Stereotactic body radiation therapy using CyberKnife for T1N0M0 lung cancer patients with severe pulmonary dysfunction

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ABSTRACT

We retrospectively investigated the efficacy and safety of stereotactic body radiotherapy (SBRT) for T1N0M0 lung cancer using CyberKnife (CK) among 13 patients with severe pulmonary dysfunction which was defined as forced expiratory volume in 1 s (FEV1.0) of <1 L. The prescribed dose was 54 Gy in 3 fractions but adjusted for some patients if their tumors were in close proximity to the organs at risk (54 Gy/3 fractions: n = 11; 50 Gy/5 fractions: n = 1; 60 Gy/8 fractions: n = 1). During follow up (median follow-up: 27 months), we evaluated local control, overall survival and toxicity, using diagnostic imaging and laboratory tests. The patients’ median FEV1.0 was 0.84 L. Of the 13 patients, 3 were diagnosed as having lung cancer histologically and 10 diagnosed clinically. The 2-year rates for overall survival and local control were 89 and 100%, respectively. So far, we have seen no adverse effects of grade 2 or higher. We concluded that CK-SBRT is effective and well tolerated for T1N0M0 lung cancer, even in patients with severe pulmonary dysfunction, but should be further evaluated with a larger cohort and longer follow-up periods.

Keywords: CyberKnife; lung cancer; pulmonary dysfunction; stereotactic body radiotherapy

INTRODUCTION

Lung cancer is a leading cause of cancer death worldwide [1, 2]. For early-stage non-small-cell lung cancer, surgery is the established treatment [3]. However, some patients are not eligible for surgery due to comorbidities or advanced age. For such patients, stereotactic body radiotherapy (SBRT) reportedly offers good disease control with acceptable toxicity [4, 5]. CyberKnife® (CK; Accuray, Sunnyvale, CA, USA) is a specialized machine for stereotactic radiotherapy that allows highly conformal irradiation with tumor motion tracking [6], and is reportedly safe and effective for early-stage lung cancer [7–9]. SBRT with CK (CK-SBRT) can provide lower radiation doses to the lung than with conventional linac-based SBRT [10], which might be especially advantageous for lung cancer patients with pre-existing pulmonary dysfunction. In this study, we defined forced expiratory volume in 1 s (FEV1.0) < 1 L as severe pulmonary dysfunction (SPD).

Absolute FEV1.0 is one commonly used predictive factor for radiation-induced lung toxicity [11]. Many clinical trials of SBRT for lung cancer are limited to patients with FEV1.0 > 0.7 L for participation [12, 13]. We think that patients with FEV1.0 0.7–1 L is the lowest subset who may be candidates for SBRT for lung cancer. Here, we report outcomes of CK-SBRT for early-stage lung cancer patients with SPD.

MATERIALS AND METHODS

Patients

We retrospectively analyzed patients with T1N0M0 lung cancer and SPD (i.e., FEV1.0 < 1 L) who were treated by CK-SBRT at our institution. Most of these lung cancer patients were clinically diagnosed because their general condition was too poor to undergo biopsies and pathological confirmation. Clinical diagnoses were...
determined by multidisciplinary discussions, based on results of multimodal examinations, such as computed tomography (CT), FDG fluorodeoxyglucose–positron emission tomography (FDG-PET) and laboratory tests. Treatments such as surgery or radiation were also discussed by the cancer board. Cancers were staged using CT, FDG-PET and gadolinium-enhanced head magnetic resonance imaging, and classified by the Union for International Cancer Control (UICC) criteria (8th edition). This study was approved by our hospital’s institutional review board (No. 18–132).

Treatment
The prescribed dose for the participants was 54 Gy in 3 fractions but was adjusted for some patients because of the proximity of the tumor to surrounding organs. If metallic marker insertion was feasible, we used fiducial markers to track tumor motion. If a patient's condition was too poor to insert fiducial markers via bronchoscopy, the patient was irradiated under free breathing towards a target volume encompassing all of the tumor motion detected by 4D CT. Gross tumor volume (GTV) encompassing internal respiratory motion was created by the maximum intensity projection method with 4D CT. Planning target volume (PTV) was created with a 2-mm margin from GTV in every direction. The planning aim was to cover the GTV with 99% of the prescribed dose and to cover 90% of the PTV with 95% of the prescribed dose. The upper limit of the PTV maximum dose was 150% of the prescribed dose. The percentage of lung volume receiving >20 Gy (lung V20) should be <20%. Dose–volume parameters, including mean lung dose (MLD), lung V20, minimum dose in the most irradiated 99% of GTV (GTV-D99) and minimum dose in the most irradiated 90% of PTV (PTV-D90), both described as percentages of prescribed doses, were evaluated and recorded prior to treatment.

