BJR

Received: 7 September 2014 | Revised: 14 November 2014 | Accepted: 8 December 2014

doi: 10.1259/bjr.20140596

Cite this article as:
Ishijima M, Nakayama H, Itonaga T, Tajima Y, Shiraishi S, Okubo M, et al. Patients with severe emphysema have a low risk of radiation pneumonitis following stereotactic body radiotherapy. Br J Radiol 2015;88:20140596.

FULL PAPER

Patients with severe emphysema have a low risk of radiation pneumonitis following stereotactic body radiotherapy

M ISHIJIMA, MD, H NAKAYAMA, MD, PhD, T ITONAGA, MD, Y TAJIMA, MD, S SHIRAISHI, MD, M OKUBO, MD, PhD, R MIKAMI, MD, PhD and K TOKUUYE, MD, PhD

Department of Radiology, Tokyo Medical University Hospital, Tokyo, Japan

Address correspondence to: Dr Hidetsugu Nakayama
E-mail: *hnakayam@tokyo-med.ac.jp*

This article has been partially presented at the Radiological Society of North America 2013 Annual Meeting held at Chicago.

Objective: To evaluate the risk of radiation pneumonitis (RP) after stereotactic radiotherapy (SBRT) for patients presenting with severe pulmonary emphysema.
Methods: This study included 40 patients with Stage I non-small-cell lung cancer who underwent SBRT, 75 Gy given in 30 fractions, at the Tokyo Medical University, Tokyo, Japan, between February 2010 and February 2013. The median age of the patients was 79 years (range, 49–90 years), and the male:female ratio was 24:16. There were 20 T1 and 20 T2 tumours. 17 patients had emphysema, 6 had slight interstitial changes on CT images and the remaining 17 had no underlying lung disease. The level of emphysema was classified into three groups according to the modified Goddard's criteria (severe: three patients, moderate: eight patients and mild: six patients). Changes in the irradiated lung following SBRT were evaluated by CT.
Results: On CT images, RP was detected in 34 (85%) patients, and not in 6 (15%) patients, during a median observation period of 313 days. Of the six patients, three had severe emphysema and three had no underlying lung disease. Patients with severe emphysema had lower risk of RP than those with moderate emphysema ($p = 0.01$), mild emphysema ($p = 0.04$) and no underlying lung disease ($p = 0.01$).
Conclusion: Patients with severe emphysema had a low risk of RP following SBRT.
Advances in knowledge: Little is known about the association between RP and pulmonary emphysema. Patients with severe emphysema had lower risk of RP than those with no underlying lung disease.

In addition to smoking, lung cancer has various causes, including emphysema and chronic obstructive pulmonary disease (COPD), which are common with underlying lung diseases.[1,2] Thus, patients with underlying lung diseases have a high possibility of having cancer.[1] Stereotactic body radiotherapy (SBRT) for Stage I non-small-cell lung cancer (NSCLC) has an excellent overall survival rate and local control; therefore, SBRT is widely considered a cure with fewer treatment-related toxicities.[3] Accordingly, an increasing number of patients with co-morbidities, especially underlying lung diseases, are undergoing SBRT.

Radiation pneumonitis (RP) is the most severe adverse event of SBRT. Some potential predictors for the risk factors of RP are reported;[4] however, little is known about the association between RP and underlying lung diseases, such as pulmonary emphysema. Thus, we evaluated the relation between RP and pulmonary emphysema following SBRT in patients with Stage I NSCLC.

METHODS

Patients

The ethical committee of the Tokyo Medical University Hospital, Tokyo, Japan, approved this study. Between February 2010 and February 2013, 40 consecutive patients with Stage I NSCLC underwent SBRT, with a total dose of 75 Gy given in 30 fractions at the Tokyo Medical University. Patients' characteristics are shown in Table 1. The median age was 79 years (range, 49–90 years). The male to female patient ratio was 24:16. 16 (40%) patients had metachronous NSCLC a median of 56 months after surgery for the first NSCLC. 26 (65%) patients had a history of smoking. There were 20 T1 and 20 T2 tumours. 20 tumours were located in the upper lobe, 4 in the middle

