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

Shih-Kai Hung,1,2 Yi-Chun Chen,2,3 Wen-Yen Chiou,1,2 Chun-Liang Lai,2,4 Moon-Sing Lee,1,2 Yuan-Chen Lo,1,2 Liang-Cheng Chen,1,2 Li-Wen Huang,1,2 Nai-Chuan Chien,2,5 Szu-Chi Li,2,6 Dai-Wei Liu,2,7 Feng-Chun Hsu,1 Shiang-Jiu Tsai,1 Michael WY Chan,8,9,10 Hon-Yi Lin1,2,8

ABSTRACT

Objective Pulmonary radiotherapy has been reported to increase the 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. Unexpectedly, we observed a higher risk of hospitalised pneumonopathy in younger irradiated-CKD patients (HR, 13.07; 95% CI, 6.61–28.53; p<0.0001). Compared with younger 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.

INTRODUCTION

Patients with lung cancer are frequently encountered in both primary and in-patient care, characterising high rates of mortality and morbidities.1–5 Radiotherapy is one of the major treatment modalities in managing lung cancer patients.1 However, irradiation has been reported to correlate with an increased incidence of several types of pneumonopathy, such as infectious pneumonia,6 7 non-infectious organic pneumonitis,8 9 and radiation pneumonitis,10 11 even after a 2-year follow-up period.12 Clinically, differentiating radiation pneumonitis from secondary pneumonia is not easy.12 13 Several aetiologies have been declared. First, the radiological finding is similar between radiation pneumonitis and secondary pneumonia14 and both of them...
showed an increased lung infiltration and/or parenchymal consolidation. Second, no reliable tools are available to diagnose radiation pneumonitis directly, its diagnosis is largely dependent on exclusion of other pulmonary diseases. Third, secondary pneumonia is frequently co-occurred in patients with radiation pneumonitis, either simultaneously or sequentially.

Remarkably, when progressive dyspnea developed, either radiation pneumonitis or secondary infectious/non-infectious pneumonia threatens a patient’s life. 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, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), thoracic surgery, chemotherapy and radiotherapy (RT). On the other hand, potential hazard factors of radiation pneumonitis have also been reported, as follows: age, gender, COPD, diabetes mellitus, thoracic surgery and chemotherapy. 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). 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, the IRB waived a requirement of written informed consents because permanent de-identification was conducted by the National Health Research Institute before data analysis.

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. 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. Briefly, we applied the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 162 to identify lung cancer patients (n=218300). And, we used a peer-reviewed data subset (ie, the Registry File for Catastrophe Illness) to validate lung cancer diagnosis. Then, we excluded previously diagnosed lung cancer patients to allocate newly onset patients (n=78722).

To purify the study population, several exclusion criteria were used, as follows: previous pneumonia/pneumonitis (n=21030), 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=49174), 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. Thus, for a better comparison, we allocated lung cancer patients treated with surgery alone as our study controls. Moreover, to create a between-group comparable condition before analysis, we used a propensity score to match 11 baseline factors simultaneously: age, gender, COPD, diabetes mellitus, thoracic surgery and chemotherapy. However, evidence from population-based studies is largely limited in irradiated lung cancer patients.

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. 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. Two reasons for this exclusion were: excluded patients with pathologically positive nodal disease, that is, pN1-3 in stage II-III; and...
avoided a confounding effect of chemotherapy on pneumonia occurrence.¹⁹

As reported previously, thirty-six 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

---

**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.
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.

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.
Statistical analysis
We analysed and reported data according to the CONSORT statement and STROBE guideline (main accordance). SAS (version 9.2; SAS Institute, Inc., Cary, NC, USA) and SPSS (version 12, IBM SPSS Inc., Chicago, USA) 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 (rather than logistic regression) was conducted to perform multivariable analysis and to estimate hazardous effects, as that of a previous report. Multivariable-analysis-identified risk factors were selected for further stratified/simplified sensitivity analysis. According to previous reports, 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, 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. 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). 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).

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 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.

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;
Hung S-K, et al. BMJ Open 2017;7:e015022. doi:10.1136/bmjopen-2016-015022

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). 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 and non-infectious pneumonia, as well as pneumonitis. A common

---

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

| Treatment received (Surgery+RT vs Surgery alone) | Hospitalised pneumonia/pneumonitis | All pneumonia/pneumonitis |
|------------------------------------------------|----------------------------------|---------------------------|
| Adjusted HR (95% CI)                           |                                  |                           |
| 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.
feature exists among these types of pneumonopathy. That is, all of them threatened a patient’s life when disease progression was noted to impair a patient’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 patients.

