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REVIEW ARTICLE

Stereotactic body radiotherapy in patients with chronic obstructive pulmonary disease and interstitial pneumonia: a review

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Abstract

Stereotactic body radiation therapy (SBRT) can yield excellent local tumor control, as well as survival benefit comparable to that of surgery for early-stage lung cancer. However, in terms of toxicity, SBRT might lead to fatal radiation pneumonitis. Lung diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), are major risk factors for lung cancer. However, these patients are typically not candidates for the gold-standard treatment option, lobectomy, because of the perioperative risks. In addition, patients with poor respiratory function can be excluded in prospective clinical trials. Thus, SBRT for patients with pulmonary diseases is still challenging, but there appears to be a clinical role for this modality as an alternative treatment. However, there are few well-documented review articles on SBRT for patients with pulmonary diseases. Therefore, we aimed to review SBRT in the context of important patient-related factors, including COPD and ILD. SBRT is an acceptable alternative treatment option for patients with lung cancer who also have COPD with an equivalent risk of radiation pneumonitis to normal lung. However, latent ILD should be detected prior to treatment. The indication for SBRT should be decided by carefully considering the risks and benefit for patients with ILD.

Keywords Chronic obstructive pulmonary disease · Interstitial lung disease · Interstitial pneumonia · Lung cancer · Stereotactic body radiotherapy · Stereotactic ablative radiotherapy

Introduction

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), has recently gained increased attention as a therapeutic modality for early-stage non-small cell lung cancer (NSCLC), which has dramatically increased the use of radiation therapy as a curative modality [1]. The major feature that distinguishes SBRT from conventional radiation treatment is the delivery of large radiation doses in a few fractions, which results in a high biologically effective dose (BED) [2, 3]. In addition, a shortened delivery time could increase cell killing [4]. The use of a high-precision technique is critical to deliver SBRT, as well as ensure larger dose gradients are located far the target, thereby achieving maximum treatment efficacy with minimal toxicity to normal tissues [5].

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The use of SBRT for extracranial tumors was developed by Blomgren et al. [6], with the techniques and clinical evidence of SBRT having been dramatically strengthened since then. The suitable fixation methods, respiratory management techniques, and dose calculation algorithms have also been improved to maximize precision and minimize errors. Moreover, not only non-coplanar three-dimensional (3D) conformal, multiple-beam irradiation techniques, but also intensity-modulated radiotherapy (IMRT) has recently been used to calculate the 3D radiation dose for volumetric prescription, to improve the radiation dose homogeneity and reduce the radiation dose for organs at risk (OARs). SBRT is now widely accepted as a treatment option achieving 80–97% local control rates for early-stage lung tumors using a BED_{10} of > 100 Gy, according to the linear quadratic (LQ) model of hypofractionated regimens [7–16].

Lung diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), are well-known major risk factors of lung cancer [17]. Intrapulmonary recurrence and second primary lung cancer often occur after a radical treatment because of the underlying

pulmonary status, with such tumors often receiving SBRT as a second radical treatment.

SBRT for small lung tumors is generally safe and can achieve high efficacy with minimal invasion, as compared to surgery, with the incidence of symptomatic radiation pneumonitis greater than common terminology criteria for adverse events (CTCAE)-grade 3 being generally < 10% [1]. However, patients with poor respiratory function, particularly those with ILD, have been considered to have a high risk of fatal radiation pneumonitis. Further, the feasibility of SBRT in patients with pulmonary disease is poorly understood and insufficiently documented at present [1, 18]. Moreover, there are few well-documented review articles on SBRT for patients with pulmonary diseases [19]. Thus, we conducted this review of lung SBRT in challenging cases, with a focus on poor pulmonary function due to COPD, ILD, and other complications.

Methods

The present research was conducted according to the systematic review and meta-analysis (PRISMA) guidelines. In this narrative review, a literature search was performed using the PubMed database to identify all relevant studies. Using the search terms "chronic obstructive pulmonary disease" or "interstitial lung disease" and "stereotactic radiotherapy", studies were identified, which included peer-reviewed studies that assessed the clinical findings in patients with pulmonary diseases (Fig. 1). The initial search was performed in July 2018 and a total of 167 articles were identified. Furthermore, other clinically challenging topics of lung SBRT were summarized with recent key references.