Table 1. Patients' characteristics

Characteristics	Patients without emphysema ($n = 23$)	Patients with emphysema ($n = 17$)	*p*-value
Sex (male:female)	9:14	15:2	0.003
Age (years), median (range)	79 (49–90)	79 (69–87)	0.910
Performance status (0:1)	21:2	15:2	0.580
Smoker:non-smoker	10:13	16:1	0.004
Diabetes mellitus:non-diabetes mellitus	5:18	3:14	1.000
Histological type	Adenocarcinoma: 11 Squamous cell carcinoma: 4 Non-small-cell lung cancer: 5 Unknown: 3	Adenocarcinoma: 5 Squamous cell carcinoma: 3 Pleomorphic carcinoma: 1 Non-small-cell lung cancer: 1 Unknown: 7	0.140
T factor	1a:7 1b:2 2a:14	1a:6 1b:5 2a:6	0.150
Right:left	12:11	12:5	0.330
Upper:middle:lower	11:3:9	9:1:7	0.760
Central:peripheral	6:17	2:15	0.430
3D-CRT:IMRT	2:21	6:11	0.050

3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiotherapy.

lobe and 16 in the lower lobe. For the underlying lung diseases, 17 patients had emphysema, 6 had slight interstitial changes at posterior site of the lung field on CT, and the remaining 17 had no underlying lung disease. Interstitial changes consisted of a variety of lung conditions, including chronic inflammation from old tuberculosis or aspiration pneumonia. Emphysema was assessed by the modified Goddard's criteria.[5] Emphysema was classified into five scores according to the three slices of CT images taken of the apex, base and middle of the lungs. In both lungs on each of the three slices of CT images, no underlying lung disease scored zero, up to 25% scored one, up to 50% scored two, up to 75% scored three and almost total involvement of the lung tissue scored four.[6] Thus, a maximum score of 24 (6×4) and a minimum score of 0 (6×0) were possible. The scores from the 17 patients with emphysema were classified into three groups according to severity: severe (>16, ≤ 24), moderate (>8, ≤ 16) and mild (≥ 0, ≤ 8). There were three severe cases of emphysema, eight moderate cases and six mild.

