



Stereotactic body radiotherapy for lung cancer in patients with interstitial lung disease

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Abstract: Stereotactic body radiotherapy (SBRT) is a highly dose-concentrated radiotherapy that can spare damage to normal organs much more than conventional radiotherapy. Severe radiation pneumonitis (RP) after stereotactic SBRT for thoracic lesions is rare but sometimes gets severe. In this review, we presented the reported frequency of severe RP after SBRT for stage I NSCLC, its risk factors, and the attempts at clarifying individual predictive risk factors. The ratio of fatal RP after SBRT for lung tumor in patients with accompanying pulmonary interstitial changes is more than 5%, and overall survival is poor. The dose to the normal lung and interstitial changes in the background lung are important predictive factors of severe RP, with idiopathic pulmonary fibrosis (IPF) being the biggest risk factor for severe RP, but these interstitial lung diseases (ILDs) are not always a contraindication for thoracic SBRT. Based on the high fatality rate, it would be reasonable to avoid prompt SBRT by watchful waiting in cases of indolent or non-aggressive tumors, such as ground-glass tumors. It would be better to use or recommend more highly precise irradiation systems or particle therapy (PT) that can reduce radiation doses to the normal lung more, in particular for the cases with IPF. Identification of biomarkers indicating an individual's risk level for severe RP, such as single nucleotide polymorphisms (SNPs), would be important in treatment decisions, but it needs further research. Though there are no reliable drugs for treating severe RP, anti-fibrotic agents, such as pirfenidone, might be effective in its prevention or alleviation.

Keywords: Stereotactic body radiotherapy (SBRT); lung cancer; radiation pneumonitis (RP); interstitial lung disease (ILD); single nucleotide polymorphisms (SNPs)

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Introduction

Stereotactic body radiotherapy (SBRT) can concentrate a high-dose to the tumor while avoiding toxicity to healthy regions, therefore SBRT is widely performed in patients with small-sized primary or oligometastatic lung tumors as a radical but minimally invasive treatment. SBRT is generally utilized in medically inoperable patients due to poor pulmonary function with chronic lung disease. Outcomes comparable to surgery were recently reported for SBRT even for medically operable patients with stage I non-small cell lung cancer (NSCLC) (1,2). However, although SBRT

is generally safe, and has no severe adverse effects in most patients, severe radiation pneumonitis (RP) can occasionally occur and cause death. Identification of the true frequency and risk factors of severe RP after SBRT is important for the evaluation of an indication of SBRT toxicity and for acquiring informed consent from the patient. The radiation dose to the normal lung and interstitial changes in the background lung are the most prevalent and significant risk factors of RP (3-8), but severe RP can occur in the absence of these risk factors as well. Further, we have experienced many cases where severe RP was not observed after SBRT for lung lesions despite severe pulmonary interstitial

Table 1 Frequency of radiation pneumonitis post stereotactic body radiotherapy for lung cancer according to the presence of pulmonary interstitial changes

Pulmonary interstitial change	First author (ref)	Study design	Patient number	Dose/fraction	Grade of radiation pneumonitis	Frequency (%)	Risk factor
No pulmonary interstitial change	Yamaguchi (3)	Retrospective	86	48 Gy/4 fr	4, 5	0.0	V25
	Ueki (4)	Retrospective	137	48–60 Gy/4–8 fr	3–5	1.4	
	Yoshitake (5)	Retrospective	242	48 Gy/4 fr	3	1.2	
					4, 5	0.0	
	Matsuo (9)	Retrospective	74	48 Gy/4 fr	3	10.6	
					4	1.9	
	Nagata (10)	Prospective	104 (inoperable)	48 Gy/4 fr	3	6.2	
			65 (operable)	48 Gy/4 fr	3	3.6	
	Glick (8)	Retrospective	498	48–60 Gy/3–8 fr	3, 4	1.0	
With pulmonary interstitial change	Yamaguchi (3)	Retrospective	16	48 Gy/4 fr	3	6.3	V5–25, MLD
					4	6.3	
					5	6.3	
	Ueki (4)	Retrospective	20	40–60 Gy/4–8 fr	3–5	10.0	
	Yoshitake (5)	Retrospective	18	48 Gy/4 fr	3	16.7	KL-6, V5, V10, MLD
					4, 5	22.3	
	Onishi (6)	Retrospective	242	Various (mainly 48 Gy/4 fr)	3–5	12.4	%VC, FEV1.0(%), V20, PS, T stage, SqCC, steroid before SBRT
					5	6.9	
	Glick (8)	Retrospective	39	48–60 Gy/3–8 fr	3–5	10.3	MLD

Vx, ratio of the lung volume irradiated with x Gy or more to the total normal lung volume. MLD, mean dose to the normal lung; SqCC, squamous cell carcinoma; PS, performance status; %VC, percent vital capacity; FEV1.0(%), percent forced expiratory volume in 1 s.

changes. Therefore, it is important to identify individual risk factors, including biomarkers such as single nucleotide polymorphisms (SNPs), in the development of severe RP after SBRT. In this review, we present the reported frequency of severe RP after SBRT for stage I NSCLC, its risk factors, and the attempts at clarifying individual predictive risk factors. Consequently, the ideal way of acquiring informed consent for SBRT in patients with stage I NSCLC and interstitial lung disease (ILD) is discussed.

