Comparison of post-chemoradiotherapy pneumonitis between Asian and non-Asian patients with locally advanced non-small cell lung cancer: a systematic review and meta-analysis

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Summary

Background Pneumonitis is a common complication for patients with locally advanced non-small cell lung cancer undergoing definitive chemoradiotherapy (CRT). It remains unclear whether there is ethnic difference in the incidence of post-CRT pneumonitis.

Methods PubMed, Embase, Cochrane Library, and Web of Science were searched for eligible studies from January 1, 2000 to April 30, 2023. The outcomes of interest were incidence rates of pneumonitis. The random-effect model was used for statistical analysis. This meta-analysis was registered with PROSPERO (CRD42023416490).

Findings A total of 248 studies involving 28,267 patients were included. Among studies of CRT without immunotherapy, the pooled rates of pneumonitis for Asian patients were significantly higher than that for non-Asian patients (all grade: 66.8%, 95% CI: 59.2%–73.9% vs. 28.1%, 95% CI: 20.4%–36.4%; $P < 0.0001$; grade ≥2: 25.1%, 95% CI: 22.9%–27.3% vs. 14.9%, 95% CI: 12.0%–18.0%; $P < 0.0001$; grade ≥3: 6.5%, 95% CI: 5.6%–7.3% vs. 4.6%, 95% CI: 3.4%–5.9%; $P = 0.015$; grade 5: 0.6%, 95% CI: 0.3%–0.9% vs. 0.1%, 95% CI: 0.0%–0.2%; $P < 0.0001$). Regarding studies of CRT plus immunotherapy, Asian patients had higher rates of all-grade (74.8%, 95% CI: 63.7%–84.5% vs. 34.3%, 95% CI: 28.7%–40.2%; $P < 0.0001$) and grade ≥2 (34.0%, 95% CI: 30.7%–37.3% vs. 24.6%, 95% CI: 19.9%–29.3%; $P = 0.001$) pneumonitis than non-Asian patients, but with no significant differences in the rates of grade ≥3 and grade 5 pneumonitis. Results from subgroup analyses were generally similar to that from the all studies. In addition, the pooled median/mean of lung volume receiving ≥20 Gy and mean lung dose were relatively low in Asian studies compared to that in non-Asian studies.

Interpretation Asian patients are likely to have a higher incidence of pneumonitis than non-Asian patients, which appears to be due to the poor tolerance of lung to radiation. Nevertheless, these findings are based on observational studies and with significant heterogeneity, and need to be validated in future large prospective studies focusing on the subject.

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Keywords: Locally advanced non-small cell lung cancer; Chemoradiotherapy; Immunotherapy; Pneumonitis; Meta-analysis

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Research in context

Evidence before this study

Recently, several studies reported a higher incidence of pneumonitis in Asian than in non-Asian patients with locally advanced non-small cell lung cancer (NSCLC) undergoing chemoradiotherapy (CRT). Nevertheless, limited by the small sample size of these studies and lack of randomized control trials, whether there is ethnic difference in the risk of pneumonitis needs further evaluation. We searched PubMed, Embase, Cochrane Library, and Web of Science for eligible studies from January 1, 2000 to April 30, 2023, mainly using the search terms "chemoradiotherapy" and "non-small cell lung cancer".

Added value of this study

To our knowledge, this is the first and most comprehensive meta-analysis focusing on ethnic difference in the incidence of post-chemoradiotherapy pneumonitis for patients with locally advanced NSCLC. Among studies examining definitive CRT, the pooled rates of all-grade, grade ≥2, grade ≥3, and grade 5 pneumonitis for Asian patients were significantly higher than that for non-Asian patients. Regarding studies of CRT plus immunotherapy, Asian patients had higher rates of all-grade and grade ≥2 pneumonitis than non-Asian patients, but with no significant differences in the rates of grade ≥3 and grade 5 pneumonitis.

Implications of all the available evidence

Asian patients are likely to have a higher incidence of pneumonitis than non-Asian patients. The results can be helpful to understand the ethnic difference in risk of post-chemoradiotherapy pneumonitis, and to optimize CRT strategy in Asian patients. Nevertheless, the findings are based on observational studies and with significant heterogeneity, and need to be validated in future large prospective studies focusing on the subject.

Introduction

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and approximately one-third of NSCLC patients have locally advanced (LA) disease at the time of diagnosis.[1] Concurrent chemoradiotherapy (cCRT) has been the historical standard of care for patients with unresectable and LA-NSCLC. However, the survival outcomes of cCRT are unsatisfactory. Given the findings in the phase III PACIFIC trial[2] that the addition of an immune checkpoint inhibitor (ICI) of durvalumab after cCRT significantly improved long-term survival (5-year survival of 42.9 vs 33.4%), the PACIFIC regimen has been the new standard of care in this setting. Nevertheless, treatment-related toxicities remain a issue of clinical concern, particular the toxicity of lung.

Radiation pneumonitis (RP) is a common complication for patients treated with thoracic radiotherapy (RT), which severely decreases patients quality of life. Many factors have been demonstrated to be predictive of RP (such as lung dose–volume parameters, RT technique, chemotherapy regimen, age, sex, history of surgery, and smoking, etc), while the predictive power of these factors appear to be moderate.[3]

Recently, several studies reported a higher rate of post-CRT pneumonitis in Asian than in non-Asian patients with LA-NSCLC. In subgroup analysis of the PACIFIC study,[4] patients who developed pneumonitis were more likely Asian (47.9% vs. 17.6%). Results from a meta-analysis of patients undergoing CRT followed by durvalumab[5] showed that the rate of all-grade pneumonitis from Asian studies was significantly higher than that from Western studies (62% vs. 22%, P = 0.017). Despite the limited sample size of the two studies, the findings suggested a potentially ethnic difference in risk of pneumonitis.

In light of this issue, we performed a systematic review and meta-analysis in LA-NSCLC patients undergoing definitive CRT with or without immunotherapy, aiming to clarify whether Asian patients were associated with a higher incidence of treatment-related pneumonitis than non-Asian patients.

Methods

Literature search

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement[6] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline,[7] and was registered with PROSPERO (CRD42023416490). PubMed, Embase, Cochrane Library and Web of Science were searched for eligible publications between January 1, 2000 and April 30, 2023 by two authors (TL and SL) independently, using the search terms presented in Supplementary File: Table S1. Abstracts of recent international meetings were also inspected, including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Lung Cancer Congress (ELCC), and American Society for Radiation Oncology (ASTRO). References of relevant studies were reviewed for additional articles.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) prospective and retrospective studies examining definitive CRT with or without immunotherapy in unresectable LA-NSCLC; (2) adopting conventionally fractionated RT (1.8–2.2Gy, once-daily) with 3-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated

radiation therapy (IMRT) technique; (3) reporting the incidence rate of pneumonitis during the study period; (4) published in English. The exclusion criteria included: (1) two-dimensional RT; (2) Co-60 or Proton or Carbon-ion RT; (3) hypofractionated or hyperfractionated or stereotactic body radiation therapy; (4) RT alone; (5) neoadjuvant or adjuvant CRT; (6) cCRT with gemcitabine based regimens; (7) endostatin or cetuximab or targeted agents concurrently used with cCRT; (8) only reporting the incidence of pneumonitis during CRT period or less than 3 months after RT; (9) only reporting the incidence of late lung toxicity such as lung fibrosis; (10) the median follow up time less than 6 months; (11) including other types of tumors such as small cell lung cancer and esophageal cancer. When multiple articles covered the similar study population, the one with the most comprehensive data was selected.

Data extraction

The following information were collected independently by three authors (TL and SL and SD): first author, publication year, study period, design, region, race, sample size, patients baseline characteristics (race, age, sex, Eastern Cooperative Oncology Group [ECOG] score, smoking, stage, interstitial lung disease [ILD], follow-up time), RT technique, total RT dose, fractionated dose, RT field, CT regimen, pneumonitis grading criteria, median or mean of lung volume receiving ≥20 Gy (V_{20}), mean lung dose (MLD), and incidence rates of pneumonitis.

Quality assessment

Methodological Index for Non-randomized Studies (MINORS) was used to assess the quality of these non-randomized studies[8] by two authors (SD and JQ) independently.

Statistics

The outcomes of interest were incidence rates of all grade, grade ≥2, grade ≥3, and grade 5 pneumonitis. The random effect model was used for statistical analysis, using the software R (version 3.5.3, R Foundation for Statistical Computing) via the meta package. The inverse variance method was used to calculate pooled estimates of the rates of pneumonitis and their 95% confidence intervals (CIs). Q test was used to test the differences between Asian and non-Asian. The Chi-square (χ^2) and I-square (I^2) test were used to detect the presence of heterogeneity, and significant heterogeneity was considered present if I^2 greater than 50%. Meta-regression was performed to search for confounding factors. The following subgroup analyses were performed: prospective studies, retrospective studies, involved-field irradiation (IFI), and CRT with consolidation durvalumab. Given the improved RT techniques, CT drugs/regimens, and CRT strategy, we also conducted a subgroup analysis of studies published after 2015 for patients undergoing CRT alone. The publication bias was estimated using Begg's test and Egger's test.

Role of funding source

There was no funding obtained for this study.

