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Irradiation enhanced risks of hospitalised pneumonopathy in lung cancer patients: a population-based surgical cohort study

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ABSTRACT

Objective Pulmonary radiotherapy has been reported to increase a risk of pneumonopathy, including pneumonitis and secondary pneumonia, however evidence from population-based studies is lacking. The present study intended to explore whether postoperative irradiation increases occurrence of severe pneumonopathy in lung cancer patients.

Design, setting and participants The nationwide population-based study analysed the Taiwan National Health Insurance Research Database (covered >99% of Taiwanese) in a real-world setting. From 2000 to 2010, 4335 newly diagnosed lung cancer patients were allocated into two groups: surgery-RT (n=867) and surgery-alone (n=3468). With a ratio of 1:4, propensity score was used to match 11 baseline factors to balance groups.

Interventions/exposure(s) Irradiation was delivered to bronchial stump and mediastinum according to peer-audited guidelines.

Outcome(s)/measure(s) Hospitalised pneumonia/pneumonitis-free survival was the primary end point. Risk factors and hazard effects were secondary measures.

Results Multivariable analysis identified five independent risk factors for hospitalised pneumonopathy: elderly (>65 years), male, irradiation, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD). Compared with surgery-alone, a higher risk of hospitalised pneumonopathy was found in surgery-RT patients (HR, 2.20; 95% CI, 1.93–2.51; 2-year hospitalised pneumonia/pneumonitis-free survival, 85.2% vs 69.0%; both p<0.0001), especially in elderly males with COPD and CKD (HR, 13.74; 95% CI, 6.61–28.53; p<0.0001). Unexpectedly, we observed a higher risk of hospitalised pneumonopathy in younger irradiated-CKD patients (HR, 13.07; 95% CI, 5.71–29.94; p<0.0001) than that of elderly irradiated-CKD patients (HR, 4.82; 95% CI, 2.88–8.08; p<0.0001).

Conclusions A high risk of hospitalised pneumonopathy is observed in irradiated patients, especially in elderly males with COPD and CKD. For these patients, close clinical surveillance and aggressive pneumonia/pneumonitis prevention should be considered. Further investigations are required to define underlying biological mechanisms, especially for younger CKD patients.

Strengths and limitations of this study

- To our best knowledge, the present study was the first investigation to apply a population-based propensity-score-matched design to explore a risk level of hospitalised pneumonopathy in the real-world medical setting.
- According to independent risk factors, the present study conducted a simplified sensitivity analysis to decrease unmeasured confounding effects.
- According to independent risk factors, the present study calculated integer risk scores to stratify high-risk patients: this approach worked well.
- Despite our efforts to decrease potential bias, this present study analysed a secondary database, which inevitably harbours some unobserved variables and may constrain the study interpretation.
- A retrospective design of the present study also limits the conclusion. Further prospective studies should be warranted for confirming the present observation.

INTRODUCTION

Patients with lung cancer are frequently encountered in both primary and in-patient care, characterising high rates of mortality and morbidities.[1–3] Radiotherapy is one of the major treatment modalities in managing lung cancer patients.[4] However, irradiation has been reported to correlate with an increased incidence of several types of pneumonopathy, such as infectious pneumonia,[5 6] non-infectious organic pneumonia[7–10] and radiation pneumonitis,[11–13] even after a 2-year follow-up period.[14]

Clinically, differentiating radiation pneumonitis from secondary pneumonia is not easy.[11 15 16] Several aetiologies have been declared. First, the radiological finding is similar between radiation pneumonitis and secondary pneumonia[17] and both of them

showed an increased lung infiltration and/or parenchymal consolidation.[16 18] Second, no reliable tools are available to diagnose radiation pneumonitis directly, its diagnosis is largely dependent on exclusion of other pulmonary diseases.[16] Third, secondary pneumonia is frequently co-occurred in patients with radiation pneumonitis, either simultaneously or sequentially.[8]

Remarkably, when progressive dyspnea developed, either radiation pneumonitis or secondary infectious/non-infectious pneumonia threatens a patient's life.[12 19–21] As a result, it is crucial to identify risk factors of severe pneumonopathy that required in–patient care. In this regard, several risk factors have been recognised in association with the occurrence of pneumonia, for example, elderly male,[22] chronic obstructive pulmonary disease (COPD),[23] chronic kidney disease (CKD),[24] thoracic surgery,[25–27] chemotherapy and radiotherapy (RT).[6 28] On the other hand, potential hazard factors of radiation pneumonitis have also been reported, as follows: age,[29 30] gender,[20] COPD,[31] diabetes mellitus,[32] thoracic surgery[33] and chemotherapy.[34] However, evidence from population-based studies is largely limited in irradiated lung cancer patients.

Hence, the population-based study intended to explore the association between irradiation and hospitalised pneumonopathy in a lung cancer surgical cohort. We hypothesised that irradiated lung cancer patients may encounter a higher risk of hospitalised pneumonopathy (ie, severe pneumonia/pneumonitis that required in-patient care) than that of non-irradiated patients.

METHODS

Database and ethic statement

The present study investigated the research database of the Taiwan National Health Insurance. The major characteristic of this database is its high coverage rate of medical care in a national population (ie, >99% Taiwanese).[35] Thus, results obtained from this population-based database largely represented an actual condition in a real medical world setting.

