

Clinical characteristics of organizing pneumonia following stereotactic body radiation therapy for lung malignancies

Masayuki Ito, MD¹, Hitoshi Takagi, PhD², Fumitaka Ito, MD, PhD³, Hidetoshi Kobayashi, MD, PhD², Shinya Hayashi, MD, PhD³, Hiroshi Toyama, MD, PhD¹

¹Department of Radiology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan, ²Division of Radiation Oncology, Ogaki Municipal Hospital, Ogaki, Gifu, Japan, ³Department of Radiation Oncology, Fujita Health University School of Medicine, Toyoake, Aichi, Japan

Abstract

Objective: Radiation pneumonitis and organizing pneumonia (OP) are the two primary forms of lung damage that can occur following lung irradiation. The goal of this study was to clarify the clinical characteristics of OP after stereotactic body radiation therapy (SBRT) for lung malignancies.

Methods: This study included 75 patients with lung malignancies who underwent SBRT from April 2013 to January 2015. The diagnosis of OP was based on lung computed tomography findings and previously established criteria.

Results: OP was observed in 6 of 75 patients (8%) and occurred in regions with a steep dose gradient ranging from 30% to 90%. The time to OP occurrence ranged from 1 to 4 months after completion of SBRT (mean, 84 days). No patients had symptoms suggestive of pneumonia, such as a fever or cough, at the time of computed tomography.

Conclusion: OP developed in regions with a steep dose gradient. This mechanism explains why the incidence of OP after SBRT was higher than that after postoperative radiation for breast cancer and non-SBRT irradiation for lung cancer.

Keywords: Radiation pneumonitis, Organizing pneumonia, Stereotactic body radiation therapy

Introduction

Stereotactic body radiation therapy (SBRT) of the lung is used to deliver radiation to the planned target volume (PTV). SBRT is a type of hypofractionated radiotherapy involving accurate deliberation of a high ablative dose to the target and a limited inconsequential dose to normal tissues. Excellent local control rates have been reported in patients treated with SBRT for multiple lung metastases.¹⁻⁶ However, the risk of pulmonary toxicity following SBRT remains unclear. Radiation pneumonitis (RP) and organizing pneumonia (OP) (i.e., bronchiolitis obliterans OP) are the two main types of lung damage that can occur following lung irradiation.⁷ RP is a common form of respiratory damage that can be fatal despite the availability of novel and conventional types of radiotherapy. RP develops along irradiated fields and results in pulmonary fibrosis. Moreover, RP is characterized by dose-limited damage; for example, the threshold percentage of lung volume receiving >5 Gy for the developing symptomatic RP is reportedly 65%.⁸ In contrast, OP was first reported following postoperative irradiation for breast cancer in 1998.⁷ The features and clinical course of OP differ from those of RP. The infiltrates of OP initially appear on the irradiated side of the lung and occur independent of the radiation dose. In our previous study, however, we first reported that OP is closely related to RP and that all OP lesions developed near the RP site.⁹ Therefore, we suspected that a high radiation dose is related to the development of RP lesions and that a steep dose gradient may be associated with the onset of OP lesions. The goal of this study was to clarify the clinical characteristics of OP.

Methods

This study included 75 patients with lung malignancies who underwent SBRT from April 2013 to January 2015 (Tables 1 and 2). The patients comprised 53 men and 22 women with a median age of 70 years. Their underlying diseases consisted of primary lung cancer (n = 39), non-small cell lung cancer (n = 37), small cell cancer (n = 2), metastatic lung cancer (n = 17), and cancer of an unknown primary site (n = 19). The lesion sites consisted of the right upper and middle lobes (n = 27), right lower lobe (n = 13), left upper lobe (n = 18), and left lower lobe (n = 17). The clinical target volume was defined as the gross tumor volume plus 1- to 18-mm internal margins superior, inferior, anterior, and posterior to the gross tumor volume and on the left and right sides of the gross tumor volume. The PTV was defined as the clinical target volume plus a 5-mm circumferential margin. A total of 64 patients had a PTV of <50 mL, and 11 had a PTV of >50 mL. The patients were administered various radiation doses: six patients received 0 to 150 Gy, 27 received 150 to 200 Gy, and 42 received 200 to 300 Gy in equivalence to the biologically effective dose [$nd(1 + d/a/\beta)$, where n, d, and a/β denote the number of divisions, the dose at a time, and 2 Gy, respectively]. The numbers of irradiation fields were 5 (n = 3), 8 (n = 67), and 10 (n = 5). The percent total lung volume receiving ≥ 20 Gy (V₂₀) ranged from 0.7% to 37.7% (median, 6.1%).

