Original Article

The CT appearance pattern of radiation-induced lung injury and tumor recurrence after stereotactic body radiation therapy in early stage non-small cell lung cancer

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Background: Radiographic changes after stereotactic body radiation therapy (SBRT) have not been well studied. The purpose of this study was to investigate the computed tomography (CT) appearance pattern of radiation-induced lung injury (RILI) and recurrence after SBRT in patients with early stage non-small cell lung cancer (NSCLC).

Methods: We retrospectively analyzed clinical data of inoperable early stage NSCLC patients undergoing SBRT treatment from February 2012 to June 2018. All patients had undergone serial CT scanning before SBRT and after completion of SBRT. An experienced radiation oncologist and radiologist reviewed all CT images, and identified the RILI and CT high-risk features (HRFs).

Results: A total of 60 patients were enrolled in this study; 55 patients had RILI (91.67%) and 7 patients had local failure. In the early CT findings of observers 1 and 2, there were diffuse ground glass opacities (GGOs) in 3 and 4 patients, diffuse consolidation in 10 and 12 patients, patchy consolidation in 22 and 15 patients, patchy GGOs in 19 and 24 patients, and no changes in 5 and 4 patients, respectively (kappa =0.706). In the late CT findings of observer 1 and 2, there were modified conventional patterns in 37 and 37 patients, mass-like patterns in 10 and 9 patients, scar-like patterns in 7 and 8 patients, and no changes in 5 and 5 patients, respectively (kappa =0.726). In the results of the CT-based HRFs of disease local failure, there were ≥1 HRFs in 7 patients, ≥2 HRFs in 7 patients, ≥3 HRFs in 6 patients, ≥4 HRFs in 5 patients, and ≥5 HRFs in 3 patients, respectively. Patients with only 1 HRF showed high sensitivity (100%) and low specificity (52.80%), with the specificity increasing and the sensitivity decreasing as the number of HRFs increased.

Conclusions: The agreement of the CT appearance on RILI between 2 observers was good. Regular follow-up and attention to HRFs are vital for better identifying RILI and local disease failure.

Keywords: Radiation-induced lung injury (RILI); tumor recurrence; stereotactic body radiation therapy (SBRT); early stage non-small cell lung cancer

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Introduction

In 2018, there were approximately 4.3 million new cancer cases and 2.9 million cancer deaths in China according to cancer statistics, and the total number of cancer cases is expected to reach around 4.51 million with 3.04 million cancer deaths by 2020 (1). Lung cancer is the most commonly diagnosed cancers (21.9% of total cases) and also causes the most cancer-related deaths (26.4% of total cases) in Chinese males. For Chinese females, lung cancer has the second highest incidence (13.3% of total cases) and the highest mortality (20.3% of total cases) (1).

Surgery and stereotactic body radiation therapy (SBRT) are considered as the main treatment options for non-small cell lung cancer (NSCLC), and SBRT in stage I NSCLC has been reported to have a 3-year local control of 92% to 98%, and a 3-year overall survival of 90% (2-4). SBRT has higher biologically effective doses (BED) irradiated during a short period, realizing the higher radiative dose of the tumor, meanwhile minimizing the exposure of the organ at risk, and achieve successful local control of lung cancer. Thus, SBRT is thought to be an optimal treatment modality for patients who have inoperable disease or who refuse operation by virtue of its good local control and low incidence of severe toxicities, with several studies finding SBRT to be an equivalent treatment option for early-stage NSCLC (2,3). This approach can also reduce overall treatment time from several weeks of conventional radiotherapy to a few days, which offering a convenience to the patients. Radiation-induced lung injury (RILI) include radiation-induced pneumonitis and lung fibrosis, and radiation pneumonitis is a predominant complication after radiotherapy while the incidence of severe radiation pneumonitis after SBRT is low (0–29%); however, more than half of patients who are treated with SBRT develop radiographic patterns of RILI (5,6). It is widely known that the CT pattern of early and late benign fibrosis is commonly observed after SBRT for lung cancer, and response evaluation criteria in solid tumor (RECIST)-defined tumor recurrence depends on the variation of lesions size. However, as some radiation-induced modifications arise from inflammation and fibrosis, it usually takes a period of time to evaluate treatment response, which limits the application of RECIST (7,8). Some changes on CT imaging can be associated with a higher risk for tumor recurrence, and these are known as high-risk features (HRFs). Huang *et al.* summarized the CT radiographic changes on acute and late lung injury after SBRT and the HRF of local recurrences, found the following characteristic patterns: an enlarging opacity of preliminary focus, a bulging margin of opacity, disappearance (including partial disappearance) of the linear edge and air bronchograms, and opacity enlarging in a craniocaudal direction and they noted that the sensitivity and specificity of identification on tumor recurrence reached up to 90% with the simultaneous presence of 2 or more HRFs (9-11).

