The radiotherapy planning CT-based multi-omics for predicting the radiation pneumonitis in lung cancer patients: A multi-center study

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Research Article

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Abstract

Background

To predict the risk of radiation pneumonitis (RP), deep learning (DL) models were built to stratify lung cancer patients. Our study also investigated the impact of RP on survival.

Methods

This study retrospectively collected 100 RP and 99 matched non-RP lung cancer patients treated with radiotherapy from two independent centers. These patients were randomly divided into training (n = 175) and validation cohorts (n = 24). The radiomics and dosiomics features were extracted from radiation planning computed tomography (CT). Clinical information was retrospectively collected from the electronic medical record database. All features were screened by LASSO cox regression. A multi-omics prediction model was developed by the optimal algorithm and estimated the area under the receiver operating characteristic curve (AUC). Overall survival (OS) between RP, non-RP, mild-RP, and severe-RP groups was analyzed by the Kaplan-Meier method.

Results

There were eventually selected 16 radiomics features, 2 dosiomics features, and 1 clinical feature to build the best multi-omics model. GLRLM_Gray Level Non Uniformity Normalized and GLCM_MCC from PTV were essential dosiomics features, and T stage was a paramount clinical feature. The optimal performance for predicting RP was the AUC of testing set [0.94, 95% confidence interval (CI) (0.939-1.000)] and the AUC of external validation set [0.92, 95% CI (0.80-1.00)]. All RP patients were divided into mild-RP and severe-RP group according to RP grade (≤ 2 grade and > 2 grade). The median OS was 31 months (95% CI, 28–39) for non-RP group compared with 49 months (95% CI, 36-NA) for RP group (HR = 0.53, P = 0.0022). Among RP subgroup, the median OS was 57months (95% CI, 47-NA) for mild-RP and 25 months (95% CI, 29-NA) for severe-RP, and mild-RP group exhibited a longer OS (HR = 3.72, P < 0.0001).

Conclusion

The multi-omics model contributed to improvement in the accuracy of the RP prediction. Interestingly, this study also demonstrated that compared with non-RP patients, RP patients displayed longer OS, especially mild-RP.

Background

Lung cancer is the most common malignant tumors worldwide, and leads to almost 25% of cancer-associated mortality in 2022 [1]. Radiation therapy (RT) is the cornerstone of lung cancer treatment, and
77% of lung cancer patients have acquired benefits from RT [2, 3]. With the continuous optimization of the radiotherapy mode, the median overall survival (OS) of patients with stage III non-small cell lung cancer (NSCLC) increased gradually from 9.8 to 40 months [4]. Nonetheless, the side effect of RT still exists because of high-doses area, which could also increase the toxicity of surrounding normal structures [3].

Radiation pneumonitis (RP) is an acute radiation-induced lung injury (RILI) occurred in 5–20% of lung cancer patients and mainly diagnosed via radiologic imaging and clinical symptoms, such as dyspnea on exertion, dry cough, and hypoxemia [5]. According to medical images, the RP area commonly appears in the high-dose radiation field [6]. Severe RP is recognized as a significant fatal factor in thoracic malignancy tumors. Dr. Akira Inoue demonstrated that the 3-year OS rate of grade 3 or higher RP was only 0 according to the Radiation Therapy Oncology Group (RTOG) criteria [7]. With the development of radiation techniques, three-dimensional conformal RT (3D-CRT), intensity-modulated RT (IMRT), volumetric arc radiotherapy (VMAT), stereotactic body RT (SBRT), stereotactic radiosurgery (SRS) and fiducial-based tracking and deep inspiratory breath hold or respiratory-gating were utilized in radiotherapy [8–12]. However, radiotherapy technology has developed more precision, which cannot completely prevent the occurrence of RP [13]. Hence, how to predict the PR is necessary for lung cancer patients [14].

Conventional wisdom holds that radiotherapy-induced the cytotoxic effect of lung tissues via ionizing radiation and induced injured tissues to secret the cytokines, including TNF-α, TNF-β1, IL-1, IL-6, et al. Inflammatory cells accumulate in the alveoli and pulmonary interstitium, further increasing capillary permeability, and leading to reversible RP [15, 16]. Dr. Zhou and his colleagues demonstrated RP risk increased with augmenting the number of peripheral lymphocytes [17]. Some hematological indicators, systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) can reflect the level of systemic inflammation and be recognized as the RP predictive factor [18].

