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Safety of daily fractionated thoracic radiosurgery

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► ***Original article***

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ABSTRACT

Background: The optimal inter-fraction interval in fractionated thoracic radiosurgery remains unclear. Several institutions maintain at least a 48-hour interval between each radiosurgery fraction. However, evidence supporting such radiosurgery schedule is lacking. Since 2014, we have performed daily fractionated thoracic radiosurgery without interruption. In this study, we evaluated the safety of daily administration of fractionated thoracic radiosurgery in patients with primary or metastatic lung cancer. ***Materials and methods***: Patients who received radical or salvage fractionated radiosurgery for treatment of primary or metastatic lung cancer were included in this study. All patients received fractionated radiosurgery divided into 2-4 fractions administered daily without interruption. Radiosurgery-induced toxicities were evaluated. ***Results***: Eighty-eight patients and 94 lung masses were treated. Radiosurgery-induced leukopenia and grade 5 toxicity did not occur. One patient experienced radiosurgery-induced grade 4 pneumonitis and dyspnea. Grade 3 pneumonitis, dyspnea, and fatigue developed in 23 (24.5%), 2 (2.1%), and 2 (2.1%) patients, respectively. Four (4.3%) patients experienced rib fracture. Dyspnea, fatigue, nausea, and pneumonitis were more common and severe in patients with central lung lesions. In contrast, dermatitis and rib fracture developed only in patients with peripheral lung lesions. ***Conclusions***: Daily fractionated radiosurgery is safe and well-tolerated in patients with primary or metastatic lung cancer. For patient convenience and better treatment outcomes, daily-fractionated thoracic radiosurgery can be considered.

INTRODUCTION

High-dose-per-fraction radiotherapy for extracranial tumors was firstly performed in patients with thoracic tumors by clinicians in Sweden and Japan, who reported promising results [1, 2]. The clinical use of fractionated body radiosurgery, also known as stereotactic ablative body radiotherapy, has since rapidly increased in patients with early-stage lung cancer or metastatic lung cancer in the last 20 years. Several institutions have conducted fractionated thoracic radiosurgery and reported excellent results and acceptable toxicities, with almost all institutions administering each radiosurgery fraction in at least 48-hour intervals [3-8]. Excessive toxicities induced by successive treatments without interruption is likely the primary reason for maintaining ≥48 hour interval between each fraction. However, definite evidence supporting such concerns is lacking. To our knowledge, there has been no studies which reported that daily fractionated radiosurgery without interruption causes more serious toxicities than intermittent fractionated radiosurgery with ≥48 hour interval between each fraction. In 2010, Videtic et al. reported favorable and acceptable toxicities after analyzing the medical records of 26 lung cancer patients who received daily fractionated radiosurgery at the Cleveland Clinic [9]. However, no studies reported the toxicity outcome of daily fractionated radiosurgery since then.

We started fractionated radiosurgery at our institution in 2014 for patients with early-stage lung cancer or metastatic lung cancer, and we had decided to administer 2-4 fractions daily without interruption. In this study, we evaluated the safety of daily administration of fractionated thoracic radiosurgery in patients with primary or metastatic lung cancer. This is one of the first studies to report the toxicity outcome of daily fractionated thoracic radiosurgery.

MATERIALS AND METHODS

Patient selection

Patients who received radical or salvage fractionated radiosurgery for the treatment of primary or metastatic lung cancer were included in this study. Eligible patients had Eastern Cooperative Oncology Group performance status ≤3 and no previous or concurrent conditions that could hinder

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the completion of fractionated radiosurgery. To appropriately evaluate radiosurgery-induced late toxicities, we only included patients followed up over a year since the completion of radiosurgery. Patients who died of other causes than radiosurgery-induced toxicity were excluded. In total, 159 patients received radiosurgery at our institution between January 2014 and August 2019. Of the initial 159 patients, 71 patients did not meet the inclusion criteria. Sixty-five patients received brain radiosurgery, and follow-up data were not available for 2 patients who were lost to follow-up or refused to be assessed after radiosurgery. Of the remaining 92 patients, 4 patients died of subdural hemorrhage, bacterial pneumonia, chronic renal failure, and coronary heart disease, respectively, within a year since the completion of radiosurgery. In total, 88 patients were finally included in this study. Hospital records, and laboratory and imaging results of all included patients were retrospectively reviewed. The Institutional Review Board of Kyung Hee University Medical Center approved this study and waived the need for written informed consent (KHUH-2021-07-018, date of approval: 20 July 2021). This study complied with the Helsinki Declaration. This study was registered in the CRIS (Clinical Research Information Service) and WHO ICTRP (International Clinical Trials Registry Platform) registration system (KCT0006478).