Results

Eligible studies

A total of 11,661 records were identified through initial database search. After removing duplicates, 5358 records were identified, and 4804 of them were excluded through titles and abstracts review. The remaining 554 articles underwent full-text assessment. Finally, 248 studies involving 28,267 patients were eligible for inclusion. The study selection process and reasons for exclusion are shown in Fig. 1. Among the 248 studies, 174 studies (85 Asian and 89 non-Asian) with 20,999 patients examined definitive CRT without immunotherapy,[9–3536–6970–7878–8889–9192–128129–159160–181] 64 studies (24 Asian and 40 non-Asian) with 6330 patients examined CRT plus immunotherapy,[182–209210–245] and 10 studies (all Asian) with 938 patients examined the both.[246–255] The majority of studies assessed cCRT (226/248, 91%), and using platinum-based doublet chemotherapy regimens. Most of pneumonitis was graded according to Common Toxicity Criteria for Adverse Events (CTCAEs) criteria. As for CRT without immunotherapy, the median age (63 years [IQR, 60–66 years] vs. 63 years [IQR, 60–65 years]), ECOG 0-2 (99% vs. 99%), stage 3 disease (99% vs. 95%), involved-field irradiation (IFI) (79% vs 84%), and the median follow-up (23 months [IQR, 15–33 months] vs. 24 months [IQR, 16–38 months]) were comparable between studies of Asian and non-Asian, while males (80% vs. 69%) and never smoking (14.6% vs. 5.7%) appeared to be unbalanced. Regarding CRT plus immunotherapy, all of studies were published after 2018. Durvalumab was the most common ICI used in studies, and other ICIs were used in 10 studies (1 of sugemalimab, 3 of atezolizumab, 3 of nivolumab, and 3 of pembrolizumab), and 5 studies adopted mixed ICIs. The median age (68 years [IQR, 64–70 years] vs. 66 years [IQR, 65–67 years]), ECOG ≥2 (99% vs. 99%), stage 3 disease (93% vs. 98%), and the median follow-up (15 months [IQR, 14–17 months] vs. 19 months [IQR, 15–21 months]) were also similar between Asian and non-Asian studies, while males (80% vs. 64%) and never smoking (13.7% vs. 7.5%) seemed to be unbalanced. There are 21 studies of Asian and 2 studies of non-Asian provided the information of preexisting ILD. Among these studies, preexisting ILD ranged from 0% to 25% for Asian studies and 0% and 2% for the two non-Asian studies. The main characteristics of studies are presented in Tables 1 and 2, and the main treatments and outcomes are

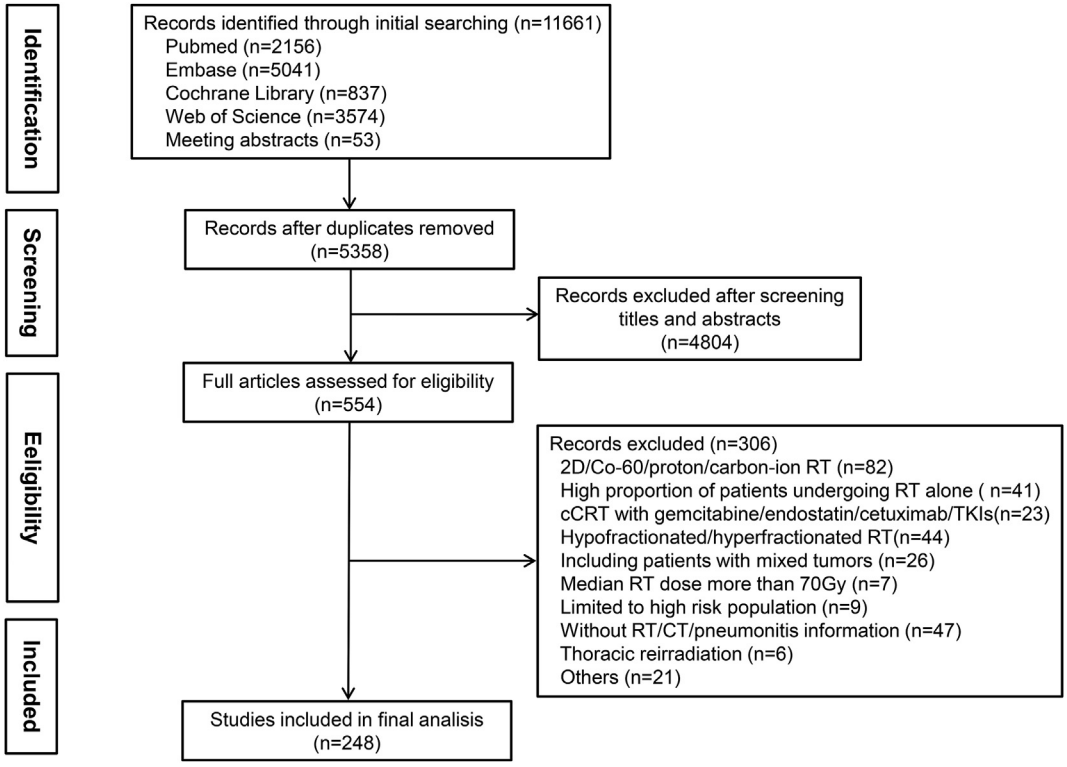

Fig. 1: Literature search and selection. 2D, two-dimensional; RT, radiotherapy; CT, chemotherapy; cCRT, concurrent chemoradiotherapy; TKIs, tyrosine kinase inhibitors.

shown in Supplementary File: Table S2 and S3, respectively.

Assessment of included studies and publication bias

All studies had a score of ≥8 by the MINORS quality assessment (ranged from 8 to 14), suggesting moderate to high quality of them (Supplementary File: Table S4).

The Begg's and Egger's test indicated significant publication bias ($P < 0.05$ for most of the pneumonitis outcomes) (Supplementary File: Table S5).

Comparison of rates of pneumonitis between Asian and non-Asian patients treated with CRT without immunotherapy

All studies

The pooled rates of all-grade (66.8%, 95% CI: 59.2%–73.9% vs. 28.1%, 95% CI: 20.4%–36.4%; $P < 0.0001$), grade ≥2 (25.1%, 95% CI: 22.9%–27.3% vs. 14.9%, 95% CI: 12.0%–18.0%; $P < 0.0001$), grade ≥3 (6.5%, 95% CI: 5.6%–7.3% vs. 4.6%, 95% CI: 3.4%–5.9%; $P = 0.015$), and grade 5 (0.6%, 95% CI: 0.3%–0.9% vs. 0.1%, 95% CI: 0.0%–0.2%; $P < 0.0001$) pneumonitis were significantly higher in Asian patients than that in non-Asian patients (Fig. 2).

Subgroup of studies published after 2015

Similar to the results from all studies, the pooled rates of pneumonitis in Asian patients were significantly higher than that in non-Asian studies (all grade: 65.9%, 95% CI: 56.5%–74.7% vs. 27.3%, 95% CI: 18.6%–37.0%, $P < 0.0001$; grade ≥2: 25.2%, 95% CI: 22.8%–27.6% vs. 15.0%, 95% CI: 11.5%–19.0%, $P < 0.0001$; grade ≥3: 6.8%, 95% CI: 5.8%–7.8% vs. 4.4%, 95% CI: 2.9%–6.2%, $P = 0.019$; grade 5: 0.6%, 95% CI: 0.3%–0.9% vs. 0.01%, 95% CI: 0.0%–0.1%, $P < 0.0001$) (Fig. 2).

Subgroup of prospective studies

The pooled rates of all-grade (54.3%, 95% CI: 44.5%–63.9% vs. 24.4%, 95% CI: 15.2%–34.9%; $P < 0.0001$), grade ≥2 (21.3%, 95% CI: 17.6%–25.2% vs. 11.9%, 95% CI: 7.5%–17.1%; $P = 0.0046$), and grade 5 (0.6%, 95% CI: 0.3%–1.1% vs. 0.04%, 95% CI: 0.0%–0.2%; $P = 0.0006$) pneumonitis rates were significantly higher in Asian patients than that in non-Asian patients. Rate of grade ≥3 pneumonitis was also numerically high in Asian vs. Non-Asian (6.0%, 95% CI: 4.7%–7.4% vs. 4.1%, 95% CI: 2.5%–5.9%), but without statistical significance ($P = 0.068$) (Fig. 2).

We also performed a subgroup analysis of phase 3 trials (Supplementary File: Figure S1). Numerically high