Radiomics, as a branch of machine learning, enables extracting the features from radiographic images to predict RP [19–21]. The accuracy of the prediction model established only by using radiomics features is not satisfactory, and the receiver operating characteristic curve (AUC) was only 0.68 [20]. Jiang et al. established an RP prediction model by combining basic clinical, dose, and radiomic features, and reached an AUC of 0.94 [22]. However, the lack of validation results reported is the major flaw in this study.

This multi-center study retrospectively collected the clinical information, radiation dose of multi-structures, and radiomics features via deep learning (DL) method to predict the RP. There are five key strengths in our study. (i) In contrast to previous studies, the comprehensive clinical indicators were included, such as the hematological biomarkers before and after radiotherapy, smoking index (SI), body mass index (BMI), and related primary diseases. (ii) Moreover, CT-based features were extracted from four regions of interest (ROIs), including the gross tumor volume (GTV), planning target volume (PTV), total lung (TL) volume minus gross tumor volume (TL-GTV), and total lung volume minus planning target volume (TL-PTV). (iii) In order to study the correlation between spatial dose distribution and RP, we
calculated both dosimetric (the percentage of irradiated lung volume), and dosiomics (the analyzation of dose- and fluence-based radiomics) [23]. (iv) External data was used to validate the efficacy of the RP multi-omics model. (v) This study further investigated the relationship between the occurrence rate of RP and OS in lung cancer patients. Therefore, we built an RP prediction model to assist radiation oncologists in designing the optimal therapeutic regimen and protecting the surrounding normal lung tissues.

Methods

1. Patient Data

Our study retrospectively collected 175 lung cancer patients treated with IMRT at Xiangya Hospital from January 2011 to January 2022, including 87 RP patients and 88 non-RP patients. The independent external validation cohort consisted of 13 RP patients and 11 non-RP patients from Changsha Central Hospital (Figure S1). All patients underwent IMRT, administered with 1.5-3 Gy per day, 5 days a week, 10–35 fractions with a total dose of 30–70 Gy. Patients will be enrolled with the following criteria: (i) Primary lung cancer diagnosed with pathology. (ii) Patients completed radiotherapy and recorded the clinical information. Clinical characteristics included age, sex, SI, BMI, tumor-node-metastasis (TNM) stage, related primary disease (chronic obstructive pulmonary disease (COPD), diabetes, and hypertension), pathology, tumor location, carcinoembryonic antigen (CEA), SII, NLR, PLR, LMR, chemotherapy regimens and total dose. SI is calculated as cigarettes per day multiply duration of smoking (years). SII, NLR, PLR and LMR are defined as follows: SII = platelet x neutrophil/lymphocyte, NLR = neutrophil/lymphocyte, PLR = platelet/lymphocyte, LMR = lymphocyte count/monocyte count. (iii) High-quality images and volumetric dose can be obtained from the radiation planning CT. (iv) The RP patients were diagnosed via radiology or symptoms, and RP was classified into mild-RP (≤ 2 grade) and severe-RP (> 2 grade) groups based on Criteria for Adverse Events (CTCAE) and RTOG criteria.

2. Image collection and ROIs delineation

All patients were scanned and located by CT analogue positioning system (SOMATOM Definition AS) with scanning voltage, tube current, helical sweep pitch, and slice thickness of 140 kV, 271 mAs, 0.6 and 3mm, respectively. Four ROIs were selected for analysis in the planning CT, including GTV, PTV, TL-GTV, and TL-PTV. The GTV was confirmed by a senior oncologist and radiologist.

3. Radiomics features extraction

The images were normalized to avoid variation, and a total of 1960 radiomics features, including shape (n = 72), texture (n = 1452), and intensity features (n = 436), were extracted from four ROIs by an open-source software, IBEX. Specifically, shape features describe geometric properties, such as diameters, volumes, and surface areas (Fig. 1). Texture features reflect the degree or abruptness of gray-level intensity fluctuations, which include the Gray Level Co-occurrence Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), et al. Intensity features represent the intensity distribution of individual voxels.
4. Dosiomics and dosimetric features extraction

The planning CT-based radiation dose was classified into two major types: dosiomics and dosimetric. The dosiomics features were extracted from the dose distributions of the four ROIs. A total of 160 dosiomics features, including GLCM (n = 96) and GLRLM (n = 64), were analyzed in our study by the 3D Slicer software. The dosimetric factors were extracted from the dose-volume histogram (DVH). The factors consisted of whole lung V5, V10, V15, V20, V25, V30, V35, V40, V45, V50. Additionally, the maximum dose, the minimum dose and the average dose in the total lung volumes, GTV and PTV were also included into the analysis.