Design and conduct of the present study were approved by the Institution Review Board (IRB) of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (approved number, B10001019). As mentioned previously,[35–37] the IRB waived a requirement of written informed consents because permanent de-identification was conducted by the National Health Research Institute before data analysis.[36 38 39]

Study design and patient allocation

For maximally reducing potential bias, the present study used a propensity score match to create a quasi-randomised condition before statistical analysis.[36 40]

From January 2000 to December 2010, a total of 4335 newly-diagnosed early-stage lung cancer patients were recruited into two groups: the surgery-RT (n=867) and surgery-alone groups (n=3468; figure 1; table 1). The identifying process was similar to our previous report.[36] Briefly, we applied the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 162 to identify lung cancer patients (n=2 18 300). And, we used a peer-reviewed data subset (ie, the Registry File for Catastrophe Illness)[38] to validate lung cancer diagnosis. Then, we excluded previously diagnosed lung cancer patients to allocate newly onset patients (n=78 723).

To purify the study population, several exclusion criteria were used, as follows: previous pneumonia/pneumonitis (n=21 030), distant metastases at the time of initial diagnosis (n=3130; ICD-9-CM codes, 196–199), patients who were treated with radiotherapy alone (ie, without surgery) or who had a treatment component of chemotherapy (n=49 174), unpaired cases (n=995) and data error (n=59).

Finally, we identified 867 early-stage lung cancer patients treated with surgery and postoperative radiotherapy into the surgery-RT group.

Propensity score match: a modern tool to create comparable groups before further statistical analysis

Surgery itself has been reported to increase a risk of pneumonia occurrence in lung cancer patients.[25 26] Thus, for a better comparison, we allocated lung cancer patients treated with surgery alone as our study controls.[36] Moreover, to create a between-group comparable condition before analysis, we used a propensity score to match 11 baseline factors simultaneously[41]: age,[29 30 42] gender,[20 22] COPD,[22 23 32] hypertension,[43] diabetes mellitus (DM),[22 32] congestive heart failure (CHF),[22] liver cirrhosis (LC),[22] CKD,[44] coronary artery disease (CAD), hyperlipidemia and tuberculosis (TB).

We paired 3468 patients who received surgery alone into the surgical-alone comparison group by using a match ratio of 1:4. We used callipers with a width of 0.2 of the SD of the logit for the propensity score match process, as previously recommended.[45] After match, patients in the two groups were compared for further analysis (table 1).[46]

Patients and treatments

The present study wished to investigate the role of irradiation in association with hospitalised pneumonopathy (ie, severe infectious/non-infectious pneumonia and/or radiation pneumonitis) in lung cancer patients who received post-operative radiotherapy. Thus, a lung cancer surgical cohort was chosen as the study population. The main reason for this selection has been declared previously.[36] Briefly, patients who were able to be treated surgically had two unique characteristics – that is, a medically operable status and technically resectable tumours.

Similarly, to maximally reduce potential bias, we excluded patients treated with chemotherapy, as reported previously.[36] Two reasons for this exclusion were: excluded patients with pathologically positive nodal disease, that is, pN1-3 in stage II-III;[47 48] and