Pretreatment evaluation

Pathologic confirmation of the initial diagnosis was made in all patients using either a percutaneous needle or endoscopic bronchial biopsy unless medically contraindicated. Clinical diagnosis was made on the basis of progressive tumor changes using serial computed tomography (CT) (Brilliance CT 64-slice, Philips, Amsterdam, Netherlands) and/or positron emission tomography (PET) (Gemini TF PET/CT Image System, Philips, Amsterdam, Netherlands) imaging in patients who could not receive pathologic confirmation. The detailed pretreatment evaluation have been described in our previous study [10].

Radiosurgery

All patients underwent a 4-dimensional CT simulation (Brilliance TM CT Big Bore, Philips, Amsterdam, Netherlands) to track the movement of the targets along the respiratory cycle. All patients were immobilized in the supine position with arms over their heads using a posterior vacuum bag restriction system (BodyFix, Medical Intelligence Medizintechnik GmBH, Schwabmünchen, Germany). All patients were asked to take shallow breaths to reduce respiratory movement of the lungs. We did not apply an abdominal compression belt to allow comfortable breathing. The detailed radiosurgery methods have been described in our previous study [10]. Briefly, all patients received daily fractionated radiosurgery divided into 2-4 fractions without interruption. Radiosurgery was performed using a Tomotherapy (TomoTherapy, Accuray Inc., Madison, WI, USA) or linear accelerator (Clinac iX, Varian Medical System Inc., Palo Alto, CA, USA). Triangulation skin marks were used before each surgical session for quick positioning of patient into the correct location. Subsequently, on-board CT images were acquired and matched with the planning CT images for comparison and correct position setup. Radiosurgery was temporarily suspended in case of patient's trunk movement during irradiation, and resumed after verification of the on-board CT images and correction of patient position. Radiation oncologist conducted the radiosurgery sessions entirely (figure 1).

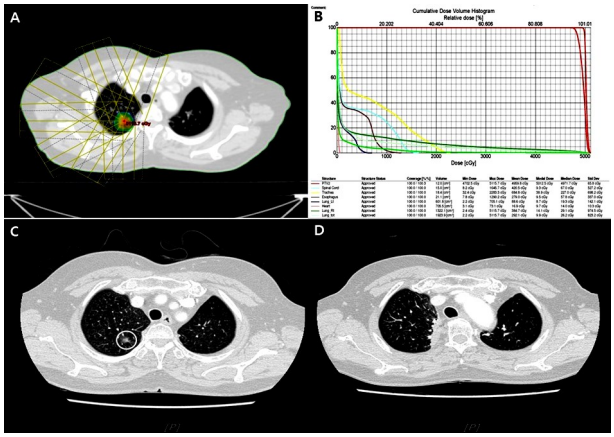

Figure 1. 70-year-old female with right upper lung adenocarcinoma. She received daily fractionated radiosurgery using linear accelerator. The dose fractionation schedule was a total 49.5 Gy in 3 fractions. **(A)** Planning target volume was covered by ≥95% isodose curve of prescription dose. **(B)** Dose-volume histogram. **(C)** Chest computed tomography (CT) image checked at 1 month before the start of radiosurgery. The lung lesion was located in white circle. **(D)** Chest CT image checked at 6 month after the completion of radiosurgery. The right upper lung lesion was well ablated.

Toxicity evaluation

Follow-up visits were scheduled 2 weeks after the completion of radiosurgery and every 2-3 months subsequently or more frequently for those who experienced treatment-related toxicities. At each follow-up visit, complete history and physical examination, basic laboratory studies, chest radiography, and chest CT imaging were conducted. Pulmonary function test and PET were also performed as needed.

Radiation pneumonitis was diagnosed based on characteristic clinical symptoms and imaging findings within the radiosurgery field and prospectively graded according to the Radiation Therapy Oncology Group toxicity criteria. Other radiosurgery-induced toxicities were prospectively evaluated using the Common Terminology Criteria for Adverse Events

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RESULTS

Of the 88 patients included in this study, 5 were treated for multiple lung masses: 4 received radiosurgery in 2 lung lesions, and 1 received radiosurgery in 3 lung lesions. Therefore, the total number of treated masses was 94. Four patients had previously undergone conventional fractionated thoracic radiotherapy before receiving radiosurgery: 3 had received lung and/or mediastinal lymph nodes radiotherapy for the treatment of lung cancer, and the other patient had received whole-breast radiotherapy for the treatment of breast cancer. Patient and tumor characteristics are summarized in table 1. All patients are Asians and were residing in South Korea. Almost all patients had underlying comorbidities such as hypertension, ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal failure. Seventy patients were considered ineligible for surgical resection after evaluation by a thoracic surgeon and a radiation oncologist, and the remaining 18 patients refused surgical resection. The lung tumor was located in the peripheral lung (>2 cm in all directions from the proximal bronchial tree) in 72 cases and in the central lung in 22 cases. The most common dose fractionation schedule was a total of 51 Gy in 3 fractions; 27 masses (28.7%) were treated with this fractionation schedule (table 2). Three lung masses were not pathologically confirmed because biopsy of these masses was medically contraindicated. The median follow-up duration for all patients was 35.6 months (range, 16.5-59.0 months).