5. Feature selection

The feature selection strategy was designed as follows: (i) Spearman's correlation analysis was used to screen the extracted features, where a correlation larger than 0.85 is considered as strongly correlated, and one of the features was removed. (ii) The variance was used to select the features, and the two features with a variance difference of less than 0.01 were regarded as solid correlations, and one of the features was removed. (iii) The Least absolute shrinkage and selector operation (LASSO) Cox regression model with 10-times repeated 5-fold cross-validation was used to select the most valuable features correlated to RP status.

6. Model validation and performance evaluation

The subject were divided into a training/validation set (n = 150, 85.7%) and a testing set (n = 25, 14.3%). To select the optimal machine learning algorithm, there used multiple algorithms, such as Support Vector Classification (SVC), Logistic Regression (LR), Gaussian Naive Bayes (GNB), Bernoulli Naive Bayes (BNB), K Nearest Neighbor (KNN), Decision Tree (DT) and Random Forest (RF) for predicting RP status. To make the distribution of the training set more reasonable, the overall data set was randomly divided into a training/testing set in a 6:1 ratio over 100 times. The 10-fold stratified cross-validation method was carried out to train classifiers. We have trained more than 5000 times to select the best performing model. The established model was evaluated in the independent external validation set (n = 24). The predictive performance of the machine learning model was evaluated using the AUC. All calculation was completed via python (version 3.6).

7. Survival analysis

According to the CTCAE and RTOG criteria, all patients were divided into two groups, which were severe-RP (> 2 grade) and mild-RP (≤ 2 grade). Kaplan–Meier method was used to compare the survival curves of non-RP and RP patients (severe-RP patients and mild-RP patients). The difference in OS was analyzed using the log-rank test and Cox regression model in all patients. Survival analysis was done with R (version 4.2.1). A two-tailed p-value < 0.05 was considered statistically significant.

Results
1. Patients characteristics

The baseline characteristics of all patients (n = 199) are shown in Table 1 and Fig. 2a. In the internal and external independent validation cohorts, males accounted for a large proportion (85% and 67%). Except M stage and TNM stage, there was no significant difference in clinical characteristics between both groups (Table 1 and Fig. 2a). Figure 2b shown an example of different grade classification RP from pre- and post-IMRT CT scans.
<table>
<thead>
<tr>
<th></th>
<th>Internal Cohort (n = 175)</th>
<th>Validation Cohort (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Mean ± SD)</strong></td>
<td>58.90 ± 8.41</td>
<td>59.50 ± 8.17</td>
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<tr>
<td><strong>Sex (n, %)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>149 (85.14%)</td>
<td>16 (66.67%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (14.86%)</td>
<td>8 (33.33%)</td>
<td></td>
</tr>
<tr>
<td><strong>T stage (n, %)</strong></td>
<td></td>
<td></td>
<td>0.778</td>
</tr>
<tr>
<td>1</td>
<td>18 (10.28%)</td>
<td>1 (4.17%)</td>
<td></td>
</tr>
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<td>2</td>
<td>46 (26.29%)</td>
<td>6 (25.00%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>55 (31.43%)</td>
<td>9 (37.50%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56 (32.00%)</td>
<td>8 (33.33%)</td>
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</tr>
<tr>
<td><strong>N stage (n, %)</strong></td>
<td></td>
<td></td>
<td>0.692</td>
</tr>
<tr>
<td>0</td>
<td>19 (10.86%)</td>
<td>2 (8.33%)</td>
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</tr>
<tr>
<td>1</td>
<td>27 (15.43%)</td>
<td>6 (25.00%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>83 (47.43%)</td>
<td>10 (41.67%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46 (26.28%)</td>
<td>6 (25.00%)</td>
<td></td>
</tr>
<tr>
<td><strong>M stage (n, %)</strong></td>
<td></td>
<td></td>
<td>0.003*</td>
</tr>
<tr>
<td>0</td>
<td>147 (84.00%)</td>
<td>14 (58.33%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (16.00%)</td>
<td>10 (41.67%)</td>
<td></td>
</tr>
<tr>
<td><strong>TNM stage (n, %)</strong></td>
<td></td>
<td></td>
<td>0.012*</td>
</tr>
<tr>
<td>I</td>
<td>3 (1.71%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (8.57%)</td>
<td>2 (8.33%)</td>
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<td>III</td>
<td>130 (74.29%)</td>
<td>12 (50.00%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>27 (15.43%)</td>
<td>10 (41.67%)</td>
<td></td>
</tr>
<tr>
<td><strong>Histology (n, %)</strong></td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