SBRT for lung cancer in COPD

COPD grade was assessed according to the global initiative for chronic obstructive lung disease criteria, with grade being determined by the severity of pulmonary function [20]. COPD is a well-known risk factor of lung cancer [21]. In addition, Jeppesen et al. reported that localized NSCLC negatively affects survival in COPD patients [22]. However, COPD can make lobectomy, a standard procedure for operable lung cancer, challenging, because COPD patients can have medical complications, including poor respiratory function. In patients with poor general condition, limited surgery has been performed and resulted in worse clinical outcomes when compared to lobectomy [23]. Therefore, SBRT can be a treatment option for patients with lung cancer and COPD, in terms of an alternative definitive treatment and in the salvage setting [24]. Rancati et al. reported that COPD and a large volume receiving low-dose radiation were correlated with high rates of radiation pneumonitis in 3D-conventional radiotherapy [25]. However, there are

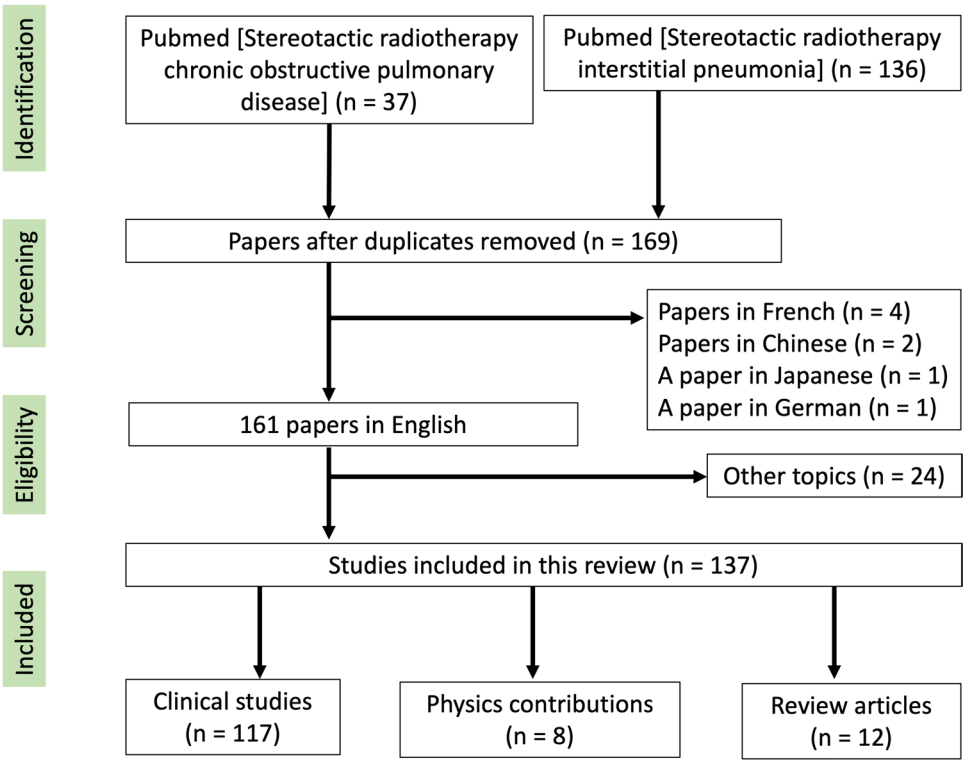

Fig. 1 Flowchart showing the article selection process. We included clinical studies, physics contributions, and review articles in this review

insufficient data regarding the feasibility and utility of SBRT in COPD patients.

Previous studies have demonstrated high local control and overall survival approaching that of surgery in patients with early-stage NSCLC [26, 27]. It has been reported that SBRT can offer significantly lower rates of post-treatment mortality in elderly patients receiving SBRT than those in patients treated with surgery [26, 28]. Louie et al. reported the potential survival benefit of SBRT for NSCLC in patients with COPD, especially for a T2 tumor in GOLD III and IV patients, using the Markov model [29]. Palma et al. reported that compared with surgery, SBRT has a lower risk of 30-day mortality in patients with severe COPD (0% vs. 10%) [30]. Thus, SBRT is reasonably offered in patients with severe COPD.