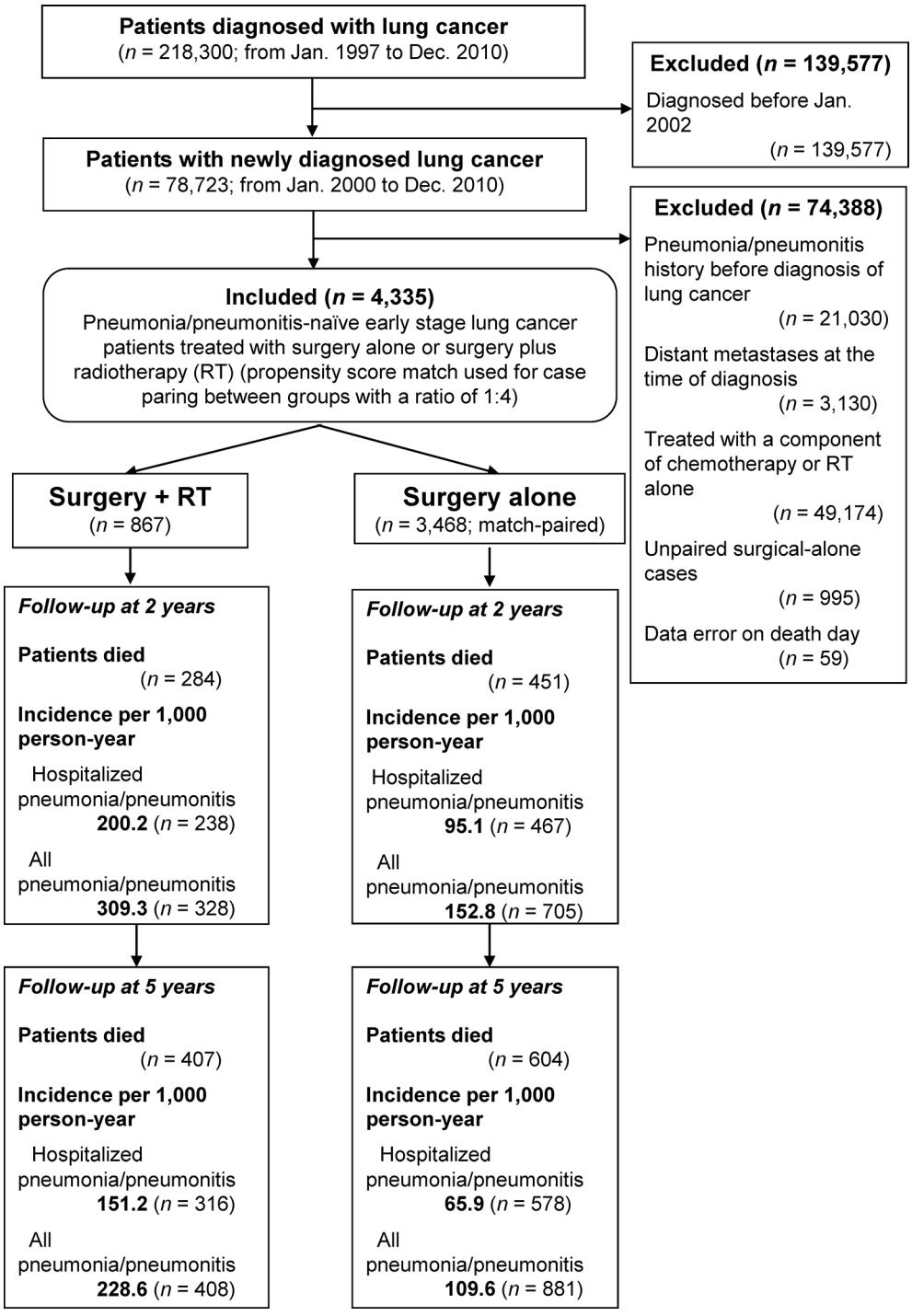

Figure 1 Flow chart of patient allocation. Using a propensity score, patients in the surgery-alone group were match-paired to those patients in the surgery-RT group, with a ratio of 1:4. Eleven baseline factors were simultaneously matched for paring cases, as shown in table 1. ICD-9-CM code 162 was used to initially identify lung cancer patients. Data-coded errors were validated by using a sub-dataset of the Registry of Catastrophe Illness.

avoided a confounding effect of chemotherapy on pneumonia occurrence.[19]

As reported previously,[36] postoperatively positive surgical margin was the main indication for post-operative radiotherapy. Thus, irradiating targets were mainly focused on the bronchial stump and adjacent mediastinum, with conventional radiation doses ranging from 45 Gy to 64.8 Gy.[16 36 48 49] Irradiation guidelines among different institutes were regularly audited by certified external peers of the Taiwan Cancer Centre Accreditation.[36 50]

Study endpoints and measurements

We defined hospitalised pneumonia/pneumonitis-free survival as the primary end point (ICD-9-CM codes: pneumonia, 480–486; and, radiation pneumonitis, 508).[51] All

Table 1 Patient and demographic characteristics according to treatment received

	Treatment received, n (%)			
	Surgery+RT	Surgery alone	p	Total, n (%)
Age*			0.96	
≤65 years	364 (42.0)	1459 (42.1)		1823 (42.1)
>65 years	503 (58.0)	2009 (57.9)		2512 (57.9)
Gender*			0.53	
Male	546 (63.0)	2144 (61.8)		2690 (62.1)
Female	321 (37.0)	1324 (38.2)		1645 (37.9)
COPD*			0.48	
Yes	363 (41.9)	1498 (43.2)		1861 (42.9)
No	504 (58.1)	1970 (56.8)		2474 (57.1)
Hypertension*			0.63	
Yes	417 (48.1)	1636 (47.2)		2053 (47.4)
No	450 (51.9)	1832 (52.8)		2282 (52.6)
Diabetes*			0.39	
Yes	224 (25.8)	946 (27.3)		1170 (27.0)
No	643 (74.2)	2522 (72.7)		3165 (73.0)
CAD*			0.93	
Yes	291 (33.6)	1159 (33.4)		1450 (33.4)
No	576 (66.4)	2309 (66.6)		2885 (66.6)
Liver cirrhosis*			0.64	
Yes	26 (3.0)	94 (2.7)		120 (2.8)
No	841 (97.0)	3379 (97.3)		4215 (97.2)
Tuberculosis*			0.75	
Yes	57 (6.6)	218 (6.3)		275 (6.3)
No	810 (93.4)	3250 (93.7)		4060 (93.7)
CHF*			0.37	
Yes	40 (4.6)	186 (5.4)		226 (5.2)
No	827 (95.4)	3282 (94.6)		4109 (94.8)
Hyperlipidemia*			0.78	
Yes	282 (32.5)	1145 (33.0)		1427 (32.9)
No	585 (67.5)	2323 (67.0)		2908 (67.1)
CKD*			0.82	
Yes	36 (4.2)	150 (4.3)		186 (4.3)
No	831 (95.8)	3318 (95.7)		4149 (95.7)
Total	867 (100)	3468 (100)		4335 (100)

All p values were calculated by using Chi-square test.
*Factors used for propensity-score match.
CAD, coronary artery heart disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; RT, radiotherapy.

pneumonia/pneumonitis-free survival was defined as the secondary endpoint.

As mentioned above, two reasons were responsible for combining infectious/non-infectious pneumonia and radiation pneumonitis as a single study endpoint. First, radiation pneumonitis and secondary pneumonia are difficult to be differentiated clinically, especially in the modern radiotherapy era.[11 15 16] Second, while severe, both of them significantly threaten the patient's life.[12 19 20] Thus, combining these two diseases as a single study end event was reasonable and suitable in secondary analysis studies, such as ours.

Hospitalised pneumonia/pneumonitis was defined as the first admission due to pneumonia/pneumonitis after surgery. All pneumonia/pneumonitis was encoded as the first diagnosis of pneumonia/pneumonitis after surgery in either an inpatient or outpatient setting.

