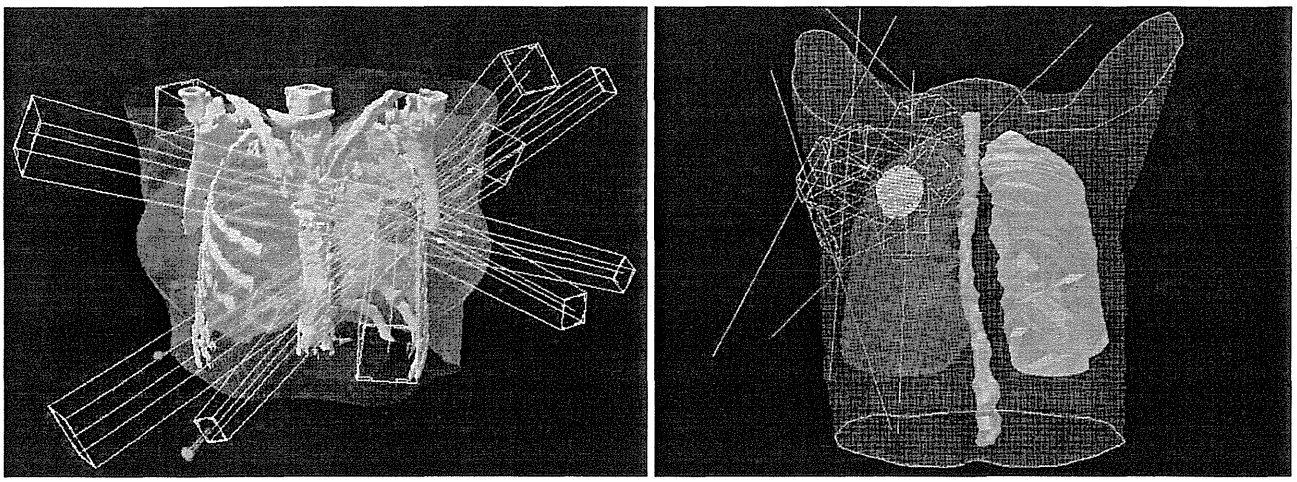

Fig. 1. A case of stereotactic body radiation therapy (SBRT) for early stage lung cancer (T1N0M0). SBRT is conducted on the left lung cancer by focusing radiation from six directions. Axial view, 3D image of radiation dose distribution.

tion point, while in Europe and the USA, the marginal dose of radiation at 80-90% is often used. It is important to note that treatment planning may differ according to the radiation field margin and the dose calculation method.

5. Pretreatment verification methods

Prior to each dose of irradiation, verification images are created and checked using a high-energy X-ray image, portal image, or in-room CT to confirm that the correct site is being irradiated. In SBRT in particular, it is essential to conduct verification prior to irradiation. To verify the reproducibility of irradiation before each treatment, verification images (confirmation images taken before irradiation using the imaging equipment) are obtained. Reproducibility of the body position with the simulation film during treatment planning is confirmed. As a result, administering irradiation within the usual error range of 2-3 mm is possible through verification of each result before each treatment. In the Japan Clinical Oncology Group (JCOG) 0403 multicenter collaborative clinical trial, a margin of 5 mm is essential. There are an increasing number of facilities that conduct pretreatment verification using either X-ray equipment attached to image-guided radiation therapy (IGRT) or by CT, with equipment set up in the same room as the radiotherapy equipment.

Clinical Results and Toxicities

1. Exposure dose and treatment outcomes

Many different fractionated irradiation techniques have been used: 12 Gy×4 fractions per radiation treatment [6], 10-12 Gy×5-6 fractions per radiation treatment [5], 7.5 Gy×8 fractions per radiation treatment [7], and 15 Gy×3 fractions per radiation treatment. Regardless of the technique used,

Table 1. Results of various clinical trials of stereotactic body radiation therapy for lung cancer

Reference	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control n (%)	Median follow-up (mo)
Uematsu et al. (2001) [5]	50-60	10	80% Margin	47/50 (94)	36
Arimoto et al. (1998) [8]	60	7.5	Isocenter	22/24 (92)	24
Timmerman et al. (2010) [9]	54	18	80% Margin	54/55 (98)	34
Onimaru et al. (2003) [7]	48-60	6-7.5	Isocenter	20/25 (80)	17
Wulf et al. (2004) [10]	45-56.2	15-15.4	80% Margin	19/20 (95)	10
Nagata et al. (2005) [6]	48	12	Isocenter	44/45 (97)	30
Xia et al. (2006) [11]	70 (50)	7 (5)	Isocenter	41/43 (95)	27
Baumann et al. (2009) [12]	45	15	67% Margin	53/57 (92)	35

when the biological effective dose (BED) is >100 Gy, the local control rate is 88-96% with some variation (Table 1) [5-12]. In these different fractionated irradiation methods, the radiation dose, total dose, and number of fractionations are often extrapolated using a linear quadratic (LQ) model calculation based on α/β values. For example, when the α/β value of the tumor is 10, a radiation dose of 12 Gy×4 fractions corresponds to 88 Gy×2 fractions. Using SBRT technology, it is possible to substantially increase the radiation dose.

Fowler [13] demonstrated that the LQ model can be clinically applied with few fractionations and that good localized control can be achieved with a BED > 100 Gy. In addition, it is unclear whether the number of radiations in SBRT can ultimately be reduced to one. However, for radiobiological reasons, fractionated irradiation is advantageous as long as hypoxic fractions exist in the tumor. Results from the USA and Europe estimate that 3-5 fractionated irradiations are the minimum number of irradiations while single irradiation is unsatisfactory.

Onishi et al. [14] examined cases from 13 medical facilities throughout Japan and reported treatment outcomes. While the local control rate was 86%, in cases able to undergo irradiation of BED > 100 Gy with surgery, the 5-year survival rate was excellent with 90% for the IA stage and 84% for the IB stage [14].

In Europe and the USA, Wulf et al. [10], Timmerman et al. [9], Xia et al. [11], and Baumann et al. [12] all report favorable local effects. However, the number of cases in these papers, when compared to cases in Japan, may have had poorer prognosis because more unfavorable cases were treated as subjects.

2. Normal tissue toxicities

In clinical results, the risk of radiation pneumonitis with symptoms greater than Common Terminology Criteria for Adverse Events (CTCAE)—grade 3 is extremely low compared with conventional radiotherapy for stage III lung cancer. In other words, provided an isolated tumor of < 4-5 cm in diameter is targeted in a lung, the irradiated volume of normal lung is within the permissible range. The majority of stage I lung cancer cases present asymptomatically, and care must therefore be taken with regard to treatment of emergent complications. However, in the subgroup of patients with poor respiratory function and in particular with underlying interstitial lung disease, there is a risk of fatal radiation pneumonitis (0.5-1.2%), and extra care must be taken [15]. Clinicians should be aware of the risk of other complications, such as rib fracture, intercostals neuralgia, pleural effusion, liver dysfunction, and brachial plexopathy. Furthermore, attention should be paid to extrapulmonary complications with central tumors close to the mediastinum. There have been reports of fatal hemoptysis [16,17] and fatal esophageal ulcers [18]. Appropriate risk management is essential in central lung cancers where irradiation of the mediastinum (heart/large artery, trachea/bronchi, and esophagus) is unavoidable.

3. Clinical trials

In Japan, a multicenter collaborative clinical trial, the "JCOG 0403 phase II clinical trial of SBRT for T1N0M0 non-small cell lung cancer" took place in 15 facilities throughout Japan. The trial evaluated the efficacy and safety of SBRT for T1N0M non-small lung cancer cases in both operable and inoperable cases. On the one hand, with cases unfit for standard surgery, the question is whether current standard therapy with a total dose of 60-70 Gy, at 2 Gy per day should be replaced. On the other hand, where surgery is possible but refused, the question is whether clinical outcomes equal to surgery can be achieved. The primary endpoint is the 3-year survival rate with secondary endpoints being the overall survival rate, the progression-free survival period, the type of recurrence, and adverse events. The treatment method comprises a total radiation dose of 48 Gy at 12 Gy per day per fraction, three or four times per week for a total of four fractions, with the total treatment period within four to eight days. The results of the operable (but rejected) cases, reported in 2010, showed that although majority of subjects were elderly individuals with a mean age of 79 years, the 3-year survival rate was 76% and the 3-year local control rate calculated as per the Radiation Therapy Oncology Group (RTOG) was 86%. There were very few adverse events over grade 3 (6%). In 2012, the results of the inoperable cases, also using elderly subjects with a mean age of 78 years, were reported. Here the 3-year survival rate was 60%; the 3-year local control rate was 88% with no grade 5 adverse events.

The RTOG 0239 results were reported in the USA in 2009. This clinical trial tested 60 Gy by 3 fractions for the purpose of local control in T1-3N0M0 inoperable lung cancers < 5 cm in size. The median observation period was 36 months, and there was a high local control rate (recurrence within the planning target volume) of 98% at 3 years. However, although there were no grade 5 adverse events, 4% were grade 4 and 24% were grade 3.

In the USA, studies currently underway include the RTOG 0618 on stereotactic irradiation (excluding partial response cases for local effectiveness) for operable lung cancer, the RTOG 0813 dose escalation study from 10 Gy×5 fractions for central hilar lung cancer, and the RTOG 0915 study comparing 12 Gy×4 fractions against 34 Gy×1. Furthermore, in Europe, a scandinavian stereotactic precision and conventional radiotherapy evaluation (SPACE) trial comparing 15

Gy×3 fractions against 2 Gy×35 fractions is currently underway.

Randomized controlled studies between surgery and SRT, including the commencement of American College of Surgeons Oncology Group (ACOSG)/RTOG trial and the randomized study to compare cyberknife to surgical Resection in stage I non-small cell lung cancer (STARS) trial are underway

The Outlook of SBRT

1. Screening and detection of early-stage lung cancer cases

Recent breakthroughs in CT imaging technology paved the way for the discovery of ground glass opacity (GGO) early-stage lesions in the lung. The only current option for such lesions is to obtain a definite diagnosis by surgery. However, it is common for patients with these lesions to be unsuitable for radical surgery because of concurrent lung disease. Studies are needed in which surgery and SBRT are compared for GGO lesions that expand during observation [19].

2. Cases with poor respiratory function

SBRT is often used for patients with poor respiratory function who are considered unsuitable for surgery. Of these patients, only those with chronic obstructive pulmonary disease are not at high risk of radiation pneumonitis following irradiation; therefore, SBRT is considered suitable. However, there is no consensus on the possibility of SRT for patients with any degree of impaired pulmonary function. An analysis of these adaptive criteria is anticipated. In cases with active interstitial pneumonia, there have been many reports of fatal irradiation pneumonitis, and it is generally accepted that they should be excluded from treatment.