Chest computed tomography (CT) was performed on all patients 1 month following completion of the irradiation to assess the therapeutic outcome and every 3 months afterward as long as the patients remained asymptomatic. CT images were obtained as needed when a patient exhibited symptoms suggestive of pneumonia. OP is generally diagnosed according to the following criteria: (1) radiation to the breast within 12 months, (2) general and/or respiratory symptoms lasting for 2 weeks, (3) radiographic lung infiltration outside the

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Corresponding author: Masayuki Ito, MD

Department of Radiology, Fujita Health University School of Medicine
1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192, Japan
E-mail: maito650@fujita-hu.ac.jp

radiation port, and (4) no evidence of a specific cause. However, because no patients exhibited respiratory symptoms in this study, patients who met the following criteria were diagnosed with OP: (1) SBRT within 12 months, (2) radiographic lung infiltration outside the radiation port and outside the PTV, (3) diagnosis of findings by three radiologists, and (4) no evidence of a specific cause. Other post-irradiation adverse events were assessed using the Common Terminology Criteria for Adverse Events v4.0.

Results

OP was observed in 6 of 75 patients (8%); their characteristics are presented in Tables 3 and 4. The time to OP occurrence ranged from 1 to 4 months after the completion of SBRT (mean, 84 days). The age at the time of OP occurrence ranged from 71 to 86 years with a median of 75 years. There were no significant differences in the incidence of OP with respect to age, sex, underlying disease, lesion site, PTV, the number of

irradiation fields, or the prescribed radiation dose. The V20 was $\leq 20\%$ in five patients and $>20\%$ in one patient. Of all patients with OP, four had a habit of smoking, one had undergone chemotherapy, and one had an allergic disease. There were no significant differences in the incidence of OP between patients with and without these factors. The relationship between the site of OP occurrence and the dose distribution was investigated in each of the six patients. OP developed in the 30% to 70% dose area (19.5–45.5 Gy) in Case 1, in the 40% to 90% dose area (20–45 Gy) in Cases 2 and 3, in the 60% to 90% dose area (36–54 Gy) in Cases 4 and 5, and in the 30% to 60% dose area (19.5–39 Gy) in Case 6. None of these patients exhibited symptoms suggestive of pneumonia (e.g., fever or coughing) at the time of CT. No patient required treatment with any drugs, including steroids. In all patients, all shadows with the exception of trabecular shadows disappeared after regular follow-up observation had been conducted without drug administration.

Table 1. The characteristics of patients

Patient character		NO. of patients(%)
Age	median age (years)(range)	39-87(Med72)
SEX	male	53(71%)
	female	22(29%)
Origin	Lung cancer	39(52%)
	Metastasis cancer	17(33%)
	Unknown	19(15%)
Location	Right upper or middle lobe	27(36%)
	Righe lower lobe	13(17%)
	Left upper lobe	18(24%)
	Left lower lobe	17(23%)
PTV size (ml)	0-20	41(54.7%)
	20-40	14(18.7%)
	40-60	11(14.7%)
	60-80	5(6.7%)
	80-100	3(4%)
	<100	1(1.3%)