Statistical analysis

We analysed and reported data according to the CONSORT statement[52] and STROBE guideline (main accordance).[53] SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA) and SPSS (version 12, IBM SPSS Inc., Chicago, USA)[36] were used for statistical analysis, accordingly. Kaplan-Meier analysis was applied to estimate survival, and the log-rank test was performed to assess curve differences between groups. The Chi-square test was used to evaluate intergroup differences for category variables.

Considering the time effect, Cox proportional regression[54] (rather than logistic regression) was conducted to perform multivariable analysis and to estimate hazardous effects, as that of a previous report.[55] Multivariable-analysis-identified risk factors were selected for further stratified/simplified sensitivity analysis.[36] According to previous reports,[56 57] regression coefficients of independent risk factors were converted into integer risk scores. These risk scores were subsequently applied to identify high-risk patient populations.

According to a recommendation of the STROBE guideline,[53] 95% confidence intervals (95% CIs) were provided in conjunction with HRs to represent hazardous size. Two biostatisticians, that is, Shiang-Jiun Tsai (for primary analysis) and Feng-Chun Hsu (for second look), independently validated all data, as reported previously.[36] A p value of <0.05 was considered as statistically significant.

RESULTS

Study group, patient and survival

We identified 4335 patients into the two groups: surgery-RT (n=867) and surgery-alone groups (n=3468; 1:4 match-paired; figure 1). The median follow-up time was 31.8 months (range, 0.1–136.1). Most patients were aged >65 years (n=2512, 57.9%). Male patients were predominate (n=2690; 62.1%). After propensity-score match, the two study groups were well balanced in terms of 11 baseline factors, i.e., age, gender, COPD, hypertension, diabetes, coronary artery disease, liver cirrhosis, tuberculosis, congestive heart failure, hyperlipidemia and CKD (table 1).

In general, 2-year and 5-year overall survival rates were statistically significantly different between the surgery-RT and surgery-alone groups, as follows: 65.6% versus 85.3%, and 48.4% versus 77.0%, respectively (p<0.0001). In addition, 2-year and 5-year distant-metastatic-free survival rates were also statistically significantly different between the two groups: 42.4% versus 86.1%, and 26.3% versus 78.1%, respectively (p<0.0001).

The primary endpoint: risk level of hospitalised pneumonopathy (pneumonia/pneumonitis) occurrence

Two observations supported a high incidence of pneumonia/pneumonitis occurrence in surgery-RT patients when compared with surgical-alone patients. First, we observed high incidences of hospitalised pneumonia/pneumonitis in surgery-RT patients, that is, per 1000

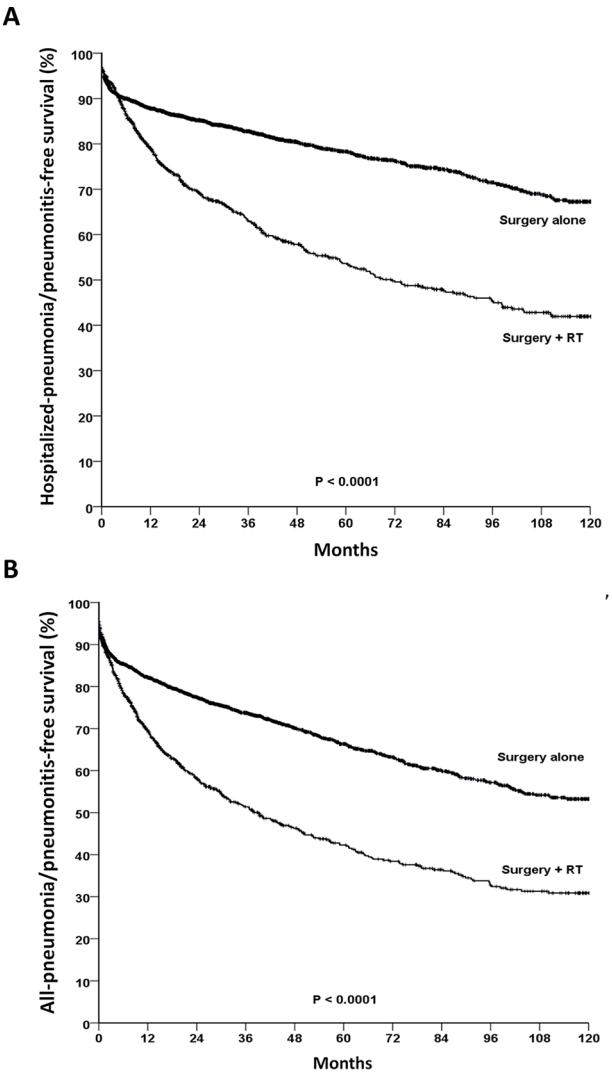

Figure 2 Kaplan-Meir estimates of pneumonia/pneumonitis-free survival between the surgery-plus-RT and surgery-alone groups: Panel A, hospitalised pneumonia/pneumonitis-free survival (p<0.0001): Panel B, all pneumonia/pneumonitis-free survival (p<0.0001).