3. Hilar lung cancer

When lung cancer develops near the pulmonary hilum, the treatment raises the risk of radiation exposure to key structures, such as the central trachea and bronchi, the esophagus, the pulmonary artery, and the spinal cord. When the tolerance dose is exceeded in these organs, there is the risk of massive hemorrhage because of ulcers in the trachea or bronchi and peripheral bronchial occlusion [16,17]. However, there is a report of no complications with standard high-dose irradiation of 10-15 Gy as far as keeping normal tissue dose constraints [20]. Clinical trials are underway with the aim of finding optimal radiation doses.

4. Expanding the indication toward advanced lung cancer

In advanced-stage lung cancer, the irradiation volume increases, meaning that it is difficult to apply SBRT technology in its current form. However, after 60-70 Gy of 3D irradiation, it may be possible to conduct additional SBRT limited to the remaining tumor. Factors that influence additional radiation exposure include volume effect, fractionation effect, and total treatment duration. Total radiation dose distribution, including these biological factors, needs to be introduced into treatment planning in the future.

5. Four-dimensional radiotherapy planning

Future planning of 4D treatment should take into consideration time factors in existing geometric plans of 3D treatment. For example, even if the same dose of radiation is administered, the therapeutic effects differ greatly depending on the fractionated radiation dose and treatment duration. Furthermore, the final treatment plan may differ depending on the sensitivity to the initial irradiation. Ideally, treatment planning would take place before each irradiation. Gating and tracking are referred to as 4D treatment, but a new 4D treatment plan, including 4D CT, is expected in the future.

6. Development of new IGRT equipment

Current advances in mechanical engineering are outstanding. The IRGT devices are new image capture devices introduced into the irradiation room that reflect images captured before and after treatment. Several devices have been developed and employed clinically: the Hokkaido University real-time tumor-tracking radiotherapy irradiation device with on board imaging on the LINAC, a new irradiation device by Varian and Elekta, Cyberknife, Hyperknife (precession motion irradiation), Tomotherapy, and Vero. Development of these new irradiation devices may enable the future development of innovative irradiation techniques. Remarkable treatment outcomes have been reported in ion beam radiotherapy [21], and a comparative study against X-rays is awaited.

7. New indications for SBRT

In Japan, SBRT is covered by public health insurance and is used for patients with primary lung cancer, metastatic lung cancer, primary liver cancer, metastatic liver cancer and

arteriovenous malformation of the spinal cord.

There are treatment results for roughly 300 cases of liver tumors in Japan. However, radical resection, transcatheter arterial chemoembolization, local ethanol injection, and local ablation using radio frequency waves and microwaves are already conducted in everyday clinical practice. The treatment indications for SBRT in comparison to these established methods of treatment need better definition and guidelines. In the USA, an RTOG clinical trial is underway to determine the dose of radiation in SBRT suitable for primary liver cancer.

In addition to these diseases covered by health insurance, SBRT technology is extremely useful for any lesion limited to a local site. Therefore, renal cancers, adrenal gland tumors, paravertebral tumors, prostate cancer, and pancreatic cancer are being targeted [22].

Conclusion

Radiation therapy is currently advancing from 3D to 4D treatment modalities using IGRT technique. In the future, we can look forward to the development and clinical application of high-precision radiotherapy, especially in SBRT.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

References

1. Blomgren H, Lax I, Goranson H, Krapelien T, Nilsson B, Naslund I, et al. Radiosurgery for tumors in the body: clinical experience using a new method. J Radiosurg. 1998;1;63-74.
2. Uematsu M, Shioda A, Tahara K, Fukui T, Yamamoto F, Tsumatori G, et al. Focal, high dose, and fractionated modified stereotactic radiation therapy for lung carcinoma patients: a preliminary experience. Cancer. 1998;82:1062-70.
3. Onishi H, Kuriyama K, Komiyama T, Tanaka S, Sano N, Aikawa Y, et al. A new irradiation system for lung cancer combining linear accelerator, computed tomography, patient self-breath-holding, and patient-directed beam-control without respiratory monitoring devices. Int J Radiat Oncol Biol Phys. 2003;56:14-20.
4. Negoro Y, Nagata Y, Aoki T, Mizowaki T, Araki N, Takayama K, et al. The effectiveness of an immobilization device in conformal radiotherapy for lung tumor: reduction of respiratory tumor movement and evaluation of the daily setup accuracy. Int J Radiat Oncol Biol Phys. 2001;50:889-98.
5. Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys. 2001;51:666-70.
6. Nagata Y, Takayama K, Matsuo Y, Norihisa Y, Mizowaki T, Sakamoto T, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. Int J Radiat Oncol Biol Phys. 2005;63:1427-31.
7. Onimaru R, Shirato H, Shimizu S, Kitamura K, Xu B, Fukumoto S, et al. Tolerance of organs at risk in small-volume, hypofractionated, image-guided radiotherapy for primary and metastatic lung cancers. Int J Radiat Oncol Biol Phys. 2003; 56:126-35.
8. Arimoto T, Usubuchi H, Matsuzawa T. Small volume multiple non-coplanar arc radiotherapy for tumors of the lund, head and neck and the abdominopelvic region. In: Lemke HU, editor. CAR'98 Computer assisted radiology and surgery. Tokyo: Elsevier; 1998. p. 257-61.
9. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303:1070-6.
10. Wulf J, Haedinger U, Oppitz U, Thiele W, Mueller G, Flentje M. Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients. Int J Radiat Oncol Biol Phys. 2004;60:186-96.
11. Xia T, Li H, Sun Q, Wang Y, Fan N, Yu Y, et al. Promising clinical outcome of stereotactic body radiation therapy for patients with inoperable Stage I/II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2006;66:117-25.
12. Baumann P, Nyman J, Hoyer M, Wennberg B, Gagliardi G, Lax I, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol. 2009;27: 3290-6.
13. Fowler JF. Sensitivity analysis of parameters in linear-quadratic radiobiologic modeling. Int J Radiat Oncol Biol Phys. 2009;73:1532-7.
14. Onishi H, Araki T, Shirato H, Nagata Y, Hiraoka M, Gomi K, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer. 2004; 101:1623-31.
15. Takeda A, Enomoto T, Sanuki N, Nakajima T, Takeda T, Sayama K, et al. Acute exacerbation of subclinical idiopathic pulmonary fibrosis triggered by hypofractionated stereotactic body radiotherapy in a patient with primary lung cancer and slightly focal honeycombing. Radiat Med. 2008;26:504-7.
16. Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y, et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiother-

apy Group. Int J Radiat Oncol Biol Phys. 2009;75:343-7.
17. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med. 2012; 366:2327-9.
18. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol. 2006;24:4833-9.
19. Inoue T, Shimizu S, Onimaru R, Takeda A, Onishi H, Nagata Y, et al. Clinical outcomes of stereotactic body radiotherapy for small lung lesions clinically diagnosed as primary lung cancer on radiologic examination. Int J Radiat Oncol Biol Phys. 2009;75:683-7.
20. Chang JY, Balter PA, Dong L, Yang Q, Liao Z, Jeter M, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2008;72:967-71.
21. Miyamoto T, Baba M, Yamamoto N, Koto M, Sugawara T, Yashiro T, et al. Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypofractionated regimen. Int J Radiat Oncol Biol Phys. 2007;67:750-8.
22. Nagata Y, Wulf J, Lax I, Timmerman R, Zimmermann F, Stojkovski I, et al. Stereotactic radiotherapy of primary lung cancer and other targets: results of consultant meeting of the International Atomic Energy Agency. Int J Radiat Oncol Biol Phys. 2011;79:660-9.

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Clinical Investigation: Thoracic Cancer

Dose–Volume Metrics Associated With Radiation Pneumonitis After Stereotactic Body Radiation Therapy for Lung Cancer

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Summary

To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer, this study analyzed 74 patients who underwent SBRT for primary lung cancer. RP grade 2 or worse was observed in 15 patients (20.3%). Lung V25 and PTV volume were significant factors. SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

Purpose: To identify dose–volume factors associated with radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for lung cancer.

Methods and Materials: This study analyzed 74 patients who underwent SBRT for primary lung cancer. The prescribed dose for SBRT was uniformly 48 Gy in four fractions at the isocenter. RP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3. Symptomatic RP was defined as grade 2 or worse. Optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were sought using the following dose–volume metrics: PTV volume (ml), mean lung dose (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40 (%) of both lungs excluding the PTV.

Results: With a median follow-up duration of 31.4 months, symptomatic RP was observed in 15 patients (20.3%), including 1 patient with grade 3. Optimal cut-offs for pulmonary dose–volume metrics were V25 and V20. These two factors were highly correlated with each other, and V25 was more significant. Symptomatic RP was observed in 14.8% of the patients with V25 <4.2%, and the rate was 46.2% in the remainder ($p = 0.019$). PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, $p = 0.020$). The patients were divided into three subgroups (patients with PTV <37.7 ml; patients with, PTV ≥37.7 ml and V25 <4.2%; and patients with PTV ≥37.7 ml and V25 ≥4.2%); the incidence of RP grade 2 or worse was 11.1%, 23.5%, and 50.0%, respectively ($p = 0.013$).

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Conclusions: Lung V25 and PTV volume were significant factors associated with RP after SBRT.

Keywords: Radiation pneumonitis, Stereotactic body radiation therapy, Dose–volume analysis

Introduction

Stereotactic body radiation therapy (SBRT) consists of two key features. One is its high degree of accuracy, which allows delivery of a high dose to a very limited volume while limiting the dose to normal tissues. The other key feature is hypofractionation. With conventional radiotherapy, schedules of 30 to 40 fractions are commonly used, with a total dose of 60 to 74 Gy for lung cancer. SBRT is usually performed in a single fraction or two to five fractions with a much higher fractional dose (6–20 Gy). These key features of SBRT lead to high control rates of local tumors (1, 2). Use of SBRT should improve the prognosis for inoperable or elderly patients with early stage non-small-cell lung cancer (NSCLC) (3).

The safety of SBRT is being confirmed in multi-institutional Phase II trials for peripheral lung cancer in both inoperable patients (1, 4) and operable patients (2). In the Radiation Therapy Oncology Group (RTOG) trial 0236 (1), protocol-specified treatment-related grade 3 and 4 adverse events occurred in 12.7% and 3.6%, respectively; no grade 5 adverse events were reported. In the Nordic Phase II study of SBRT (4), grade 3 toxicity was seen in 21%; no grade 4 or 5 toxicity was reported. Nagata *et al.* reported grade 3 toxicity in 6.2% of operable patients in the Japan Clinical Oncology Group (JCOG) 0403 (2).

Radiation pneumonitis (RP) is one of the most common toxicities after SBRT, as well as after conventional radiotherapy to the lung. The reported rates of symptomatic RP after SBRT range from 9% to 28% (5–11). Although most of the RP was grade 2 and manageable, a few cases were severe, and there is a potential risk of mortality (5). It is very important to develop a method to predict the risk of RP after SBRT for the lung.