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
Asian											
Tsujino/2003[9]	1999–2000	retrospective	Japan	71	8	67	82	13	NR	96	RP
Lee/2005[10]	2002–2003	phase 2	Korea	31	24	59	85	NR	100	100	ORR
Kim/2005[11]	2000–2002	phase 2	Korea	135	24	60	90	NR	100	100	ORR
Sekine/2006[12]	2001–2003	prospective	Japan	93	30	60	82	NR	100	100	efficacy, safety
Yuan/2007[13]-ENI	1997–2001	prospective	China	100	27	63	64	NR	100	100	LCR
Yuan/2007[13]-IFI	1997–2001	prospective	China	100	27	64	67	NR	100	100	LCR
Sekine/2007[14]	2003–2004	phase 1	Japan	18	NR	63	78	NR	100	100	safety
Naito/2008[15]	2000–2004	retrospective	Japan	73	35	63	86	7	100	100	efficacy, safety
Hanna/2008[16]	2002–2006	prospective	India	147	42	NR	NR	NR	100	100	OS
Ohyanagi/2009[17]	2005–2007	phase 2	Japan	48	25	63	86	NR	100	100	ORR
Nakamura/2009[18]	1998–2004	prospective	Japan	34	NR	61	94	NR	100	100	safety
Cho/2009[19]	2003–2005	phase 2	Korea	49	37	64	90	NR	100	100	OS
Harada/2009[20]	2002–2006	retrospective	Japan	59	30	NR	80	NR	100	100	OS
Shi/2010[21]	2005–2006	retrospective	China	94	11	NR	78	50	85	100	RP
Ichinose/2011[22]	2006–2007	phase 2	Japan	55	28	63	80	4	100	100	ORR
Xu/2011[23]	2008–2009	phase 2	China	21	15	59	76	NR	NR	100	ORR,safety
Lin/2011[24]	2008–2010	prospective	China	37	12	64	59	NR	NR	65	safety
Kim/2011[25]	2000–2010	retrospective	Korea	49	NR	63	90	18	100	100	RP
Wang/2012[26]-EP	2004–2007	phase 2	China	33	46	55	76	NR	100	100	OS
Wang/2012[26]-PC	2004–2007	phase 2	China	32	46	61	79	NR	100	100	OS
Shukuya/2012[27]-SP	2002–2010	retrospective	Japan	39	NR	66	87	13	100	100	efficacy, safety
Shukuya/2012[27]-NP	2002–2010	retrospective	Japan	50	NR	64	74	16	100	100	efficacy, safety
Saitoh/2012[28]	2000–2006	phase 2	Japan	116	62	65	85	NR	100	100	OS
Wang/2012[29]	2006–2010	retrospective	China	135	9	60	79	NR	84	97	RP
Chen/2013[30]-IFI	2002–2011	prospective	China	45	34	56	82	NR	100	100	efficacy
Chen/2013[30]-ENI	2002–2011	prospective	China	54	34	56	89	NR	100	100	efficacy
Kaira/2013[31]	2007–2013	phase 2	Japan	41	15	64	88	NR	100	100	ORR
Sugawara/2013[32]-UP	2006–2009	phase 2	Japan	35	20	62	80	NR	100	100	ORR
Sugawara/2013[32]-NP	2006–2009	phase 2	Japan	31	20	61	84	NR	100	100	ORR
Lin/2013[33]	2008–2010	phase 1	China	18	10	67	78	NR	100	78	safety
Oh/2013[34]-TP	2005–2007	phase 3	Korea	33	≥36	64	91	3	100	100	ORR
Oh/2013[34]-DP	2005–2007	phase 3	Korea	29	≥36	62	90	10	100	100	ORR
Park/2013[35]	2003–2010	retrospective	Korea	60	21	65	85	13	100	93	RP
Zhu/2014[36]	2006–2008	phase 2	China	34	21	59	85	NR	100	100	OS
Ji/2014[37]	2010–2012	retrospective	China	48	20	58	77	31	96	100	efficacy, safety
Dang/2014[38]	2009–2013	retrospective	China	369	≥6	NR	71	38	100	100	RP
Tsujino/2014[39]	2001–2008	retrospective	Japan	122	15	63	89	12	NR	98	RP
Liu/2015[40]	2001–2010	retrospective	China	203	23	56	84	NR	100	100	efficacy, safety
Liang/2015[41]-CTV	2008–2012	retrospective	China	55	NR	59	76	NR	100	100	efficacy, safety
LiangG/2015[41]-NCTV	2008–2012	retrospective	China	50	NR	62	80	NR	100	100	efficacy, safety
Nogami/2015[42]	2006–2009	phase 2	Japan	48	54	66	77	NR	100	100	ORR
Yao/2015[43]	2009–2011	prospective	China	20	NR	60	75	NR	100	100	efficacy, safety
Takase/2016[44]	2006–2014	retrospective	Japan	114	15	61	96	6	100	100	OS,PFS
Wang/2016[45]-PP	NR	phase 3	Multicentre	44	NR	54	59	52	100	100	OS
Wang/2016[45]-EP	NR	phase 3	Multicentre	46	NR	57	62	43	100	100	OS
Feng/2016[46]	2012–2014	prospective	China	36	NR	63	67	NR	100	100	ORR
Lin/2016[47]	2006–2013	phase 3	China	130	23	NR	82	NR	100	100	ORR
Noh/2016[48]-3DRT	2010–2012	retrospective	Korea	48	22	62	73	29	100	100	PFS,OS
Noh/2016[48]-IMRT	2010–2012	retrospective	Korea	29	22	59	62	41	100	100	PFS,OS
He/2016[49]	2011–2013	retrospective	China	35	26	NR	86	NR	100	100	efficacy, safety
Hasegawa/2016[50]	2013–2014	prospective	Japan	10	8	73	90	10	100	100	ORR
Oh/2017[51]	2003–2012	retrospective	Korea	204	NR	NR	70	NR	100	100	OS
Liang/2017[52]-EP	2007–2011	phase 3	China	95	73	59	84	26	100	100	OS

(Table 1 continues on next page)

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
(Continued from previous page)											
Liang/2017[52]-PC	2007–2011	phase 3	China	96	73	57	89	24	100	100	OS
Ding/2017[53]	2010–2015	retrospective	China	40	NR	64	73	25	100	100	RP
Lee/2017[54]	2010–2015	retrospective	Korea	61	12	68	92	28	100	100	RP
Xu/2017[55]	2009–2012	retrospective	China	87	25	61	89	17	100	100	efficacy, safety
Sasaki/2018[56]-SP	2009–2011	phase 2	Japan	54	32	60	78	11	100	100	OS
Sasaki/2018[56]-NP	2009–2011	phase 2	Japan	54	32	62	80	13	100	100	OS
Jiang/2018[57]-NS	2009–2014	retrospective	China	47	41	57	94	NR	100	100	efficacy, safety
Jiang/2018[57]-S	2009–2014	retrospective	China	50	41	57	94	NR	100	100	efficacy, safety
Taira/2018[58]	2005–2010	phase 2	Japan	39	70	66	80	10	100	100	OS
Xiao/2018[59]	NR	prospective	China	42	9	NR	67	36	100	100	RP
Bi/2019[60]	2011–2015	phase 2	China	51	50	60	76	24	100	100	OS
Zhou/2019[61]	2013–2019	retrospective	China	122	NR	61	88	18	100	100	RP
Wang/2019[62]-SIB	2014–2016	retrospective	China	128	25	62	79	29	100	100	OS,PFS
Wang/2019[62]-IMRT	2014–2016	retrospective	China	298	25	62	80	23	100	100	OS,PFS
Sakaguchi/2019[63]	2011–2018	retrospective	Japan	73	NR	69	85	NR	100	100	efficacy, safety
Sheng/2019[64]	2010–2017	retrospective	China	328	NR	62	92	NR	NR	100	RP
Zhao/2020[65]	2006–2012	prospective	China	69	33	57	78	NR	100	100	OS
Xu/2020[66]	2008–2017	retrospective	China	59	20	NR	97	14	100	100	efficacy
Niho/2020[67]-SP	2013–2016	phase 2	Japan	52	32	65	67	23	100	100	PFS
Niho/2020[67]-PP	2013–2016	phase 2	Japan	50	32	64	66	24	100	100	PFS
Fukui/2020[68]	2012–2018	retrospective	Japan	108	21	65	75	10	100	100	efficacy, safety
Zhang/2010[69]	2013–2017	retrospective	China	749	22	NR	82	27	95	100	efficacy
Jung/2020[246]	2018–2019	retrospective	Korea	40	NR	67	90	15	100	100	PFS
Katsui/2020[70]	2004–2018	retrospective	Japan	45	20	63	91	2	100	100	RP
Shimokawa/2021[71]-SP	2011–2014	phase 2	Japan	53	NR	63	79	21	100	100	OS
Shimokawa/2021[71]-DP	2011–2014	phase 2	Japan	53	NR	66	77	15	100	100	OS
Park/2021[72]	2009–2019	retrospective	Korea	40	11	68	80	NR	88	100	OS
Tanaka/2021[73]	2016–2018	phase 2	Japan	28	33	66	96	NR	100	100	OS
Watanabe/2021[74]-UP	2010–2017	phase 2	Japan	43	54	62	74	9	100	100	OS
Watanabe/2021[74]-PP	2010–2017	phase 2	Japan	42	54	63	81	14	100	100	OS
Zhang/2021[75]	NR	retrospective	China	57	23	NR	93	NR	100	100	efficacy, safety
Meng/2021[76]	2017–2019	retrospective	China	64	18	64	97	8	NR	100	RP
Sakaguchi/2021[77]	2011–2018	retrospective	Japan	103	NR	68	86	9	95	100	RP
Yang/2021[78]-Train	2013–2017	retrospective	China	356	40	60	82	24	100	100	efficacy
Yang/2021[78]-Test	2013–2017	retrospective	China	177	40	60	85	20	100	100	efficacy
Tsukita/2021[247]	2018–2019	retrospective	Japan	20	14	NR	NR	NR	100	100	RP,PFS
Saito/2021[248]	2018–2019	retrospective	Japan	77	8	NR	NR	NR	100	84	RP
Jang/2021[249]	2018–2020	retrospective	Korea	55	12	66	89	18	NR	91	RP
Abe/2021[250]	2007–2018	retrospective	Japan	76	26	70	86	NR	NR	86	LCR
Fujiwara/2021[251]	2016–2019	phase 2	Japan	22	15	NR	NR	NR	100	100	RP,OS
Watanabe/2021[252]	2018–2020	retrospective	Japan	16	16	71	73	NR	NR	NR	RP
Kashihara/2021[79]	2014–2017	retrospective	Japan	145	24	68	72	NR	100	95	RP
Imano/2021[80]	2008–2019	retrospective	Japan	124	NR	69	81	NR	100	NR	RP
Wu/2021[81]	2014–2015	retrospective	China	153	10	63	92	39	100	100	RP
Zhang/2021[82]	2017–2019	retrospective	China	81	23	61	48	65	NR	37	RP
Kim/2021[83]	2016–2018	retrospective	Korea	194	22	62	77	23	100	100	OS
Wu/2022[84]	2019–2020	phase 3	China	81	NR	64	82	43	100	100	safety
Yang/2022[85]	2019–2021	retrospective	China	91	NR	59	78	29	100	92	RP
Yang/2022[78]	2013–2017	retrospective	China	533	40	60	83	23	100	100	OS
He/2022[86]	2014–2019	retrospective	China	122	30	62	88	25	NR	100	OS,safety
Kim/2022[87]	2020–2017	phase 3	Korea	124	71	67	92	11	100	100	OS
Harada/2022[88]	NR	phase 2	Japan	21	NR	67	82	5	100	100	safety
Huang/2022[253]	2013–2020	retrospective	Singapore	45	22	66	84	22	100	100	PFS,OS