Radiation pneumonitis in patients with COPD

The majority of previous reports have found no evidence of COPD being a significant risk factor for radiation pneumonitis after SBRT. Inoue et al. have reported the existence of COPD and the Brinkman index as risk factors of prolonged minimal radiation-induced pneumonitis, but concluded that SBRT for early lung cancer can be tolerated in COPD patients [31]. Notably, patients with COPD had significantly lower rates of 1-year cumulative probabilities for grade 1 radiation-induced pneumonitis than those without COPD ($n=62$ vs. 74, 48.4% vs. 83.8%, $p=0.0004$).

Lindberg et al. have reported that 1 out of 57 patients, including 65% patients with COPD, experienced grade 4 dyspnea at 36 months after treatment, leading to hospital admission due to respiratory failure and death after almost 6 years after receiving SBRT [32]. The cause of death was considered to be COPD and hence was not classified as attributed to SBRT. Grade 2 COPD-exacerbation and pneumonitis were found in 6% and 11% of patients, respectively. Kimura et al. reported that following SBRT, patients with emphysema developed symptomatic radiation pneumonitis less frequently than those without emphysema ($n=18$ vs. 29, grade ≥ 2 in any grades of radiation pneumonia, 27.8% vs. 58.6%, $p=0.0394$) [33]. Ishijima et al. documented 40 early-stage lung cancer patients who underwent SBRT using a conventional schedule and reported that patients with emphysema had no difference in the incidence of radiation pneumonitis compared with those with normal lung. In their report, patients with severe emphysema had a low risk of radiation pneumonitis [34]. Yamamoto et al. assessed the correlation between the percentage of low attenuation area (%LAA) in lung and radiation pneumonitis, and they reported that high %LAA was associated with a lower rate of grade 1 radiation pneumonitis but not with grade 2–3 radiation pneumonitis. Their data seem consistent with those of previous reports [31, 33–35]. Therefore, previous reports indicated an equivalent risk of radiation pneumonitis in patients with COPD and those without COPD. We summarized the available comparison data in patients with or without COPD from the previous series in Table 1.

The severity of emphysema varies in different areas of the lung. Pauwels et al. showed that pulmonary emphysema occurred more frequently in the upper lung regions in milder cases and extended throughout the entire lung in advanced cases [20]. Ishijima et al. reported that radiation pneumonitis developed earlier in patients with tumors of the lower lobe than in the upper or middle lobe ($p=0.04$) [34]. Kyas et al. found that the dose–response curve shifted to the left when the lower part of the lung was irradiated, which had a tendency to increase the risk of radiation pneumonitis [40]. As severe emphysema causes a reduction in the volume of the parenchyma, the total dose absorbed by the lung decreases, which may be related to the low incidence of radiation pneumonitis. Indeed, previous studies have shown that the patients with tumors in the lower lobe had a higher risk of radiation pneumonitis than those with tumors in the upper lobe [34, 40–42].

Dosimetric information, such as V20 (the volume of the lungs receiving ≥ 20 Gy) and mean lung dose, has historically been considered predictive for the occurrence of radiation pneumonitis [43]. However, the tumor location associated with the severity of emphysema might provide more information to predict radiation pneumonitis.

Pulmonary dysfunction after SBRT in patients with COPD

A minimal reduction in pulmonary function after SBRT has been described, although a report by Guckenberger et al. did find that the decline of pulmonary function after SBRT was significantly correlated with pre-SBRT pulmonary function [44]. Takeda et al. investigated the relationship between pneumonitis and COPD severity [37]. In their reports, the global initiative for chronic obstructive lung disease (GOLD) stage was negatively correlated with decreased respiratory function. The authors concluded that patients with COPD had a lower risk of radiation pneumonitis. The same group has also reported that lower forced expiratory volume % in 1 s (FEV1) and forced vital capacity (FVC) were significant in patients with normal function or mild to moderate COPD, but not significant in patients with severe COPD (GOLD stage III–IV). SBRT had a limited effect on decreased long-term pulmonary function ≥ 1 year after SBRT [45]. Wang et al. also assessed whether poor pulmonary function was associated with pneumonitis and concluded that poor pulmonary function did not increase the risk of radiation pneumonitis [46]. Stephans et al. reported that there was no significant decline observed in pulmonary functional tests after

Table 1 Incidence and severity of radiation pneumonitis in patients with or without chronic obstructive pulmonary disease