The dose–volume metrics from a treatment plan might be a predictor for RP. In conventional radiotherapy for the lung, many dose–volume data are available, and dose constraints have been proposed to reduce the risk of pneumonitis. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommended a lung V20 $\leq$30% to 35% and mean lung dose (MLD) $\leq$20 to 23 Gy to limit the risk of RP to $\leq$20% in definitive radiotherapy for NSCLC with conventional fractionation (12). However, there are no established criteria regarding dose–volume factors in hypofractionated SBRT. Therefore, we searched for dose–volume factors associated with RP after SBRT for lung cancer.

Methods and Materials

This study analyzed consecutive 74 patients who underwent SBRT for pathology-proven NSCLC from September 2003 to March 2008. All patients were diagnosed with Stage I lung cancer based on CT. The eligibility criteria for SBRT for Stage I lung cancer were as follows: surgery was contraindicated or refused; maximal tumor diameter was 40 mm or less; the tumor was not adjacent to mediastinal organs (spinal cord, esophagus, heart, and main bronchus); the patient could remain stable for longer than 30 min with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; the patient had no active interstitial pneumonitis; and written informed consent was obtained. Patient characteristics are shown in Table 1. For these patients, the prescribed dose of SBRT was uniformly 48 Gy in four fractions at the isocenter. A median in overall treatment time was 5 days (range, 4–12 days). Chemotherapy was not administered unless disease progression was confirmed.

SBRT procedure

Details of our SBRT procedure have been described in our previous reports (13, 14). The patient was immobilized with a stereotactic body frame (Elekta AB, Stockholm, Sweden). Irradiation was performed with 6-MV x-ray beams from a linear accelerator (Clinac 2300 C/D; Varian Medical Systems, Palo Alto, CA) with multiple non-coplanar static ports (range, five to eight ports). The beams were shaped into a planning target volume (PTV) plus 5-mm margins using multi leaf collimators.

The SBRT was planned with the Eclipse (Varian Medical Systems) treatment planning system. An internal target volume (ITV) was determined using computed tomography (CT) with a slow-scan technique, considering tumor motion assessed by x-ray fluoroscopy. The PTV was defined as the ITV with a 5-mm margin for setup uncertainty. To delineate lung volumes, the segmentation wizard in Eclipse was applied to the slow-scan CT images with a threshold value of −300 Hounsfield units (HU). The lung

Table 1 Patient characteristics

Sex	
Male	55
Female	19
Age (y)	
Median (range)	77 (63–88)
ECOG performance status	
0	37
1	30
2	7
Operability	
Operable	24
Inoperable	50
Histology	
Adenocarcinoma	36
Squamous cell carcinoma	30
Other*	8
T-stage (7th UICC staging)	
T1a	26
T1b	27
T2a	21

Abbreviation: UICC = Union for International Cancer Control.
* Other included three large-cell carcinomas and five non-small-cell carcinomas not otherwise specified.

volumes were then trimmed manually to remove overlapping regions involving the PTV and bronchi.

RP grading

The patients were followed up 1, 2, 4, 6, 9, and 12 months after the SBRT, then every 3 months for Years 2 to 5, and then every 6 months thereafter. CT was performed every 2 to 4 months in the first year, every 6 months between Years 1 and 5 after the treatment, and annually thereafter.

Radiation pneumonitis was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v.3 for pneumonitis, which consists of the following grades: grade 1, asymptomatic with radiographic findings only; grade 2, symptomatic and not interfering with the activities of daily living (ADL); grade 3, symptomatic, interfering with the ADL and O_2 indicated; and grade 4, life-threatening, ventilatory support indicated. We defined symptomatic RP as grade 2 or worse.

Statistical analysis

The dose–volume metrics were re-calculated using the Analytical Anisotropic Algorithm (AAA) with the same monitor units as used in the clinical setting. The grid size for the calculation was $2.5 \times 2.5 \times 2.5$ mm^3.

The following dose–volume metrics were evaluated in this study: PTV volume (ml), MLD (Gy), and V5, V10, V15, V20, V25, V30, V35, and V40, where Vd is the relative volume of normal lung (%) that received more than a threshold dose of d Gy. We defined normal lung as both lungs excluding the PTV.

The optimal cut-offs dividing the patient population into two subgroups based on the incidence of symptomatic RP were searched using the recursive partitioning method. After dividing the groups, the occurrence rates for symptomatic RP were compared using Fisher's exact test. R version 2.13.1 with the rpart package (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses. Statistical significance was defined as $p < 0.05$.

Results

With a median follow-up duration of 31.4 months (range, 4.2–65.0 months), symptomatic RP was observed in 15 patients (20.3%), consisting of 14 patients with grade 2 and 1 patient with grade 3. RP was diagnosed based on symptoms with radiologic findings. The median time to symptomatic RP was 4.5 months (range, 1.1–16.1 months).

Table 2 summarizes the dose–volume metrics of the PTV and normal lung. The PTV ranged from 9.9 to 86.6 ml (median, 32.5 ml). The median MLD was 3.2 Gy (range, 1.6–7.6 Gy). The median lung V20 and V25 were 4.4% and 2.9%, respectively. The lung metrics (MLD and V5–40) were highly correlated with each other, with correlation coefficients (R) of 0.61 to 0.99. In contrast, the correlations between the PTV volume and lung metrics were weak (R = 0.37–0.59). The PTV volume, MLD, V20, and V25 were respectively 42.1 ml, 3.7 Gy, 5.4%, and 3.8% in mean for patients with grade 2 RP. Those values were respectively 38.1 ml, 4.0 Gy, 5.0%, and 3.3% for a patient with grade 3 RP.

The optimal cut-offs for the dose–volume metrics are shown in Table 3. Lung V25 and V20 were significant factors, and V25 was more significant. The rate of symptomatic RP was 14.8% in the patients with V25 <4.2%, whereas the rate was 46.2% in the remainder (p = 0.019). The PTV volume was another significant factor. The symptomatic RP rate was significantly lower in the group with PTV <37.7 ml compared with the larger PTV group (11.1% vs. 34.5%, p = 0.020). On classifying the patient population into three subgroups (patients with PTV <37.7 ml, n = 45; patients with PTV ≥37.7 ml and V25 <4.2%, n = 17; and patients with PTV ≥37.7 ml and V25 ≥4.2%, n = 12), the incidence of symptomatic RP was 11.1%, 23.5%, and 50.0%, respectively (p = 0.013).

Table 2 Dose–volume metrics

		Median (range)
PTV	Volume (ml)	32.5 (9.9–86.6)
Lung	Mean dose (Gy)	3.2 (1.6–7.6)
	V40 (%)	0.7 (0–2.9)
	V35 (%)	1.4 (0.2–4.8)
	V30 (%)	2.0 (0.5–6.6)
	V25 (%)	2.9 (0.9–9.5)
	V20 (%)	4.4 (1.7–13.1)
	V15 (%)	6.7 (2.6–18.2)
	V10 (%)	10.3 (4.4–25.1)
	V5 (%)	16.7 (7.1–37.3)

Abbreviation: PTV = planning target volume.

Discussion

We investigated the dosimetric factors associated with symptomatic RP (≥grade 2) after SBRT, and found that PTV and lung V25 were significant factors. The optimal cut-offs for these factors (PTV <37.7 ml and V25 <4.2%) were much lower than prespecified constraints that other SBRT trials used to mainly limit the risk of grade 3 toxicities (*e.g.*, MLD <18 Gy, lung V40 <100 ml, V15 <25%, and V20 <20% for the JCOG 0403 trial; and lung V20 <10% for RTOG 0236). As only 1 patient in our cohort had grade 3 RP, it was difficult to build a model for predicting severe RP (*e.g.*, grade 3 or worse). Severe RP is uncommon after SBRT for the lung. Grade 3 RP was observed in 3.6% of the patients in RTOG

Table 3 Optimal cut-off values and crude rates of symptomatic RP

	Cut-off values	Symptomatic RP		p values
		<Cut-off	≥Cut-off	
PTV (ml)	37.7	11.1%	34.5%	0.020*
MLD (Gy)	4.7	17.2%	40.0%	0.110
V40 (%)	1.6	17.6%	50.0%	0.093
V35 (%)	1.9	15.3%	40.0%	0.066
V30 (%)	2.8	15.3%	40.0%	0.066
V25 (%)	4.2	14.8%	46.2%	0.019*
V20 (%)	5.8	15.0%	42.9%	0.030*
V15 (%)	4.9	5.3%	25.5%	0.096
V10 (%)	10.1	11.4%	28.2%	0.089
V5 (%)	26.8	17.9%	42.9%	0.143

Abbreviations: MLD = mean lung dose; PTV = planning target volume; RP = radiation pneumonitis.
* Statistically significant.

Table 4 Summary of reports on dose–volume factors associated with radiation pneumonitis grade 2 or worse after stereotactic body radiation therapy

First author, reference	Year	*n*	Dose fractionation (total dose/fractions)	Heterogeneity correction algorithm	PTV volume (ml), median (range)	RP grade 2 or worse (crude rate)	Scoring system	Suggested factors
Yamashita (5)	2007	25	48 Gy/4–6 fr	CC	43.9 (7.5–239.4)	28.0%	CTCAE v3	CI
Ricardi (6)	2009	60	45 Gy/3 fr or 26 Gy/1 fr	CC	*NA*	14.3%	RTOG	MLD† (ipsilateral lung-CTV)
Borst (7)	2009	128	35–60 Gy/4–8 fr	CS	9.6 (0.2–106.9) in GTV	10.9%	CTC v2	MLD† (bilateral lung-GTV)
Guckenberger (8)	2010	59	26 Gy/1 fr or 37.5 Gy/3 fr	AAA	33 (2–236)	18.6%	SWOG	MLD† and V2.5–50 (ipsilateral lung-CTV)
Ong (9)	2010	18	55 Gy/5 fr or 60 Gy/8 fr	AAA	137 (87–286)	27.8%	CTCAE v4	V5 (contra-lateral lung)
Barriger (10)	2010	251	24–66 Gy/3–5 fr	*NA**	48.3 (8–401)	9.4%	CTC v2	MLD and V20 (bilateral lung-GTV)
Stauder (11)	2011	84	32–60 Gy/3–5 fr	*NA**	42.9 (5.3–321.5)	12.5%	CTCAE v3	PTV maximal dose
Present study		74	48 Gy/4 fr	AAA	32.5 (9.9–86.6)	20.3%	CTCAE v3	PTV volume and V25 (bilateral lung-PTV)

Abbreviations: AAA = analytical anisotropic algorithm; CC = collapsed cone convolution superposition; CI = conformity index; CS = convolution–superposition; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; fr = fractions; MLD = mean lung dose; NA = not available; RP = radiation pneumonitis; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group.

* Authors reported that tissue heterogeneity was corrected in some patients, but information on heterogeneity correction algorithm was not available.

† MLD was evaluated using normalized total dose, which is the equivalent dose in 2-Gy fractions.

0236 (1) and in 3.1% of the operable patients in JCOG 0403 (2). Baumann *et al.* reported that no one developed grade 3 pneumonitis in their Phase II trial of SBRT (4).

Table 4 summarizes published reports that focused on the dose–volume metrics associated with RP grade 2 or worse after SBRT. The RP rates varied from 9.4% to 28.0%, and the suggested dose–volume factors for RP differed among the reports. This variation might be caused by differences in the PTV volume, dose fractionation schedule, and RP scoring system.