Definition of abbreviations: LUSC = lung squamous cell carcinoma; LUAD = lung adenocarcinoma; SCLC = small cell lung cancer; SI = smoking index; SII = systemic immune inflammation index; RP = radiation pneumonitis; NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; MLR = monocyte to lymphocyte ratio; CEA = carcinoembryonic antigen; pre- = before radiotherapy; post- = after radiotherapy. *p < 0.05
<table>
<thead>
<tr>
<th></th>
<th>Internal Cohort (n = 175)</th>
<th>Validation Cohort (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUSC</td>
<td>103 (58.86%)</td>
<td>15 (62.50%)</td>
<td></td>
</tr>
<tr>
<td>LUAD</td>
<td>22 (12.57%)</td>
<td>6 (25.00%)</td>
<td></td>
</tr>
<tr>
<td>SCLC</td>
<td>50 (28.57%)</td>
<td>3 (12.50%)</td>
<td></td>
</tr>
<tr>
<td>SI (Median, IQR)</td>
<td>700 (200–1000)</td>
<td>0 (0-525)</td>
<td>0.949</td>
</tr>
<tr>
<td>BMI (Median, IQR)</td>
<td>23.00 (21.30-23.88)</td>
<td>23.03 (21.93–24.91)</td>
<td>0.281</td>
</tr>
<tr>
<td>COPD (n, %)</td>
<td></td>
<td></td>
<td>0.242</td>
</tr>
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<td>Yes</td>
<td>34 (19.43%)</td>
<td>7 (29.17%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>141 (80.57%)</td>
<td>17 (70.83%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td></td>
<td></td>
<td>0.264</td>
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<td>18 (10.29%)</td>
<td>1 (4.17%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>157 (89.71%)</td>
<td>23 (95.83%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (16.00%)</td>
<td>6 (25.00%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>147 (84.00%)</td>
<td>18 (75.00%)</td>
<td></td>
</tr>
<tr>
<td>RP (n, %)</td>
<td></td>
<td></td>
<td>0.267</td>
</tr>
<tr>
<td>Yes</td>
<td>87 (49.71%)</td>
<td>13 (54.17%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>88 (50.29%)</td>
<td>11 (45.83%)</td>
<td></td>
</tr>
<tr>
<td>Haematological index (Median, IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-SII</td>
<td>487.73 (303.98-759.55)</td>
<td>660.90 (515.76-927.63)</td>
<td>0.205</td>
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<tr>
<td>Pre-NLR</td>
<td>2.41 (1.76–3.36)</td>
<td>2.98 (2.37–3.74)</td>
<td>0.400</td>
</tr>
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<td>Pre-PLR</td>
<td>144.21 (114.23-194.37)</td>
<td>168.80 (150.62-230.45)</td>
<td>0.910</td>
</tr>
<tr>
<td>Pre-LMR</td>
<td>2.71 (2.00-3.67)</td>
<td>3.61 (2.91–4.90)</td>
<td>0.613</td>
</tr>
<tr>
<td>Post-SII</td>
<td>1260.00 (725.14-2090.67)</td>
<td>290.00 (197.13-1067.06)</td>
<td>0.142</td>
</tr>
<tr>
<td>Post-NLR</td>
<td>7.33 (5.00-12.85)</td>
<td>4.06 (3.21–6.79)</td>
<td>0.157</td>
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<tr>
<td>Post-PLR</td>
<td>366.00 (247.01-541.25)</td>
<td>0.84 (0.57-321.23)</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Definition of abbreviations: LUSC = lung squamous cell carcinoma; LUAD = lung adenocarcinoma; SCLC = small cell lung cancer; SI = smoking index; SII = systemic immune inflammation index; RP = radiation pneumonitis; NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; MLR = monocyte to lymphocyte ratio; CEA = carcinoembryonic antigen; pre- = before radiotherapy; post- = after radiotherapy. *p < 0.05
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<th>Validation Cohort (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-LMR</strong></td>
<td>1.00 (0.67–1.67)</td>
<td>0.74 (0.45–1.16)</td>
<td>0.510</td>
</tr>
<tr>
<td><strong>CEA</strong></td>
<td>2.45 (1.62–3.67)</td>
<td>2.82 (1.87–9.07)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Chemotherapy (n, %)</strong></td>
<td></td>
<td></td>
<td>0.456</td>
</tr>
<tr>
<td>Yes</td>
<td>153 (87.43%)</td>
<td>15 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (12.57%)</td>
<td>9 (37.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Chemotherapy Regimens (n, %)</strong></td>
<td></td>
<td></td>
<td>0.496</td>
</tr>
<tr>
<td>Platinum-based</td>
<td>107 (61.14%)</td>
<td>21 (87.50%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>46 (30.07%)</td>
<td>3 (12.50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Immunotherapy (n, %)</strong></td>
<td></td>
<td></td>
<td>0.969</td>
</tr>
<tr>
<td>Yes</td>
<td>15 (8.57%)</td>
<td>2 (8.33%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>160 (91.43%)</td>
<td>22 (91.67%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total dose (cGy)</strong></td>
<td></td>
<td></td>
<td>0.082</td>
</tr>
<tr>
<td>&lt;=4500</td>
<td>29 (16.57%)</td>
<td>1 (4.17%)</td>
<td></td>
</tr>
<tr>
<td>4500–5500</td>
<td>30 (17.14%)</td>
<td>13 (54.17%)</td>
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<tr>
<td>5500–6500</td>
<td>114 (65.14%)</td>
<td>9 (37.50%)</td>
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</tr>
<tr>
<td>&gt;6500</td>
<td>2 (1.14%)</td>
<td>1 (4.17%)</td>
<td></td>
</tr>
</tbody>
</table>