**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.

| 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.
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.

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, acute pneumonitis and/or late fibrosis. 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. Thus, an increased risk of secondary infectious pneumonia occurrence is reasonable, as this phenomenon has been observed in irradiated nasopharyngeal cancer patients.

Second, a high incidence of radiation pneumonitis was observed in irradiated lung cancer patients with a comorbidity of COPD. Third, COPD itself induces barrier defects of the lung and increases a risk of secondary pneumonia occurrence, especially in those patients aged >65 years. Our results agreed with these observations. A high risk of hospitalised pneumonopathy (ie, Table 4 Estimated hazards for pneumonia-free and overall survival: stratified by treatment groups, CKD, and age

| Treatment Group          | CKD (+)          | CKD (-)          |
|--------------------------|------------------|------------------|
| Hospitalised pneumonia/pneumonitis |                  |                  |
| ≥65 years                | 4.82 (2.88–8.08) | 4.59 (3.69–5.71) |
| p<0.0001**               | p<0.0001**       |                  |
| ≤65 years                | 13.07 (5.71–29.94) | 3.14 (2.44–4.02) |
| p<0.0001**               | p<0.0001**       |                  |
| All pneumonia/pneumonitis |                  |                  |
| ≥65 years                | 3.85 (2.42–6.14)  | 3.43 (2.89–4.07)  |
| p<0.0001**               | p<0.0001**       |                  |
| ≤65 years                | 9.07 (4.03–20.40) | 2.50 (2.05–3.04)  |
| p<0.0001**               | p<0.0001**       |                  |

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.
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).

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, even after a renal transplantation. 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, which is considered as a risk factor of developing radiation pneumonitis. Second, inhibiting the Renin-Angiotensin system may reduce the development of symptomatic radiation pneumonitis. 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. 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, 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. First, resected lung cancer patients characterise ‘technically resectable’ tumours and a ‘medically operable’ physical status, minimising confounding effects. 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.

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

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. Moreover, a population-based study is recommended in exploring a rare-event association and in demarcating what is actually achieved in the real medical world. 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.

Next, to overcome potential limitations of regression analysis, we conducted a propensity score match to balance study groups before statistical analysis. After an effective match, we created a near head-to-head condition before statistical analysis (table 1). 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. Moreover, we used an integer risk score to further stratify high-risk patients. As shown in figure 4, this risk-stratified model worked well.

Study limitations

We declared several limitations of the present study, as reported previously. 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. First, we used ‘COPD’ to represent ‘smoking habits’ at
least partly. Second, we applied ‘charge code of radiotherapy’ to estimate ‘radiation doses’. Third, we excluded ‘patients who were treated with chemotherapy’ to narrow down the study population and to decrease potentially confounding effects. Fourth, to further reduce potential bias, though an extensive sensitivity analysis cannot be done because of our relatively small sample size, we still applied a simplified sensitivity analysis that stratified by independent factors.

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.

Author affiliations

1Department of Radiation Oncology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
2School of Medicine, Tzu Chi University, Hualien, Taiwan
3Division of Nephrology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
4Chest Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
5Thoracic Surgery, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
6Haematology-Oncology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Chia-Yi, Taiwan
7Department of Radiation Oncology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan
8Institute of Molecular Biology, National Chung Cheng University, Chia-Yi, Taiwan
9Department of Life Science, National Chung Cheng University, Chia-Yi, Taiwan
10Human Epigenomics Centre, National Chung Cheng University, Chia-Yi, Taiwan

Acknowledgements This study utilises research data from the Taiwan National Health Insurance Research Database provided by the Bureau of Taiwan National Health Insurance (NHI), Department of Health and managed by National Health Research Institutes (registry number 99029). Results were validated by using another independent dataset (registry number 100266; data not shown). The interpretation and conclusions contained herein are not those of the Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

Contributors Conception or design (S-KH; Y-CC; M-SL; W-YC; C-LL; D-WL; N-CC; S-CL; Y-CL; MWYC; H-YL); or data acquisition (L-CC; L-WH), data analysis (F-CH; L-SJT); or data interpretation (H-YL). Drafting (S-KH; S-JT) or revising the work (L-SJT; Y-CL; MWYC; H-YL); or data acquisition (L-CC; L-WH), data analysis (F-CH; L-SJT); or data interpretation (H-YL). Drafting (S-KH; S-JT) or revising the work (L-SJT; Y-CL; MWYC; H-YL); or data acquisition (L-CC; L-WH), data analysis (F-CH; L-SJT); or data interpretation (H-YL). Final approval (H-YL). Co-first authors: S-KH and S-JT contributed equally.