The scoring criteria for RP differ among toxicity grading systems. Steroid use for pneumonitis is scored as grade 3 in the RTOG system, whereas the Common Toxicity Criteria (CTC) v.2 scores symptomatic patients requiring steroids as grade 2. CTCAE v.3 removed steroid use from the pneumonitis scoring system. From CTCAE v.3 to v.4, the pneumonitis score was modified slightly. Grade 2 pneumonitis in CTCAE v.4 was defined as "symptomatic, medical intervention indicated or limiting instrumental ADL." The number of patients considered to have RP depends on which system is used to evaluate RP. Tucker *et al.* retrospectively evaluated 442 patients who received definitive radiotherapy for NSCLC using the three RP grading systems: RP grade 2 or worse was observed in 129 (29%), 109 (25%), and 195 (44%) patients according to RTOG, CTC v.2, and CTCAE v.3, respectively (15). The rate of grade 2 to 3 RP according to CTCAE v.3 seemed to be slightly higher (20.3%) in our study compared with other studies that evaluated it using CTC v.2 or the RTOG system. Nevertheless, we administered steroids to 6 patients (8.1%) only. Scoring systems should be considered when interpreting the results regarding RP.

This study indicated that a large PTV is a significant risk factor for symptomatic RP after SBRT. Ong *et al.* treated large tumors in 18 patients with a PTV >80 ml (median, 137 ml) with SBRT using volumetric modulated arc therapy (9). The investigators reported 5 patients (27.8%) with RP grade 2 to 3. We speculate that the large PTV volume was one of the reasons for their relatively high risk of pneumonitis. From our results, minimizing the PTV is one way to limit the RP risk. When a lung tumor has large respiratory motion, respiration management will contribute to the prevention of RP by reducing the PTV.

To correct for differences in dose fractionation, three reports (6–8) in Table 4 used normalized total doses (NTD), which were equivalent doses in 2-Gy fractions in terms of pulmonary toxicity. Borst *et al.* evaluated the relationship between the MLD and the incidence of RP after SBRT (7). They calculated the MLD in the NTD form using the linear-quadratic model with an α/β ratio of 3 Gy. A significant dose–response relationship was found between RP and MLD. We used a uniform dose fractionation of 48 Gy in four fractions for all of our patients, and we evaluated dosimetric factors in the form of a nominal dose. Although we cannot apply normalization to our data exactly, the median MLD was roughly estimated to be 3.7 Gy in NTD. The usefulness of NTD evaluation for pulmonary toxicity after SBRT should be validated in future studies.

Heterogeneity correction and the definition of lung volume may influence the dose–volume factors of the lung. De Jaeger *et al.* evaluated differences between the equivalent–pathlength and convolution–superposition algorithms in MLD and V20 for 68 patients treated with conformal radiotherapy for NSCLC (16). MLD and V20 differed between the two algorithms by 16.9% and 12.0% on average, respectively. The TD_{50} for RP grade 2 or worse in MLD was estimated to be 34.1 Gy with the equivalent-pathlength algorithm, whereas the value was 29.2 Gy with the

convolution–superposition algorithm. Because most related reports have used convolution–superposition algorithms, we applied the AAA, which is a convolution–superposition algorithm, to recalculate the dose–volume data so as to limit the influences of heterogeneity correction.

Our definition of lung volume was both lungs segmented with a threshold value of −300 HU on slow-scan CT from which PTV was excluded. Lung volume can vary depending on which lung is evaluated (ipsilateral, contralateral, or bilateral), exclusion of tumor volume (GTV or PTV), type of planning CT (slow-scan CT, 4D CT, or breath-hold CT), and the threshold HU for segmentation. When the PTV is subtracted from the lung volume, a high-dose volume within the PTV margin is not evaluated as dose–volume factors for the lung. These conditions were not always stated in the previous papers, and future articles should include this information.

Factors other than the dose–volume metrics also affect the occurrence of pneumonitis after SBRT. The serum level of Krebs von den Lungen-6 (KL-6) is a predictor of RP. Hara *et al.* evaluated 16 patients who received single-fraction SBRT with 20 to 35 Gy (17). The relative increase in the serum KL-6 between before and at 2 months after SBRT was significantly correlated with the occurrence of grade 3 RP by the RTOG criteria. Iwata *et al.* reported that the pretreatment serum KL-6 levels, gender, and PTV volume were correlated with symptomatic RP in a univariate analysis, and the pretreatment KL-6 levels remained significant in a multivariate analysis (18). They concluded that patients with a pretreatment KL-6 level ≥300 U/ml should be followed carefully for the occurrence of RP. CT or x-ray imaging before and after SBRT should help to predict severe RP. Yamashita *et al.* recommended prescreening of interstitial pneumonitis on CT, in addition to checking the serum KL-6 and surfactant protein-D (SP-D) levels to limit the risks of severe RP (19). They reported that after introducing the prescreening, the occurrence rate of RP grade 4 to 5 decreased from 18.8% to 3.5%. Takeda *et al.* reported that the early appearance of RP on chest x-ray after SBRT was correlated with the severity of RP (20). The radiographic appearance of RP during the initial 2 months indicated a 40% risk for grade 3 RP, whereas the risk was only 1.2% when the radiologic change appeared 3 months after SBRT. Considering biomarkers (KL-6 and SP-D) and radiologic imaging as well as dose–volume factors helps us to limit the risks for severe pneumonitis after SBRT.

Our study has several limitations. First, this study was based on a retrospective review; thus, it was prone to selection bias. Second, the number of RP events was limited in the present study. Third, that clinical factors other than dose–volume metrics were not taken into consideration. Prospective data are awaited to investigate a correlation between pulmonary toxicities and dosimetric factors.

Conclusion

In conclusion, this study found that the lung V25 and PTV volumes were significant factors associated with RP after SBRT. Use of SBRT with PTV ≥37.7 ml and lung V25 ≥4.2% indicated a 50% risk of RP grade 2 or worse.

References

1. Timmerman R, Paulus R, Galvin J, *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070–1076.
2. Nagata Y, Hiraoka M, Shibata T, *et al.* A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group (JCOG0403). *Int J Radiat Oncol Biol Phys* 2010;78:S27–S28.
3. Palma D, Visser O, Lagerwaard FJ, *et al.* Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. *J Clin Oncol* 2010;28:5153–5159.
4. Baumann P, Nyman J, Hoyer M, *et al.* Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer—a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. *Radiother Oncol* 2008;88:359–367.
5. Yamashita H, Nakagawa K, Nakamura N, *et al.* Exceptionally high incidence of symptomatic grade 2-5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. *Radiat Oncol* 2007;2:21.
6. Ricardi U, Filippi AR, Guarneri A, *et al.* Dosimetric predictors of radiation-induced lung injury in stereotactic body radiation therapy. *Acta Oncol* 2009;48:571–577.
7. Borst GR, Ishikawa M, Nijkamp J, *et al.* Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy. *Radiother Oncol* 2009;91:307–313.
8. Guckenberger M, Baier K, Polat B, *et al.* Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol* 2010;97:65–70.
9. Ong CL, Palma D, Verbakel WFAR, Slotman BJ, Senan S. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy (SBRT): Planning considerations and early toxicity. *Radiother Oncol* 2010;97:431–436.
10. Barriger RB, Forquer JA, Brabham JG, *et al.* A dose–volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2012;82:457–462.
11. Stauder MC, Macdonald OK, Olivier KR, *et al.* Early pulmonary toxicity following lung stereotactic body radiation therapy delivered in consecutive daily fractions. *Radiother Oncol* 2011;99:166–171.
12. Marks LB, Bentzen SM, Deasy JO, *et al.* Radiation dose–volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76:S70–S76.
13. Takayama K, Nagata Y, Negoro Y, *et al.* Treatment planning of stereotactic radiotherapy for solitary lung tumor. *Int J Radiat Oncol Biol Phys* 2005;61:1565–1571.
14. Hiraoka M, Matsuo Y, Takayama K. Stereotactic body radiation therapy for lung cancer: Achievements and perspectives. *Jpn J Clin Oncol* 2010;40:846–854.
15. Tucker SL, Jin H, Wei X, *et al.* Impact of toxicity grade and scoring system on the relationship between mean lung dose and risk of radiation pneumonitis in a large cohort of patients with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010;77:691–698.
16. De Jaeger K, Hoogeman MS, Engelsman M, *et al.* Incorporating an improved dose-calculation algorithm in conformal radiotherapy of lung cancer: Re-evaluation of dose in normal lung tissue. *Radiother Oncol* 2003;69:1–10.
17. Hara R, Itami J, Komiyama T, Katoh D, Kondo T. Serum levels of KL-6 for predicting the occurrence of radiation pneumonitis after stereotactic radiotherapy for lung tumors. *Chest* 2004;125:340–344.
18. Iwata H, Shibamoto Y, Baba F, *et al.* Correlation between the serum KL-6 level and the grade of radiation pneumonitis after stereotactic body radiotherapy for stage I lung cancer or small lung metastasis. *Radiother Oncol* 2011;101:267–270.
19. Yamashita H, Kobayashi-Shibata S, Terahara A, *et al.* Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy. *Radiat Oncol* 2010;5:32.
20. Takeda A, Ohashi T, Kunieda E, *et al.* Early graphical appearance of radiation pneumonitis correlates with the severity of radiation pneumonitis after stereotactic body radiotherapy (SBRT) in patients with lung tumors. *Int J Radiat Oncol Biol Phys* 2010;77:685–690.

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Physics Contribution

Functional Image-Guided Radiotherapy Planning in Respiratory-Gated Intensity-Modulated Radiotherapy for Lung Cancer Patients with Chronic Obstructive Pulmonary Disease

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Summary

We investigated the incorporation of functional lung image-derived low attenuation area (LAA) based on 4D-CT into respiratory-gated IMRT or VMAT in treatment planning for lung cancer patients with COPD. Respiratory-gated plans (anatomic and functional) were compared and the lung V20 found to be lower in the functional than the anatomic plan through a reduction in MLD. Functional image-guided planning appears to be helpful in preserving functional lung in lung cancer patients with COPD.

Purpose: To investigate the incorporation of functional lung image-derived low attenuation area (LAA) based on four-dimensional computed tomography (4D-CT) into respiratory-gated intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) in treatment planning for lung cancer patients with chronic obstructive pulmonary disease (COPD).

Methods and Materials: Eight lung cancer patients with COPD were the subjects of this study. LAA was generated from 4D-CT data sets according to CT values of less than than −860 Hounsfield units (HU) as a threshold. The functional lung image was defined as the area where LAA was excluded from the image of the total lung. Two respiratory-gated radiotherapy plans (70 Gy/35 fractions) were designed and compared in each patient as follows: Plan A was an anatomical IMRT or VMAT plan based on the total lung; Plan F was a functional IMRT or VMAT plan based on the functional lung. Dosimetric parameters (percentage of total lung volume irradiated with ≥20 Gy [V20], and mean dose of total lung [MLD]) of the two plans were compared.