References	Total dose/number of fractions for SBRT (median) (range/variation)	Grade	COPD	*n*	Incidence of radiation pneumonitis (%)
[33]	48 Gy/4 fr (48–60 Gy/4–14 fr) (54 Gy/14 fr, 60 Gy/10 fr, 60 Gy/8 fr, 50 Gy/5 fr, 48 Gy/4 fr)	2–3	+[a]	18	27.8
		2	−	29	58.6
[36]	45 Gy/3fr (67% isodose of the PTV)	1–2	+	40	17.5
			−[b]	17	17.6
[37]	40 or 50 Gy/5 fr	≥2	+ GOLD I–II	78	0.96 (0.50–1.82)[c]
			+ GOLD III–IV	48	0.59 (0.25–1.39)[c]
			−	139	1
[38]	42–50 Gy (relative biological effectiveness) in 3–5 fractions[d]	3	+	8	12.5
			−	7	0.0
[34]	75 Gy/30 fr	1	+	23	87.0[e]
			−	17	82.4
[31]	48 Gy/4 fr (44–70 Gy/4–16 fr) (44 Gy/4 fr, 60 Gy/10 fr, 50 Gy/5 fr, 54 Gy/9 fr, 57.6/16 fr, 58.5 Gy/9 fr, 57.6 Gy/16 fr, 58.5 Gy/9 fr, 60 Gy/8 fr, 60 Gy/12 fr, 70 Gy/14 fr)	1[f]	+	62	48.4
			−	74	83.8
[39]	50 Gy/5 fr (40–60 Gy/5–10 fr)	≥2	+	28	10.7
			−	43	7.0
[35]	40 Gy/4 fr, 48 Gy/4 fr	2–3	+[g]	NA	0.51 (0.14–1.88)[c]
			−	NA	1

COPD, chronic obstructive pulmonary disease CT, computed tomography; fr, fraction; SBRT, stereotactic body radiotherapy; Rf., reference; PTV, planning target volume; NA, not applicable

[a]Pulmonary emphysema on CT

[b]Patients with cardiovascular disease

[c]Hazard ratios and the corresponding 95% confidence intervals were indicated. No significant differences were observed

[d]SBRT was performed using a proton

[e]In the text, the authors state that the incidence of radiation pneumonitis in patients with severe emphysema was significantly lower than in those with no underlying lung disease ($p = 0.008$)

[f]The 1-year cumulative probabilities for the development of grade 1 radiation-induced pneumonitis

[g]Percentage of the lung area with attenuation of 860 Hounsfield units > 62%

SBRT for early-stage lung cancer in 92 patients, including 81 patients with COPD [47].

Moreover, Stanic et al. reported that poor baseline pulmonary function tests did not predict pulmonary toxicity after SBRT in a phase 2, multicenter study, with the authors concluding that poor baseline pulmonary function alone should not be used to exclude patients with early-stage lung cancer from SBRT treatment [48]. Hara et al. reported the clinical experience of SBRT for early-stage NSCLC in 24 patients receiving home oxygen therapy (HOT), with no grade 3 or worse pneumonitis observed in 23 of the patients [49]. Notably, no reduction in pulmonary function tests after SBRT was observed over 14 months (range 10–28 months) after SBRT. Contrarily, Ishihara et al. reported that preexisting pulmonary disease was a predictive factor for decreased respiratory function. In their report, most cases of pulmonary disease were COPD (23 of 26) [50]. Furthermore, Binkley et al. have identified that the volume reduction of the treated lobe was positively correlated with the volume receiving a BED ≥ 60 Gy ($r^2 = 0.45$), and the authors hypothesized an ability to achieve therapeutic volume reduction if applied in patients with emphysema [51].

Pitfalls of lung SBRT in patients with COPD

COPD patients can have interstitial change that is known as combined pulmonary fibrosis and emphysema [52]. Further, the combination of pulmonary fibrosis and emphysema has been considered to have a poor prognosis, similar to idiopathic pulmonary fibrosis [53]. Hara et al. reported that 1 of 24 patients who received SBRT under HOT use developed fatal radiation pneumonitis, with this patient