Evaluation
Patients were followed up every 3 months for the first year and every 6 months thereafter. Chest X-rays, CTs and laboratory tests were taken periodically. Acute toxicity was defined as adverse events (AEs) that occurred within 90 days after treatment; late toxicity was defined as AEs that occurred thereafter. All AEs were classified by the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0. Overall survival (OS) was defined as the interval from start of treatment to death or last follow-up date. Local control was defined as no local recurrence in the irradiated field.

Statistical analysis
Cumulative OS rate and local control rate were calculated using the Kaplan–Meier method. Mean parameters in two groups were compared with Student's t test. These statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (SPSS Inc., Armonk, NY, USA).

RESULTS
Patient and treatment characteristics
We analyzed 13 patients (6 men and 7 women) with T1N0M0 lung cancer who had SPD (FEV1.0 < 1 L) and were treated with CK-SBRT at our hospital between July 2015 and May 2019. Their median age was 75 years (range: 71–85 years). Their median follow-up was 27 months (range: 5–55 months) and median the FEV1.0 was 0.84 L (range: 0.49–0.9 L). Diffusing capacity for carbon monoxide (DLCO) was measured in 9 patients. Among 9 patients, median %DLCO, which was calculated by dividing absolute DLCO by predicted DLCO, was 22.5% (range: 14.5–107.4%). Lung vital capacity (VC) was measured in all patients and %VC, which was calculated by dividing absolute VC by predicted VC, was 78.7% (range: 64.5–90.0%). Regarding the cause of pulmonary dysfunction, 11 patients had a history of smoking, 1 patient had a history of chronic obstructive pulmonary disease (COPD) with moderate hypoxemia [14]. In their study, the median FEV1.0 was 0.83 L, which was similar to our study. The 2-year OS rate in our study was 89%, which indicates that,
**Table 1. Patient and treatment characteristics (N = 13)**

| Characteristic                         | n (%)          |
|----------------------------------------|----------------|
| Age, years\(^c\)                       | 75 (71–85)     |
| FEV\(_{1.0}\), L\(^c\)                 | 0.84 (0.49–0.9) |
| FEV\(_{1.0}\), % as predicted\(^d\)    | 39.7 (27.5–72.1) |
| Blinkman Index\(^e\)                   | 800 (0-1680)   |
| Home oxygen therapy                    |                |
| Yes                                    | 4 (31)         |
| No                                     | 9 (69)         |
| Sex                                    |                |
| Male                                   | 6 (46)         |
| Female                                 | 7 (54)         |
| Histopathological type                 |                |
| Adenocarcinoma                         | 1 (8)          |
| Squamous cell carcinoma                | 1 (8)          |
| Non-small cell lung cancer             | 1 (8)          |
| Not identified                         | 10 (76)        |
| T classification                       |                |
| T1b                                    | 6 (46)         |
| T1c                                    | 7 (54)         |
| Diameter of tumor, mm                  |                |
| 21 (14–28)                             |                |
| Radiation dose                         |                |
| 50 Gy in 5 fractions                   | 1 (8)          |
| 54 Gy in 3 fractions                   | 11 (84)        |
| 60 Gy in 8 fractions                   | 1 (8)          |
| Tumor motion tracking                  |                |
| Yes                                    | 3 (23)         |
| No                                     | 10 (77)        |
| Lung V20, %\(^b\)                     | 3.4 (±2.5)     |
| Mean lung dose, Gy\(^b\)               | 3.2 (±1.4)     |
| GTV D99, %\(^b\)                       | 98.2 (±4.0)    |
| PTV D90, %\(^b\)                       | 96.9 (±4.3)    |
| Maximum dose in PTV, %\(^b\)           | 137.7 (±11.6)  |

\(^a\) Shown as median (range).

\(^b\) Shown as mean (± Standard deviation).

\(^c\) described as percentage for prescribed dose.