Herein, we discuss our investigation of the CT appearance pattern of RILI and recurrence after SBRT in patients with early stage NSCLC in order to better identify RILI and local disease failure.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-609).

Methods

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained at institutional review board of Shanghai Pulmonary Hospital for this retrospective study (approval ID: K20-174Y). Informed consent was waived.

Patients and radiotherapy

We selected 60 patients with early stage NSCLC who received SBRT treatment in Shanghai Pulmonary Hospital and Cancer Hospital affiliated to the University of the Chinese Academy of sciences from February 2012 to June 2018, and retrospectively analyzed their clinical data. The study cohort comprised 44 males and 16 females, and the median age was 76 (range, 52–88) years. The specific information of enrolled patients is shown in *Table 1*. The median prescription dose was 50 Gy/5 fraction (range, 40–70 Gy/4–10 fraction). All patients had a biologically effective dose (BED_{10}) of ≥100 Gy, and the total dose covered 95% of the planning target volume (PTV).

Follow-up

All patients had undergone serial CT scanning before SBRT and every 3 months for the first half year, every 6 months for the next half year (at 3, 6, 12, 18, and 24 months post-treatment), and then annually after completion of SBRT. The frequency of CT scan increased when relapse was highly suspected, and the relapse was verified with ^{18}F-FDG (positron emission tomography) PET/CT or biopsy. In the

Table 1 The specific information of enrolled patients

Characteristics	Number (%)
Patients	60
Age	
Median [range]	76 [52–88]
<65	50 (83.33)
≥65	10 (16.67)
Sex	
Male	44 (73.33)
Female	16 (26.67)
Pack-years smoked	
Pack-years ≤30	29 (48.33)
Pack-years >30	31 (51.67)
ECOG PS	
PS 0	12 (20.00)
PS 1	45 (75.00)
PS 2	3 (5.00)
Chronic pulmonary disease	15 (25.00)
Tumor type	
Central	3 (5.00)
Non-central	57 (95.00)
Pathological type	
Adenocarcinoma	19 (31.67)
Squamous carcinoma	13 (21.67)
NSCLC	8 (13.33)
No pathology	20 (33.33)
Disease stage	
Ia	53 (88.33)
Ib	7 (11.67)

NSCLC, non-small cell lung cancer.

present study, all the enrolled patients underwent ^{18}F-FDG PET/CT scanning. A standard uptake value (SUV) greater than 5 or an initial value (as measure by initial 18F-FDG PET/CT scanning) was diagnosed as tumor relapse according to the literature (10,12). In the present study, 7 patients were diagnosed with relapse, and of these patients, 1 patient had the relapse verified by pulmonary fine needle puncture pathology, while 6 patients failed biopsy because of cardiopulmonary dysfunction or old age. In this instance, the diagnostic criteria of relapse were opacity increase on CT scanning after SBRT, SUV measurements by ^{18}F-FDG PET/CT revealed as positive and higher than those before treatment. An experienced radiation oncologist and radiologist who were blinded reviewed all CT images and identified acute or late RILI and HRF.

Statistical analysis

Statistical analysis was conducted using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). The chi-squared was used to assess the consistency between the two observers and to compare radiographic changes between the recurrence and non-recurrence groups. P value <0.05 was considered statistically significant.

Results

Patients data

The median follow-up was 36.7 months (3–70 months). There were 7 patients with recurrence after treatment in 60 patients, and 1 patient with RECIST-indicated progressive disease. 1- and 3-year overall survival were 95.2%, 86.3%, and 1- and 3-year progression-free survival were 85.9%, 69.4%. There were 55 patients with radiation injury, and the incidence of RILI was 91.67%. The median time for the occurrence of RILI was 4 months (1–12 months), and the median time for the endpoint of the RILI progression was 12 months (4–34 months).