having the complication of ILD [49]. In addition, patients with a complication of ILD showed significantly poor survival (3-year survival rate, 67% vs. 0%). Ozawa et al. investigated the clinical characteristics and predictive factors for developing acute extended radiation pneumonitis with a focus on the presence and radiological characteristics of preexisting ILD and concluded that the presence of preexisting ILD on the CT scan before radiotherapy was a significant predictive factor [54]. Onishi et al. reviewed 23 of 1789 patients who received SBRT for lung cancer and reported that the 6-month overall survival rates of patients with and without interstitial change on the CT scan before SBRT were 50.0% and 14.3%, respectively ($p = 0.08$). Their data suggest that interstitial change on the pre-treatment CT scan can be associated with increased severity of radiation pneumonitis [55]. Notably, several factors such as a usual interstitial pneumonia (UIP) pattern on CT scans were indicated in the high-risk group of acute exacerbation of ILD after pulmonary resection for lung cancer [56]. The risk factors of acute exacerbation of ILD after surgery for lung cancer likely had common denominators including an elevated Krebs von den Lungen-6 (KL-6) level with severe pneumonitis after SBRT in patients with ILD [57, 58]. Thereafter, we suggest that suspected ILD on a pretreatment CT scan and elevated serum KL-6 level are key ways of detecting latent ILD even if the patient has no medical history of ILD.

Interstitial changes and latent ILD can be associated with lethal radiation pneumonitis, as we describe in the following section. Therefore, we suggest the necessity to pay attention to the existence of latent ILD, to evaluate the risk of radiation pneumonitis.

In terms of tumor control, Takenaka et al. have analyzed 50 patients receiving SBRT for lung tumors and reported that the patients with emphysema had lower local control rates than those without emphysema ($p = 0.044$) [59]. Ochiai et al. analyzed the dose–volume histograms (DVHs) of lung SBRT plans using an isocenteric dose prescription [60]. In their report, there was a tendency to decrease dose for both the PTV and lung, due to it being delivered in the low-density tissue of emphysema. Taken together, we hypothesize that volume-based prescription may improve radiation dose homogeneity, to achieve excellent tumor control in COPD patients (Fig. 2).