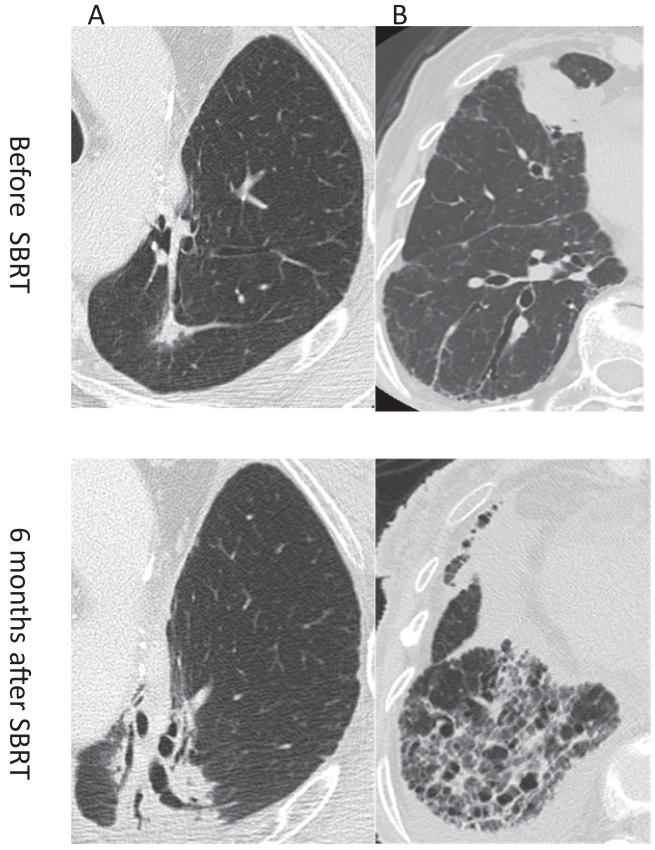
Radiotherapy methods

An immobilization device that compressed the abdomen to restrict the respiratory movement was used. Then, the tumour respiratory motions were observed to be within the limit of 1.0 cm using an X-ray simulator for this treatment. The clinical target volume (CTV) was defined as the gross tumour volume plus 0.7 cm in all directions on the lung image of the treatment planning system (Xio v. 4.6; Elekta AB, Stockholm, Sweden). The planning target volume (PTV) was then defined as the CTV plus 1.5 cm in the craniocaudal direction and 0.5 cm in all other directions. The left and right lungs were delineated as organs at risk. SBRT was performed using five non-coplanar directions. In the three-dimensional conformal radiotherapy (3D-CRT) plan, the PTV was coincident with the shape from the beam. In the intensity-modulated radiation therapy (IMRT) plan, the intensity modulation was generated by a compensated filter according to the IMRT planning. In the 3D-CRT plan, 100% doses were prescribed to the isocentre; while in the IMRT plan, the 95% dose line was set to cover the entire PTV. Prescribed doses were both 75 Gy in 30 fractions. 8 and 32 patients underwent radiotherapy using 3D-CRT and IMRT, respectively. The median percent of total lung volume irradiated with >20 Gy (V20 value) was 9.1% (range, 0.6–16.3).

Follow-up and statistical analysis

RP after SBRT was assessed according to common terminology criteria for adverse events (CTCAE v. 4.0). The diagnosis of grade 1 RP was made only when radiographic findings showed asymptomatic conditions not interfering with activities of daily living. Physical, laboratory, chest radiograph and chest CT examinations were performed every 3 months for the first year and every 6 months thereafter. When the tumour recurred or RP appeared, the follow-up schedule was modified depending on the patient. Factors associated with RP were evaluated with the χ^2 test and Fisher's exact test for categorical variables and Wilcoxon's rank-sum test for continuous variables. A probability value (*p*-value) <0.05 was considered statistically significant. The time to RP development was calculated from the beginning of SBRT. Kaplan–Meier's methods and log-rank tests were also used to evaluate the incidence of RP using STATA v. 12 (StataCorp, College Station, TX).

Figure 1. High-resolution CT images of a 72-year-old male with no underlying lung disease (a) and an 89-year-old female with interstitial changes (b). After stereotactic body radiotherapy (SBRT) radiation pneumonitis developed.



RESULTS

During the median observation period of 313 days, 34 (85%) patients experienced grade 1 RP according to the CTCAE (Figure 1). No patient suffered from grade 2 or more RP. The median time to RP development was 89 days. Six (15%) patients did not experience RP; of these patients, three had severe emphysema and three had no underlying lung disease (Figure 2). The incidence of RP in patients with severe emphysema was statistically significantly lower than in patients with no underlying lung disease ($p = 0.008$) by Fisher's exact test.

When examining the underlying lung conditions affecting RP, patients with interstitial changes suffered from RP earlier than those with no underlying lung disease ($p = 0.02$) or emphysema ($p = 0.02$) (Figure 3). Further analysis showed that patients with severe emphysema had lower risk of RP than those with moderate ($p = 0.01$) and mild ($p = 0.04$) emphysema (Figure 4). In addition, RP developed earlier for patients who underwent radiotherapy in the lower or middle lobe than in the upper lobe ($p = 0.04$) (Figure 5).

The patient's smoking history (presence *vs* absence; $p = 0.73$), Brinkman index ($\geq$1000 *vs* $<$1000; $p = 0.21$), age ($\geq$75 *vs* $<$75 years; $p = 0.33$), sex (male *vs* female; $p = 0.41$), performance status (1 *vs* 2; $p = 0.19$), tumour location (peripheral *vs* central; $p = 0.48$), T-factor (T1 *vs* T2; $p = 0.28$), treatment method (IMRT *vs* 3D-CRT; $p = 0.21$) and V20 value ($\geq$10 *vs* $<$10; $p = 0.85$) showed no statistically significant association with RP.