The acute and late RILI

In the follow-up of 7 patients with recurrence, 1 case had no RILI, 2 cases had diffuse consolidation, 4 cases had patchy consolidation and GGO, 3 cases had mass-like pattern, and 3 cases had modified conventional pattern. The characteristics CT changes of patients with recurrence are shown in *Table 2*. The CT features of acute and late RILI are shown in *Figure 1*.

There were differences between the 2 observers in judging the grade of RILI, as shown in *Table 3*. The Chi-squared test was used to analyze the consistency between the 2 observers on the grade of RILI, and the Kappa coefficient was 0.89, indicating that the judgment of RILI grade by the 2 observers had good consistency. The grade 1 and grade 2 RILI were considered the primary event.

Table 2 CT features and follow-up results of 7 patients with recurrence

Characteristics	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7
Bulging margin of opacity	+	+	+	+	+	+	+
Opacity enlarged in craniocaudal direction	+	–	+	+	+	+	–
Opacity expanded after 12 months	+	+	+	+	+	+	+
Disappearance of air bronchograms	–	+	+	–	+	–	–
Disappearance of linear edge	–	+	–	–	–	–	–
Enlarging opacity of preliminary focus	+	+	+	+	+	–	–
The period of time for RILI appearance	5 months	3 months	2 months	No injury	2 months	2 months	3 months
The period of time for cease of RILI progress	7 months	9 months	10 months	No injury	9 months	12 months	12 months
CT features of acute RILI	Diffuse consolidation	Diffuse consolidation	Patchy consolidation and GGO	No injury	Patchy consolidation and GGO	Patchy consolidation and GGO	Patchy consolidation and GGO
CT features of late RILI	Mass-like pattern	Modified conventional pattern	Modified conventional pattern	No injury	Modified conventional pattern	Mass-like pattern	Mass-like pattern

GGO, ground glass opacity; RILI, radiation-induced lung injury. +, appearance of the HRF; –, no appearance of the HRF.

The CT characteristics of acute and late RILI are shown in *Tables 4* and *5*. The Chi-squared test was used to analyze the consistency between the 2 observers on CT characteristics of acute and late RILI, and the Kappa coefficients were 0.706 and 0.72. These showed that the judgement of 2 observers on CT characteristics of acute and late RILI had good consistency. Observer 1 found the patchy consolidation and GGO to be the main CT feature on acute RILI, while observer 2 found patchy GGO to be the main feature. The modified conventional pattern was the main CT feature on late RILI.

High-risk features

The enlarging opacity of preliminary focus (29, 48.33%) and bulging margin of opacity (19, 31.67%) were the primary HRFs among the CT images of 60 patients. The bulging margin of opacity and the opacity expanding after 12 months had the highest sensitivity (both of 100%), while disappearance of air bronchograms had the highest specificity (100%). There was no statistically significant difference between the disappearance of linear edge and the enlarging opacity of preliminary focus. The odds ratio (OR) value of the disappearance of linear edge was less than 1, and the OR value of the opacity expanding after 12 months reached up to 216.4. The incidence of high-risk features was detailed in *Table 6*.

The accumulated sensitivity and specificity of HRFs are shown in *Table 7*. Patients with only 1 HRF showed high sensitivity (100%) and low specificity (52.80%), and the specificity increased with the number of HRFS while the sensitivity decreased. The CT images with diagnosis, follow-up, and relapse of 1 patient are shown in *Figure 2*. The tumor relapse was confirmed by PET/CT on the 53rd month, and we found 2 HRFs on follow-up CT image, including the opacity expanding after 12 months and the bulging margin of opacity.