(Table 1 continues on next page)

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
(Continued from previous page)											
Kim/2022[89]-1	2018–2020	retrospective	Korea	23	NR	65	87	17	NR	74	RP
Kim/2022[89]-2	2018–2020	retrospective	Korea	31	NR	60	77	19	NR	90	RP
Wu/2023[90]	2013–2017	retrospective	China	113	63	62	87	19	NR	100	RP
Lee/2023[91]	2012–2020	retrospective	Korea	317	30	66	16	NR	100	100	RP
Abe/2023[254]	2008–2022	retrospective	Japan	17	22	68	88	NR	NR	100	efficacy
Park/2023[255]	2020–2021	prospective	Korea	27	27	69	96	7	NR	100	PFS OS
Park/2023[92]	2014–2020	retrospective	Korea	294	18	67	93	14	100	100	PFS OS
Non-Asian											
Rosemman/2002[93]	1996–1999	phase 1-2	USA	48	43	57	61	NR	100	100	OS
Semrau/2003[94]	1997–2002	retrospective	Germany	33	NR	65	NR	NR	91	70	efficacy, safety
Vergnen'egre/2005[95]	2000–2001	phase 2	France	40	35	55	93	NR	100	100	ORR
Fay/2005[96]	1999–2001	retrospective	Australia	156	14	NR	65	72	NR	NR	RP
Petris/2005[97]	1999–2001	retrospective	Sweden	32	14	63	56	NR	100	100	safety
Gandara/2006[98]-9504	1996–1998	phase 2	USA	83	71	60	73	NR	100	100	OS
Gandara/2006[98]-9019	1996–1998	phase 2	USA	50	71	58	82	NR	100	100	OS
Yom/2006[99]-IMRT	2002–2005	retrospective	USA	68	8	62	59	10	100	90	RP
Yom/2006[99]-3DRT	2002–2005	retrospective	USA	222	9	61	52	5	100	90	RP
Kosmidis/2007[100]	2000–2003	phase 2	Greece	32	44	63	93	NR	100	100	efficacy, safety
Semrau/2007[101]	1998–2005	retrospective	Germany	66	13	68	85	NR	NR	88	efficacy, safety
Tell/2008[102]	NR	phase 2	Multicentre	64	NR	63	63	NR	100	100	efficacy, safety
Krzakowski/2008[103]	2002–2003	phase 2	Multicentre	54	37	58	76	NR	100	100	ORR
Steven/2009[104]	2003–2005	phase 2	USA	20	36	67	NR	NR	100	100	efficacy, safety
Crvenkova/2009[105]-S	2005–2008	prospective	Macedonia	45	13	59	89	NR	100	100	OS
Crvenkova/2009[105]-C	2005–2008	prospective	Macedonia	40	22	57	88	NR	100	100	OS
Kocak/2009[106]	2003–2007	retrospective	Turkey	90	16	60	100	NR	100	100	ORR
Garrido/2009[107]	2001–2006	phase 2	Spain	135	23	61	91	NR	100	100	OS
Schallier/2009[108]	2001–2005	phase 2	Belgium	64	59	66	80	NR	100	100	OS
Huber/2010[109]	2002–2003	phase 1	Germany	23	NR	59	91	NR	100	100	OS
Jiang/2010[110]	2005–2006	retrospective	USA	165	17	63	59	5	NR	76	OS,safety
Bastos/2010[111]	2004–2007	phase 2	USA	32	34	58	66	NR	100	100	OS,safety
Barriger/2010[112]	2002–2006	prospective	USA	243	16	63	83	54	NR	100	RP
Descourt/2011[113]	2006–2007	phase 2	France	38	NR	57	88	NR	100	100	ORR
Govindan/2011[114]	2005–2008	phase 2	USA	50	32	65	56	NR	100	100	OS
Shirish/2011[115]	2006–2009	phase 2	USA	28	41	60	68	NR	100	100	OS
Senan/2011[116]	2004–2005	phase 2	Multicentre	70	14	NR	83	NR	100	100	safety
Phernambucq/2011[117]	2003–2008	retrospective	Netherlands	89	17	64	60	NR	100	100	OS,safety
Poudenx/2012[118]	2004–2007	phase 2	France	34	39	61	75	NR	100	100	ORR
Scotti/2012[119]	2003–2007	retrospective	Italy	43	18	63	77	NR	100	100	efficacy, safety
Phernrmbucq/2012[120]	2003–2010	retrospective	Netherlands	87	NR	60	70	NR	NR	100	RP
Yirmibesoglu/2012[121]	2000–2010	retrospective	USA	121	17	60	63	8	NR	86	RP
Stenmark/2012[122]	NR	prospective	USA	58	18	69	88	2	NR	NR	RP
Stephanie/2012[123]	2008–2011	retrospective	Netherlands	86	12	67	NR	NR	NR	97	OS,safety
Spina/2013[124]	1994–2009	retrospective	Australia	105	NR	64	71	9	98	100	OS
Liew/2013[125]-PC	2000–2011	retrospective	Netherlands	44	52	71	80	7	100	100	OS,safety
Liew/2013[125]-EP	2000–2011	retrospective	Netherlands	31	52	63	65	3	100	100	OS,safety
Choy/2013[126]	2007–2009	phase 2	USA	46	NR	63	65	NR	NR	100	OS
Garrido/2013[127]	2001–2006	phase 2	Spain	139	57	62	91	NR	100	100	ORR
Terry/2013[128]	2004–2011	retrospective	Netherlands	121	38	63	69	NR	100	100	OS,safety
Leprieur/2013[129]	2007–2010	retrospective	France	47	NR	70	79	7	NR	NR	RP
Lerouge/2014[130]	2005–2008	phase 2	France	70	19	61	84	NR	100	100	ORR
Mertsoylu/2014[131]	2006–2012	retrospective	Turkey	97	24	58	90	4	100	100	OS,PFS
Juan/2014[132]	2010–2011	phase 2	Spain	48	19	61	90	44	100	100	efficacy, safety
Trinh/2014[133]	2004–2012	prospective	Australia	107	44	65	67	3	100	100	efficacy, safety

(Table 1 continues on next page)

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
(Continued from previous page)											
Bradley/2015[134]	2007–2011	phase 3	USA/ Canada	217	23	64	59	7	100	100	OS
Garrido/2015[135]	2009–2011	phase 2	Multicentre	75	25	61	57	8	100	100	PFS
Chajon/2015[136]	2011–2014	retrospective	France	21	18	NR	NR	NR	NR	100	oesophagitis
Jaksic/2015[137]	2011–2016	retrospective	France	59	NR	65	75	32	NR	88	efficacy, safety
Rodrigues/2015[138]-SD	1995–2010	retrospective	Multicentre	143	89/40	61	74	12	100	100	OS
Rodrigues/2015[138]-ID	1995–2010	retrospective	Multicentre	131	40	61	78	4	100	100	OS
Singhal/2015[139]	2008–2013	phase 2	Multicentre	43	NR	64	67	NR	100	100	PFS
Scher/2015[140]	2007–2013	retrospective	USA	55	13	NR	49	NR	NR	75	RP
Fournel/2016[141]-I	NR	phase 2	France	64	77	57	91	NR	100	100	ORR
Fournel/2016[141]-C	NR	phase 2	France	63	77	59	87	NR	100	100	ORR
Ozcelik/2016[142]-PC	2004–2014	retrospective	Turkey	87	13	64	82	NR	100	100	efficacy, safety
Ozcelik/2016[142]-EP	2004–2014	retrospective	Turkey	50	13	60	90	NR	100	100	efficacy, safety
Ozcelik/2016[142]-DP	2004–2014	retrospective	Turkey	90	13	60	93	NR	100	100	efficacy, safety
Flentje/2016[143]	2005–2009	phase 3	Germany	279	16	60	71	NR	100	100	PFS
Brade/2016[144]	2007–2009	phase 2	Canada	39	29	62	46	NR	100	100	OS
Yılmaz/2016[145]	2008–2012	retrospective	Turkey	82	40	57	96	NR	100	100	OS
Ling/2016[146]-ENI	1994–2014	retrospective	USA	65	13	NR	NR	NR	100	100	OS,safety
Ling/2016[146]-IFI	1994–2014	retrospective	USA	43	13	NR	NR	NR	100	100	OS,safety
Ling/2016[146]-IMRT	1994–2014	retrospective	USA	37	13	NR	NR	NR	100	100	OS,safety
Sen/2016[147]-EP	2004–2012	retrospective	Turkey	50	27	54	92	NR	100	100	OS,safety
Sen/2016[147]-DP	2004–2012	retrospective	Turkey	55	19	55	96	NR	NR	100	OS,safety
Matthew/2016[148]	2000–2007	retrospective	New Zealand	43	12	70	56	NR	NR	88	OS,safety
Wijsman/2016[149]	2008–2014	retrospective	Netherlands	188	18	63	79	NR	NR	100	efficacy, safety
Morth/2016[150]	2009–2012	retrospective	Sweden	71	NR	71	46	11	100	92	RP
Hansen/2017[151]-60Gy	2009–2013	phase 2	Denmark	59	33	67	61	3	100	100	PFS
Hansen/2017[151]-66Gy	2009–2013	phase 2	Denmark	58	33	65	55	3	100	100	PFS
Hughes/2017[152]	2007–2010	phase 2	Australia	27	60	63	56	NR	100	100	efficacy, safety
Alharbi/2017[153]	2007–2015	retrospective	Germany	732	NR	NR	NR	NR	NR	100	RP
Soler/2017[154]	2009–2014	retrospective	Spain	64	16	64	86	6	NR	97	efficacy, safety
Okumus/2017[155]	2009–2012	retrospective	Turkey	68	NR	59	93	3	100	91	OS,safety
Rivas/2018[156]	2012–2017	phase 2	Spain	48	21	60	79	NR	100	100	ORR
Zhang/2018[157]	2004–2014	phase 1	UK	25	27	61	54	NR	100	100	safety
Liao/2018[158]	2009–2014	prospective	USA	92	24	NR	51	10	100	78	RP
Yegya-Raman/2018[159]-CBCT	2007–2015	retrospective	USA	76	41	64	61	NR	100	76	RP
Yegya-Raman/2018[159]-Okv	2007–2015	retrospective	USA	48	76	66	46	NR	100	88	RP
Sculier/2018[160]	2007–2013	phase 3	Multicentre	120	62	60	77	NR	100	100	OS
Topkan/2019[161]	2007–2012	retrospective	Turkey	956	26	63	77	8	100	100	OS
Isla/2019[162]-NP	2011–2014	phase 2	Spain	69	24	64	87	3	100	97	PFS
Isla/2019[162]-EP	2011–2014	phase 2	Spain	71	24	61	86	0	100	97	PFS
Yegya-Raman/2019[163]	2009–2016	retrospective	USA	82	38	65	59	NR	100	74	PFS
Yu/2019[164]	2016–2018	retrospective	USA	46	11	69	52	20	85	83	efficacy, safety
Luna/2019[165]	2008–2016	retrospective	USA	203	23	63	45	8	72	100	RP
Kaderbhaï/2020[166]	2005–2014	retrospective	France	89	58	63	84	6	100	100	efficacy, safety
Nestle/2020[167]-Con	2009–2016	prospective	Germany	99	29	64	72	NR	100	94	PFS
Nestle/2020[167]-PET	2009–2016	prospective	Germany	105	29	66	74	NR	100	92	PFS
Ergen/2020[168]	2009–2015	retrospective	Turkey	268	≥6	60	89	12	100	94	RP
Harris/2020[169]	2011–2016	retrospective	USA	78	NR	65	39	17	NR	100	RP
Spencer/2021[170]	2011–2014	retrospective	UK	141	21	63	54	NR	96	100	OS,safety
Remmerts de Vries/2021[171]	2015–2017	retrospective	Netherlands	64	29	67	50	5	100	100	OS,safety