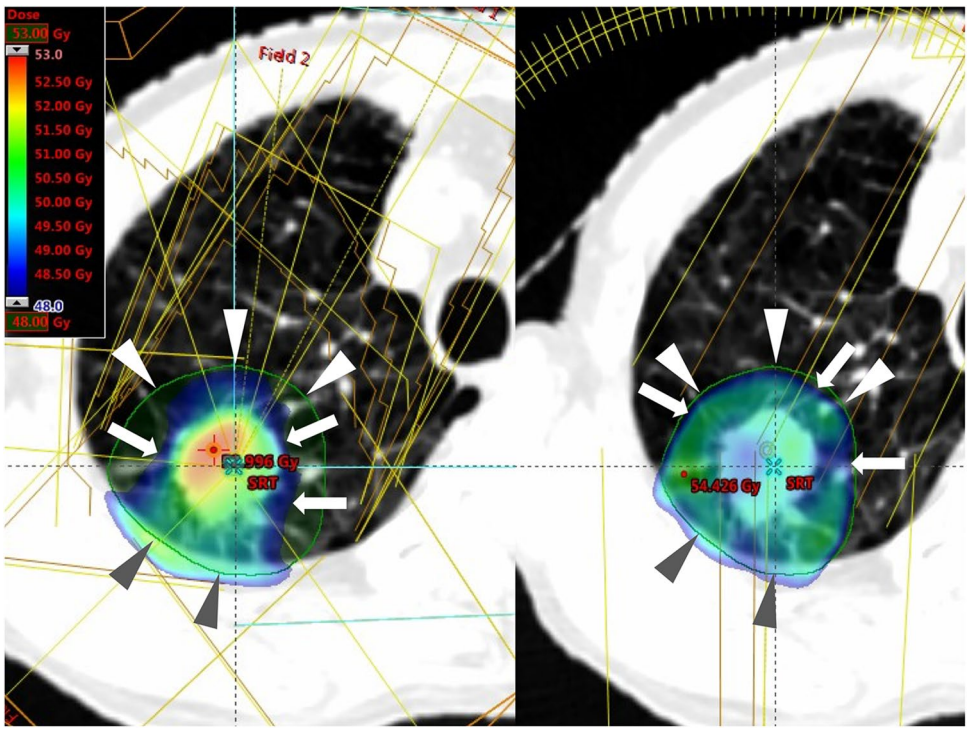

Fig. 2 Comparison of dose distribution between plans utilizing multiple non-coplanar conformal beams and those using volume metric arc therapy. The patient was an 83-year-old man with squamous cell carcinoma of the right lung. SBRT was performed with a total dose of 52 Gy to the isocenter in four fractions using eight conformal beams (left). A VMAT plan using two arcs was generated to deliver 48 Gy in four fractions using D95 for the prescription (right). PTV is indicated by white and grey arrowheads. In the dose distributions of both plans, the blue color wash and white arrows indicate the 48 Gy isodose. In the isocenter-based prescription, homogeneity is lower than that of the volume-based prescription, such that the cold area that would receive < 48 Gy. Only a small cold spot exists in the VMAT plan (right). SBRT, stereotactic body radiotherapy; VMAT, volumetric-modulated arc therapy; PTV, planning target volume; D95, the dose to cover 95% of the PTV

In COPD patients, SBRT can yield good tumor control with an equivalent risk of radiation pneumonitis to normal lung and can be an alternative treatment option for early-stage lung cancer patients who have COPD. Volume-based prescription may improve the homogeneity of the target. Latent ILD should be detected prior to treatment.

SBRT in interstitial lung disease

ILD can cause acute exacerbation from lung cancer treatment including surgery, chemotherapy, and radiotherapy [17]. Therefore, the treatment of lung tumors in ILD patients is challenging. In conventional fractionated radiotherapy, the occurrence rate of acute exacerbation or severe radiation pneumonitis has been reported as 26–43% [61, 62]. Moreover, ILD has been considered to have a high risk of fatal radiation pneumonitis (0.5–1.2%) [1, 18]. Generally, the indication criteria for SBRT to treat lung tumors include early-stage disease, such as stage I non-small cell lung cancer or lung oligo-metastasis, medically inoperable or refusal of surgery, tumor not adjacent to critical organs, and without contraindication for radiotherapy of the lung, such as ILD [63]. According to a landmark prospective study in Japan, SBRT was contraindicated for patients with ILD [7].

It has been reported that patients with ILD have a significantly high-risk of radiation pneumonitis after SBRT for early-stage lung cancer compared to patients with no underlying lung disease although there is a limited number of retrospective studies comparing the incidence of radiation pneumonia after SBRT for lung tumors [34, 39, 64–73]. We summarized the available comparison data in patients with or without ILD from the previous series in Table 2 [39, 64–73]. We reviewed SBRT in patients with ILD in terms of the risk of radiation pneumonitis. However, it is difficult to differentiate interstitial pneumonia from ILD, and no reports have indicated the differences of specific types of ILD in terms of the risk of radiation pneumonitis because ILD is a group of several lung conditions, including interstitial pneumonia [74]. The previous reports on SBRT and ILD are retrospective series, and they include little information on the details of the classification of ILD. Only a few reports have focused on the classification of ILD for risk factors of acute exacerbation of ILD in patients receiving radiotherapy. The UIP pattern has been known as the risk factor for acute exacerbation of ILD [75]. Previous reports have indicated that the incidence of exacerbation of ILD after treatments including surgery, chemotherapy, and chemoradiotherapy was significantly higher in patients with lung cancer with the UIP pattern detected by CT than in those with a non-UIP pattern [56, 76, 77]. Moreover, a specific diagnosis of idiopathic pulmonary fibrosis may influence SBRT-related mortality and toxicity [78].

In previous reports, the presence of ILD was associated with the incidence and severity of radiation pneumonitis, although various definitions of ILD existed among the series. Among 23 patients who developed fatal radiation pneumonitis in a nationwide cohort study of 1789 patients in Japan, 14 of 19 cases (73.7%) in which CT could be reviewed showed pulmonary interstitial change [79]. Tsurugai et al. reported inferior survival in ILD patient group, despite an equivalent local control being achieved, and they concluded that SBRT achieved excellent local control with acceptable pulmonary toxicity in lung cancer patients with ILD [72]. Glick et al. reported that the incidences of both grade ≥ 2 and grade ≥ 3 radiation pneumonitis were significantly higher in patients with ILD, but no significant impact of the presence of ILD was found on survival [73].