Discussion

We found 1- and 3-year overall survival in the 60 patients were 95.2% and 86.3%. The therapeutic effectiveness

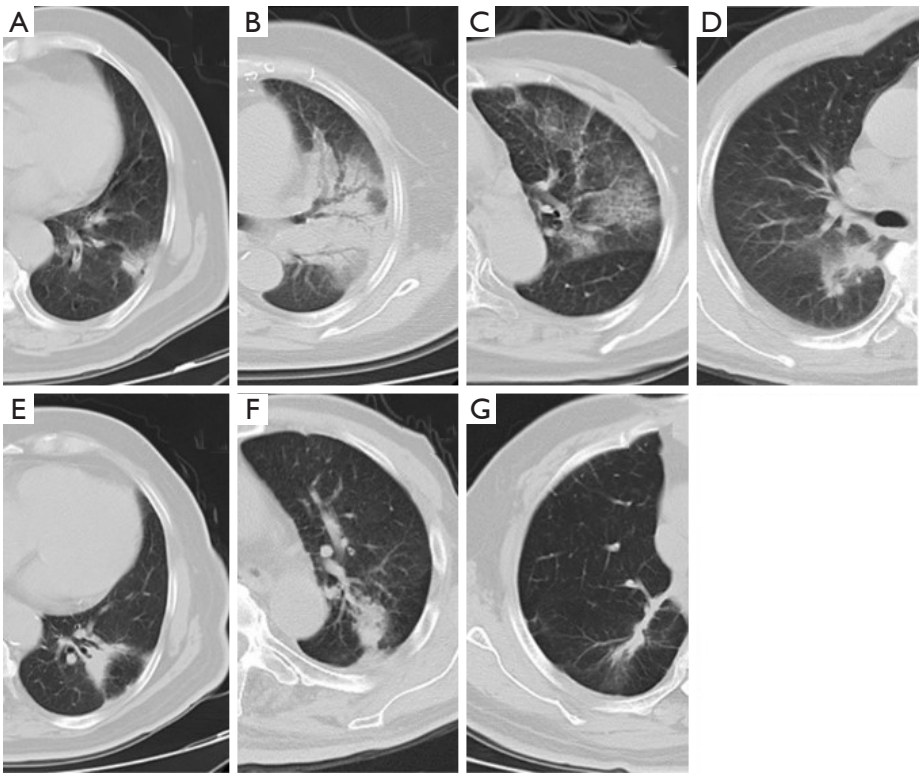

Figure 1 CT features of acute and late RILI. (A) Patchy GGO; (B) diffuse consolidation; (C) diffuse ground glass opacity; (D) patchy consolidation and GGO; (E) modified conventional pattern; (F) mass like pattern; (G) scar-like pattern. RILI, radiation-induced lung injury; GGO, ground glass opacity.

Table 3 The judgement between two observers on the grade of RILI

Observer 2	Observer 1				
	Grade 0	Grade 1	Grade 2	Grade 3	Total
Grade 0	5	1	0	0	6
Grade 1	0	23	2	0	25
Grade 2	0	1	26	0	27
Grade 3	0	0	0	2	2
Total	5	25	28	2	60

RILI, radiation-induced lung injury.

SBRT was desirable and the incidence of RILI was 91.67%. The 2 observers had a good agreement on the grade of RILI, and the CT pattern of acute and late RILI. We found that the incidence of severe RILI after SBRT was extremely low, and grade 1 and grade 2 RILI were the primary pulmonary toxicities. Patchy consolidation and GGO was the most common CT pattern on acute RILI, and the modified conventional pattern was mainly found with late RILI. The specificity of relapse tumor increased with the number of HRFS while the sensitivity decreased, which was important for the diagnosis of tumor recurrence.

One retrospectively study analyzed the SBRT outcomes of 88 operable patients with early-stage NSCLC. For toxicities, grades 0, 1, 2 and 3 radiation pneumonitis occurred in 37.5%, 47.7%, 13.6%, and 1.1% of patients, respectively, and no grade 4 or 5 radiation pneumonitis occurred (2). In the present study, observer 1 found that grades 0, 1, 2, and 3 RILI were 10%, 41.7%, 45%, and 3.3%, respectively, while observer 2 found that grades 0, 1, 2, and 3 RILI were 8.3%, 41.7%, 46.7%, and 3.3%, respectively. Thus, the incidence rate of severe RILI after SBRT is low, and mild RILI after SBRT warrants greater attention.