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### 2. Features extraction and filtration

The main workflow of multi-omics model building was summed in Fig. 1 and Figure S1. A total of 1960 radiomics and 179 dose-related features were extracted from the four ROIs, as described in Table S1. After selection, 8 features were used in radiomics model (Model R), 16 features were used in the dose and clinical model (Model D + C), and 19 features were used in radiomics, dose, and clinical model (Model R + D + C). Furthermore, the best Model R + D + C consisted of 16 radiomics features, 2 dosiomics features (GLRLM_Gray Level Non Uniformity Normalized and GLCM_MCC from PTV), and 1 clinical characteristic (T stage) (Table S1). Simultaneously, we further found that 5 features overlapped in Model R and Model R + D + C, and there were 3 common elements in Model D + C and Model R + D + C (Fig. 3a).
3. Compared the performance of the prediction models

To build the most predictive model, 7 different classifiers were estimated by the confusion matrices (Figure S2-S7, Fig. 4) and ROC curves (Fig. 3c) in a testing set. As summarized in Table 2, the predictive performance of all models was compared based on the accuracy, precision, sensitivity, specificity, and mean AUC, which was sufficient to derive the optimal model and LR became the final choice. The performance of models in the internal testing cohort and external validation cohort are shown in Fig. 3d-e. In the internal testing cohort, the AUC of Model R and Model D + C were 0.83 (95% CI, 0.769–0.854) and 0.73 (95% CI, 0.654–0.758), respectively. After combining radiomics, dose, and clinical features, the AUC of the model (Model R + D + C) was improved to 0.94 (95% CI, 0.939-1.000). In the validation set, 0.92 (95% CI, 0.800-1.000) of the AUC (Model R + D + C) was yielded to evaluate the risk of overfitting. The relatively small difference between the external validation and internal testing sets suggests the models had less risk of overfitting. In confusion matrices of testing set, the accuracy, precision, sensitivity, specificity of LR also shown the same trend and Model R + D + C had higher value (accuracy = 96%, precision = 100%, sensitivity = 90%, specificity = 100%) (Fig. 4). The Pearson correlation between selected features was shown in Supplementary Figure S8.
## Table 2
The classification results of different machine learning models