person-year at 2 years (200.2 vs 95.1, 2.11 folds) and at 5 years (151.2 vs 65.9, 2.29 folds; figure 1). Second, we found a low 2-year hospitalised pneumonia/pneumonitis-free survival rate in surgery-RT patients (69.0% vs 85.2%, p<0.0001; figure 2A). Data from all pneumonia/pneumonitis-free survival showed similar findings (figure 2B). However, in patients who were treated with RT, a higher estimated dose level wasn't associated with a lower 2-year hospitalised pneumonia/pneumonitis-free survival (68.9% vs 68.6%, p=0.586). This may be due to a relatively low threshold dose (when compared with therapeutic dose) that potentially increases a risk of pneumonia/pneumonitis occurrence.[58]

Multivariable analysis confirmed five independent risk factors for hospitalised pneumonia/pneumonitis occurrence

As shown in table 2, multivariable analysis identified five independent risk factors for predicting hospitalised pneumonia/pneumonitis occurrence: irradiation (HR, 2.20;

Table 2 Adjusted hazards for hospitalised and all pneumonia/pneumonitis occurrence

	Adjusted HR (95% CI)	
	Hospitalised pneumonia/ pneumonitis	All pneumonia/pneumonitis
Treatment received (Surgery+RT vs Surgery alone)	2.20 (1.93–2.51), p<0.0001**	1.94 (1.73–2.17), p<0.0001**
Age (>65 vs ≤65 years)	1.86 (1.60–2.16), p<0.0001**	1.53 (1.36–1.73), p<0.0001**
Gender (male vs female)	2.00 (1.72–2.32), p<0.0001**	1.78 (1.57–2.00), p<0.0001**
COPD (Yes vs No)	1.28 (1.12–1.46) p=0.0002*	1.26 (1.13–1.40), p<0.0001**
Hypertension (Yes vs No)	1.06 (0.92– 1.22), p=0.39	1.02 (0.90–1.15), p=0.79
Diabetes (Yes vs No)	1.02 (0.89–1.18), p=0.69	1.05 (0.93–1.19), p=0.40
CAD (Yes vs No)	1.06 (0.91–1.22), p=0.42	1.11 (0.98–1.25) p=0.10
Liver cirrhosis (Yes vs No)	0.91 (0.61–1.36), p=0.65	0.87 (0.62–1.22), p=0.42
Tuberculosis (Yes vs No)	1.05 (0.84– 1.33), p=0.62	1.07 (0.88–1.30), p=0.52
CKD (Yes vs No)	1.41 (1.10– 1.82) p=0.006*	1.20 (0.95–1.51) p=0.12
CHF (Yes vs No)	1.13 (0.87–1.45) p=0.33	0.97 (0.77–1.22) p=0.77

HR with 95% CI was estimated by using Cox proportional hazard analysis.
*p<0.05, **p<0.01.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CAD, coronary heart disease; CKD, chronic kidney disease; RT, radiotherapy.

95% CI, 1.93–2.51; p<0.0001), age >65 years (HR, 1.86; 95% CI, 1.60–2.16; p<0.0001), male gender (HR, 2.00; 95% CI, 1.72–2.32; p<0.0001), COPD (HR, 1.28; 95% CI, 1.12–1.46; p=0.0002) and CKD (HR, 1.41; 95% CI, 1.10–1.82; p=0.006; table 2 and figure 3A–D).

To further demarcate the risk levels of hospitalised pneumonia/pneumonitis occurrence, we performed simplified sensitivity analysis among three major independent factors: irradiation, age and gender (table 3). A risk-increasing trend was observed in eight stratified patient subgroups. Remarkably, a very high risk was observed in irradiated elderly males (HR, 9.22; 95% CI, 6.44–13.19; p<0.0001), when compared with non-irradiated younger females (reference =1). The analysed results were similar when the reference group was defined as 'non-irradiated younger male' or 'irradiated younger female'. Intergroup *p* values in the above two conditions were both ranged between 0.01 and <0.0001.

An unexpected finding

Unexpectedly, we found a higher risk of hospitalised pneumonia/pneumonitis occurrence in younger irradiated-CKD patients (HR, 13.07; 95% CI, 5.71–29.94; p<0.0001) than that of elderly irradiated-CKD patients (HR, 4.82; 95% CI, 2.88–8.08; p<0.0001; table 4), This unexpected observation created a biological interest for further investigation.

Integer risk score analysis

Furthermore, independent factors were used to construct a risk-predicting model, according to integer risk score (table 5).[56] Three groups were classified: the high-risk group, patients with a score of >18; the medium-risk group, patients with a score of 13–17; and the low-risk group, patients with a score of <12. As shown in figure 4, this model works well. Remarkably, the highest risk of hospitalised pneumonia/pneumonitis was observed in irradiated elderly males with COPD and CKD (HR, 13.74; 95% CI, 6.61–28.53; p<0.0001), when compared with non-irradiated younger female patients without COPD and CKD (reference group, HR=1).