(Table 1 continues on next page)

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
(Continued from previous page)											
Owen/2021[172]-3DRT	2007–2013	retrospective	USA	58	NR	NR	78	NR	NR	79	RP
Owen/2021[172]-VMAT	2007–2013	retrospective	USA	30	NR	NR	60	NR	NR	93	RP
Provencio/2021[173]	2017–2018	phase 2	Spain	54	29	62	77	5	100	100	PFS
Tsakiridis/2021[174]	2014–2019	phase 2	Canada	28	NR	65	43	NR	100	100	efficacy
Skinner/2021[175]	2014–2016	phase 2	Canada	75	28	64	59	NR	100	100	OS,safety
Mantel/2021[176]	2010–2018	retrospective	Germany	138	18	63	68	NR	NR	83	LCR,safety
Lim/2021[177]	2015–2018	phase 2	USA	19	24	68	45	5	NR	84	RP
Lutz/2021[178]-60Gy	2009–2013	prospective	Denmark	59	NR	67	61	5	100	88	RP
Lutz/2021[178]-66Gy	2009–2013	prospective	Denmark	58	NR	65	55	5	100	95	RP
McFarlane/2021[179]	2012–2019	prospective	USA	1302	NR	68	51	4	NR	84	RP
Szejniuk/2021[180]	2012–2016	prospective	Denmark	41	12	66	56	5	100	78	RP
Bourbons/2021[181]	2015–2018	retrospective	France	165	≥12	65	67	NR	100	100	RP

Abbreviations: ECO, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; LCR, local control rate; RP, radiation pneumonitis; NR, not reported.

Table 1: **Characteristics of studies examining chemotherapy without immunotherapy.**

rates of pneumonitis were observed for Asian vs. non-Asian (all grade: 48.0%, 95% CI: 32.9%–63.2% vs. 41.7%, 95% CI: 32.9%–50.5%; P = 0.48; grade ≥2: 19.1%, 95% CI: 7.8%–30.3% vs. 12.0%, 95% CI: 0.4%–23.6%; P = 0.39; grade ≥3: 7.3%, 95% CI: 4.1%–10.6% vs. 3.8%, 95% CI: 1.4%–6.2%; P = 0.091; grade 5: 2.2%, 95% CI: 1.0%–3.8% vs. 0.1%, 95% CI: 0.0%–0.6%; P < 0.0001), but without statistical significance (except grade 5) (Fig. 2).

Subgroup of retrospective studies

Similar to the results from prospective studies, Asian patients were associated with higher rates of all-grade (79.4%, 95% CI: 71.2%–86.6% vs. 33.3%, 95% CI: 20.8%–47.0%; P < 0.0001), grade ≥2 (27.4%, 95% CI: 24.7%–30.0% vs. 17.0%, 95% CI: 13.9%–20.1%; P < 0.0001), and grade 5 (0.6%, 95% CI: 0.3%–1.0% vs. 0.08%, 95% CI: 0.0%–0.3%; P = 0.002) pneumonitis compared to non-Asian patients, but with no significant difference in rate of grade ≥3 pneumonitis (6.9%, 95% CI: 5.8%–8.0% vs. 5.2%, 95% CI: 3.5%–7.3%; P = 0.15) (Fig. 2).

Subgroup of patients undergoing cCRT

There were also higher rates of all-grade (65.5%, 95% CI: 57.2%–73.4% vs. 26.4%, 95% CI: 18.7%–35.0%; P < 0.0001), grade ≥2 (24.7%, 95% CI: 21.8%–27.7% vs. 13.3%, 95% CI: 10.0%–16.9%; P < 0.0001), and grade 5 (0.6%, 95% CI: 0.3%–0.9% vs. 0.04%, 95% CI: 0.0%–0.2%; P < 0.0001) pneumonitis in Asian patients than that in non-Asian patients, and without significant difference in rate of grade ≥3 pneumonitis (6.0%, 95% CI: 5.0%–7.0% vs. 4.7%, 95% CI: 3.4%–6.1%; P = 0.10) (Fig. 2).

Subgroup of patients undergoing CRT with IFI

Similarly, Asian patients were associated with higher rates of all-grade (66.0%, 95% CI: 57.0%–74.4% vs. 31.9%, 95% CI: 18.7%–46.9%; P = 0.0001), grade ≥2 (24.0%, 95% CI: 21.3%–26.7% vs. 15.1%, 95% CI: 12.1%–18.1%; P < 0.0001), and grade 5 (0.4%, 95% CI: 0.2%–0.8% vs. 0.1%, 95% CI: 0.0%–0.3%; P = 0.014) pneumonitis compared to non-Asian patients, but with no significant difference in rate of grade ≥3 pneumonitis (7.1%, 95% CI: 5.9%–8.3% vs. 5.2%, 95% CI: 3.5%–7.1%; P = 0.09) (Fig. 2).

Comparison of pneumonitis rates between Asian and non-Asian patients undergoing CRT plus immunotherapy

All studies

The pooled rates of all-grade (74.8%, 95% CI: 63.7%–84.5% vs. 34.3%, 95% CI: 28.7%–40.2%; P < 0.0001) and grade ≥2 (34.0%, 95% CI: 30.7%–37.3% vs. 24.6%, 95% CI: 19.9%–29.3%; P = 0.001) pneumonitis were significantly higher in Asian patients than that in non-Asian patients; while there were no significant differences in rates of grade ≥3 (4.7%, 95% CI: 3.6%–5.9% vs. 6.0%, 95% CI: 4.7%–7.5%; P = 0.24) and grade 5 (0.1%, 95% CI: 0.0%–0.5% vs. 0.1%, 95% CI: 0.0%–0.2%; P = 0.28) pneumonitis (Fig. 3).

Subgroup of prospective studies

Different from the results of all studies, only rate of all-grade pneumonitis was significantly higher in Asian patients than in non-Asian patients (70.7%, 95% CI: 47.6%–86.6% vs. 38.9%, 95% CI: 23.9%–56.4%; P = 0.031), but with no significant differences in the rates of grade ≥2 (26.5%, 95% CI: 15.4%–37.6% vs.