<table>
<thead>
<tr>
<th>Classifier</th>
<th>Model</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC</td>
<td>Model R</td>
<td>88%</td>
<td>76.9%</td>
<td>100%</td>
<td>80%</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Model D + C</td>
<td>60%</td>
<td>58.3%</td>
<td>58.3%</td>
<td>61.5%</td>
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Definition of abbreviations: Model R = Radiomics model; Model D + C = Dose and Clinical model; Model R + D + C = Radiomics, Dose and Clinical model; SVC = Support Vector Classification; LR = Logistic Regression; GNB = Gaussian Naive Bayes; BNB = Bernoulli Naive Bayes; KNN = K Nearest Neighbor; DT = Decision Tree; RF = Random Forest.

### 4. Feature importance
In Model R + D + C, features normalized importance was evaluated. The bar graphs showed the top 10 features in terms of contribution in Fig. 3b. There were 9 radiomics features from three ROIs (TL-PTV, PTV, and GTV) and 1 dosiomics feature from PTV. Radiomics features extracted from TL-PTV have a large proportion, and Shape Mean Breadth played a vital role (distribution rate = 80%) in Model R + D + C.

5. Survival analysis

The influence of RP on survival outcomes was further investigated in these patients. The median follow-up time was 28 months. At the time of data cutoff, 16 patients were lost to follow-up, and 93 patients (50.8%) had died. All patients (n = 183) were divided into non-RP group (n = 97) and RP group (n = 86). The RP group was further subdivided into a severe-RP group (n = 20) and a mild-RP group (n = 66). As shown in Fig. 5a, the median OS was 49 months for RP group (95% CI, 36-NA), 31 months for non-RP group (95% CI, 28-39), and RP group was significantly higher than non-RP group with regard to OS (HR = 0.53, 95% CI, 0.35-0.80, p = 0.0022). Figure 5b-d shows the survival data of RP subgroups. Compared with mild-RP, severe-RP patients exhibited worse OS in Fig. 5b (57 vs. 25 months, HR, 3.72; 95% CI, 1.35-10.23, p < 0.0001). Although the OS was not significantly different between severe-RP and non-RP patients (25 vs. 31 months, HR, 1.33; 95% CI, 0.67-2.64, p = 0.36, Fig. 5c), the mild-RP group had a longer survival time than non-RP patients in Fig. 5d (57 vs. 31 months, HR, 2.46; 95% CI, 1.59-3.80, p < 0.0001).

Discussion

In this study, a novel RP predicting model was developed and validated using the machine-learning algorithm. This model consisting of radiomics, the dose distribution of ROIs, and clinical signatures provided an individualized prediction of RP in NSCLC patients treated with IMRT. Our results showed that 0.94 of the AUC in Model R + D + C outperformed 0.83 of the AUC in Model R and 0.73 of the AUC in Model D + C. Our research effectively improved the performance of RP model prediction and provided a route toward RP individualized management strategies.

Radiomics can capture hidden information from CT-based features which were hard recognized by the radiologist and oncologist. There were many common risk factors in the occurrence of RP, including interstitial lung disease, COPD, and abnormal pulmonary function, which could be detected by radiomics [24]. In our study, the radiomics features were extracted from 4 ROIs. Previous research has also proved that the radiomics features extracted from the ROI (total lung volumes minus PTV) can achieve better performance [22, 25]. The TL-PTV could determine the occurrence of RP, and this region should be further investigated.

Additionally, radiation dose was another critical factor in predicting RP [26]. Although recent studies focused on the relationship between RP and dosimetric factors, dosimetric factors consist only of discrete data from the DVH curve without spatial information and ignore the 3-dimensional spatial features of radiation dose [27, 28]. Bin Liang et al. have also noted the limitation of dosimetric and utilized dosiomics to predict RP. Nevertheless, the performance of the dosiomics prediction model was
only 0.78 of AUC [29]. Our dose prediction model improves predictive ability in combination with
dosiomics and dosimetric. Clinical characteristics were also included. The T stage was selected as an
essential role in the prediction of RP because tumor size can affect high-dose radiation volume. There
were a few studies indicating tumor size is one of the risk factors for the prediction of RP [26, 30].
Haematological parameters may be another factor for the prediction of RP. Consistent with Lu Wang's
study, our study also collected the results of blood routine tests pre-/post-radiotherapy [31]. Therefore, the
level of systemic inflammation might be one predictor, but the right time point should be further
determined in the future.