DISCUSSION

Main finding: a high risk of hospitalised pneumonopathy occurrence in irradiated lung cancer patients

In irradiated lung cancer patients, radiotherapy has been reported to increase incidences of pneumonopathy, including infectious[5] and non-infectious pneumonia,[7] as well as pneumonitis.[11] A common

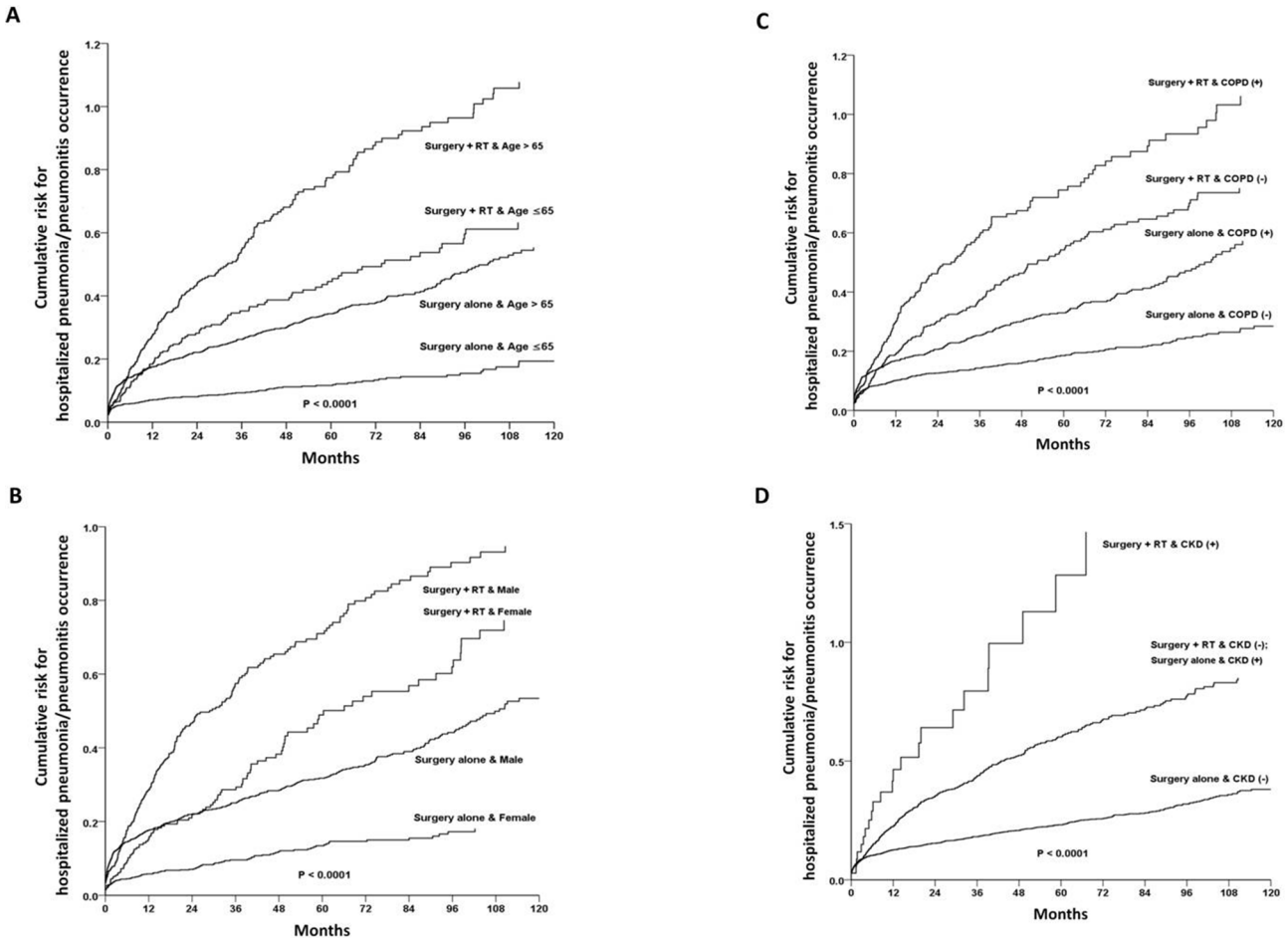

Figure 3 Cumulative risk estimates of hospitalised pneumonia occurrence between the surgery-RT and surgery-alone groups, stratifying according to independent factors: Panel A, age; Panel B, gender; Panel C, COPD; Panel D, CKD.

feature exists among these types of pneumonopathy. That is, all of them threatened a patient's life when disease progression was noted to impair apatient's lung function significantly. Thus, investigating adverse risk factors to identify high-risk patients is critical. However, population-based evidence is largely lacking in this issue.

In the present study, three observations supported a high risk of hospitalised pneumonia/pneumonitis occurrence in postoperatively irradiated lung cancer

Table 3 Estimated hazards for hospitalised and all pneumonia/pneumonitis: stratified by treatment groups, age and gender

	Male		Female	
	>65 years	≤65 years	>65 years	≤65 years
The surgery+RT group (n=867)				
Hospitalised pneumonia/pneumonitis	9.22 (6.44–13.19), p<0.0001**	6.20 (4.18–9.17), p<0.0001**	5.90 (3.90–8.91), p<0.0001**	4.78 (3.07–7.44), p<0.0001**
All pneumonia/pneumonitis	4.84 (3.76–6.23), p<0.0001**	4.06 (3.07–5.36), p<0.0001**	3.31 (2.43–4.50), p<0.0001**	2.69 (1.92–3.76), p<0.0001**
The surgery-alone group (n=3468)				
Hospitalised pneumonia/pneumonitis	5.30 (3.76–7.45) p<0.0001**	2.34 (1.61–3.40) p=0.01*	2.14 (1.45–3.16) p=0.0001	1
All pneumonia/pneumonitis	3.08 (2.45–3.87), p<0.0001**	1.67 (1.30–2.16), p<0.0001**	1.48 (1.13–1.93), p=0.004	1

HR with 95% CI was estimated by using Cox proportional hazard analysis. Young female patients (≤65 years) treated with surgery alone were selected as reference (value=1).
*p<0.05; **p<0.01.
RT, radiotherapy.