Trovo *et al.* (13) enrolled 68 patients who accepted SBRT and found some patients had acute RILI at 6 weeks after SBRT, most patients had no findings (37, 54.4%), and 11 patients had patchy GGO. In their follow-up,

Table 4 The judgement between two observers on CT characteristics of acute RILI

Observer 2	Observer 1					
	Diffuse GGO	Diffuse consolidation	Patchy consolidation and GGO	Patchy GGO	No changes	Total
Diffuse GGO	3	0	0	1	0	4
Diffuse consolidation	0	9	3	0	0	12
Patchy consolidation and GGO	0	1	13	1	0	15
Patchy GGO	0	0	6	17	1	24
No changes	0	0	0	0	4	4
Total	3	10	22	19	5	59

GGO, ground glass opacity; RILI, radiation-induced lung injury.

Table 5 The judgement between two observers on CT characteristics of late RILI

Observer 2	Observer 1				
	Modified conventional pattern	Mass-like pattern	Scar-like pattern	No changes	Total
Modified conventional pattern	33	2	2	0	37
Mass-like pattern	2	7	0	0	9
Scar-like pattern	2	1	5	0	8
No changes	0	0	0	5	5
Total	37	10	7	5	59

RILI, radiation-induced lung injury.

Table 6 The incidence of high-risk features

High-risk feature	Case (%)	Relapse (%)	Non-relapse (%)	P	Sensitivity (%)	Specificity (%)	OR
Bulging margin of opacity	19 (31.67)	7 (36.84)	12 (63.16)	<0.01	100	77.40	49.8
Opacity enlarged in craniocaudal direction	9 (15.0)	5 (55.56)	4 (44.44)	<0.01	71.40	92.50	30.6
Opacity expanding after 12 months	10 (16.67)	7 (70.00)	3 (30.00)	<0.01	100	94.30	216.4
Disappearance of air bronchograms	3 (5.00)	3 (100.00)	0 (0.00)	<0.01	42.90	100	83.2
Disappearance of linear edge	10 (16.67)	1 (10.0)	9 (90.0)	1.000	14.30	83.00	0.81
Enlarging opacity of preliminary focus	29 (48.33)	5 (17.24)	24 (82.76)	0.369	71.40	54.70	3

patchy consolidation and GGO was the primary pattern 2–6 months after SBRT, and the modified conventional pattern was the main pattern in late RILI 7–18 months after treatment. The findings are consistent with those of the present study. Hayashi *et al.* (8) investigated 81 NSCLC patients after SBRT, and 6 patients had tumor relapse, including 5 case of mass-like opacity pattern and 1 case of modified conventional pattern. The present study had 3 cases of mass-like pattern, 3 cases of modified conventional pattern, and 1 case of no injury. That is to say, the mass-

Table 7 The accumulated sensitivity and specificity of HRFs

Number of HRFs	Cases (%)	Relapse (%)	Non-relapse (%)	P	Sensitivity (%)	Specificity (%)
≥1	32 (53.33)	7 (21.88)	25 (78.13)	0.026	100	52.80
≥2	22 (36.67)	7 (31.82)	15 (68.18)	0.01	100	71.70
≥3	13 (21.67)	6 (46.15)	7 (53.85)	<0.01	85.70	86.80
≥4	8 (13.33)	5 (62.50)	3 (37.50)	0.01	71.40	94.30
≥5	5 (8.33)	3 (60.00)	2 (40.00)	0.005	42.90	96.20

HRFs, high-risk features.