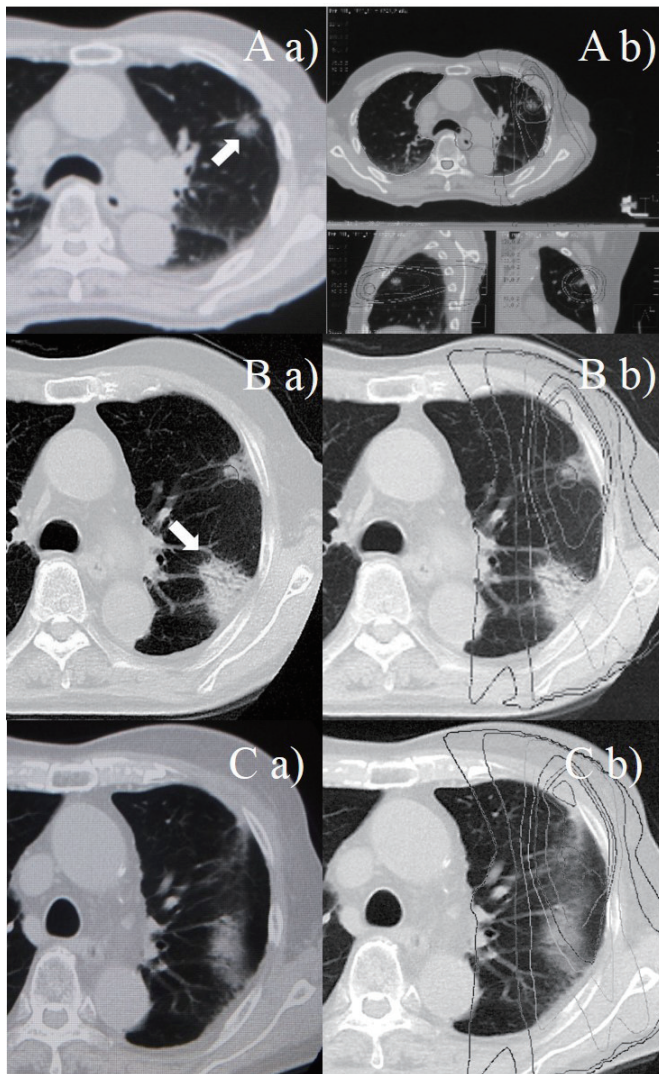
Table 2. Dose fraction and Biological Effective Dose (BED)

Radiation therapy details	BED (calculated as $a/\beta = 2$)	No. of patients(%)
25 Gy in 5 fractions	87.5	1(1.3%)
30 Gy in 5 fractions	120	1(1.3%)
35 Gy in 5 fractions	157.5	1(1.3%)
40 Gy in 5 fractions	200	1(1.3%)
40 Gy in 10 fractions	120	1(1.3%)
44 Gy in 11 fractions	132	1(1.3%)
48 Gy in 12 fractions	144	1(1.3%)
50 Gy in 10 fractions	175	25(33.3%)
56 Gy in 7 fractions	280	14(18.7%)
58 Gy in 10 fractions	226.2	1(1.3%)
60 Gy in 10 fractions	240	21(28%)
60 Gy in 20 fractions	150	1(1.3%)
65 Gy in 10 fractions	276.25	6(8%)

Table 3. Summary of clinical characteristics of OP patients

Case no.	Age	Sex	Diagnosis	Irradiated breast	irradiated dose	Period before onset after RT(days)
1	86	male	primary lung cancer (adenocarcinoma)	left upper lobe	65Gy/10Fr	123
2	71	female	primary lung cancer (adenocarcinoma)	left upper lobe	50Gy/10Fr	79
3	74	male	colon cancer	left lower lobe	50Gy/10Fr	97
4	75	male	primary lung cancer (SCC)	right lower lobe	60Gy/10Fr	41
5	81	male	primary lung cancer (adenocarcinoma)	right upper lobe	60Gy/10Fr	76
6	82	male	primary lung cancer (SCC)	right upper lobe	65Gy/10Fr	90

Figure 1.