Table 4 Estimated hazards for pneumonia-free and overall survival: stratified by treatment groups, CKD, and age

	CKD (+)		CKD (-)	
	>65 years	≤65 years	>65 years	≤65 years
The surgery+RT group (n=867)				
Hospitalised pneumonia/ pneumonitis	4.82 (2.88–8.08) p<0.0001**	13.07 (5.71–29.94) p<0.0001**	4.59 (3.69–5.71) p<0.0001**	3.14 (2.44–4.02) p<0.0001**
All pneumonia/pneumonitis	3.85 (2.42–6.14), p<0.0001**	9.07 (4.03–20.40), p<0.0001**	3.43 (2.89–4.07), p<0.0001**	2.50 (2.05–3.04), p<0.0001**
The surgery-alone group (n=3468)				
Hospitalised pneumonia/ pneumonitis	3.17 (2.21–4.56) p<0.0001**	3.23 (1.50–6.93) p=0.003*	2.34 (1.92–2.85) p<0.0001**	1
All pneumonia/pneumonitis	2.70 (2.00–3.64), p<0.0001**	2.15 (1.06–4.36), p=0.03	1.99 (1.73–2.30), p<0.0001**	1

HR with 95% CI was estimated by using Cox proportional hazard analysis. Young female patients (≤65 years) treated with surgery alone were selected as reference (value=1).
*, p<0.05; **, p<0.01.
RT, radiotherapy.

patients when compared with that of non-irradiated patients: a higher incidence of hospitalised pneumonia/pneumonitis at 2 years (200.2 vs 95.1 per 1000 person-year); a lower rate of 2-year hospitalised pneumonia/pneumonitis-free survival, 69.0% vs 85.2% (p<0.0001; figure 2); and a higher adjusted HR of 2.20 (95% CI, 1.93–2.51; p<0.0001; table 2).

Moreover, we observed a high risk in irradiated elderly male patients (HR, 9.22; 95% CI, 6.44–13.19; p<0.0001; table 3), especially in those with COPD and CKD (HR, 13.74; 95% CI, 6.61–28.53; p<0.0001). Integer risk score further stratified three risk groups (table 5 and figure 4). Aggressive clinical surveillance and pneumonia/pneumonitis prevention should be critically considered for high-risk patient populations.

Table 5 Independent predictors for hospitalised pneumonia/pneumonitis occurrence

Baseline predictor for any cancer occurrence	Regression co-efficient	Risk score	p
Age (each 5 years' increment)	0.19	1	<0.001
Gender			
Female	Reference	0	
Male	0.64	3	<0.001
COPD			
No	Reference	0	
Yes	0.23	1	<0.001
CKD			
No	Reference	0	
Yes	0.34	2	0.006
RT			
No	Reference	0	
Yes	0.78	4	<0.001

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; RT, radiotherapy.

Biological reasoning: radiation-associated lung injury may further damage innate immune and then increase a risk of infectious pneumonia in irradiated lung cancer patients

The present study generates a biological hypothesis: irradiation may further damage innate immune, induce more barrier defects, and then increase a risk of secondary infectious pneumonia occurrence in irradiated lung cancer patients, *especially in those with COPD*.

Three reasons supported this hypothesis. First, several lines of evidence have been reported to support that irradiation may induce several forms of pathological pneumonopathy, such as post-irradiation organising pneumonia,[7 8] acute pneumonitis and/or late fibrosis.[28 34 59–61] These irradiation-induced pathological changes are able to damage resident lung cells, to disrupt local barriers and to disturb local immune of the irradiated lung.[62 63] Thus, an increased risk of secondary infectious pneumonia is reasonable, as this phenomenon has been observed in irradiated nasopharyngeal cancer patients.[64] In molecular biology, several genetic variants of irradiation-responsive genes (eg, polymorphisms of *XRCC1*,[65] *P53*,[66] *ATM*[66] and *APEX1*[65 67]) and TGF-β1[68] have been reported to be as potential biomarkers or predictors in predicting radiation-associated pneumonitis and pneumonia. Thus, these genes might be involved in the underlying pathological processes. However, further in vitro and in vivo studies are required to validate their real roles.

Second, a high incidence of radiation pneumonitis was observed in irradiated lung cancer patients with a comorbidity of COPD.[31 69 70] Third, COPD itself induces barrier defects of the lung[71] and increases a risk of secondary pneumonia occurrence,[23] especially in those patients aged >65 years.[72 73] Our results agreed with these observations. A high risk of hospitalised pneumonopathy (ie,

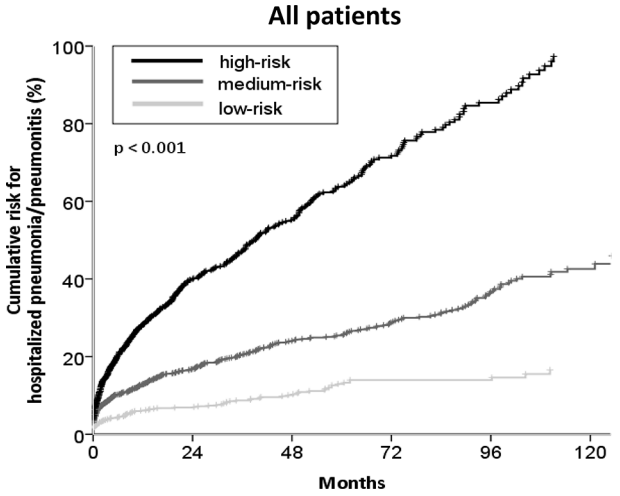

Figure 4 Cumulative risk estimates of hospitalised pneumonia/pneumonitis occurrence according to regression-based risk grouping: the high-risk group, patients with a score of >18; the medium-risk group, patients with a score of 13–17; and the low-risk group, patients with a score of <12. Note that score is calculated and summed according to individual regression co-efficient (table 5), with respect to five independent factors (age, gender, COPD, CKD and irradiation).

pneumonia/pneumonitis) was found in irradiated lung cancer patients, especially in those with COPD (table 2 and figure 3C). Detailed biological mechanisms should be further investigated.