Results: V20 was lower in Plan F than in Plan A (mean 1.5%, $p = 0.025$ in IMRT, mean 1.6%, $p = 0.044$ in VMAT) achieved by a reduction in MLD (mean 0.23 Gy, $p = 0.083$ in IMRT, mean 0.5 Gy, $p = 0.042$ in VMAT). No differences were noted in target volume coverage and organ-at-risk doses.

Conclusions: Functional IGRT planning based on LAA in respiratory-guided IMRT or VMAT appears to be effective in preserving a functional lung in lung cancer patients with COPD.

Keywords: Functional imaging, 4D-CT, IMRT, COPD

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Introduction

One of the most severe complications in radiotherapy for lung cancer is radiation pneumonitis (RP). Reduction of the incidence of severe RP requires a reduction of the lung dose, such as V20 which is defined as the percentage of pulmonary volume irradiated to ≥20 Gy. It is also one of the significant dosimetric risk factors for the incidence and severity of RP (1). Chronic obstructive pulmonary disease (COPD) is a recognized risk factor for RP (2). There has been a worldwide increase of the prevalence of COPD and as the population ages, the incidence of COPD is expected to increase (3). Pulmonary emphysema (PE) is a subtype of COPD, and defined pathologically as a group of diseases that demonstrate anatomic alterations in the lung, characterized by enlargement of airspaces distal to the terminal bronchioles, accompanied by destructive changes of alveolar walls (4). These lesions are seen as low-attenuation areas (LAAs) on CT scans, and are established findings on the imaging diagnosis of COPD (5, 6). Kimura *et al.* reported a correlation between the incidence of RP and the extent of LAAs in the whole lung fields (7). From these results, the functional lung image-derived LAA based on four-dimensional computed tomography (4D-CT) was developed for planning of radiation treatment to reduce the risk of RP in patients with COPD.

Several authors have described functional imaging modalities for planning of radiation treatment, such as ventilation imaging with 4D-CT (8) and single-photon emission computed tomography (SPECT) lung perfusion imaging (9). All of these authors showed that functional lung regions could be identified with imaging and then avoided with IMRT treatment planning techniques. Matsuoka (6) suggested that paired inspiratory and expiratory CT imaging can be used to define LAA volumes in patients with COPD. Therefore, these two approaches were combined in order to address the respiratory problem. This study investigated the ability of functional lung image-derived LAA based on 4D-CT, and its incorporation into respiratory-gated intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) in treatment planning for lung cancer patients with COPD.

Methods and Materials

Patient background

In this study, 8 male patients with lung cancer were enrolled who had undergone 4D-CT scanning and definitive radiotherapy at Hiroshima University from 2009 to 2010. Pathological diagnosis, stage (Union International Contre le Cancer [UICC] 7th edition), and the primary tumor location are summarized in Table 1. All patients received [18F] fluorodeoxyglucose–positron emission tomography (FDG-PET) for staging.

Functional lung image-derived LAA based on 4D-CT

At first, 4D-CT scans were acquired with 2.5-mm-thick slices using multi detector-row CT (MDCT; LightSpeed, GE Medical systems, Waukesha, WI) in cine mode with the Varian Real-time Position Management (RPM) Respiratory Gating system (Varian Medical Systems, Palo Alto, CA). After image acquisition, the CT image data set was sorted into 10-phase bins of the respiratory cycle, and phase by phase evaluation was performed on a workstation (AdvantageSim, GE Healthcare, Princeton, NJ). The 10-phase set consisted of 0 to 90% in steps of 10%, and 0 or 90% was in the end-inspiratory phase and 50% in the end-expiratory phase. All 10-phase CT data sets were imported into the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). Several authors reported that the threshold CT value for the detection and quantification of LAA ranged from -850 to -950 HU (10, 11). Matsuoka *et al.* concluded that the threshold of -860 HU correlated closely with airway dysfunction in COPD on paired inspiratory and expiratory CT (6). Therefore LAAs were generated from 10-phase 4D-CT data sets according to CT values lower than -860 Hounsfield units (HU) as a threshold on Eclipse.

For respiratory gated planning in this study, three expiratory phases (40-60%) were selected with the phase gating method. Figure 1 shows the three steps involved in making the functional lung image-derived LAA based on 4D-CT in Case 1: *(1)* acquisition of LAA at each phase (the threshold of -860HU); *(2)* fusion of LAA at three expiratory phases (40–60%), and trimming the ROI as LAA image (40–60%); and *(3)* the functional lung image was defined as the area where LAA image (40–60%) was excluded from fusion images of the total lung volumes on each of the 40–60% phases.

This technique did not use any sort of deformable image registration algorithm in any of the steps.

Respiratory gated IMRT and VMAT planning with functional lung image

In this simulation study, two respiratory-gated radiotherapy plans were designed and compared for each patient as follows: *(1)* Plan A was an anatomical IMRT or VMAT plan based on the total lung; *(2)* Plan F was a functional IMRT or VMAT plan based on the functional lung. RapidArc (Varian Medical Systems, Palo Alto, CA) was used as VMAT. In this study, IMRT was defined as fixed, nonrotational IMRT, and VMAT was defined as rotational IMRT. All dose calculations were done on the full expiration (50%) phase.

For target delineation of each plan, a physician delineated the target volume on each 10-phase CT image. Gross tumor volume (GTV) included the primary tumor and metastatic lymph nodes, and clinical target volume (CTV) margin of 3 to 5 mm was added to GTV according to the pathology. Elective nodal irradiation was omitted (so-called "involved-field"). Internal target volume (ITV)

Table 1 Characteristics of study patients

Case patient	Age (y)	Sex	Histology	TNM	Stage	Tumor location
1	81	M	Non-small	T2aN1M0	IIB	R.S8
2	86	M	SCC	T2aN0M0	IB	L.S8
3	56	M	Adeno	T4N2M0	IIIB	R.S1
4	68	M	Small	T2aN1M0	IIB	R.S10
5	71	M	SCC	T2aN3M0	IIIB	R.S10
6	74	M	Small	T2aN2M0	IIIA	L.S8
7	68	M	SCC	T3N2M0	IIIA	R.S6
8	84	M	Non-small	T1N0M0	IA	L.S8

Abbreviations: Non-small = non-small cell carcinoma; SCC = squamous cell carcinoma; Small = small cell carcinoma; Adeno = adenocarcionoma; F = female; M = male.

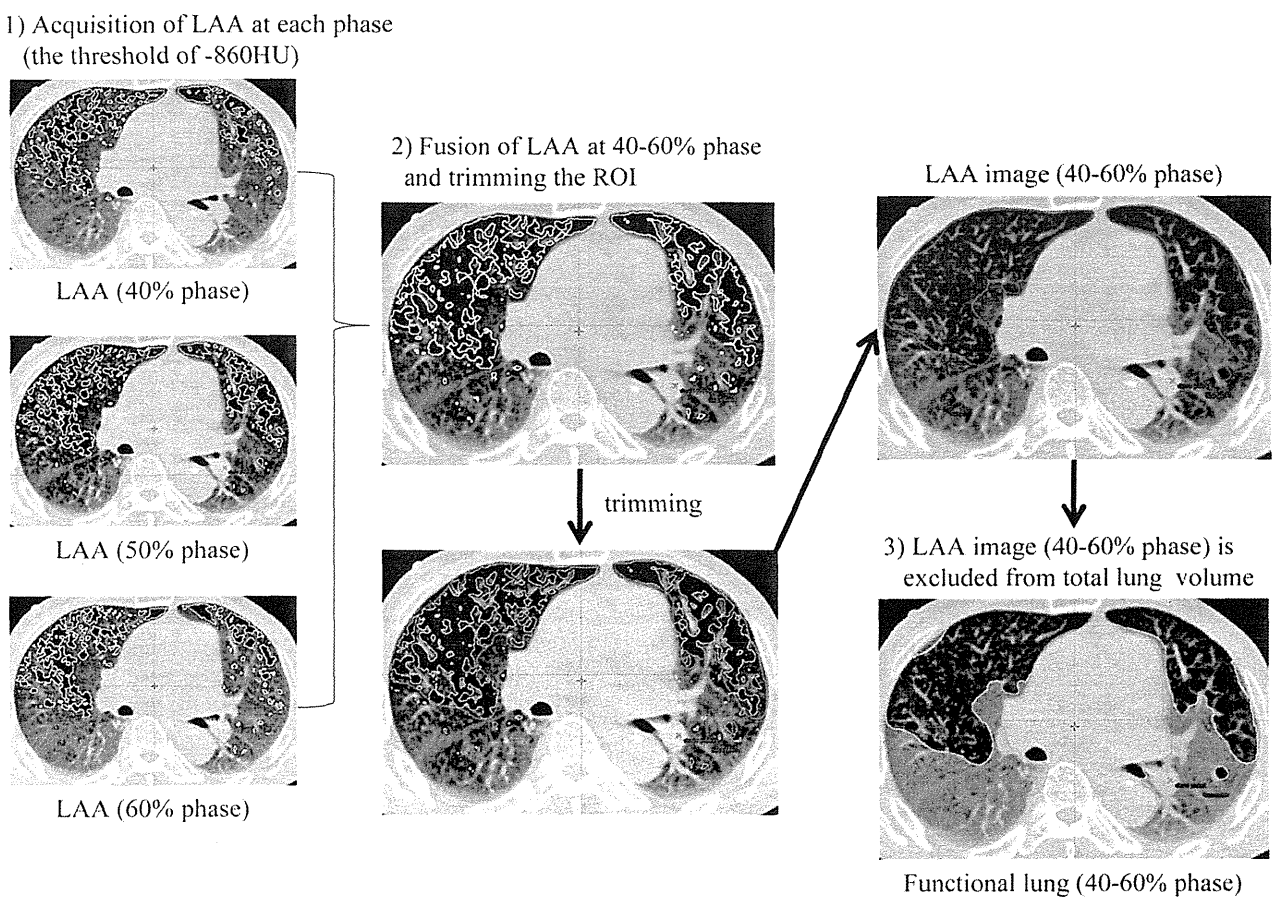

Fig. 1. Three steps to make the functional lung image-derived low attenuation area (LAA) based on four-dimensional computed tomography (4D-CT) in Case 1.