\(^d\) FEV\(_{1.0}\) = forced expiratory volume in one second, Lung V20 = normal lung volumes that received more than 20 Gy, GTV D99 = minimum dose in most irradiated 99% of gross tumor volume described as percentage for prescribed dose, PTV D90 = minimum dose in most irradiated 90% of planning target volume described as percentage for prescribed dose.

at least, our treatment did not worsen patient prognosis. In this study, mean pre-treatment SpO\(_2\) was 96.1% and mean post-treatment SpO\(_2\) was 95.9% (\(P = 0.296\)), with a median interval of 24 months between pre- and post-treatment measurement. This result also indicates that CK-SBRT has low invasiveness for lung cancer with SPD. Although optimal treatment is affected by the patient’s general condition, tumor aggressiveness and the patient’s cooperation, CK-SBRT is an attractive option for lung cancer patients with SPD.

In this study, 1-year and 2-year OS rates were 100 and 89%, respectively. Hara et al. reported that respective 1-year and 2-year OS rates were 87 and 70% after 40–60 Gy in 5 fractions of linac-based SBRT for lung cancer with COPD [15]. Temming et al. reported that the 2-year OS rate was 77% after CK-SBRT for patients with early-stage lung cancer and pulmonary dysfunction [7]. Results of SBRT for lung cancer patients with pulmonary dysfunction are summarized in Table 2 [16, 17]. We believe our result are comparable to these studies, although our patients had SPD.

We saw no AEs of grade 2 or higher in this study. Treatment-related lung AEs and deterioration of daily living activities were the most concerning problems after SBRT for lung cancer patients with SPD. Reported incidences of grade ≥ 2 RP were 3–28% after SBRT for lung cancer patients with pulmonary dysfunction [7, 18]. In our study, lung V\(_{20}\) was 3.5% and MLD was 3.2 Gy, which were adequately low. The AE profile and treatment details in the literature are summarized in Table 3. We believe 54 Gy in 3 fractions of CK-SBRT is safe even for patients with SPD.

Only 1 of our patients developed local recurrence. This patient was treated with a total SBRT dose of 60 Gy in 8 fractions because of the
Table 2. Treatment efficacy of stereotactic body radiotherapy for lung cancer patients with pulmonary dysfunction in the literature

| Authors            | Number of patients | Pre-treatment pulmonary function | Total dose/fractions | Treatment machine | Treatment outcome |
|--------------------|--------------------|----------------------------------|----------------------|-------------------|------------------|
| Hara et al. [12]   | 24                 | Median FEV1.0 = 1.12 L           | 40-60 Gy/5 fractions | Linac             | 3y-OS 49%, 3y-LC 93% |
| Palma et al. [13]  | 176                | Median FEV1.0 = 0.94 L           | 54-60 Gy/3-8 fractions | Linac            | 3y-OS 47%, 3y-LC 89% |
| Temming et al. [7] | 106                | NA                               | 51-60 Gy/3-8 fractions | CyberKnife       | 2y-OS 77%, 2y-LC 88% |
| Present study      | 13                 | Median FEV1.0 = 0.84 L           | 50-60 Gy/3-8 fractions | CyberKnife       | 2y-OS 89%, 2y-LC 100% |

FEV1.0 = forced expiratory volume in one second, OS = overall survival, LC = local control, NA = not applicable.

Table 3. Toxicity profile in the literature

| Authors            | Number of patients | Pre-treatment pulmonary function | Treatment machine | Dose-volume parameters of the lung | Lung toxicity |
|--------------------|--------------------|----------------------------------|-------------------|-----------------------------------|---------------|
| Hara et al. [12]   | 24                 | Median FEV1.0 = 1.12 L           | Linac             | Median MLD = 3.3 Gy               | Grade 2 = 17% |
| Baumann et al. [14]| 60                 | Mean FEV1.0 (%) = 49             | Linac             | Median V20 = 8-12%, Median MLD = 6-8 Gy | Grade 1,2 = 17.5% |
| Temming et al [7]  | 106                | NA                               | CyberKnife        | NA                                | Grade 2 = 3%  |
| Present study      | 13                 | Median FEV1.0 = 0.84 L           | CyberKnife        | Mean V20 = 3.4 %                  | Grade 2 = 0%  |
|                    |                    | Median FEV1.0 (%) = 40           |                   | Mean MLD = 3.2 Gy                 |               |

FEV1.0 = forced expiratory volume in one second, MLD = mean lung dose, V20 = normal lung volumes that received more than 20 Gy, NA = not applicable.

Fig. 1. Dose distribution of a representative patient. Prescribed dose was 54 Gy in 3 fractions. The thick red line shows 95% of the prescribed dose and the thick purple line shows the 20 Gy isodoseline. Gross tumor volume is shown with pink mesh.