DISCUSSION

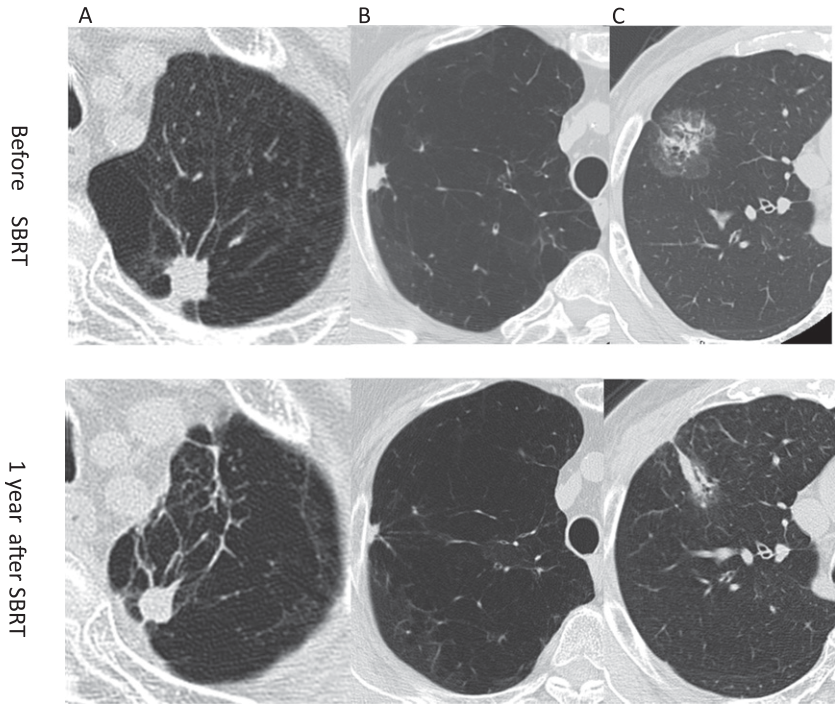
Patients with Stage I NSCLC who are inoperable owing to underlying lung diseases have become candidates for SBRT. RP can be a life-threatening event when radiotherapy is performed in the lung. SBRT provides radiation to a limited area of the tumour while reducing it to the surrounding lung tissues. This allows patients with underlying lung diseases to be treated. In this study, all patients were medically inoperable owing to poor pulmonary functions. To reduce serious RP, we used fractionated SBRT at a dose of 75 Gy given in 30 fractions. All patients had good tolerance, and no grade 2 or higher RP was observed.

Kimura et al[7] reported that following SBRT, patients with emphysema developed RP less frequently. Using the χ^2 test, they reported that patients with emphysema had a much lower incidence of RP than patients without emphysema. Their data were consistent with our results. To further investigate the relationship between RP and emphysema, we used the Goddard criteria for emphysema severity.

Pauwels et al[8] showed that pulmonary emphysema occurred more frequently in the upper lung regions in milder cases, and extended throughout the entire lung in advanced cases. Here, we showed that the patients with tumours in the lower lobe had greater chance of suffering from RP than those with tumours in the upper lobe. This finding appears consistent with others.[9–11] Severity of emphysema varied in different areas of the lungs. 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 RP. Yamada et al[11] reported similar results and found an increased risk of RP by multivariate analysis when chemoradiotherapy was performed in the lower lobe. Palma et al[10] conducted an individual meta-analysis to clarify the risk of RP following chemoradiotherapy for NSCLC. They showed fatal RP was related not only to dosimetric factors but also to the irradiated location. Kyas et al[9] denoted 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 RP. Two others reported that irradiation of the upper part of the lung was associated with a low risk of RP. Addition of dosimetric information such as V20 and mean lung dose to location of tumour more accurately predicted RP.[12,13] The tumour location may be an independent risk factor from dosimetric parameters.

COPD is a physiological deterioration in the lung that is diagnosed through a lung physiological function test.[14] By contrast, emphysema is a morphological condition that is

Figure 2. High-resolution CT images of a 75-year-old male (a) and a 74-year-old female (b) with severe emphysema and a 79-year-old female with no underlying lung disease (c). There were no fibrotic changes after stereotactic body radiotherapy (SBRT).



diagnosed with dilatation and destruction of the respiratory bronchioles. Destruction of the lung parenchyma in patients with COPD typically causes centrilobular emphysema.[15] Therefore, COPD and emphysema represent different aspects of lung injuries. Emphysema was recognized on CT images, meeting the parameters needed to modify a treatment, however, COPD diagnosed by physiologically tests did not meet the necessary parameters.