Any interstitial changes in pre-treatment CT can be associated with severe radiation pneumonitis. Although CT is a gold standard imaging modality to assess ILD, CT findings do not completely agree with pathological findings because of the presence of minor interstitial changes [80]. The role of serum markers of ILD, such as KL-6, for the prediction of radiation pneumonitis might be controversial [57, 58, 64, 73]. However, Iwata et al. suggested that a cutoff level of 300 U/mL may be appropriate for preventing the occurrence of grade ≥ 2 radiation pneumonitis from SBRT, according to receiver operating characteristic curve analysis [57]. Yamashita et al. recommended prescreening for ILD with CT scans and serum KL-6 and SP-D levels, which successfully reduced the incidence of grade 4 and 5 radiation pneumonitis from 18.8 to 3.5% [58]. Seto et al. documented several factors for predicting the acute exacerbation of ILD after pulmonary resection for lung cancer [56]. The risk factors of acute exacerbation of ILD after surgery for lung cancer likely have common denominators including the UIP pattern on CT scans and elevated KL-6 level with severe pneumonitis after SBRT in ILD patients [57, 58]. However, it is difficult to distinguish severe radiation pneumonitis and acute exacerbation in ILD patients. However, the UIP pattern might be a significant risk among ILD patients; nevertheless, further analyses may indicate the specific pathological condition in ILD.

Only a few reports have compared SBRT to other modalities in ILD patients. Chen et al. analyzed ILD-specific toxicity after various radical treatments including SBRT and surgery in a systematic review, and they reported that patients receiving SBRT and particle beam therapy showed a higher mortality rate than those receiving surgery among patients with coexisting ILD [78]. Additionally, the proportions of treatment-related mortality and ILD-specific toxicity were 15.6% and 25%, 4.3% and 18.2%, and 8.7% and 25% in SBRT, particle beam therapy, and radiofrequency ablation (RFA), respectively. In medically inoperative patients,

Table 2 Incidence and severity of radiation pneumonitis in patients with or without interstitial pneumonia

Ref.	Total dose/number of frs for SBRT (median) (range/variation)	Grade	IP	*n*	Incidence of radiation pneumonitis	
					(%)	(Grade 5, *n*)
[64]	48 Gy/4 fr	≥4	+[a]	13	53.8	7
			−	104	1.9	
[65]	50 Gy/5 fr (40–60 Gy/fr, 50 Gy/10 fr)	3	+[b]	3	33.3	
			−	130	2.3	
[66]	48 Gy/4 fr (50 Gy/4 fr, 52 Gy/4 fr, 30 Gy/3 fr, 60 Gy/10 fr, 50.4 Gy/4 fr, 62.5 Gy/10 fr)	≥2	+[c]	16	18.8	1
			−	84	11.9	
[67]	60 Gy/3 fr (60 Gy/5 fr, 50 Gy/4 fr, 50 Gy/5 fr, 40 Gy/5 fr)	5	+[b]	5	60.0	
		3	−	145	1.4[h]	
[68]	48 Gy/4 fr (56 Gy/4 fr, 60 Gy/8 fr, 50 Gy/4 fr, 60 Gy/4 fr)	≥2 (≥3)	+[d]	20	55.0 (10.0)	
			−	137	13.1 (1.5)	1
[69]	48 Gy/4 fr	≥2 (≥3)	+[e]	18	50.0 (38.9)	3
			−	242	5.8 (1.2)	
[70]	BED10 = 180 (72–180)	≥3 (≥4)	+[d]	28	32.1 (21.4)	
			−	476	2.1 (0.0)	
[71]	48–56 Gy/4 fr	≥2	+[f]	7	28.6	
			−	49	8.2	
[39]	50 Gy (40–60 Gy) in 5 fr (5–10 fr)	≥2	+[g]	11	45.5	2
			−	60	1.7	
[72]	50 Gy/5 fr (40 or 50 Gy/5 fr)	≥2 (≥3)	+[b]	42	19.0 (11.9)	1
			−	466	14.8 (2.6)	2
[73]	48 Gy/4 fr (60 Gy/8 fr, 54–60 Gy/3 fr)	≥2 (≥3)	+[d]	39	20.5 (10.3)	2
			−	498	5.8 (1.0)	1

CT, computed tomography; fr, fraction; SBRT, stereotactic body radiotherapy; IP, interstitial pneumonia; Ref., reference

[a]Interstitial pneumonia was identified as a CT shadow

[b]Idiopathic pulmonary fibrosis

[c]Subclinical interstitial pneumonia means an untreated and oxygen-free status

[d]Interstitial lung disease

[e]Pulmonary interstitial changes detected by CT

[f]Interstitial pneumonia

[g]Interstitial lung disease detected by CT

[h]Two patients with grade 3 pneumonitis, but the idiopathic pulmonary fibrosis status is unclear in these patients

particle beam therapy has the potential to provide relatively safer treatment for early-stage NSCLC than SBRT and RFA.