Funding The present study is supported by several research grants of our institute, that is, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (grant number: DTCRD100-1-14 and DTCRD101-E-18). The funding source fully supported requirement of the present work but did not interact with any of the research process, for example, design and interpretation.

Competing interests None declared.

Ethics approval The Institution Review Board (IRB) of the Buddhist Dalin Tzu Chi Hospital (approved number, B10001019)

REFERENCES

1. Torre LA, Sauer AM, Chen MS, et al. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016. Converging incidence in males and females. CA Cancer J Clin 2016;66:182–202.
2. Siegel RL, Miller KD, Jemal A, et al. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
3. Torre LA, Siegel RL, Jemal A, et al. Lung cancer statistics. Adv Exp Med Biol 2016;893:1–19.
4. NCCN.org. Clinical practice guidelines in oncology: non-small cell lung cancer, Version 4. (NCCN Guidelines™) 2016 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
5. Maimon N, Barski L, Sion-Vardy N, et al. A man with interstitial pneumonia and pancycopenia during radiotherapy. Chest 2004;126:1368–71.
6. Reckzeh B, Merte H, Pflüger KH, et al. Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small-cell lung cancer. J Clin Oncol 1996;14:1071–6.
7. Ochiai S, Nomoto Y, Yamashita Y, et al. Radiation-induced organizing pneumonia after stereotactic body radiotherapy for lung tumor. J Radiat Res 2015;56:904–11.
8. Y-Saito Y, Kato M, et al. Relationship between radiation pneumonitis and organizing pneumonia after radiotherapy for breast cancer. Radiat Oncol 2013;8:56.
9. Epler GR. Post-breast cancer radiotherapy bronchiolitis obliterans organizing pneumonia. Expert Rev Respir Med 2013;7:109–12.
10. Murai T, Shibamoto Y, Nishiyama T, et al. Organizing pneumonia after stereotactic ablative radiotherapy of the lung. Radiat Oncol 2012;7:123.
11. Leprieur EG, Fernandez D, Chatellier G, et al. Acute radiation pneumonitis after conformational radiotherapy for nonsmall cell lung cancer: clinical, dosimetric, and associated-treatment risk factors. J Cancer Res Ther 2013;9:447–51.
12. Arrieta O, Gallardo-Rincón D, Villarreal-Garza C, et al. High frequency of radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent radiotherapy and gemcitabine after induction with gemcitabine and carboplatin. J Thorac Oncol 2009;4:845–52.
13. Yamaguchi S, Ohguri T, Matsuki Y, et al. Radiotherapy for thoracic tumors: association between subclinical interstitial lung disease and fatal radiation pneumonitis. Int J Clin Oncol 2015;20.
14. Tokuda Y, Takigawa N, Kozuki T, et al. Long-term follow-up of phase II trial of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer, Acta Oncol 2012;51:537–40.
15. Yrimbesoglu E, Higginson DS, Fayda M, et al. Challenges scoring radiation pneumonitis in patients irradiated for lung cancer. Lung Cancer 2012;76:350–3.
16. Phillips TL, Hoppe RT, Roach M. Leibler and Phillips Textbook of Radiation Oncology. 3rd ed. Philadelphia: Saunders, an imprint of Elsevier Inc., 2010.
17. Kocak Z, Evans ES, Zhou SM, et al. Challenges in defining radiation pneumonitis in patients with lung cancer. Int J Radiat Oncol Biol Phys 2005;62:635–8.
18. Anderson EJ. Respiratory infections. Cancer Treat Res 2014;161:203–36.
19. Akinosoglou KS, Karkoulias K, Marangos M. Infectious complications in patients with lung cancer. Eur Rev Med Pharmacol Sci 2013;17:9–18.
20. Robnett TJ, Machtay M, Vines EF, et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000;48:89–94.
21. Khalil AA, Hoffmann L, Moeller DS, et al. New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy. *Acta Oncol* 2015;54:1343–9.