Table 2 Dose constraints for intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT)

	Plan A: Anatomical plan			Plan F: Functional		
	Volume (%)	Dose (cGy)	Priority	Volume (%)	Dose (cGy)	Priority
PTV						
Upper	0	7,350	70	0	7350	70
	10	7,200	70	10	7200	70
Lower	98	7,000	80	98	7000	80
	100	6,650	70	100	6650	70
Cord						
Upper	0	4,500	90	0	4500	90
Esophagus						
Upper	0	7,350	50	0	7350	50
	35	5,500	50	35	5500	50
Heart						
Upper	50	4,500	50	50	4500	50
Body						
Upper	0	7,500	50	0	7500	50
Lung						
Upper	10–30	2,000	90			
Functional lung						
Upper				10–30	2000	120
Low-functional lung (LAA†)						
Upper				10–30	2000	90

Table 3 Target (planning target volume [PTV]), normal tissue, and dosimetric characteristics of study patients

Case	PTV (cm^3)	Total lung volume (cm^3)	Functional lung volume (cm^3)	Defect size (as % of total lung)	Dose constraints of V20 or fV20
1	158.8	3354.5	1,617.6	51.8	<20%
2	228.3	2819.6	1,717.3	39.1	<10%
3	207.3	3258.1	2,302.3	29.3	<10%
4	278.4	2719.1	2,012.5	26	<30%
5	505.9	2490	2,264.1	9.1	<20%
6	256.4	2885.4	1,586.6	45	<25%
7	561.1	2517.1	1,903.4	24.4	<25%
8	62.4	3124.2	866.8	72.3	<10%
Mean	282.3	2896	1,810.4	37.1	

was defined as the sum of CTV at three expiratory phases (40-60%) in this respiratory gated planning. A planning target volume (PTV) margin of 5-10 mm was added allowing for reproducibility of respiratory motion and setup error to ITV.

The IMRT plans consisted of five coplanar fixed beams with gantry angles of 20°, 320°, 240°, 180°, and 135° at the right lung, and 340°, 40°, 120°, 180°, and 215° at the left lung. The VMAT plans consisted of two coplanar arcs with gantry angles were moved 220° from 180° to 40° in the right lung, and from 180° to 320° in the left lung in clockwise and counter clockwise directions. Treatment plans were delivered using 6-MV photons generated by a linear accelerator (Clinac iX, Varian Medical Systems, Palo Alto, CA) with continuous changes in the gantry speed, multi-leaf collimator position, and dose rate. The collimator angle was fixed at 45° throughout the arc. The same beam arrangements were used for both plans.

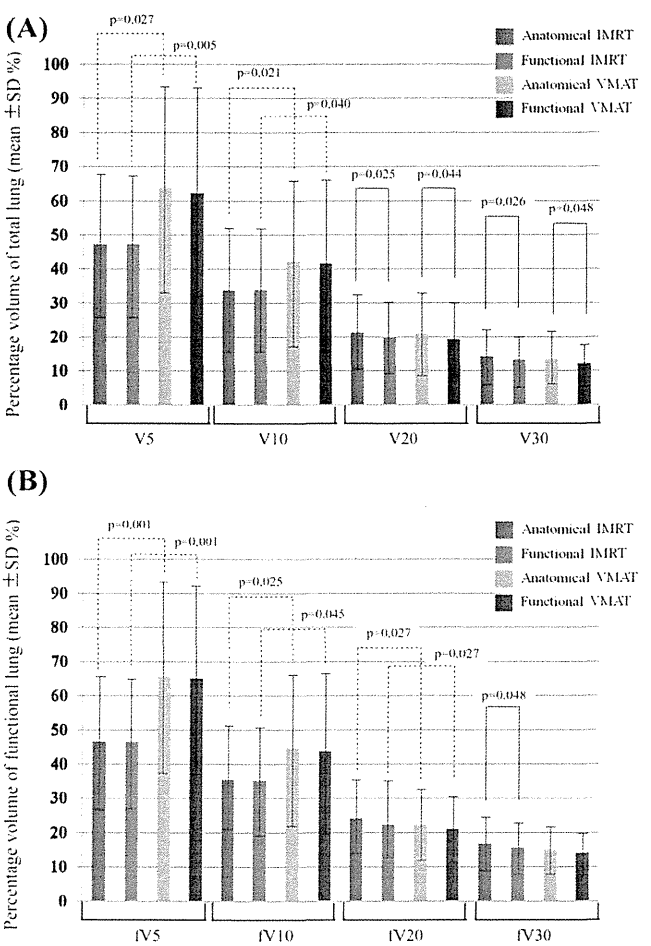

Fig. 2. Comparison of V5-30 and fV5-30 in Plans A and F using intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) (mean ± SD). The *p* values shown are only for statistically significant differences.

A total dose of 70 Gy in 35 fractions to 95% of the PTV was prescribed. The prescribed dose was calculated with a heterogeneous dose calculation algorithm (the Eclipse anisotropic analytical algorithm; AAA). Table 2 shows the dose constraints for each structure. The constraints on the total lung were used in Plan A, and those on the two functional lung regions were used in Plan F. V20 or functional V20 (fV20) was calculated by lung-PTV and its dose constraints were defined as less than 10-30%. Therefore the background of patients included all stages. The minimal value of V20 which could be achieved in the anatomical plan of each patient was selected according to the field size of each patient, and the value of fV20 was also the same. Several IMRT and VMAT plans were made to maintain clinical acceptability, and the plans which most suitably satisfied the dose constraints in Table 2 were selected for Plans A and F.

Data analysis and statistical methods

The dosimetric parameters of Plans A and F using respiratory guided IMRT and VMAT planning were evaluated by examining the following: *(1)* Lung V5-30 and fV5-30: the percentage of total or functional lung volumes irradiated with ≥5 to 30 Gy; *(2)* Lung MLD and functional MLD (fMLD): mean dose to total or functional lung; *(3)* mean dose, homogeneity index (HI), and conformity index (CI) of PTV; HI = maximum dose of PTV/minimum dose to PTV; CI = treated volume/PTV; it is implied that treated volume completely encompasses the PTV; *(4)* mean or maximum dose of organ-at-risk (heart, esophagus, and spinal cord); and *(5)* monitor units for each plan.

For comparison of statistical significance, the Mantel–Haenzel χ^2 or *t*-test was used. All statistical analysis was performed using StatMate for Windows (StatMate version 4.01; ATMS, Tokyo, Japan). Statistical significance was defined as $p < 0.05$.

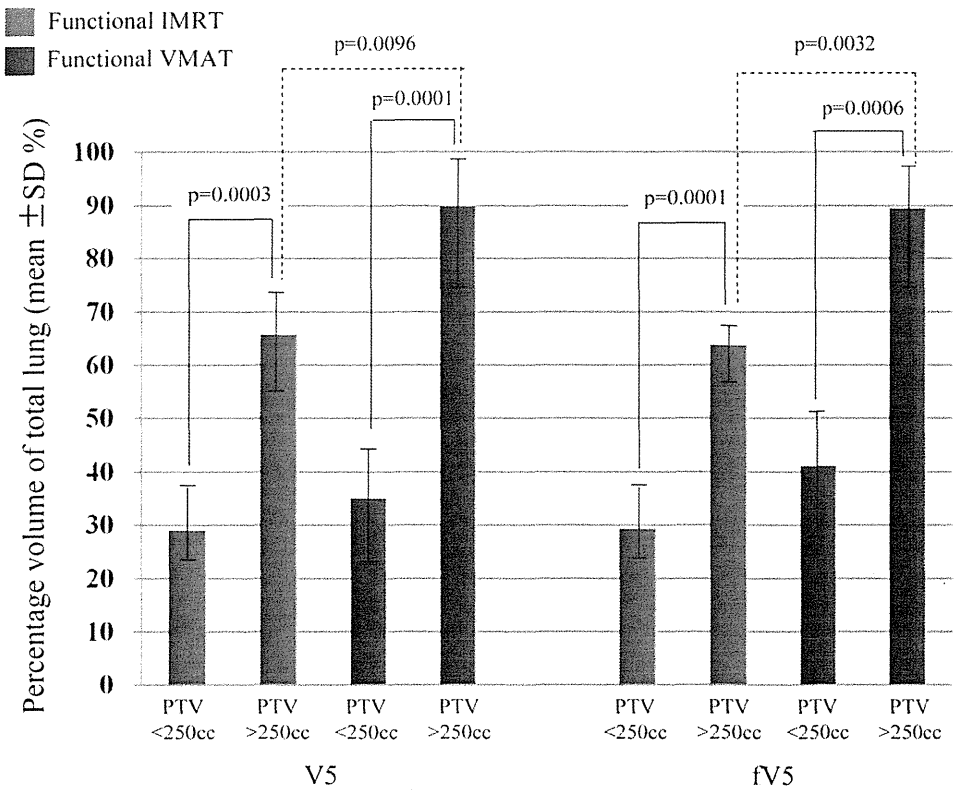

Fig. 3. Comparison of V5 and fV5 in intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) of Plan F according to planning target volume (PTV). The p values shown are only for statistically significant differences.

Results

Details of target characteristics

The details of target characteristics used in both plans are presented in Table 3.

Comparison of dosimetric parameters for lung

Figs 2A and B show the mean percentage volumes of total lung (A) or functional lung (B) receiving ≥5, ≥10, ≥20 and ≥30 Gy (V5, V10, V20, V30, and fV5, fV10, fV20, fV30, respectively) for both IMRT and VMAT. Compared with Plan A, Plan F reduced V20 in IMRT (mean 1.5%, p= 0.025), in VMAT (mean 1.6%, p = 0.044), V30 in IMRT (mean 1.0%, p = 0.026), in VMAT (mean 1.3%, p = 0.048) and fV30 in IMRT (mean 1.3%, p = 0.048). Small reductions were noted in MLD (mean 0.23 Gy, p = 0.083 in IMRT, mean 0.5 Gy, p = 0.042 in VMAT) and fMLD (mean 0.3 Gy, p = 0.106 in IMRT, mean 0.5 Gy, p = 0.092 in VMAT).

On the other hand, compared with IMRT, VMAT reduced fV20 in Plan A (mean 2.0%, p = 0.027), and in Plan F (mean 1.3%, p = 0.027), but increased V5 in Plan A (mean 16.4%, p = 0.027), in Plan F (mean 15.1%, p = 0.005); V10 in Plan A (mean 8.4%, p = 0.021), in Plan F (mean 7.7%, p = 0.040); fV5 in Plan A (mean 19.0%, p = 0.001), in Plan F (mean 18.7%, p = 0.001) and fV10 in Plan A (mean 9.3%, p = 0.025), in Plan F (mean 8.4%, p = 0.045). Significant increases were also seen in MLD (mean 1.1 Gy, p = 0.013 in Plan A, mean 0.8 Gy, p = 0.010 in Plan F) and fMLD (mean 1.1 Gy, p = 0.037 in Plan A, mean 0.9 Gy, p = 0.002 in Plan F).

Fig 3 shows V5 and fV5 in IMRT and VMAT of Plan F according to PTV. Compared with PTV < 250 cc, IMRT and VMAT significantly increased V5 and fV20 in PTV ≥ 250 cc. In addition, compared with IMRT, VMAT also increased V5 and fV5 in PTV ≥ 250 cc significantly (p = 0.0096 in V5, p = 0.0032 in fV5).

Comparison of dosimetric parameters for PTV and organs at risk

Table 4 (upper) shows the dosimetric parameters for PTV, organ-at-risk and monitor units (MU) between Plans A and F. There were no differences of PTV mean dose, HI, CI, mean or maximum dose to organ-at-risk, such as heart, esophagus and spinal cord and MU between Plans A and F in both IMRT and VMAT.