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
Asian											
Jung/2020[246]	2018–2019	retrospective	Korea	21	NR	66	90	24	100	100	PFS
Zhang/2020[182]	2018–2020	prospective	China	20	11	61	80	30	NR	95	efficacy, safety
Saito/2020[183]	2018–2019	retrospective	Japan	36	7	72	75	NR	NR	75	RP
Miura/2020[184]	2018–2019	retrospective	Japan	41	23	72	80	20	100	100	Safety
Inoue/2020[185]	2018–2019	retrospective	Japan	30	8	68	63	23	NR	100	pneumonitis
Chu/2020[186]	2018–2019	retrospective	China	31	NR	64	84	26	100	100	PFS
Tsukita/2021[247]	2018–2019	retrospective	Japan	87	14	70	71	14	100	100	pneumonitis
Saito/2021[248]	2018–2019	retrospective	Japan	225	8	NR	NR	NR	100	84	pneumonitis
Jang/2021[249]	2018–2020	retrospective	Korea	51	12	62	78	28	100	90	RP
Oshiro/2021[187]	2018–2020	retrospective	Japan	91	15	68	74	10	98	90	pneumonitis
Shintani/2021[188]	2018–2019	retrospective	Japan	146	16	70	82	14	100	86	RP
Abe/2021[250]	2018–2019	retrospective	Japan	44	17	73	77	NR	NR	82	PFS/OS
Abe/2021[189]	2019–2020	retrospective	Japan	20	8	71	75	NR	NR	90	pneumonitis
Fujiwara/2021[251]	2016–2019	prospective	Japan	20	15	NR	NR	NR	100	100	RP
Watanabe/2021[252]	2018–2020	retrospective	Japan	21	16	NR	NR	NR	NR	NR	pneumonitis
Sugimoto/2022[190]	2019	prospective	Japan	35	16	69	72	11	100	100	safety
Mayahara/2022[191]	2018–2019	retrospective	Japan	56	14	72	66	20	100	100	RP
Yamamoto/2022[192]	2016–2021	retrospective	Japan	36	14	71	81	13	100	NR	PFS
Zhou/2022[193]	2018–2020	prospective	China	255	14	61	93	16	100	100	PFS
Tanzawa/2022[194]	2019–2020	prospective	Japan	51	22	68	86	9	100	100	PFS
Huang/2022[253]	2013–2020	retrospective	Singapore	39	15	64	80	21	100	100	PFS,OS
Araki/2022[195]	2018–2021	retrospective	Japan	76	17	70	71	17	100	100	PFS,OS
Nishimura/2022[196]	2018–2020	retrospective	Japan	82	15	70	66	18	NR	100	pneumonitis
Harada/2022[197]	2018–2020	retrospective	Japan	26	15	66	77	12	100	100	pneumonitis
Kawanaka/2022[198]	2012–2019	retrospective	Japan	20	NR	NR	NR	NR	100	100	RP,PFS
Lu/2022[199]	2016–2021	retrospective	China	196	18	61	82	27	94	78	pneumonitis
Abe/2022[200]	2020–2021	retrospective	Japan	28	14	71	71	14	100	100	RP
Nakamichi/2022[201]	2020	prospective	Japan	47	NR	65	87	NR	100	100	PFS
Mamesaya/2022[202]	2019–2021	prospective	Japan	29	NR	NR	NR	NR	100	100	ORR
Morimoto/2022[203]	2018–2019	retrospective	Japan	34	13	73	73	NR	100	74	NR
Abe/2023[254]	2008–2022	retrospective	Japan	12	14	70	67	NR	NR	100	efficacy, safety
Park/2023[255]	2020–2021	prospective	Korea	23	27	67	87	4	NR	100	PFS,OS
Wang/2023[204]	2018–2022	retrospective	China	75	22	65	89	16	100	100	PFS,OS
Park/2023[205]	2018–2020	retrospective	Korea	157	19	65	85	20	98	100	PFS
Non-Asian											
Lin/2019[206]	2016–2018	prospective	USA	40	15	67	68	22	100	85	safety
Shaverdian/2020[207]	2017–2019	retrospective	USA	62	13	66	58	3	100	100	RP
Durm/2020[208]	2015–2016	prospective	USA	92	32	66	64	5	NR	100	TMDD
Faehling/2020[209]	2017–2018	retrospective	Germany	126	25	62	65	4	100	94	efficacy, safety
Offin/2020[210]	2017–2019	retrospective	USA	62	12	66	58	3	100	100	efficacy, safety
Hassanzadeh/2020[211]	2017–2019	retrospective	USA	34	12	68	54	5	100	94	pneumonitis
Yan/2020[212]	2017–2019	prospective	USA	25	NR	62	NR	NR	NR	100	safety
Moore/2020[213]	2018–2019	retrospective	Canada	39	NR	69	NR	NR	NR	100	pneumonitis
Jain/2020[214]	2018–2019	retrospective	UK	28	21	NR	NR	NR	NR	100	efficacy, safety
Jegannathen/2020[215]	2018–2019	retrospective	Multicentre	18	NR	NR	44	22	NR	100	efficacy, safety
Landman/2021[216]	2018–2020	retrospective	Israel	39	20	67	64	15	100	100	PFS,OS
Jabbour/2021[217]-PC	2018–2020	prospective	Multicentre	112	19	66	68	5	100	100	ORR/pneumonitis
Jabbour/2021[217]-PP	2018–2020	prospective	Multicentre	102	14	64	61	5	100	100	ORR,pneumonitis
Peters/2021[218]	2016–2018	prospective	Multicentre	77	21	62	67	4	100	100	PFS,OS
Desilets/2021[219]	2018–2019	retrospective	Canada	147	16	67	67	10	100	100	PFS,OS,safety
Taugner/2021[220]	2018–2020	retrospective	Germany	26	21	68	65	NR	NR	96	PFS,OS
Bruni/2021[221]	2018–2020	retrospective	Italy	155	14	66	70	36	100	100	PFS,OS,safety
Jabbour/2021[222]	2016–2018	prospective	USA	21	16	70	48	5	100	100	safety
Kartolo/2021[223]	2018–2020	retrospective	Canada	63	17	NR	51	5	NR	100	OS

(Table 2 continues on next page)

Author/published year	Time range	Study design	Study region	Sample size	Median follow-up (months)	Median age	Males (%)	Never smoking (%)	ECOG 0-2 (%)	Stage III (%)	Primary endpoint/main purpose
(Continued from previous page)											
Sally/2021[224]	2018–2020	retrospective	Canada	82	NR	NR	NR	NR	NR	100	PFS,OS,safety
Kauffmann-Guerrero/2021[225]	NR	prospective	Germany	38	NR	NR	NR	NR	NR	100	pneumonitis
Ross/2021[226]	2017–2019	prospective	USA	64	24	64	48	11	100	100	DCR
Koffer/2021[227]	NR	retrospective	USA	40	19	NR	NR	NR	NR	90	pneumonitis
Hanayneh/2021[228]	NR	retrospective	USA	119	NR	NR	NR	NR	NR	NR	pneumonitis
Gao/2022[229]	2018–2021	retrospective	USA	190	15	67	49	0	100	90	pneumonitis
Herbst/2022[230]	2019–2020	phase 2	Multicentre	183	12	65	68	7	100	100	ORR
LeClair/2022[231]	2018–2019	retrospective	USA	83	NR	70	58	2	100	100	pneumonitis
Saad/2022[232]	2017–2020	retrospective	Israel	71	19	67	63	10	91	100	PFS,OS,safety
Garassino/2022[233]	2019–2020	prospective	Multicentre	117	13	68	62	8	100	100	safety
Raez/2022[234]	2018–2021	retrospective	Multicentre	125	20	66	47	17	100	100	safety
Guberina/2022[235]	2017–2020	retrospective	Germany	39	26	62	67	5	NR	100	safety
Riudavets/2022[236]	2015–2020	retrospective	Multicentre	323	19	66	71	6	100	100	PFS,OS
Denault/2022[237]	2018–2020	retrospective	Canada	205	NR	NR	56	9	100	100	OS
Stevens/2022[238]	2018–2021	retrospective	Australian	145	19	67	63	NR	100	100	safety
Gabelica/2022[239]	2019–2020	retrospective	Croatia	42	NR	63	79	NR	NR	NR	NR
Rimner/2022[240]	2019–2021	prospective	USA	27	12	82	NR	NR	100	93	PFS
Tavara/2022[241]	2018–2021	retrospective	Spain	37	20	67	78	49	NR	100	NR
Saade/2022[242]	2018–2022	retrospective	USA	14	NR	65	50	25	NR	100	pneumonitis
Girard/2023[243]	2017–2021	retrospective	Multicentre	1399	24	66	67	8	99	95	PFS
Diamond/2023[244]	2018–2021	retrospective	USA	62	17	67	48	0	NR	90	pneumonitis
Käsmann/2023[245]-Niv	2016–2020	prospective	Germany	11	23	59	73	NR	100	100	PFS,OS,safety
Käsmann/2023[245]-Dur	2016–2020	prospective	Germany	28	27	68	71	NR	100	100	PFS,OS,safety

Abbreviations: EOCG, Eastern Cooperative Oncology Group; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TMDD, time to metastatic disease or death; RP, radiation pneumonitis; NR, not reported.

Table 2: **Characteristics of studies examining chemotherapy with immunotherapy.**

23.8%, 95% CI: 16.1%–31.5%; P = 0.69), grade ≥3 (2.8%, 95% CI: 1.2%–4.4% vs. 5.3%, 95% CI: 3.3%–7.3%; P = 0.058) and grade 5 (0.0%, 95% CI: 0.0%–0.6% vs. 0.4%, 95% CI: 0.0%–1.3%; P = 0.25) pneumonitis (Fig. 3).

Subgroup of retrospective studies

Similar to the results from all studies, Asian patients were associated with higher rates of all-grade (76.2%, 95% CI: 65.8%–85.2% vs. 32.5%, 95% CI: 26.2%–39.1%; P < 0.0001) and grade ≥2 (35.1%, 95% CI: 31.8%–38.3% vs. 24.5%, 95% CI: 18.9%–30.2%; P = 0.002) pneumonitis compared non-Asian patients, but without significant differences in rates of grade ≥3 (5.4%, 95% CI: 4.2%–6.8% vs. 6.2%, 95% CI: 4.6%–7.9%; P = 0.79) and grade 5 (0.2%, 95% CI: 0.0%–0.7% vs. 0.1%, 95% CI: 0.0%–0.2%; P = 0.089) pneumonitis (Fig. 3).