22. Welte T. Risk factors and severity scores in hospitalized patients with community-acquired pneumonia: prediction of severity and mortality. *Eur J Clin Microbiol Infect Dis* 2012;31:33–47.

23. Yamada Y, Sekine Y, Suzuki H, et al. Trends of bacterial colonisation and the risk of postoperative pneumonia in lung cancer patients with chronic obstructive pulmonary disease. *Eur J Cardiothorac Surg* 2010;37:752–6.

24. Viasus D, Garcia-Vidal C, Cruzado JM, et al. Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011;26:2899–906.

25. Lee JY, Jin SM, Lee CH, et al. Risk factors of postoperative pneumonia after lung cancer surgery. *J Korean Med Sci* 2011;26:979–84.

26. Pool KL, Munden RF, Vapourciyan A, et al. Radiographic imaging features of thoracic complications after pneumonectomy in oncology patients. *Eur J Radiol* 2012;81:165–72.

27. Takeda S, Maeda H, Sawabata N, et al. Clinical impact of interstitial pneumonia following surgery for lung cancer. *Thorac Cardiovasc Surg* 2006;54:268–72.

28. Minami-Shimmyo Y, Ohe Y, Yamamoto S, et al. Risk factors for treatment-related death associated with chemotherapy and thoracic radiotherapy for lung cancer. *J Thorac Oncol* 2012;7:177–82.

29. Dang J, Li G, Zang S, et al. Risk and predictors for early radiation pneumonitis in patients with stage III non-small cell lung cancer treated with concurrent or sequential chemoradiotherapy. *Radiat Oncol* 2014;9:172.

30. Dang J, Li G, Ma L, et al. Predictors of grade ≥ 2 and grade ≥ 3 radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with three-dimensional conformal radiotherapy. *Acta Oncol* 2013;52:1175–80.

31. Inoue T, Shiomi H, Oh RJ. Stereotactic body radiotherapy for Stage I lung cancer with chronic obstructive pulmonary disease: special reference to survival and radiation-induced pneumonitis. *J Radiat Res* 2015;56:727–34.

32. Zhang XJ, Sun JG, Sun J, et al. Risk of prediction of radiation pneumonitis in lung cancer patients: a systematic review. *J Cancer Res Clin Oncol* 2012;138:2103–16.

33. Dang J, Li G, Zang S, et al. Comparison of risk and predictors for early radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with radiotherapy with or without surgery. *Lung Cancer* 2014;86:329–33.

34. Parashar B, Edwards A, Mehta R, et al. Chemotherapy significantly increases the risk of radiation pneumonitis in radiation therapy of advanced lung cancer. *Am J Clin Oncol* 2011;34:160–4.

35. Wei KC, Lin HY, Hung SK, et al. Leukemia risk after cardiac fluoroscopic interventions stratified by procedure number, exposure latent time, and a nationwide population-based case-control study. *Medicine* 2016;95:e2953.

36. Hung SK, Lee MS, Chiu WY, et al. High incidence of ischemic stroke occurrence in irradiated lung cancer patients: a population-based surgical cohort study. *PLOS One* 2014;9:e94377.

37. Chiu WY, Hung SK, Lai GL, et al. Effect of 23-valent pneumococcal polysaccharide vaccine inoculated during anti-cancer treatment period in elderly lung cancer patients on community-acquired pneumonia hospitalization: a nationwide population-based cohort study. *Medicine* 2015;94:e1022.

38. Chen PC, Muo CH, Lee YT, et al. Lung cancer and incidence of stroke: a population-based cohort study. *Stroke* 2011;42:3034–9.

39. Tsai SJ, Huang YS, Tung CH, et al. Increased risk of ischemic stroke in cervical cancer patients: a nationwide population-based study. *Radiat Oncol* 2013;8:41.

40. Kalinick T, Horakova D, Spelman T, et al. Switch to natalizumab versus fingolimod in active relapsing-remitting multiple sclerosis. *Ann Neurol* 2015;77:425–35.

41. Katz MH. Evaluating clinical and public health interventions: a practical guide to study design and statistics. Cambridge: Cambridge University Press, 2010.

