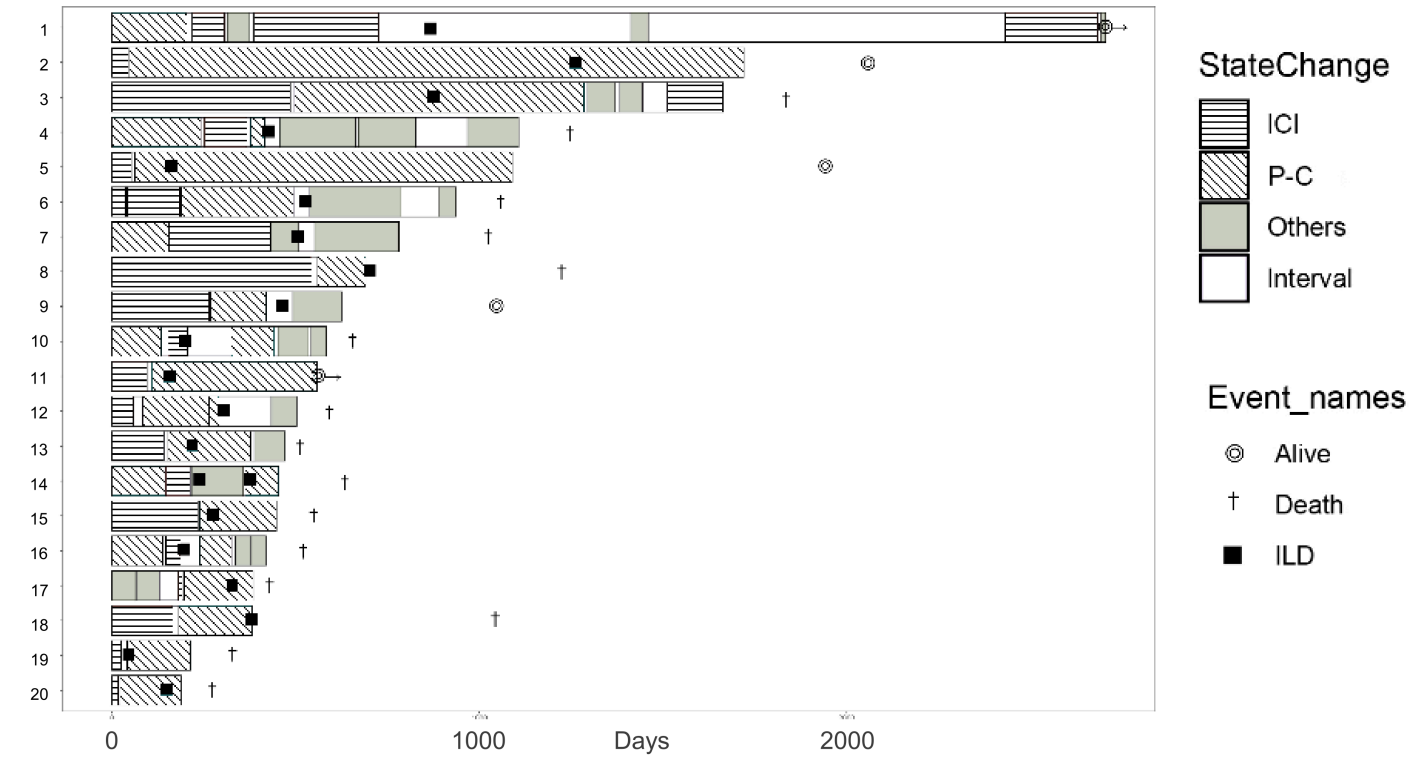



**Figure 2**

**Swimmer plot of cases with ILD**

Swimmer plot showing the courses of chemotherapy, ILD, and survival. Boxes with diagonal lines represent administration of ICIs (nivolumab or pembrolizumab). Boxes with horizontal lines represent administration of cetuximab and/or paclitaxel. Gray boxes represent administration of other anticancer drugs. Black squares indicate ILD onset.