Treatment-related toxicities in all cases are summarized in table 3. Radiosurgery-induced leukopenia and grade 5 toxicities were not observed. One patient experienced radiosurgery-induced grade 4 pneumonitis and dyspnea. This 78-year old male patient had primary lung cancer in the left lower peripheral lung and had received radiosurgery with a total of 48 Gy in 4 fractions. He had underlying ischemic heart disease, interstitial lung disease, and bronchial asthma. This patient's pre-radiosurgery forced expiratory volume in 1 second was 88% and diffusing capacity for carbon monoxide was 30%. Dyspnea began to aggravate at 7 months after completion of radiosurgery; therefore, this patient was managed with steroid agents and conservative treatment. However, because he did not achieve symptomatic relief, he was intubated and placed on a ventilator. The remaining patients experienced acceptable toxicities and were successfully treated with conservative management.

Adverse events by cancer location are summarized in table 4. Overall, the patients who received radiosurgery for the treatment of central lung cancer experienced worse treatment-related toxicities. Dyspnea, fatigue, nausea, and pneumonitis were more common and more severe in patients with central lung lesions. In contrast, dermatitis and rib fracture developed only in patients with peripheral lung lesions.

Table 1. Patient and tumor characteristics.

Characteristics	Variables
Number of patients	88
Number of treated masses	94
Age (years) Median (range)	76.0 (45.1-87.7)
Sex Male/Female	57/31
ECOG performance status 0/1/2	23/51/14
Smoking status Current/Former or never	31/57
Pretreatment FEV1 (%) Median (range)	81 (30-134)
Pretreatment DLCO (%) Median (range)	74 (30-122)
Location Right/Left Upper/Lower or middle Central/Peripheral	 55/39 43/51 22/72
Histology Adeno/SqCC/HCC/SCLC/CCC/Not confirmed	66/21/2/1/1/3
Primary site Lung/Colo-rectum/Liver/Esophagus/ Kidney/Thymus	84/5/2/1/1/1
Surgery modality Tomo/Linac	71/23
GTV (cc) Median (range)	11.19 (1.89-100.8)
Daily dose (Gy) Median (range)	16 (11-22)
Total dose (Gy Median (range)	51 (44-60)

ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity for carbon monoxide; Adeno, adenocarcinoma; SqCC, squamous cell carcinoma; HCC, hepatocellular carcinoma; SCLC, small cell lung cancer; CCC, clear cell carcinoma; Tomo, tomotherapy; Linac, linear accelerator; GTV, gross tumor volume.

Table 2. Dose fractionation schedules in all cases.

Dose fractionation schedule			Number of targets (n=94)
Total dose (Gy)	Number of fractions	Daily dose (Gy)	
51	3	17	27
50	4	12.5	20
48	4	12	13
54	3	18	10
52	4	13	7
48	3	16	5
49.5	3	16.5	3
45	3	15	3
60	3	20	1
60	4	15	1
57	3	19	1
56	4	14	1
44	2	22	1
44	4	11	1

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Table 3. Radiosurgery-induced toxicities in all cases.

Toxicities	Grade			
	1	2	3	4
Pneumonitis	19 (20.2%)	50 (53.2%)	23 (24.5%)	1 (1%)
Dyspnea	12 (12.8%)	11 (11.7%)	2 (2.1%)	1 (1%)
Chest wall pain	11 (11.7%)	13 (13.8%)	0	0
Fatigue	18 (19.1%)	16 (17%)	2 (2.1%)	0
Nausea	3 (3.2%)	3 (3.2%)	0	0
Dermatitis	7 (7.4%)	6 (6.4%)	0	0
Esophagitis	3 (3.2%)	2 (2.1%)	0	0
Rib fracture	4 (4.3%)			

Table 4. Radiosurgery-induced toxicities by cancer location.