Frequency of severe RP after SBRT

As per previous reports, incidence rates of severe RP in

the cases with and without pulmonary interstitial change after SBRT for lung cancer, are shown in *Table 1* (3–6,8–10). Severe (grade 3 or more) RP were observed in 10–40% of patients who had pulmonary interstitial change and grade 5 was observed in more than 5% of these patients in mostly retrospective studies, and the true rates would be higher in a prospective setting. The reason of the widely ranged incidences in these reports might be caused by differences of the study design (prospective or retrospective) and the definition of “interstitial lung change” among them. Interstitial lung change was judged with only an abnormal interstitial lung shadow in one report (6), but was diagnosed as a disease according to the classification according

to American Thoracic Society/European Respiratory Society guidelines (11) in another report (8). The true and reproducible incidence rate should be examined by a prospective setting using a common standard definition.

In regards to the relationship between severe RP and radiotherapy planning, Timmerman *et al.* (12) reported a higher incidence of fatal RP after SBRT in the cases of which tumors located more centrally than peripherally. Yamashita *et al.* (13) reported a high incidence of fatal RP (3 of 25 patients) after SBRT. In that study, the three fatal cases had poor respiratory function, ILD, and recurrence after surgery, respectively, and fatal RP related to a large volume of high dose area in their lung parenchyma. Hope *et al.* (14) and Matsuo *et al.* (9) also found that fatal RP occurrence correlated with the higher dose volume; however, Takeda *et al.* (15) insisted that severe RP was associated to a shorter (less than 3 months) latency period for RP symptom development and not related to lung dose. Nagata *et al.* (16) reported 11 (0.5%) cases with fatal RP in 2,004 patients treated by SBRT on lung lesions in a survey of SBRT in Japan. Onishi *et al.* (17) reported a case series of 23 fatal RP cases after SBRT in 1,789 patients with stage I NSCLC or lung metastases. They showed that the median time duration to respiratory symptom appearance after SBRT was 75 days (ranged widely, 14–204) and the median survival time after onset of the symptoms was 53 days (ranged widely, 4–802). More than half of the 23 patients had interstitial lung shadow before SBRT and idiopathic pulmonary fibrosis (IPF) was the most frequent type. However, immediately progressive fatal RP was also observed in patients without pulmonary interstitial change. Three of the four patients who died within three months after SBRT had no pulmonary fibrosis before SBRT but did experience chronic heart failure. Onishi *et al.* (6) also reviewed only cases of SBRT for patients with stage I NSCLC accompanying pulmonary interstitial change. They showed that one and two-year overall survival rates were 82.1% and 57.1%, respectively and fatal RP was produced in 6.9% of all patients. In the report, the worse overall survival rate was associated with percent vital capacity <70%, mean percentage normal lung volume receiving more than 20 Gy (V20) >10%, performance status of 2–4, presence of squamous cell carcinoma, clinical T2 stage, regular use of steroid before SBRT, and percentage predicted forced expiratory volume in one second <70%. Kong *et al.* (7) thoroughly reviewed risk factors of radiation-induced lung toxicity (RILT), including RP and pulmonary fibrosis after thoracic SBRT, and demonstrated that patients

with ILD appear to be especially susceptible to severe RILT, and safe treatment with a rate of symptomatic RILT <10–15% can be acquired with a mean lung dose <8 Gy in 3–5 fractions and V20 <10–15%. Pre- and post-SBRT monitoring of KL-6 is one of the biomarkers popularly used for prediction of severe RP after SBRT, and Iwata *et al.* (18) reported a correlation between the serum sialylated carbohydrate antigen KL-6 level and the grade of RP after SBRT for stage I lung cancer or small lung metastasis.

Mechanism and efforts for clarifying individual risk factors of severe RP

The mechanism of RP induction and lung fibrosis is considered as follows (19,20). According to the radiation, alveolar epithelial and vascular endothelial cells are damaged at first, and accordingly M2 macrophages are activated releasing inflammatory mediators such as Th2-derived cytokines, mainly IL-4 and IL-13. They drive the conversion of the immune response into an abnormal wound healing response that promote fibrosis through the production of TGF-beta and leads to substantial lung tissue damage. In relation to this mechanism, some biomarkers that predict high grade RP and its prognosis after thoracic radiation therapy have been found. Some cytokine levels (21,22) and genetic variants of inflammation-related genes such as SNPs in microRNA-related genes, vascular endothelial growth factor, and TGF-beta 1, have also been found to be predictors of RP (23–27). In the summarized overview of the frequency of RP post SBRT for small sized lung cancer according to the presence of pulmonary interstitial change shown in *Table 1*, though most of the reports were from Japan (3–6,9,10), the frequency of severe RP if them was almost higher than that from Canada (8). It might be due to the ethnic or genetic difference between Japan and Canada.