ICI, immune checkpoint inhibitors; Cmab/PTX, cetuximab and/or paclitaxel; ILD, interstitial lung disease

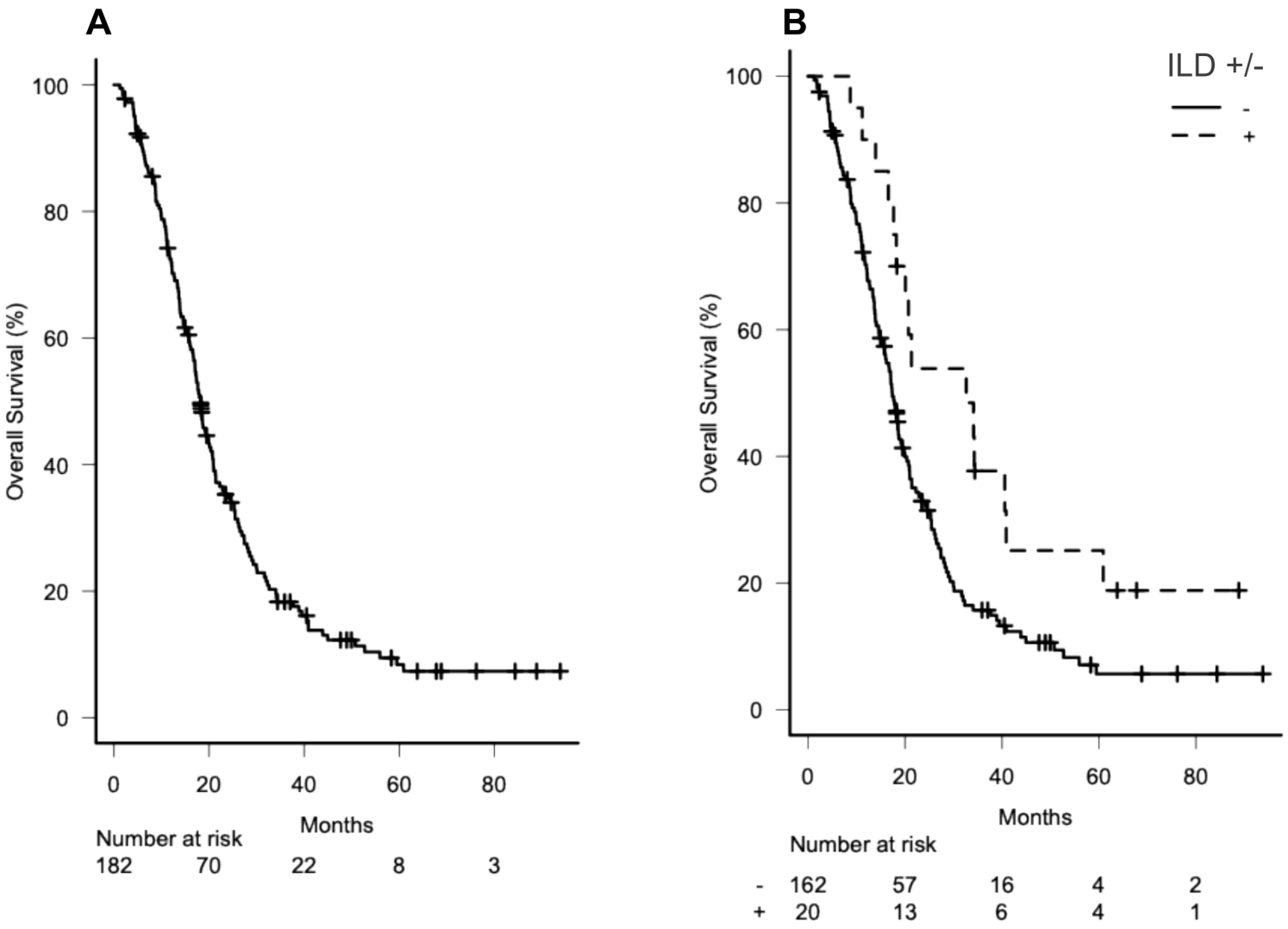



**Figure 3**

**Overall survival**

Overall survival curves for all patients treated with immune checkpoint inhibitors and cetuximab and/or paclitaxel (A) and for patients stratified by ILD and non-ILD status (B).

ILD, interstitial lung disease

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ILDfiguresupple20260701.pptx