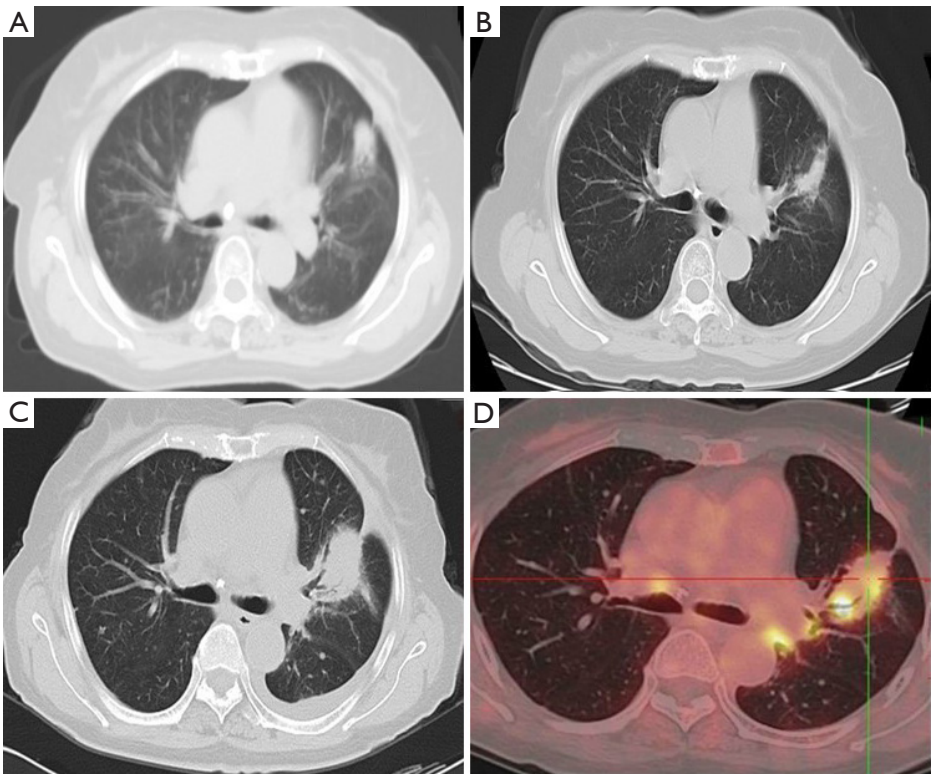

Figure 2 The radiological images of one patient with local recurrence after SBRT. (A) The CT image with tumor diagnosis of a female patient (68 years old) with NSCLC stage IB; (B) a mass-like fibrosis was found on follow-up CT image on the 18th month after SBRT; (C) there were 2 HFRs including the opacity expanding after 12 months and bulging margin of opacity on the 53rd month after SBRT; (D) the PET/CT on the 53rd month after SBRT indicated tumor relapse, with an SUV_{max} of 13.3. SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; HFRs, high-risk features.

like and modified conventional pattern were the main CT patterns of late RILI. We also found that among the 7 patients with relapse of acute RILI, there were 2 cases of diffuse consolidation, 4 cases of patchy consolidation and GGO, and 1 case of no injury. The radiological changes developed in most patients after SBRT, but several researchers have reported slightly different results concerning the main CT pattern. These differences may depend on which delivery technique was chosen, as the frequency and timing of the radiological changes can vary according to the delivery technique (14). Ronden *et al.* (11) described the typical radiological changes in patients who had undergone SBRT with an older fixed-beam delivery approach, and the most frequent acute radiological changes

were diffuse consolidation and patchy consolidation. However, many institutions currently use a modern delivery technique, for which late radiological changes are more common, with the main CT pattern being a modified conventional pattern (62%) that is difficult to distinguish from local recurrence (11,14).

Huang *et al.* retrospectively analyzed a total of 88 patients who were treated with SBRT using volumetric-modulated arc therapy, and they found that the most frequently observed HRFs in non-recurrence patients were enlarging opacity (64.8%) and enlarging opacity after 12 months (50.0%) (9). The present study indicated that the enlarging opacity of preliminary focus (48.33%) also had the highest incidence, while there were 7 patients who were diagnosed with tumor recurrence. We also found that opacity expanding after 12 months had the highest OR (216.4) which was the important indicator for recurrence diagnosis. We can thus definitively conclude that enlarging opacity or opacity expanding after 12 months alone cannot be depended on to determine tumor recurrence. In our study, we also found that the specificity increased while the sensitivity decreased as the number of HRFs increased. Therefore, regular follow-up and attention to high-risk HRFs are crucial.

The radiomics approach may detect early changes associated with local recurrence by extracting quantitative features, and these features are not typically considered by physicians (9). Moran *et al.* (6) found radiomics features significantly correlated with radiation oncologist-scored post-SBRT lung injury and showed a significant dose-response relationship. Thus, radiomics may help us have a better understanding of pulmonary toxicity and tumor relapse and may facilitate the earlier intervention of local recurrences after SABR (6,9). In the future, our group will also use the radiomics method to investigate pulmonary toxicity after SBRT.

In summary, regular follow-up and attention to high-risk HRFs are vital in better identifying RILI and local disease failure.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained at institutional review board of Shanghai Pulmonary Hospital for this retrospective study (approval ID: K20-174Y). Informed consent was waived.

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