Cases with reasonable watchful waiting policy or prompt radical treatment

The natural course of stage I NSCLC described varies widely among available literature. Detterbeck *et al.* reported the natural history of lung cancer and median survival time of untreated patients with stage I NSCLC varied from 9 to 25 months, and it depended on the tumor doubling time that was related to the tumor density (28). Tsurugai *et al.* (29) reported that the ratio of consolidation to total

tumor diameter (CTR) predicted the outcomes of patients who received SBRT for NSCLC and demonstrated that the 3-year OS for the CTR <0.5 group was 87.5%. The possible reason of the good survival rate was that the group had minimally invasive tumors. Lafata *et al.* (30) reported an association of pre-treatment radiomic findings with the recurrence in lung cancer patients treated with SBRT indicating that relatively dense tumors with a homogenous coarse texture might be associated with higher rates of local recurrence. Takeda *et al.* (31) reported a case of acute exacerbation of subclinical idiopathic pulmonary fibrosis produced by SBRT in a patient with slight focal honeycomb changes in the lung and argued that attention must be paid to the cases with such findings, even if it is minimal. In a case with stage I NSCLC with an invasive type tumor, the fatality rate of natural course might be higher than the incidence ratio of fatal RP after SBRT. In regard to the risk of surgery for patients with ILD, Lee *et al.* (32) reported a high fatality rate due to respiratory failure after resection of lung cancer in patients with IPF. Therefore, the fatality ratios of SBRT and surgery would be similar in patients with IPF, but these radical procedures must not be excluded from the treatment choices. According to these data, a watchful waiting policy would be reasonable for indolent (minimally invasive) or very early stage tumors, particularly in cases with ILD. However, a prompt radical treatment policy would be ideal in cases of invasive or large size tumors without ILD.

Measures for managing RP

The measures for managing RP are as follows: better radiotherapy techniques for dose-sparing to the normal lung, symptomatic agents, and preventive agents. First, higher dose concentrations that spare normal lung tissue could be achieved using more precise irradiation systems enabling a small setup and internal margin or PT. Kadoya *et al.* (33) and Ebara *et al.* (34) respectively reported that proton and carbon ion therapy are useful for sparing the background lung from high radiation doses. Chen *et al.* (35) performed a systematic review of the 3,056 records in 50 journal articles regarding treatment-related toxicity in patients with early-stage NSCLC and coexisting ILD treated with SBRT, PT, and radiofrequency ablation (RFA). In the results, treatment-related mortality of SBRT, PT and RFA in primarily medically inoperable patients was 15.6%, 4.3%, and 8.7%, respectively, and the authors insisted that a cautious approach to the active treatment or best supportive

care should be indicated in patients with coexisting ILD. Second, basic management of mild RP using antitussive or expectorant drugs itself is a symptomatic treatment. When the symptoms progress, corticosteroids need to be administered in combination with antibiotics on a case-by-case basis. Most cases where disease leads to acute exacerbation of symptoms and the inflammatory shadow expands onto the irradiated volume result in death. Third, several medications have been evaluated for their ability to prevent or reduce RP in animals and humans, including corticosteroids, amifostine, ACE inhibitors or angiotensin II type 1 receptor blockers, pentoxifylline, melatonin, carvedilol, and manganese superoxide dismutase-plasmid/liposome (36). Recently, anti-fibrotic agents such as pirfenidone have been used in clinical trials for evaluating the efficacy and safety of perioperative pirfenidone for preventing the acute exacerbation of ILDs in lung cancer patients after surgery (37), and the initial reports showed a safe and promising effect. Research on the effects of RP is still experimental (38,39), a clinical trial is warranted in the future. For other methods of therapeutic management, immunosuppressive agents or plasmapheresis may be used, although scant evidence exists on their success.

Conclusions

Generally, the dose to the normal lung and interstitial changes in the background lung are important risk factors of severe RP in cases of lung cancer treated with SBRT. The ratio of fatal RP after SBRT for stage I NSCLC in patients with accompanying pulmonary interstitial change was reported to be more than 5%. IPF is the biggest risk factor for severe RP. Chronic heart failure might exacerbate RP, but further research is mandatory to reach a definitive conclusion. It would be reasonable to avoid prompt SBRT by employing a watchful waiting policy in cases of indolent or non-aggressive type tumors, such as ground-glass tumors. While pulmonary interstitial disease is an important risk factor of severe RP, it is not always a contraindication for thoracic SBRT. Patients need to be provided proper information, including an adequate explanation of the risk of severe RP post SBRT according to the condition and characteristics of their tumors, before they provide consent, and the final decision must be selected by the patients' judgement. It would be better to use or recommend more highly precise irradiation technique, PT, or radio-frequency ablation, that can reduce radiation doses to the normal lung more, in particular for the cases with IPF. Identification

of biomarkers indicating an individual's risk level for severe RP, such as SNPs, would be important in treatment decisions, but it needs further researches. Though there are no reliable drugs for treating severe RP, anti-fibrotic agents, such as pirfenidone, might be effective in its prevention or alleviation. Further clinical trials to explore the efficacy of anti-fibrotic agents is mandatory.

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Footnote

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Ethical Statement: The author is 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.

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