Studies with patients with COPD have often produced contradictory results in clinical practice and clinical trials. Rancati et al[16] reported patients with COPD are associated with a higher risk of RP. By contrast, some reported that COPD did not increase RP. Takeda et al[17] investigated the relationship between RP and COPD grade according to the Global Initiative for Chronic Obstructive Lung Disease criteria, which were determined by the severity of pulmonary functions. They concluded that patients with COPD had lower risk of suffering from RP than do patients

Figure 3. A Kaplan–Meier curve shows development of radiation pneumonitis among patients with no underlying lung disease, interstitial change and emphysema. The median times for developing radiation pneumonitis for patients with no underlying lung disease, interstitial change and emphysema were 150, 63 and 127 days, respectively. Patients with interstitial changes suffered from radiation pneumonitis earlier than those with no underlying lung disease ($p = 0.02$) and emphysema ($p = 0.02$).

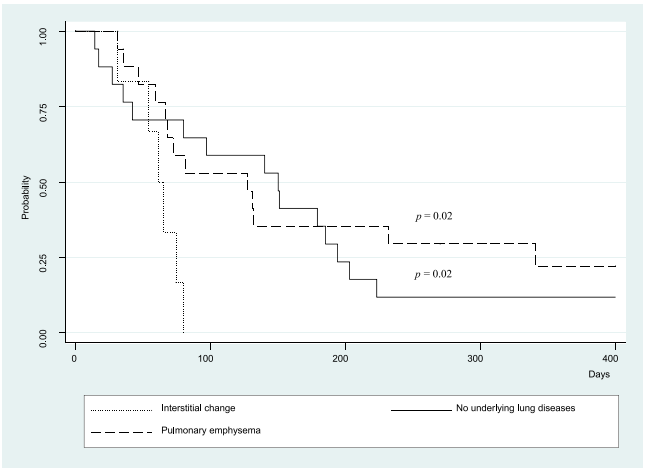


Figure 4. Patients with severe emphysema had lower risk of radiation pneumonitis than those with moderate ($p = 0.01$) and mild emphysema ($p = 0.04$).

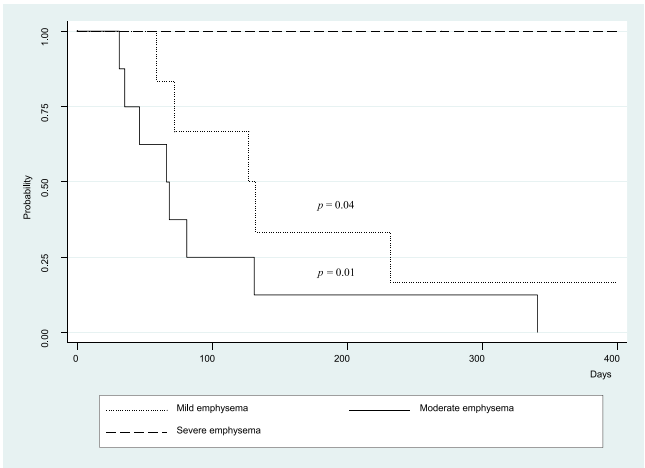
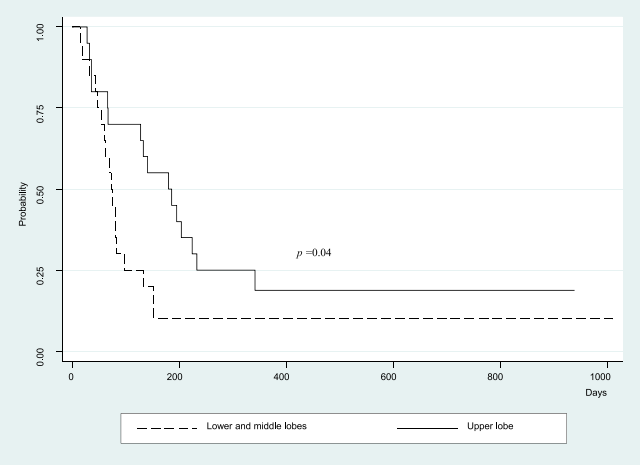


Figure 5. The median time to radiation pneumonitis in the treatment of tumours in the lower or middle lobe, and the upper lobe were 73 and 182 days, respectively. Radiation pneumonitis developed earlier in patients with tumours in the lower lobe than in the upper or middle lobe ($p = 0.04$).



with no underlying lung diseases, and moreover, severe COPD was a negative risk factor for RP following SBRT. Wang et al[18] also assessed whether poor pulmonary function was associated with RP. In their analysis, the risk of RP increased with high mean lung doses, the absence of COPD and high forced expiratory volume 1s. They concluded that poor pulmonary function did not increase the risk of RP. These results showed radiotherapy may be a good treatment option for patients with NSCLC who have COPD.