So far as we know, few studies have reported the relationship between RP and overall survival. Compared
to non-RP patients, RP patients had a higher OS rate. In our study, we further divided RP patients into
mild-RP and severe-RP patients. The mild-RP patients had a better prognosis. Interestingly, there was a
significant difference in the survival time of the patients with mild-RP and non-RP (p < 0.0001). Although
some researches have been conducted on the survival analysis of mild- and severe-RP, few studies
understand the mechanism of the survival difference between mild-RP and non-RP [7]. The mild-RP might
be a protective factor in lung cancer patients underwent radiotherapy, mainly because (i) Radiation-
induced RP often occurs in the high-dose area. Dose escalation was regarded as substantially increasing
locoregional tumor control [32]. (ii) Radiation can stimulate a local inflammatory response, which may
act as an immunological protective method to awaken the systemic effect [33]. In addition to the direct
injury of cancer cells, radiation can affect the tumor microenvironment (TME) [34]. MHC-I expression on
the surface of the tumor cells and the ability of dendritic cells (DCs) to present antigens can be increased
after radiation. Miaomiao Yang et al. proposed that RP tissue had less naive CD8+ T cells, more effector
T cells, and a more diverse B cell subtype [35]. Based on available evidence, radiation-induced RP can
activate the immune response to some extent, which could be beneficial for the survival of lung cancer
patients.

This study suffers from several limitations. (i) The pulmonary functional (PF) metrics, including an
exhaled fraction of nitric oxide (FeNO) and lung diffusion capacity for the carbon monoxide (DLCO),
enabled to prediction of the risk of RP [6, 36]. More serum markers should be included in the prediction
model in the future, such as interleukin-6 (IL-6), C-reaction protein (CRP), and procalcitonin (PCT) [37]. (ii)
This model included a slightly larger number of features, which could cause overfitting. (iii) This study
was retrospective research. The prospective clinical trial could be conducted in the future to distinguish
non-RP and RP patients. (iv) Genetic sequencing was not integrated into the prediction model. The effect
of microRNAs (miRNAs) and some cytokines on the improved prediction of RP have been documented
[38].

Our study aims to develop a prediction model to aid oncologists in identifying patients at high risk of
developing RP and designing optimal treatment plans. Although severe-RP is an independent prognostic
risk factor for survival, mild-RP can prolong the patients’ OS. Therefore, mild RP is acceptable.

Conclusion
In the present study, our results establish and validate an RP prediction model using radiomics, dosimetric, dosiomics, and clinical features based on planning CT. The survival outcome of RP patients was also discussed, and mild-RP patients displayed the most prolonged OS rate.

**Abbreviations**

RP: Radiation pneumonitis

DL: Deep learning

CT: Computed tomography

ROC: Receiver operating characteristic curve

AUC: Area under the curve

OS: Overall survival

CI: Confidence interval

RT: Radiation therapy

NSCLC: Non-small cell lung cancer

RILI: Radiation-induced lung injury

RTOG: Radiation Therapy Oncology Group

3D-CRT: Three-dimensional conformal radiation therapy

IMRT: Intensity-modulated radiation therapy

VMAT: Volumetric arc radiotherapy

SBRT: Stereotactic body radiation therapy

SRS: Stereotactic radiosurgery

SII: Systemic immune inflammation index

NLR: Neutrophil to lymphocyte ratio

PLR: Platelet to lymphocyte ratio

MLR: Monocyte to lymphocyte ratio

SI: Smoking index
BMI: Body mass index
ROI: Region of interest
GTV: Gross tumor volume
PTV: Planning target volume
TL: Total lung
TL-GTV: Volume minus gross tumor volume
TL-PTV: Total lung volume minus planning target volume
TNM: Tumor-node-metastasis
COPD: Chronic obstructive pulmonary disease
CEA: carcinoembryonic antigen
CTCAE: Criteria for Adverse Events
GLCM: Gray Level Co-occurrence Matrix
GLRLM: Gray Level Run Length Matrix
DVH: Dose-volume histogram
LASSO: Least absolute shrinkage and selector operation
SVC: Support Vector Classification
LR: Logistic Regression
GNB: Gaussian Naive Bayes
BNB: Bernoulli Naive Bayes
KNN: K Nearest Neighbor
DT: Decision Tree
RF: Random Forest
TME: Tumor microenvironment
DC: dendritic cell
PF: Pulmonary functional