Subgroup of patients undergoing cCRT with consolidation durvalumab

Consistently, the rates of all-grade (78.6%, 95% CI: 68.9%–86.9% vs. 35.0%, 95% CI: 27.8%–42.6%; P < 0.0001) and grade ≥2 (34.4%, 95% CI: 31.6%–37.1% vs. 25.6%, 95% CI: 19.3%–31.8%; P = 0.011) pneumonitis rates were significantly higher in Asian vs. non-Asian patients; there were no significant differences in rates of grade ≥3 (5.2%, 95% CI: 3.9%–6.7% vs. 6.0%, 95% CI: 4.4%–7.6%; P = 0.86) and grade 5 (0.1%, 95% CI: 0.0%–0.5% vs. 0.1%, 95% CI: 0.0%–0.3%; P = 0.22) pneumonitis (Fig. 3).

Comparison of grade ≥2 pneumonitis between Asian and non-Asian patients based on lung V_{20}/MLD

There were 37 studies of Asian and 26 studies of non-Asian reporting data of V_{20} as well as the incidence of grade ≥2 pneumonitis for the study population. Among these studies, the pooled median/mean of V_{20} for Asian was 23.0% (IQR, 20.0%–25.7%) vs. 27.9% (IQR, 25.9%–30.0%) for non-Asian, with the pooled rate of grade ≥2 pneumonitis of 30.3% (95% CI, 27.0%–33.6%) vs. 22.3% (95% CI, 18.2%–26.4%, P = 0.003) (Fig. 4). In addition, there were 25 studies of Asian and 30 studies of non-Asian providing data of MLD (the pooled median/mean of 13.6 Gy [IQR, 11.9Gy–15.1Gy] vs. 16.0 Gy [IQR, 14.9Gy–17.2Gy]) with the incidence of grade ≥2 pneumonitis of 32.5% (95% CI, 28.4%–37.0%) vs. 20.7% (95% CI, 16.4%–25.4%, P = 0.0002) (Fig. 4).

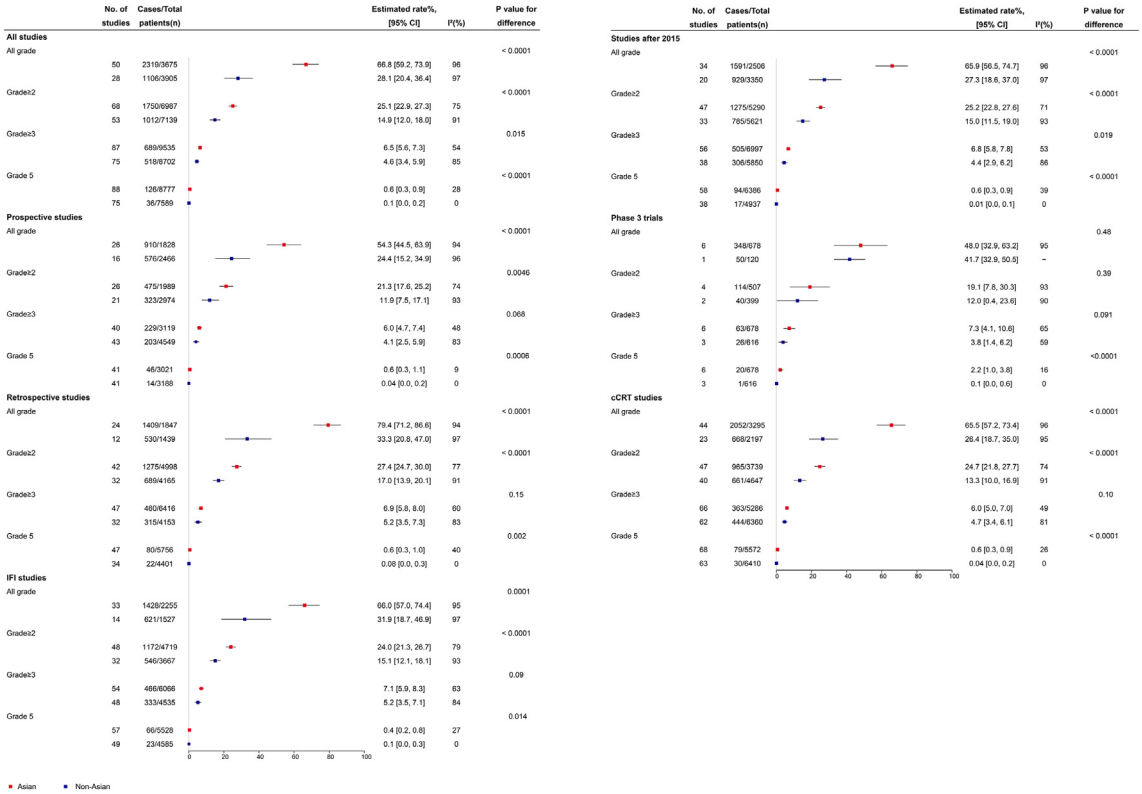

Fig. 2: Comparison of rates of pneumonitis between Asian and non-Asian patients treated with CRT without immunotherapy. CRT, chemoradiotherapy; cCRT, concurrent chemoradiotherapy; IFI, involved-field irradiation; No., number; CI, confidence intervals. P-values of <0.05 were defined as statistically significant.

The forest plots for the results

The forest plots for all results of meta-analysis are presented in Supplementary File: Figure S2–S47.

Heterogeneity

There were significant heterogeneity among studies, particularly for all-grade (I^2 range, 90%–97%) and grade ≥2 (I^2 range, 11%–94%) pneumonitis. The heterogeneity reduced somewhat in some subgroup analyses (Figs. 2 and 3). No significant heterogeneity were observed for grade 5 pneumonitis (I^2 range, 0%–40%) (Figs. 2 and 3).

Meta-regression analysis

Meta-regression was conducted to investigate the influence of sex, smoking status, and stage on the incidence of pneumonitis (Supplementary File: Table S6). Due to too many missing data, we carried out meta-regression analyses with race (Asian) and then sex (model 1), smoking (model 2), and stage (model 3) separately as predictors of pneumonitis. As for CRT alone, race was significantly associated with the incidence of pneumonitis ($P < 0.05$ for each result), except grade ≥3 pneumonitis ($P = 0.91$) in model 2; sex significantly influenced the incidence of grade ≥2 ($P = 0.01$) and grade ≥3 ($P = 0.03$) pneumonitis; stage was an predictor of grade ≥2 pneumonitis ($P = 0.01$). Regarding CRT plus immunotherapy, race and sex were predictors of all-grade and grade ≥2 pneumonitis ($P < 0.05$ for each result).

Discussion

This study summarized incidence of pneumonitis after definitive CRT with or without immunotherapy in Asian and non-Asian patients with LA-NSCLC, respectively. As for CRT without immunotherapy, the pooled incidence rates of all-grade (66.8% vs. 28.1%, $P < 0.0001$), grade ≥2 (25.1% vs. 14.9%, $P < 0.0001$), grade ≥3 (6.5% vs. 4.6%, $P < 0.015$), and grade 5 (0.6% vs. 0.1%, $P < 0.0001$) pneumonitis were significantly higher in Asian than that in non-Asian patients. Regarding CRT plus immunotherapy, significantly higher rates of all-grade (74.8% vs. 34.3%, $P < 0.0001$) and grade ≥2 (34.0% vs. 24.6%, $P = 0.001$) pneumonitis was observed in Asian than in non-Asian patients; while, there were no significant differences in rates of grade ≥3 (4.7% vs. 6.0%, $P = 0.24$) and grade 5 (0.1%