42. Palmut AA, Saukoriipi A, Snellman M, et al. Incidence and etiology of community-acquired pneumonia in the elderly in a prospective population-based study. *Scand J Infect Dis* 2014;46:250–9.

43. Ishigami K, Okuro M, Koizumi Y, et al. Association of severe hypertension with pneumonia in elderly patients with acute ischemic stroke. *Hyperension* 2012;63:494–50.

44. James MT, Quan H, Tonelli M, et al. CKD and risk of hospitalization and death with pneumonia. *Am J Kidney Dis* 2009;54:24–32.

45. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–61.

46. Nagami Y, Shiba M, Tominaga K, et al. Locoregional steroid injection prevents surgical fistulation after endoscopic submucosal dissection for esophageal cancer: a propensity score matching analysis. *Surg Endosc* 2016;30:1441–9.

47. Greene FL, AJCC cancer staging atlas. 6 edn. New York, NY: Springer, 2006.

48. NCCN.org. Clinical Practice Guidelines in Oncology: Non-small cell lung cancer. Version 3. (NCCN Guidelines™). 2014 http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

49. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. *Ann Thoracic Cardiovasc Surg* 2009;15:4–9.

50. Institutes TNHR. Taiwan cancer center accreditation. 2014 4 http://www.nthri.org.tw/nthri/ org/ ca/ accredit/index.htm (accessed 12 Mar 2014).

51. Monge V, González A. Hospital admissions for pneumonia in Spain. *Infection* 2001;29:3–6.

52. Schultz KF. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726–32.

53. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007;4:e296.

54. Steyerberg EW. Clinical prediction models: a practical approach to development, validation, and updating. New York; London: Springer, 2009.

55. Tsai YF, Lee CH, Ho WC, et al. Statins and the risk of hepatocellular carcinoma in patients with hepatitis C virus infection. *J Clin Oncol* 2013;31:1514–21.

56. Lee MH, Yang HI, Liu J, et al. Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. *Hepatology* 2013;58:546–54.

57. Sullivan LM, Massaro JM, D’Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004;23:1631–60.

58. Trodella L, Ramella S, Salvi G, et al. Dose and volume as predictive factors of pulmonary toxicity. *Radiology* 2005;30:175–80.

59. Werner-Wasik M, Paulus R, Curran WJ, et al. Acute esophagitis and late lung toxicity in concurrent chemoradiation therapy trials in patients with locally advanced non-small-cell lung cancer: analysis of the radiation therapy oncology group (RTOG) database. *Clin Lung Cancer* 2011;12:245–51.

60. Palma DA, Sanes S, Tsuijno K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2013;85:444–50.

61. Omer H, Suleiman A, Alizammi K. Risks of lung fibrosis and pneumonitis after postmastectomy electron radiotherapy. *Radiat Prot Dosimetry* 2015;165:499–502.

62. Tsoutsou PG. The interval between radiation and the immune system in the field of post-radical pneumonitis and fibrosis and why it is important to understand it. *Expert Opin Pharmacother* 2014;15:1781–3.

63. Cappuccini F, Eldh T, Bruder D, et al. New insights into the molecular pathology of radiation-induced pneumopathy. *Radiother Oncol* 2011;101:86–92.

64. Yen TT, Lin CH, Jiang RS, et al. Incidence of late-onset pneumonia in patients after treatment with radiotherapy for nasopharyngeal carcinoma: a nationwide population-based study. *Head Neck* 2015;37:1756–61.

65. Yin M, Liao Z, Liu Z, et al. Functional polymorphisms of base excision repair genes XRCC1 and APE1 predict risk of radiation pneumonitis in patients with non-small cell lung cancer treated with definitive radiation therapy. *Int J Radiat Oncol Biol Phys* 2011;81:e67–73.

66. Yang M, Zhang L, Bi N, et al. Association of PS3 and ATM polymorphisms with risk of radiation-induced pneumonitis in lung cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1402–7.

67. Li H, Liu G, Xia L, et al. A polymorphism in the DNA repair domain of APEX1 is associated with the radiation-induced pneumonitis occurrence in locally advanced non-small cell lung cancer patients treated with concurrent or sequential chemoradiotherapy. *Cancer* 2011;12:245–51.