FeNO: Exhaled fraction of nitric oxide

DLCO: Lung diffusion capacity for the carbon monoxide

DLCO: Interleukin-6

CRP: C-reaction protein

PCT: procalcitonin

MiRNAs: MicroRNAs

**Declarations**

**Acknowledgements**

Not applicable.

**Funding**

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**Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The research followed the principles of the Helsinki Declaration. Informed consent was exempted because of the retrospective nature of the study and minimal risk of harm to the study subjects. Ethics approval and consent was obtained from the Xiangya Hospital ethics committee (202208192).

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Not applicable.

**Authors’ contributions**
LN and XC collected the clinical and radiotherapy planning dataset and had contributed equally to the manuscript. HZ analyzed the data and built the deep learning model. LN wrote the article. LC, XY, FD and ZL revised and polished the article. DJ and RZ conceived the project and edited the article. All authors reviewed and approved the final manuscript.

**Corresponding authors**

Correspondence to Di Jing and Rongrong Zhou.

**References**


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Figures
Figure 1

**Workflow and illustration of multi-omics.** Standardized pre-IMRT CT images, radiation treatment planing, and clinical information from RP and non-RP patients were input. Then optimal features were selected via Spearman's correlation analysis, variance analysis and LASSO cox regression, and used to construct three models (Model R = Radiomics model; Model D+C = Dose and Clinical model; Model R+D+C = Radiomics, Dose and Clinical model). The performance of the three models were all validated by ROC curves. The survival rate of lung cancer patients were further analyzed.
**Clinical characteristics and the classification of lung patients.** (a) Lung cancer patients in the external validation and internal training/testing cohorts (LUSC: lung squamous cell carcinoma, LUAD: lung adenocarcinoma, SCLC: small cell lung cancer, SI: smoking index, SII: systemic immune inflammation index, RP: radiation pneumonitis, ICI: immune checkpoint inhibitor, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, CEA: carcinoembryonic antigen, pre-: before radiotherapy, post-: after radiotherapy). (b) Patients were divided into non-RP group, mild-RP group, and severe-RP group according to the clinical symptoms and CT images. An representative CT images were collected from pre-IMRT and post-IMRT in lung cancer patients.
Figure 3

The features and performance of multi-omics models. (a) The overlapping features were selected from the models. (b) Univariate importance of features in models (top 10). The different colors represented the features from various structures. (c) The values of area under the curve (AUC) in different machine learning algorithms. (d-e) Receiver operating characteristic (ROC) curves on testing set and external validation set (Black, blue and red lines represent ROC of Model R, Model D+C and Model R+D+C, separately. Model R: radiomics model, Model D+C: dose and clinical model, Model R+D+C: radiomics, dose and clinical model, SVC: Support Vector Classification, LR: Logistic Regression, GNB: Gaussian Naive Bayes, BNB: Bernoulli Naive Bayes, KNN: K Nearest Neighbor, DT: Decision Tree, RF: Random Forest).
Figure 4

Confusion matrices of Logistic Regression to predict the risk of RP. LR confusion matrices for radiomics model (a), dose and clinical model (b), and radiomics, dose and clinical model (c). Confusion matrix represents the performance of classifier. Each row in the confusion matrix is predicted number and percentages of sample, while each column is actual class and their percentages. The last columns and rows represent the recall and precision for per class, respectively. Every classifiers’ accuracy and loss is shown in the bottom-right cell.

Figure 5
Overall survival (OS) of the patients stratified via the non-RP patients and the classification of RP. Kaplan-Meier analysis of OS in the (a) RP vs. non-RP patients, (b) severe-RP vs. mild-RP patients, (c) severe-RP vs. non-RP patients, and (d) mild-RP patients and non-RP patients (HR: hazard ratio, NA: not available).

Supplementary Files

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- supplement.docx