Table 4 (lower) shows the dosimetric parameters for PTV, organ-at-risk and MU between IMRT and VMAT. Compared with IMRT, VMAT improved HI and CI of PTV, especially in Plan F (p = 0.040) without change in mean dose to PTV. However, there was no difference in mean or maximum doses to heart and spinal cord between IMRT and VMAT, and VMAT increased mean dose to esophagus (mean 3.9 Gy, p = 0.002 in Plan A, mean 3.6 Gy, p = 0.003 in Plan F) in both Plans A and F. However, IMRT resulted in greater MU than in VMAT in both Plans A and F (p = 0.008 and 0.003).

Figure 4 shows dose distribution in Case 4.

Table 4 Comparison of dosimetric parameters of planning target volume (PTV) and normal tissue between anatomical and functional plans, for intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) (mean ± SD)

	IMRT			VMAT		
(upper)	Anatomical	Functional	*p* Value	Anatomical	Functional	*p* Value
PTV						
Mean dose (Gy)	72.6 ± 1.2	72.9 ± 0.9	0.155	72.2 ± 1.0	72.3 ± 1.1	0.629
Homogeneity index*	1.52 ± 0.08	1.59 ± 0.08	0.056	1.51 ± 0.10	1.51 ± 0.10	1
Conformity index†	2.74 ± 0.72	3.17 ± 1.07	0.128	2.44 ± 0.49	2.53 ± 0.49	0.356
Heart						
Mean dose (Gy)	19.7 ± 9.7	20.6 ± 10.6	0.214	19.1 ± 10.2	19.9 ± 11.1	0.356
Esophagus						
Mean dose (Gy)	15.6 ± 11.4	15.6 ± 11.6	0.951	19.5 ± 13.1	19.2 ± 13.2	0.522
Spinal cord						
Mean dose (Gy)	9.1 ± 6.3	9.2 ± 6.3	0.456	10.3 ± 5.4	9.9 ± 5.8	0.257
Maximum dose (Gy)	40.6 ± 21.2	40.6 ± 20.5	0.954	42.0 ± 14.6	41.1 ± 15.9	0.269
MU	786.8 ± 214.3	817.3 ± 203.1	0.378	496.5 ± 60.9	529.9 ± 56.5	0.149
	Anatomical			Functional		
(lower)	IMRT	VMAT	*p* Value	IMRT	VMAT	*p* Value
PTV						
Mean dose (Gy)	72.6 ± 1.2	72.2 ± 1.0	0.275	72.9 ± 0.9	72.3 ± 1.1	0.129
Homogeneity index*	1.52 ± 0.08	1.51 ± 0.10	0.831	1.59 ± 0.08	1.51 ± 0.10	0.077
Conformity index†	2.74 ± 0.72	2.44 ± 0.49	0.23	3.17 ± 1.07	2.53 ± 0.49	0.04
Heart						
Mean dose (Gy)	19.7 ± 9.7	19.1 ± 10.2	0.639	20.6 ± 10.6	19.9 ± 11.1	0.671
Esophagus						
Mean dose (Gy)	15.6 ± 11.4	19.5 ± 13.1	0.002	15.6 ± 11.6	19.2 ± 13.2	0.003
Spinal cord						
Mean dose (Gy)	9.1 ± 6.3	10.3 ± 5.4	0.117	9.2 ± 6.3	9.9 ± 5.8	0.281
Maximum dose (Gy)	40.6 ± 21.2	42.0 ± 14.6	0.711	40.6 ± 20.5	41.1 ± 15.9	0.888
MU	786.8 ± 214.3	496.5 ± 60.9	0.008	817.3 ± 203.1	529.9 ± 56.5	0.003

Abbreviation: MU = monitor units.

* Maximum dose of PTV/minimum dose of PTV.

† Irradiated volume that is covered by minimum dose of PTV/PTV.

Discussion

This study showed that planning of functional image-guided radiotherapy based on LAA can improve the dosimetric parameters for lung without a major change of PTV coverage and increasing other organ-at-risk doses. IMRT appears to be a good treatment planning based on favorable outcomes and maintenance of dosimetric predictors of toxicity at acceptable levels for patients who have larger tumors with difficult geometry in critical locations (12). However, inasmuch as reductions in MLD, V20, and V10 have been shown by IMRT, it can also increase the volume of lung receiving low doses, such as V5, which may potentially increase lung toxicity (13, 14). For delivering safe IMRT for lung cancer, it is important for dosimetric factors to be carefully considered. In fact, severe radiation pneumonitis may be easily induced by a lower dose in patients with COPD, which seldom comprises normal lung tissue (7). It is especially in these patients that the functional IMRT described here may contribute to minimize the effect of lower doses.

Several authors have reported on functional imaging modalities for planning of radiation treatment. Ventilation imaging is one of the modalities, which is generated from CT image volumes of the thorax representing exhale and inhale phases obtained from components of the 4D-CT sets using a deformable image registration algorithm (8, 15). Yaremko *et al.* reported generation of high functional regions, comprising the 90th percentile of the functional volume and 10% of the lung volume where the highest ventilation occurred. IMRT plans were generated using constraints on the high-functional regions. This method led to the result in which the mean dose to the high-functional region was reduced by 2.9 Gy (8). Yamamoto *et al.* also reported the effectiveness of the ventilation imaging-based functional planning (15). In their study, functional lung was divided into high-, moderate-, and low-functional regions, and the average reductions of the mean dose in the high-functional lung were 1.8 Gy for IMRT and 2.0 Gy for VMAT. This was achieved by using constraints on each region, for patients who had high-function lungs adjacent to the PTV.

SPECT lung perfusion imaging is the other functional imaging modality, which provides information about the function of pulmonary vascular and alveolar subunits. Shioyama *et al.* reported that the functional plans reduced the median dose of the 50th and 90th percentile hyperperfusion lung to 2.2 and 4.2 Gy, respectively, compared with anatomic plans by incorporating perfusion information in IMRT planning (9).

An advantage of these modalities is that several degrees of functional regions can be described according to the degree of

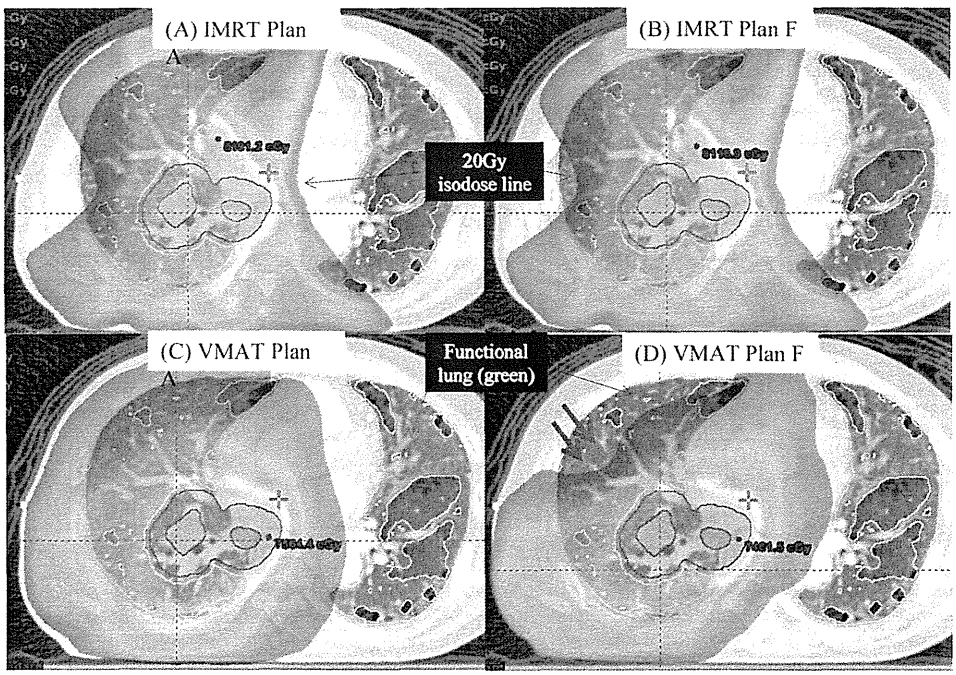

Fig. 4. Dose distribution of Case 4. (A) Intensity-modulated radiotherapy (IMRT) plan A, (B) IMRT plan F, (C) volumetric modulated arc therapy (VMAT) plan A, and (D) VMAT plan F show isodose line ≥20 Gy (blue) and functional lung area (green). The isodose line ≥20 Gy was decreased at the functional lung in VMAT Plan F (red arrows).

its regional volume change or perfusion distribution. However, the regional physiologic accuracy has not been validated in the ventilation imaging because of the uncertainty regarding the use of deformable image registration. In addition, the use of SPECT lung perfusion imaging is limited by the need for separate imaging sessions or fusions in radiotherapy planning.

The functional lung image-derived LAA based on 4D-CT of this study focused only on describing nonfunctional lung regions. The advantages of this method are as follows: *(1)* Actual lung function may be easily recognized especially in patients with COPD by using LAA-based images. *(2)* Our LAA approach can be done simply, without the need of a sophisticated deformable image registration algorithm. *(3)* This method may be less affected by respiratory motion because of the respiratory-gated technique. Consequently, there was limited description of several degrees of functional regions. However, CT quantitation using LAA is already an established tool for *in vivo* assessment of COPD, and has been correlated with pulmonary function (10, 11). Especially in CT findings of patients with COPD, LAA appears as areas of decreased lung attenuation because of an air-trapping phenomenon, which is characterized by progressive air way obstruction and airflow limitation that are not reversible with the administration of bronchodilator drugs (16). Therefore Zaporozhan *et al.* reported that PE volumes measured from expiratory MDCT scans better reflect abnormalities in pulmonary function tests in patients with severe PE than those from inspiratory scans (17). Considering the better reproducibility of lung motion, expiratory phases of 4D-CT were selected for this study. A problem remains in that 4D-CT data acquisition by this method is affected by respiratory motion. Thus, the proper thresholds of CT values for the detection and quantification of LAA and the correlations with pulmonary function using this method need to be evaluated. Nevertheless, the advantage of this respiratory gated method is that it can reduce not only the artifact of respiratory motion but also the total lung dose to a minimum.

Fixed-beam IMRT and VMAT plans were also compared. An advantage of VMAT over IMRT is the improvement of target conformity and the potential reduction in delivery time, especially in stereotactic body radiotherapy for lung cancer, which requires a large number of beams and monitor units (18). On the other hand, Schallenkamp *et al.* reported that larger volumes of lungs treated with lower doses may be more critical in predicting adverse events than smaller volumes treated with higher doses, especially when using the IMRT technique which delivers low doses of radiation to large lung volumes (19). Yamamoto *et al.* reported that functional IMRT and VMAT planning had a similar impact on each other for high-functional lung dose, PTV metrics, and doses to other critical organs (15). In our comparison with IMRT, although VMAT reduced fV20 and MU and improved HI and CI of PTV, VMAT increased the low-dose areas in both plans, especially in patients with large PTV. Increasing the low-dose area of lung using VMAT in patients with large PTV needs to be approached with caution.