68. Bayard D, Truong VA, Cronin W. The Framingham heart study. *Ann Intern Med* 2016;165:499–502.

69. Jarolimek W, van Eijk JJ, Truong VA. The Framingham heart study. *Ann Intern Med* 2016;165:499–502.
69. Kimura T, Togami T, Takashima H, et al. Radiation pneumonitis in patients with lung and mediastinal tumours: a retrospective study of risk factors focused on pulmonary emphysema. Br J Radiol 2012;85:135–41.
70. Rancati T, Ceresoli GL, Gagliardi G, et al. Factors predicting radiation pneumonitis in lung cancer patients: a retrospective study. Radiother Oncol 2003;67:275–83.
71. Roy MG, Livraghi-Butrico A, Fletcher AA, et al. Muc5b is required for airway defence. Nature 2014;505:412–6.
72. Müllerova H, Chigbo C, Hagan GW, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med 2012;106:1124–33.
73. Ryan M, Suaya JA, Chapman JD, et al. Incidence and cost of pneumonia in older adults with COPD in the United States. PLoS One 2013;8:e78887.
74. Chou CY, Wang SM, Liang CC, et al. Risk of pneumonia among patients with chronic kidney disease in outpatient and inpatient settings: a nationwide population-based study. Medicine 2014;93:174.
75. Nielsen LH, Jensen-Fangel S, Jespersen B, et al. Risk and prognosis of hospitalization for pneumonia among individuals with and without functioning renal transplants in Denmark: a population-based study. Clin Infect Dis 2012;55:679–86.
76. Santos PC, Krieger JE, Pereira AC. Renin-Angiotensin system, hypertension, and chronic kidney disease: pharmacogenetic implications. J Pharmacol Sci 2012;120:77–88.
77. Mahmoud J, Jelveh S, Zaidi A, et al. Targeting the Renin-Angiotensin system combined with an antioxidant is highly effective in mitigating radiation-induced lung damage. Int J Radiat Oncol Biol Phys 2014;89:227–33.
78. Ghosh SN, Zhang R, Fish BL, et al. Renin-Angiotensin system suppression mitigates experimental radiation pneumonitis. Int J Radiat Oncol Biol Phys 2009;75:528–36.
79. Bracci S, Valeriani M, Agoll L, et al. Renin-Angiotensin system inhibitors might help to reduce the development of symptomatic radiation pneumonitis after stereotactic body radiotherapy for lung cancer. Clin Lung Cancer 2016;17:189–97.
80. Bracci S, Valeriani M, Agoll L, et al. Renin-Angiotensin system inhibitors might help to reduce the development of symptomatic radiation pneumonitis after stereotactic body radiotherapy for lung cancer. Clin Lung Cancer 2016;17:189–97.
81. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11–19.
82. Granone P, Trodella L, Margaritora S, et al. Radiotherapy versus follow-up in the treatment of pathological stage Ia and Ib non-small cell lung cancer. Early stopped analysis of a randomized controlled study. Eur J Cardiothorac Surg 2006;18:418–24.
83. Hall EJ, Giaccia AJ. Radiobiology for the radiologist. 7th edn. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.
84. Rosenbaum PR. Design of observational studies. New York; London: Springer, 2010.
85. Maruyama K, Kawahara N, Shin M, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. N Engl J Med 2005;352:146–53.
86. Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. Lancet Oncol 2011;12:900–4.
87. Lee CC, Ho HC, Hsiao SH, et al. Infectious complications in head and neck cancer patients treated with cetuximab: propensity score and instrumental variable analysis. PLoS One 2012;7:e50163.
88. Owonikoko TK, Ragan C, Chen Z, et al. Real-world effectiveness of systemic agents approved for advanced non-small cell lung cancer: a SEER-Medicare analysis. Oncologist 2013;18:800–10.
89. Choudhury G, Mandal P, Singanayagam A, et al. Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia—a propensity-adjusted analysis. Clin Microbiol Infect 2011;17:1852–8.
90. VanderWeele TJ. Unmeasured confounding and hazard scales: sensitivity analysis for total, direct, and indirect effects. Eur J Epidemiol 2013;28:113–7.
91. Stang P, Lydick E, Silverman C, et al. The prevalence of COPD: using smoking rates to estimate disease frequency in the general population. Chest 2000;117(S Suppl 2):354S–9.