Fig. 2. CT image of same patient as in Fig. 1 taken 27 months after treatment showed no evidence of disease.

3 fractions produces good local control, even for patients with SPD. Additionally, our planning aim and dose constraint, such as to cover 99% of GTV with the prescribed dose and to allow high maximum dose to the PTV, may also improve local control, although longer follow-up with a larger study cohort is necessary to clarify the dose effect on local control and OS.

This study had some limitations. First, it was a retrospective analysis with a small number of patients. Second, most of the patients were not histologically diagnosed, which may have ultimately affected treatment outcomes such as local control and OS.

In conclusion, CK-SBRT is effective and well tolerated for stage T1N0M0 lung cancer patients even with SPD. However, our findings should be verified with a larger cohort and longer follow-up.
CONFLICT OF INTEREST
None declared.

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REFERENCES
1. Mao Y, Yang D, He J et al. Epidemiology of lung cancer. Surg Oncol Clin N Am 2016;25:439–45.
2. Cheng TY, Cramb SM, Baade PD et al. The international epidemiology of lung cancer: Latest trends, disparities, and tumor characteristics. J Thorac Oncol 2016;11:1653–71.
3. Ettinger DS, Wood DE, Aisner DL et al. Non-small cell lung cancer, version 5. 2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15:504–35.
4. Timmerman R, Paulus R, Galvin J et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070–6.
5. Zheng X, Schipper M, Kidwell K et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: A meta-analysis. Int J Radiat Oncol Biol Phys 2014;90:603–11.
6. Nuyttens JJ, van de Pol M. The CyberKnife radiosurgery system for lung cancer. Expert Rev Med Devices 2012;9:465–75. doi: 10.1586/erd.12.35.
7. Temming S, Kocher M, Stoelben E et al. Risk-adapted robotic stereotactic body radiation therapy for inoperable early-stage non-small-cell lung cancer. Strahlenther Onkol 2018;194:91–7.
8. Brown WT, Wu X, Fayad F et al. CyberKnife radiosurgery for stage I lung cancer: Results at 36 months. Clin Lung Cancer 2007;8:488–92.
9. Awano N, Ikushima S, Izumo T et al. Efficacy and safety of stereotactic body radiotherapy using CyberKnife in stage I primary lung tumor. Jpn J Clin Oncol 2017;47:969–75.
10. Atalar B, Aydin G, Gungor G et al. Dosimetric comparison of robotic and conventional linac-based stereotactic lung irradiation in early-stage lung cancer. Technol Cancer Res Treat 2012;11:249–55.
11. Robnett TJ, Machtay M, Vines EF et al. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000;48:89–94.
12. Kimura T, Nagata Y, Eba J et al. A randomized phase III trial of comparing two dose-fractionations stereotactic body radiotherapy (SBRT) for medically inoperable stage IA non-small cell lung cancer or small lung lesions clinically diagnosed as primary lung cancer: Japan clinical oncology group study JCOG1408 (J-SBRT trial). Jpn J Clin Oncol 2017;47:277–81.
13. Nagata Y, Hiraoka M, Shibata T et al. Prospective trial of stereotactic body radiation therapy for both operable and inoperable T1N0M0 non-small cell lung cancer: Japan clinical oncology group study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989–96.
14. Górecka D, Gorzelak K, Sliwiński P et al. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52:674–9.
15. Hara Y, Takeda A, Eriguchi T et al. Stereotactic body radiotherapy for chronic obstructive pulmonary disease patients undergoing or eligible for long-term domiciliary oxygen therapy. J Radiat Res 2016;57:62–7.
16. Palma D, Lagerwaard F, Rodrigues G et al. Curative treatment of stage I non-small-cell lung cancer in patients with severe COPD: Stereotactic radiotherapy outcomes and systematic review. Int J Radiat Oncol Biol Phys 2012;82:1149–56.
17. 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;88:359–67.
18. Doi H, Nakamatsu K, Nishimura Y. Stereotactic body radiotherapy in patients with chronic obstructive pulmonary disease and interstitial pneumonia: A review. Int J Clin Oncol 2019;24:899–909.
19. Stamm B, Peulen H, Guckenberger M et al. Dose to heart substrates is associated with non-cancer death after SBRT in stage I-II NSCLC patients. Radiother Oncol 2017;123:370–5.
20. Stephans KL, Woody NM, Reddy CA et al. Tumor control and toxicity for common stereotactic body radiation therapy dose-fractionation regimens in stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2018;100:462–9.