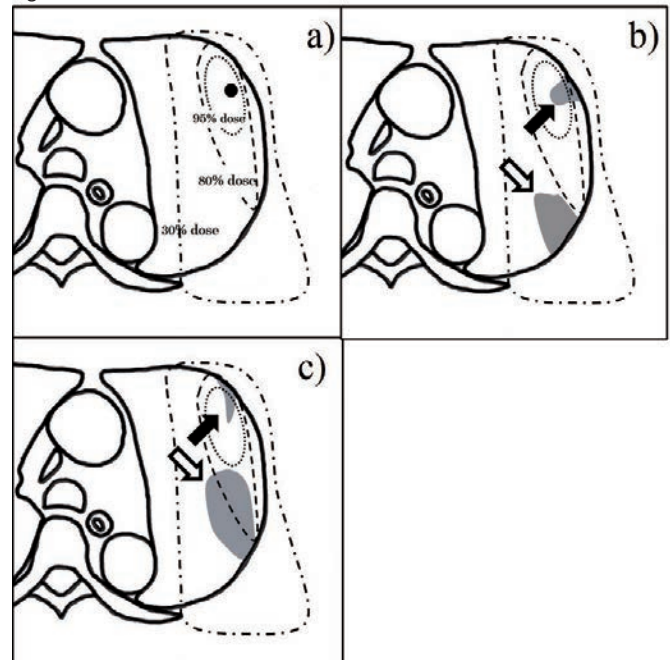


(A) a) Computed tomography (CT) images before stereotactic body radiation therapy (SBRT). b) Fusion of CT images before SBRT and the treatment plan with isodose lines. (B) a) CT images 4 months after SBRT. b) Fusion of CT images 4 months after SBRT and the treatment plan with isodose lines. Organizing pneumonia (OP) appeared along the 30% to 70% dose line (→). Radiation pneumonitis (RP) appeared around the primary lesion. (C) a) CT images 1 year after SBRT. b) Fusion of CT images 1 year after SBRT and the treatment plan with isodose lines. The OP had diminished and become fibrotic and shrunken. The RP had diminished and the primary lesion had disappeared.

A representative case (Case 1) is presented in Table 3. This patient underwent irradiation with 65 Gy in 10 fractions for primary lung cancer (adenocarcinoma) in the upper lobe of the left lung (Figure 1A). In a CT image taken 4 months after completion of the irradiation (Figure 1B), infiltrative shadows appeared in the 30% to 70% dose area (19.5–45.5 Gy), indicating the onset of OP. Infiltrative shadows were also observed surrounding the primary lesion, indicative of the development of RP. On a CT image obtained 1 year after the completion of irradiation (Figure 1C), the infiltrative shadows due to OP had faded and become fibrotic and shrunken. The primary tumor was no longer noticeable, and the RP around the primary lesion had also decreased in size.

Figure 2 shows a close-up schema of changes in RP and OP

Figure 2.



Close-up schema of changes in radiation pneumonitis (RP) and organizing pneumonia (OP) over time after stereotactic body radiation therapy (SBRT) for lung malignancy. a) Before SBRT. b) RP (→) appeared 4 months after lung SBRT mainly in the primary lesion. OP (⇨) appeared in the 30% to 70% dose region 4 months after lung SBRT. c) The RP was reduced in size 1 year thereafter. The OP shadow had become diminished, fibrotic, and shrunken 1 year thereafter.

over time after SBRT for lung malignancy. Figure 2a shows the time period before SBRT, and Figure 2b shows the changes 4 months after SBRT. OP occurred in regions with a steep dose gradient ranging from 30% to 70%, and RP simultaneously emerged in high-dose regions surrounding the tumor. Figure 2c shows the changes 1 year after SBRT. Both OP and RP improved over time; the shadows became lighter and the OP shadows moved ventrally, presumably because RP underwent fibrosis and shrank.

Discussion

Abnormal shadows in the lung following radiation can be caused by two major classes of underlying diseases distinct from each other based on various clinical characteristics, including the time to onset, occurrence site, and course following onset. These two major classes of lung damage are RP and OP. RP is inflammation of the lung caused by radiation therapy to the chest. Such damage is presumed to be caused by different mechanisms and is affected by a variety of factors.⁷ Moreover, RP develops in a dose-dependent manner above an approximate threshold of 20 Gy, generally within the radiation field, and occurs 3 months after completion of the irradiation. There are no observed differences in the disease or irradiated site of the lung. In addition, RP can progress into pulmonary fibrosis, although recurrence is rare. While symptoms during the acute phase (e.g., coughing and fever) are mild, breathing difficulties that develop after RP has advanced to pulmonary fibrosis depend on the lung volume affected by RP. Therefore, a history of emphysema and the ratio of the lung volume subjected to radiation of >20 Gy to the total lung volume are

important risk factors in radiation therapy.¹⁰⁻¹⁵

OP shows no dose dependency, occurs 6 months to 2 years after irradiation (even at sites remote from the radiation field), and recurs frequently. The incidence is 2% to 3% on the remnant breast in patients who have undergone postoperative irradiation. Moreover, there are substantially higher rates compared with the incidence of OP following irradiation for lung cancer; however, there have been reported cases. Symptoms of pneumonia (e.g., cough and fever) are intense and do not depend on the dose or irradiated field.^{9,17-25} OP reportedly requires treatment with steroids and often recurs, but it does not develop into extensive pulmonary fibrosis and is not fatal except during the acute phase.²⁶⁻²⁸