Biology interesting: an increased risk of hospitalised pneumonia/pneumonitis occurrence in lung cancer patients with CKD

Patients with CKD are at a high risk of encountering hospitalised pneumonia,[24 74] even after a renal transplantation.[75] On the other hand, very few studies reported an association of CKD with radiation pneumonitis. In the literature, we observed that the Renin-Angiotensin system may be contributed as a key factor to link CKD and radiation pneumonitis. First, CKD patients have been reported to demonstrate a relatively hyperactive Renin-Angiotensin system,[76] which is considered as a risk factor of developing radiation pneumonitis.[77 78] Second, inhibiting the Renin-Angiotensin system may reduce the development of symptomatic radiation pneumonitis.[79 80] However, evidence in defining this issue is largely lacking. Therefore, by combined severe pneumonopathy as a whole, our data confirmed CKD increased a small but substantial risk of hospitalised pneumonia/pneumonitis occurrence in post-operative irradiated lung cancer patients (adjusted HR, 1.41; 95% CI, 1.10–1.82; p=0.006; table 2 and figure 3D), supporting a potential hazard effect of CKD in radiation-associated pneumonopathy.

More interestingly, as shown in table 4, we observed an unexpectedly higher risk of hospitalised pneumonia/pneumonitis occurrence in younger irradiated-CKD patients (HR, 13.07; 95% CI, 5.71–29.94; p<0.0001) than that of elderly irradiated-CKD patients (HR, 4.82; 95% CI, 2.88–8.08; p<0.0001). This finding was similar with a prior observation.[44] However, detailed biological mechanisms are largely unknown in this phenomenon. Further exploration should be warranted.

A population-based surgical cohort is suitable to explore a risk level of pneumonia/pneumonitis occurrence in irradiated lung cancer patients

As mentioned above and previously,[36] to explore the risk level of pneumonia/pneumonitis in irradiated lung cancer patients, two reasons led us to select patients who were treated with surgery as the study population.[48 81 82] First, resected lung cancer patients characterise 'technically resectable' tumours and a 'medically operable' physical status, minimising confounding effects.[36] Second, resected lung cancer patients had a significant longer survival rate than that of un-resected patients, allowing a more likely observation of late events of pneumonia/pneumonitis.[36 83]

Moreover, lung cancer itself and thoracic surgery have been reported as risk factors of pneumonia/pneumonitis occurrence.[19 25–27 33] Thus, the present study identified lung cancer patients who were treated with surgery alone as a comparison cohort, as reported previously.[36]

Study strength

A population-based study has several advantages in conducting clinical research. For example, it is suitable to investigate clinical questions that are unethical or difficult to be answered by using randomised clinical trials.[84 85] Moreover, a population-based study is recommended in exploring a rare-event association[36 53 86 87] and in demarcating what is actually achieved in the real medical world.[36 84 85 88] Thus, we used a population-based design to explore a risk level of hospitalised pneumonopathy in irradiated lung cancer patients, being similar with our previous report.[36]

Next, to overcome potential limitations of regression analysis,[41 54] we conducted a propensity score match to balance study groups before statistical analysis.[54 84 89] After an effective match, we created a near head-to-head condition before statistical analysis (table 1)[46].This approach led to a more clear inference in answering our study question.

Finally, to decrease unmeasured confounding effects, we conducted a simplified sensitivity analysis according to independent risk factors.[36 55 90] Moreover, we used an integer risk score to further stratify high-risk patients.[56] As shown in figure 4, this risk-stratified model worked well.

Study limitations

We declared several limitations of the present study, as reported previously.[36] For example, unobserved variables do exist, such as smoking habits, infectious pathogens, the dialysis period and cancer stage. For minimising effects of this limitation, we used several strategies.[36 55] First, we used 'COPD' to represent 'smoking habits' at

least partly.[36 55 91] Second, we applied 'charge code of radiotherapy' to estimate 'radiation doses'.[36] Third, we excluded 'patients who were treated with chemotherapy' to narrow down the study population and to decrease potentially confounding effects.[36 47 48] Fourth, to further reduce potential bias, though an extensive sensitivity analysis cannot be done because of our relatively small sample size,[36 55] we still applied a simplified sensitivity analysis that stratified by independent factors.[36]

However, despite the above efforts, intrinsic limitations of the present study cannot be fully eliminated. Thus, interpreting the present data should be done carefully as additional studies are required.

CONCLUSION

A high incidence of severe pneumonopathy, that is, pneumonia and/or pneumonitis that required in-patient care, was observed in postoperatively irradiated lung cancer patients, especially in elderly males with COPD and CKD. For these patients, close clinical surveillance and aggressive prevention for pneumonia/pneumonitis should be critically considered. Further bench studies are encouraged to explore underpinning biological mechanisms.

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