The limitation of this study is that there are only a small number of patients with severe emphysema. It is reported there are few patients with severe criteria of COPD,[19] therefore incidence of severe emphysema was predicted to be low. Further multi-institutional studies are needed to demonstrate our results. In this study CT scans were performed every 3 months, so grade I RP could have occurred before.

This report focuses on the morphological changes affecting RP. Therefore, this study is limited by the lack of physiological data. Combined morphological and physiological data, as well as morphological data by site, are needed to further investigate RP. In conclusion, patients with severe emphysema have a lower risk of RP when SBRT is performed for stage I NSCLC.

REFERENCES

1. Punturieri A, Szabo E, Croxton TL, Shapiro SD, Dubinett SM. Lung cancer and chronic obstructive pulmonary disease: needs and opportunities for integrated research. *J Natl Cancer Inst* 2009; **101**: 554–9. doi: 10.1093/jnci/djp023
2. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008; **178**: 738–44. doi: 10.1164/rccm.200803-435OC
3. Hiraoka M, Nagata Y. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the Japanese experience. *Int J Clin Oncol* 2004; **9**: 352–5.
4. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005; **63**: 5–24.
5. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. *Clin Radiol* 1982; **33**: 379–87.
6. Makita H, Nasuhara Y, Nagai K, Ito Y, Hasegawa M, Betsuyaku T, et al. Characterisation of phenotypes based on severity of emphysema in chronic obstructive pulmonary disease. *Thorax* 2007; **62**: 932–7.
7. Kimura T, Matsuura K, Murakami Y, Hashimoto Y, Kenjo M, Kaneyasu Y, et al. CT appearance of radiation injury of the lung and clinical symptoms after stereotactic body radiation therapy (SBRT) for lung cancers: are patients with pulmonary emphysema also candidates for SBRT for lung cancers? *Int J Radiat Oncol Biol Phys* 2006; **66**: 483–91.
8. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001; **163**: 1256–76.
9. Kyas I, Hof H, Debus J, Schlegel W, Karger CP. Prediction of radiation-induced changes in the lung after stereotactic body radiation therapy of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007; **67**: 768–74.
10. Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2013; **85**: 444–50. doi: 10.1016/j.ijrobp.2012.04.043
11. Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* 1998; **34**: 71–5.
12. Hope AJ, Lindsay PE, El Naqa I, Alaly JR, Vicic M, Bradley JD, et al. Modeling radiation pneumonitis risk with clinical, dosimetric, and spatial parameters. *Int J Radiat Oncol Biol Phys* 2006; **65**: 112–24.
13. Seppenwoolde Y, De Jaeger K, Boersma LJ, Belderbos JS, Lebesque JV. Regional differences in lung radiosensitivity after radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004; **60**: 748–58.
14. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; **176**: 532–55.
15. McLean KH. The pathogenesis of pulmonary emphysema. *Am J Med* 1958; **25**: 62–74.
16. Rancati T, Ceresoli GL, Gagliardi G, Schipani S, Cattaneo GM. Factors

predicting radiation pneumonitis in lung cancer patients: a retrospective study. *Radiother Oncol* 2003; **67**: 275–83.
17. Takeda A, Kunieda E, Ohashi T, Aoki Y, Oku Y, Enomoto T, et al. Severe COPD is correlated with mild radiation pneumonitis following stereotactic body radiotherapy. *Chest* 2012; **141**: 858–66. doi: 10.1378/chest.11-1193
18. Wang J, Cao J, Yuan S, Ji W, Arenberg D, Dai J, et al. Poor baseline pulmonary function may not increase the risk of radiation-induced lung toxicity. *Int J Radiat Oncol Biol Phys* 2013; **85**: 798–804. doi: 10.1016/j.ijrobp.2012.06.040
19. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan: the Nippon COPD Epidemiology study. *Respirology* 2004; **9**: 458–65.