We previously reported that OP occurs following tangential irradiation on the remnant breast, with a 1.7% frequency at sites located outside the irradiated area, with a steep radiation dose gradient, and adjacent to RP.⁹ In addition, we speculated that OP occurs close to RP. In the present study, we investigated the development of OP following lung SBRT. The incidence of OP following lung SBRT was 8%, which is higher than the incidence of OP following irradiation for breast cancer. The differences in the dose distribution in patients with lung cancer, breast cancer, and SBRT are speculated to

be related to the onset of OP. OP developed following lung SBRT in regions with a steep dose gradient. We found that a portion of OP occurred near RP; however, this was not true in all cases. Additionally, RP occurred near the mass while OP occurred both near the mass and at sites far from the mass. When the regions of RP and OP were compared with the dose distributions, the RP regions were associated with a high dose area and the OP regions were associated with the dose gradient. Thus, our findings indicate that RP is not an essential factor for the onset of OP and that the onset of OP is dependent on the dose gradient.

Figure 2 shows that OP occurred in regions with a steep dose gradient ranging from 30% to 90% and that RP simultaneously emerged in high-dose regions surrounding the tumor. While both OP and RP improved over time and the shadows became lighter, the OP shadows moved ventrally, presumably because RP underwent fibrosis and shrank. Additionally, the onset of OP occurred within the first 5 months after radiation, which is earlier than previously reported. Patients had virtually no symptoms of pneumonia (e.g., cough and fever) and improved without treatment. Because CT is generally performed after symptoms have appeared, the previous findings that OP can develop outside of the radiation field²³⁻²⁵ may correspond to

Table 4. Univariate analysis of factors associated with OP

patient character		NO. of All patient	NO. of OP patients	p value
Age		39-87(Med72)	71-86(Med75)	
	under 70y	27	0	p=0.055
	over 70y	48	6	
SEX	male	53	5	p=0.477
	female	22	1	
Origin	LK	39	5	p=0.440
	Meta	17	1	
Location	upper of middle lobe	45	4	p=0.728
	lower lobe	30	2	
PTV size(ml)		2.5-157(med: 25)	9.2-157(med: 46)	
	under 60ml	63	3	p=0.094
	over 60ml	12	3	
BED($\alpha / \beta = 2$)	0 ~ 150	6	0	p=0.491
	150 ~ 200	27	2	
	200 ~ 300	42	4	p=0.761
Number of irradiate gantries	5	3	0	p=0.588
	8	67	6	
	10	5	0	p=0.485
V20%		0.7-37.7(Med6.1)	5.9-26.2(Med10.5)	
	under 20(%)	71	5	p=0.210
	over 20(%)	4	1	
Smoking	+	46	4	p=0.278
	-	29	2	
Chemotherapy	+	25	1	p=0.367
	-	50	5	
Allergic disease	+	4	1	p=0.210
	-	71	5	

sites of recurrence rather than primary lesions. Moreover, although OP occurred at a high frequency, it was associated with virtually no symptoms over time and did not recur in some patients. This may be attributed to the more frequent follow-up observations than described in previous studies. Based on the present observation that all primary sites corresponded to steep dose gradients, the pathogenesis of OP is likely associated with damage to the lung secondary to the steep radiation dose gradient. Presuming that the onset of OP is facilitated by other factors in addition to lung damage, we investigated whether age, sex, underlying disease, irradiated site, PTV size, radiation dose (in equivalence to the biologically effective dose), number of irradiation fields, V20, smoking, chemotherapy, or allergic disease was correlated with the occurrence of OP. We found no correlation between the occurrence of OP and any of these factors (Table 4).

Conclusions

The incidence of OP was higher than that after postoperative radiation for breast cancer and non-SBRT for lung cancer. OP developed following lung SBRT in regions with a steep dose gradient. The optimal irradiation method for lung SBRT may be identified in future studies by investigating how the dose gradient results in lung damage and what factors influence such damage.

Competing interests

The authors declare that they have no competing interests.

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