The use of functional lung image-derived LAA into respiratory-gated IMRT or VMAT in planning for lung cancer patients may remove the uncertainties of quantifying LAA because of respiratory motion, and may result in further reductions of total and functional lung doses in functional planning. However, several problems need to be addressed for clinical use. Prospective clinical trials will be necessary to determine whether treatment results, such as survival and complications, are improved by using this functional avoidance treatment planning.

Conclusion

In conclusion, functional IGRT planning based on LAA in respiratory-guided IMRT or VMAT appears to be effective in

preserving a functional lung in lung cancer patients with COPD. Further investigations are needed, including those to clarify several technical problems mentioned above, and to conduct prospective clinical trials.

References

1. Graham MV, Purdy JA, Emami B, *et al.* Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45: 323–329.
2. Rancati T, Ceresoli GL, Gagliardi G, *et al.* Factors predicting radiation pneumonitis in lung cancer patients: A retrospective study. *Radiother Oncol* 2003;67:275–283.
3. Fukuchi Y, Nishimura M, Ichinose M, *et al.* COPD in Japan: The Nippon COPD Epidemiology study. *Respirology* 2004;9:458–463.
4. American Thoracic Society. Standard for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225–232.
5. Orlandi I, Moroni C, Camiciottoli G, *et al.* Chronic obstructive pulmonary disease: Thin-section CT measurement of airway wall thickness and lung attenuation. *Radiology* 2005;234:604–610.
6. Matsuoka S, Kurihara Y, Yagihashi K, *et al.* Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. *AJR Am J Roentgenol* 2008;190:762–769.
7. Kimura T, Togami T, Takashima H, *et al.* Radiation pneumonitis in patients with lung and mediastinal tumors: A retrospective study of risk factors focused on pulmonary emphysema. *Br J Radiol* (in press).
8. Yaremko BP, Guerrero TM, Noyola-Martinez J, *et al.* Reduction of normal lung irradiation in locally advanced non-small cell lung cancer patients, using ventilation images for functional avoidance. *Int J Radiat Oncol Biol Phys* 2007;68:562–571.
9. Shioyama Y, Jang SY, Liu HH, *et al.* Preserving functional lung using perfusion imaging and intensity-modulated radiation therapy for advanced-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;68:562–571.
10. Park KJ, Bergin CJ, Clausen JL. Quantitation of emphysema with three-dimensional CT densitometry: Comparison with two-dimensional analysis, visual emphysema scores, and pulmonary function test results. *Radiology* 1999;211:541–547.
11. Gevenois PA, Vuyst PD, Sy M, *et al.* Pulmonary emphysema: Quantitative CT during expiration. *Radiology* 1996;1999: 825–829.
12. Sura S, Gupta V, Yorke E, *et al.* Intensity-modulated radiation therapy (IMRT) for inoperable non-small cell lung cancer: The Memorial Sloan-Kettering Cancer Center (MSKCC) experience. *Radiother Oncol* 2008;87:17–23.
13. Liu HH, Wang X, Dong L, *et al.* Feasibility of sparing lung and other thoracic structures with intensity-modulated radiotherapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1268–1279.
14. Murshed H, Liu HH, Liao Z, *et al.* Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1257–1267.
15. Yamamoto T, Kabus S, Berg JV, *et al.* Impact of four-dimensional computed tomography pulmonary ventilation imaging-based functional avoidance for lung cancer radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;79:279–288.
16. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;152:S77–S83.
17. Zaporozham J, Ley S, Eberhardt R, *et al.* Paired inspiratory/expiratory volumetric thin-slice CT scans for emphysema analysis. *Chest* 2005; 128:3212–3220.
18. Matuszak MM, Yan D, Grills I, *et al.* Clinical applications of volumetric modulated arc therapy. *Int J Radiat Oncol Biol Phys* 2010;77:608–616.
19. Schallenkamp JM, Miller RC, Brinkmann DH, *et al.* Incidence of radiation pneumonitis after thoracic irradiation: Dose-volume correlates. *Int J Radiat Oncol Biol Phys* 2007;67:410–416.

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CLINICAL INVESTIGATION **Lung**

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR OPERABLE STAGE I NON–SMALL-CELL LUNG CANCER: CAN SBRT BE COMPARABLE TO SURGERY?

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Purpose: To review treatment outcomes for stereotactic body radiotherapy (SBRT) in medically operable patients with Stage I non–small-cell lung cancer (NSCLC), using a Japanese multi-institutional database.

Patients and Methods: Between 1995 and 2004, a total of 87 patients with Stage I NSCLC (median age, 74 years; T1N0M0, *n* = 65; T2N0M0, *n* = 22) who were medically operable but refused surgery were treated using SBRT alone in 14 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. Total dose was 45–72.5 Gy at the isocenter, administered in 3–10 fractions. Median calculated biological effective dose was 116 Gy (range, 100–141 Gy). Data were collected and analyzed retrospectively.

Results: During follow-up (median, 55 months), cumulative local control rates for T1 and T2 tumors at 5 years after SBRT were 92% and 73%, respectively. Pulmonary complications above Grade 2 arose in 1 patient (1.1%). Five-year overall survival rates for Stage IA and IB subgroups were 72% and 62%, respectively. One patient who developed local recurrences safely underwent salvage surgery.

Conclusion: Stereotactic body radiotherapy is safe and promising as a radical treatment for operable Stage I NSCLC. The survival rate for SBRT is potentially comparable to that for surgery. © **2011 Elsevier Inc.**

Stereotactic body radiotherapy, Lung cancer, Non–small-cell, Operable, Stage I.

INTRODUCTION

With the popularization of computed tomography (CT) screening, lung cancers are increasingly detected at an early stage. For patients with Stage I (T1 or 2, N0, M0) non–small-cell lung cancer (NSCLC), resection of the set of full lobar and systemic lymph nodes represents standard treatment. Five-year overall survival rates for clinical Stage IA and IB treated surgically are approximately 60–75% and 40–60%, respectively (1–3). However, a proportion of patients who meet the criteria for surgery refuse such intervention for various reasons. Radiotherapy offers a therapeutic alternative in such cases, but the effects of conventional radiotherapy in patients with Stage I NSCLC are unsatisfactory, with local control rates of approximately 50% during a short 5-year survival period in 15–30% of patients (4–7). Survival rates for conventional radiotherapy for a statistically sufficient number of cases of operable Stage I NSCLC have not been reported, because most

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patients receiving radiotherapy are inoperable. The poor local control rates with conventional radiotherapy have been attributed to doses of conventional radiotherapy that are too low to control the tumor. Mehta *et al.* (8) provided a detailed theoretical analysis of NSCLC responses to radiotherapy and a rationale for dose escalation. They concluded that higher biologically effective doses (BED) irradiated during a short period must be administered to achieve successful local control of lung cancer. To provide a higher dose to the tumor without increasing adverse effects, three-dimensional conformal radiotherapy techniques have been used, and better local control and survival have recently been reported (9–11). Over the last decade, hypofractionated high-dose stereotactic body radiotherapy (SBRT) has been actively performed for early-stage lung cancer, particularly in Japan (12–17). We have previously reported preliminary results for a Japanese multi-institutional review of 257 patients with Stage I NSCLC treated with SBRT (18). The results showed that local control and survival rates were better with BED ≥100 Gy than with <100 Gy, and survival rates were much better for medically operable patients than for medically inoperable patients. These results were encouraging, but the duration of follow-up for the study was somewhat short (median, 38 months), and we have not presented a detailed analysis of medically operable patients as a distinct subgroup. Although the standard therapy for operable Stage I NSCLC remains surgery, the effect of SBRT on medically operable patients is an issue of great concern. We provide herein detailed and matured results of SBRT (BED ≥100 Gy) for medically operable patients with Stage I NSCLC, using a retrospectively collected Japanese multi-institutional database.

PATIENTS AND METHODS

Eligibility criteria

All patients who satisfied the following eligibility criteria were retrospectively collected from 14 major Japanese institutions in which SBRT for lung cancer was actively performed: (*1*) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdominal CT, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging; (*2*) histopathologic confirmation of NSCLC; (*3*) medically operable cancer but selection of SBRT after refusal to undergo surgery. Medical operability was discussed within the multidisciplinary tumor board of each institution according to respiratory function, age, and complicating diseases. Basic cutoff values for medical operability were World Health Organization performance status ≤2, pressure of arterial oxygen ≥65 mm Hg, predicted postoperative forced expiratory volume in 1 s ≥800 mL, no heart failure requiring pharmacotherapy, no diabetes requiring insulin, no severe arrhythmia, and no history of cardiac infarction. Positron emission tomography was not essential in the staging procedures.

Patients were informed of the concept, methodology, and rationale of this treatment, which was performed in accordance with the 1983 revision of the Declaration of Helsinki.

Table 1. Patient characteristics

Number (14 institutions)	87
Male	63
Female	24
Age (y), median (range)	74 (43–87)
ECOG performance status	
0	51
1	30
2	6
Histology	
Adenocarcinoma	54
Squamous cell carcinoma	25
Other	8
Stage	
IA	64
IB	23
Tumor diameter (mm), median (range)	25 (7–50)
IA	21
IB	39
Chronic lung disease	
Positive	38
Negative	49

Abbreviation: ECOG = Eastern Cooperative Oncology Group. Values are number unless otherwise noted.

Patient characteristics

A summary of patient pretreatment characteristics is given in Table 1. From April 1995 to March 2004, a total of 87 medically operable patients with primary NSCLC were treated using hypofractionated high-dose SBRT in 14 major Japanese institutions. Each of these 87 cases was judged medically operable, and surgery was initially recommended, but the patients declined surgery and selected SBRT as a radical treatment. Pathology of all tumors was confirmed as NSCLC by transbronchial or CT-guided percutaneous biopsy. The 14 participating institutions were these: Hokkaido University; Kyoto University; Cancer Institute Hospital; Tokyo Metropolitan Komagome Hospital; Kitasato University; Tohoku University; Hiroshima University; Tokyo Metropolitan Hiroo Hospital; Sapporo Medical University; Institute of Biomedical Research and Innovation; International Medical Center of Japan; Tenri Hospital; Kitami Red Cross Hospital; and Yamanashi University.

Treatment methods

Although the techniques to accomplish stereotactic methods differed among these institutions, all "stereotactic radiotherapy techniques" fulfilled the following five requirements: (*1*) reproducibility of the isocenter (setup error ≤5 mm), as confirmed by image guidance for every fraction; (*2*) respiratory motion (internal margin) suppressed using as much as possible, to <5 mm; (*3*) slice thickness on CT ≤3 mm for three-dimensional treatment planning; (*4*) irradiation with multiple noncoplanar static ports or dynamic arcs; and (*5*) single high dose ≥5 Gy.

Gross target volume (GTV) was delineated on CT images displayed with a lung window level. Clinical target volume (CTV) marginally exceeded GTV by 0–5 mm as judged by the individual radiation oncologist. Internal margin was