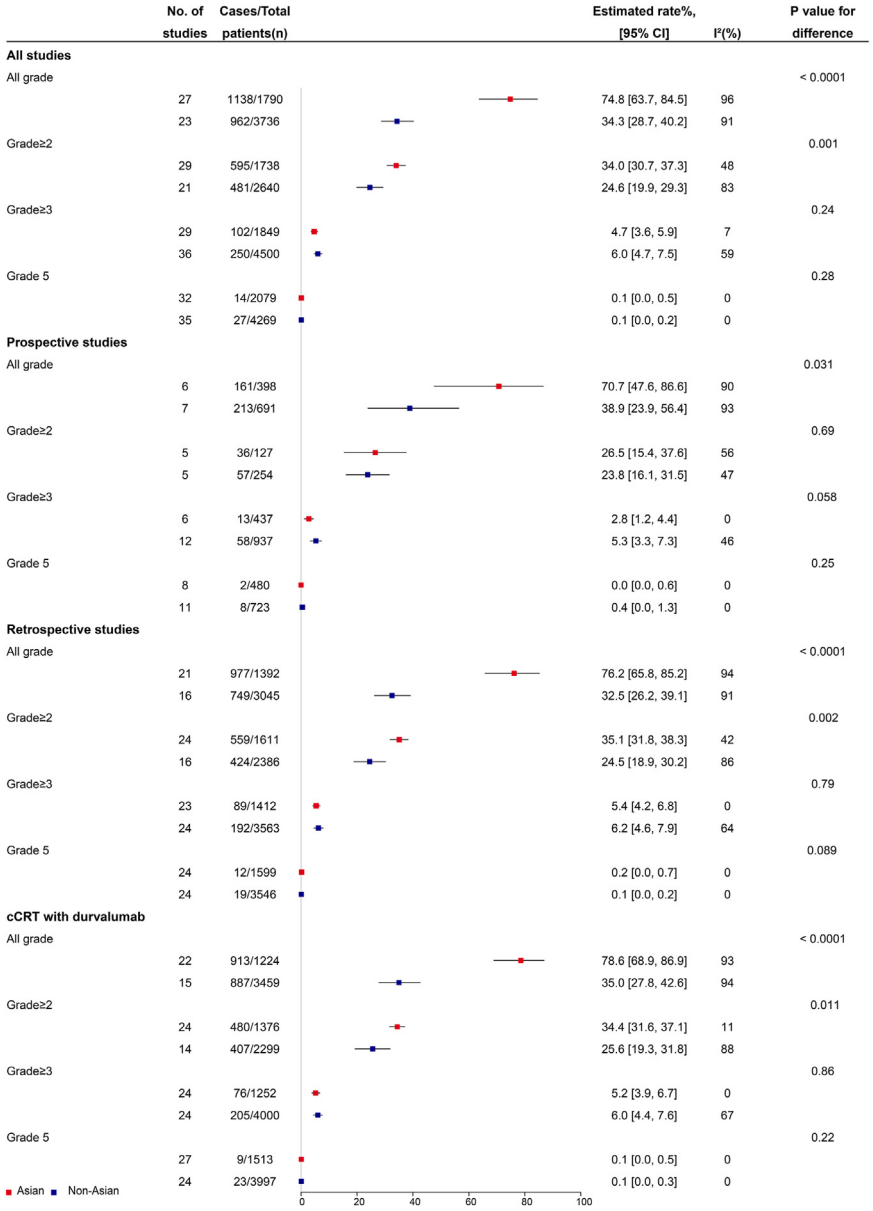

Fig. 3: Comparison of rates of pneumonitis between Asian and non-Asian patients treated with CRT plus immunotherapy. CRT, chemoradiotherapy; cCRT, concurrent chemoradiotherapy; No., number; CI, confidence intervals. P-values of <0.05 were defined as statistically significant.

vs. 0.1%, P = 0.28) pneumonitis between the two population.

One of the explanations for the difference in incidence of pneumonitis is different genetic backgrounds between Asian and non-Asian patients, such as ethnic difference in single nucleotide polymorphisms (SNPs) of the TGF-β1 gene,[256,257] epidermal growth factor receptor (EGFR) mutations,[258] and Toll-like receptor 2 (TLR2) and TLR4 gene polymorphisms.[259] For example, TGF-β1 rs1982073:T869C gene has been demonstrated to be associated with lower risk of radiation pneumonitis (RP) in white but not in Chinese NSCLC patients treated with definitive CRT.[256,257] In addition, EGFR mutations are more common in Asian patients than in non-Asian patients with NSCLC (38.4% vs. 14.1%),[258] and patients with EGFR mutations were found to have a higher risk of pneumonitis compared to EGFR wild-type patients (11.0% vs. 3.8%) in the subgroup analysis of PACIFIC study.[4]

However, there is also a possibility that Asian patients received higher lung dose than non-Asian

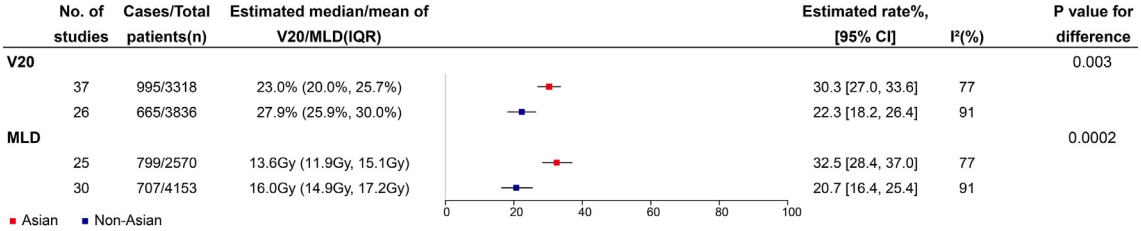

Fig. 4: Comparison of grade ≥2 pneumonitis between Asian and non-Asian patients based on lung V_{20}/MLD. $V_{20,}$ lung volume receiving ≥20 Gy, MLD, lung mean dose; No., number; CI, confidence intervals; IQR, interquartile range. P-values of <0.05 were defined as statistically significant.

patients, leading to the higher incidence of pneumonitis. In the present meta-analysis, a total of 63 studies reported the median/mean of lung V_{20} and 55 studies reported median/mean of MLD for the study population. In these studies, we found that although the pooled median/mean of V_{20} was relatively low for studies of Asian compared to that for studies of non-Asian (23% vs. 27.9%), rate of grade ≥2 pneumonitis was significantly higher in Asian vs. non-Asian studies (30.3% vs. 22.3%, P = 0.003). Similarly, the pooled median/mean MLD was 13.6Gy for Asian studies vs. 16.0Gy for non-Asian studies, with rate of grade ≥2 pneumonitis of 32.5% vs. 20.7% (P < 0.0002). These findings suggested the poor tolerance of lung to radiation in Asian patients.

It should be noted that there were no ethnic differences in rates of grade ≥3 and grade 5 pneumonitis in patients treated with CRT plus immunotherapy. Differences in ICI drugs used and combination therapy strategy adopted between Asian and non-Asian studies might account for the results, at least in part. For studies of Asian, cCRT followed by consolidation durvalumab was the common regimen. However, PD-1 inhibitors (pembrolizumab or nivolumab) and concurrent CRT and ICIs strategy were frequently adopted in the studies of non-Asian, which might result in the increased lung toxicity, leading to the comparable incidence of grade ≥3 pneumonitis to Asian patients. Nevertheless, there was also a possibility that Asian patients were only associated with an increased risk of moderate pneumonitis (grade 2) but not severe pneumonitis (grade 3–5) compared to non-Asian patients in the case of CRT plus immunotherapy.

There were significant heterogeneity among studies. To explore potential sources of heterogeneity, we conducted a number of subgroup analyses for both CRT alone and CRT plus immunotherapy. As for CRT alone, results from these subgroup analyses were similar to that from the all studies. Regarding CRT plus immunotherapy, subgroup analyses of retrospective studies and studies of cCRT followed by durvalumab showed comparable results to the all studies. However, rate of grade ≥2 pneumonitis in prospective studies was similar between Asian and non-Asian patients (26.5% vs. 23.8%, P = 0.69), which appeared to be due to the limited number of studies and small sample size in this subgroup. Overall, the findings from the subgroup analyses further supported that Asian patients were more likely to have a higher risk of pneumonitis compared to non-Asian patients.

To our knowledge, the present study is the first and most comprehensive meta-analysis focusing on ethnic differences in the incidence of post-chemoradiotherapy pneumonitis for patients with locally advanced NSCLC. It included a total of 248 studies involving 28,267 patients, and summarized the rates of all-grade, grade ≥2, grade ≥3, and grade 5 pneumonitis, respectively. In addition, a comprehensive subgroup analyses were conducted, with the results generally in agreement with that from the overall study population. Nevertheless, there are some limitations in this meta-analysis. First, due to lack of RCTs and cohort studies directly comparing the incidence of pneumonitis between Asian and non-Asian patients, this meta-analysis was performed based on cross-study comparisons between single-arm studies. This methodological limitation prevented us from drawing a firm conclusion. Second, pneumonitis grading criteria adopted in individual studies were inconsistent, which might result in bias in collection and reporting of pneumonitis. Third, the majority of studies reported incidence of pneumonitis during the study period. Studies only reporting the incidence of pneumonitis during CRT period or less than 3 months after RT, or only providing data of late lung toxicity such as lung fibrosis, were excluded from our analysis. The exclusion of these studies might lead to bias. Fourth, there were significant heterogeneity among studies. By subgroup analyses, we found that study design, RT field, CRT strategy, study published years appeared to account for some heterogeneity. In addition, CT regimens, RT techniques, RT dose, and PTV volume might also be confounding factors. However, we could not evaluate their effects on the incidence of pneumonitis between Asian and non-Asian patients due to insufficient data. Fifth, in the case of multiple articles covered the similar study population, the one with the most comprehensive data was selected.

Nevertheless, there might be also studies of overlap patients which were not recognized and were included in our study, especially for some multi-center studies which were difficult to determine whether they had overlap patients or not. This might result in bias of the results. Sixth, meta-regression analyses showed that some patients baseline characteristics (sex and stage) were potential confounders for the incidence of pneumonitis, which might also lead to bias of the results. In addition, baseline ILD is also a risk factor for pneumonitis. However, the majority of included studies did not provide the information of the preexisting ILD. Thus, we could not evaluate its effects on the results. Finally, the primary endpoints or main purpose of the included studies were various (such as OS, and/or PFS, and/or safety), which might affect the results of pneumonitis. There might be difference somewhat in the frequency of pneumonitis depending on whether the purpose of the study is about treatment effects or mainly about side effects.

In conclusion, Asian patients are likely to have a higher incidence of pneumonitis than non-Asian patients treated with CRT with or without immunotherapy, which appears to be due to the poor tolerance of lung to radiation. These results can be helpful to understand the ethnic difference in risk of pneumonitis, and to optimize CRT strategy in Asian patients. Nevertheless, the findings are based on observational studies and with significant heterogeneity, and need to be validated in future large prospective studies focusing on the subject.

Contributors

The study was designed by JD, ZH, and GL. Literature search and data collection were done by TL, SL, SD, JQ, JC, CR, HW, and XW. Statistical analyses were done by TL, SL, and SD, and JQ. JD, ZH, TL, SL, SD, and JQ contributed to data analysis and interpretation. TL, SL, and HW verified the underlying data. All authors had full access to all of the data. The manuscript was drafted by JD, TL, SL, SD, and JQ. All authors read and approved the final version of the manuscript. JD had the final responsibility to submit for publication.

Data sharing statement

All data extracted and generated in this study can be shared with others on reasonable request via email to the corresponding author.

Declaration of interests

The authors declare no competing interests.

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None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102246.

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