There is still a lack of strong data regarding the prediction of radiation pneumonitis in patients with ILD, as well as no established pharmacological approaches to prevent radiation pneumonitis. In terms of dosimetric parameters, mean dose and V20 are well-known risk factors of symptomatic radiation pneumonitis [38]. However, grade 3 or higher radiation pneumonitis might occur with lower radiation doses since the dose relationship may be unclear [60]. In terms of preventing fatal pneumonitis in ILD patients, Takeda et al. reported that clarithromycin administration significantly reduced the rates of grade ≥3 radiation pneumonitis after lung SBRT in patients with ILD [81].

Patients with ILD can be excluded from prospective clinical trials, due to relatively high risk of lethal radiation pneumonitis, although there are insufficient data to indicate the exact risk of radiation pneumonitis. In addition, ILD may have a poor prognosis [82]. Therefore, the indication of SBRT should be decided under careful consideration of the risk and benefit with prescreening for latent ILD, and after the discussion of specialists, including oncologists and pulmonologists.

Normal lung-sparing SBRT theory and the use of IMRT in SBRT

In terms of functional lung-sparing SBRT theory, the lower lung has a greater propensity for motion than the upper or middle lobes [83, 84]. Bahig et al. reported that lobar function derived from a dual-energy CT iodine map correlates well with single-photon emission CT/CT, with its integration in lung treatment planning being associated with significant differences in V5 and mean lung dose to the functional lung [85]. Further, Faught et al. quantified the potential toxicity reduction from CT ventilation-based functional avoidance planning [86]. As described above, the lower lobes could develop radiation pneumonitis more often than the upper lobes [34, 40–42]. The distribution of emphysema and functional lung area seem correlated with these clinical outcomes. However, contrary opinions also exist. Otsuka et al. reported that the radiation dose delivered to poorly ventilated areas of the lung was associated with grade ≥ 2 radiation pneumonitis [87]. Functional-sparing SBRT seems warranted to minimize the reduction of pulmonary function, as well as the risk of radiation pneumonitis. Future work is needed to establish functional avoidance planning.

Lu et al. documented nine studies in a meta-analysis and indicated V5 and V20 as major risk factors for radiation pneumonitis after SBRT treatment for a lung tumor [88]. Chen et al. reported that V20 $\leq 6.5\%$ and mean lung dose ≤ 4.5 Gy were found to be associated with reduced mortality in ILD patients [78]. In general, IMRT reduces the volume of the whole lung receiving more than 20 Gy (V20), but the effect of IMRT on lower doses to the lung such as V5 seems controversial [89]. Further, optimal dose distribution to the lung with lung disease is necessary. Thus, when using an inverse planning technique, efforts to reduce the radiation doses to the lung are needed.

SBRT using IMRT can have dose variation from the interplay effect between the multileaf collimator (MLC) sequence and tumor motion. Court et al. showed that dose error could be $> 5\%$ for the area of 40% in the target with 2-cm motion using the volumetric modulated arc therapy (VMAT) plan [90]. Tyler et al. found that SBRT using dynamic MLC deliveries minimizes the effects of both interplay and gradient on gross tumor dose coverage in comparison with VMAT [91]. However, Kubo et al. recently reported that patients who breathe > 40 times during irradiation of two partial arc VMAT (16 breaths per minute in a typical case) may be suitable to undergo VMAT–SBRT for lung cancer [92]. Breathing control is an important factor to minimize the dose variation to defeat the interplay effect in SBRT using IMRT.

Conclusion

SBRT is a treatment option for small-sized lung cancer tumors in patients with pulmonary disease. SBRT is an acceptable alternative treatment option for patients with lung cancer and COPD that does not increase the risk of radiation pneumonitis. The presence of ILD was verified as a risk factor for severe radiation pneumonitis. The presence of latent ILD should be considered prior to SBRT with the aim of avoiding lethal radiation pneumonitis.

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Compliance with ethical standards

Conflict of interest None declared.

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