Toxicities	Location	Grade			
		1	2	3	4
Pneumonitis	Central	3 (13.6%)	10(45.5%)	9 (40.9%)	0
	Peripheral	16(22.2%)	40(55.5%)	14(19.4%)	1(1.4%)
Dyspnea	Central	3 (13.6%)	2 (9.1%)	1 (4.5%)	0
	Peripheral	9 (12.5%)	9 (12.5%)	1 (1.4%)	1(1.4%)
Chest wall pain	Central	1 (4.5%)	2 (9.1%)	0	0
	Peripheral	10(13.9%)	11(15.3%)	0	0
Fatigue	Central	9 (40.9%)	4 (18.2%)	1 (4.5%)	0
	Peripheral	9 (12.5%)	12(16.7%)	1 (1.4%)	0
Nausea	Central	1 (4.5%)	1 (4.5%)	0	0
	Peripheral	2 (2.8%)	2 (2.8%)	0	0
Dermatitis	Central	0	0	0	0
	Peripheral	7 (9.7%)	6 (8.3%)	0	0
Esophagitis	Central	3 (13.6%)	2 (9.1%)	0	0
	Peripheral	0	0	0	0
Rib fracture	Central	0			
	Peripheral	4 (5.6%)			

DISCUSSION

How long interval between each fractions are need when conducting fractionated thoracic radiosurgery? Owing to the lack of pertinent studies, the optimal inter-fraction interval in fractionated thoracic radiosurgery remains unclear. Several institutions maintain at least a 48-hour interval between each radiosurgery fraction because of possible toxicities induced by successive treatments without interruption [3-8]. However, evidence supporting such radiosurgery schedule is lacking. Since 2014, we have performed daily fractionated thoracic radiosurgery without interruption in patients with early-stage lung cancer or metastatic lung cancer. To evaluate the safety of our fractionation schedule, we retrospectively assessed the incidence of radiosurgery-induced adverse events in 88 patients who received daily fractionated radiosurgery at our institution between January 2014 and August 2019. One patient experienced grade 4 pneumonitis and dyspnea; however, this patient had poor pre-radiosurgery lung function and pre-existing lung conditions, which would have contributed to the severe toxicity. All other patients experienced acceptable toxicities and were successfully treated with conservative management (table 3). Although there is no control group in this study, the incidence and severity of toxicities induced by daily fractionated radiosurgery were comparable to those induced by intermittent fractionated radiosurgery which have been reported in several previous studies [3-8]. Moreover, of the total 94 treated masses, 22 were located in the central lung. Although the patients who received radiosurgery for the treatment of central lung cancer experienced worse toxicities than the patients with peripheral lung cancer (table 4), all toxicities were acceptable and successfully treated. Therefore, we believe that daily fractionated radiosurgery is safe and can be conducted in clinical field. This is one of the first studies to report the toxicity outcomes of daily fractionated thoracic radiosurgery.

Daily fractionated radiosurgery offers several advantages compared to intermittent fractionated radiosurgery with temporary interruption. First, it results in a shorter total treatment duration, which minimizes patient inconvenience and allows for early initiation of adjuvant systemic therapy.

Second, daily fractionated radiosurgery can suppress repopulation of cancer cells. The tumor cells in the stationary phase proliferate to compensate for the loss of cell populations after depletion of cell population by ionizing radiation injury. Although the time to repopulation onset would vary depending on pathologic cell types and fractionated radiation doses, it is known that repopulation occurs 2-3 weeks after initiation in conventional fractionated radiotherapy and earlier in fractionated radiosurgery than conventional fractionated radiotherapy [11-16]. Daily administration of each radiosurgery fraction without interruption results in a total treatment duration of <1 week. Therefore, daily fractionated radiosurgery can more effectively suppress cancer cell repopulation.

Third, daily fractionated radiosurgery can suppress sublethal or potentially lethal DNA damage repair. Tumor cells are known to overcome radiation-induced sublethal or potentially lethal DNA damage by DNA damage repair process after a certain period, and continue to proliferate [16-18]. A long interval between each radiosurgery fraction will be conducive to sublethal or potentially lethal DNA damage repair. Daily fractionated radiosurgery can suppress radiation-induced sublethal or potentially lethal DNA damage repair by maintaining a short interval between each radiosurgery fraction, which would yield better tumor control and prognosis. Of course, the aforementioned second and third advantages are based on radiobiological theories. We are planning on conducting additional pre-clinical and clinical researches to confirm these advantages.

Videtic *et al.* analyzed the records of 26 patients with inoperable early-stage lung cancer who received daily fractionated radiosurgery with a total 50 Gy in 5 fractions. They reported that daily fractionated thoracic radiosurgery showed favorable toxicity outcomes, with no grade ≥4 toxicity, grade 3 dyspnea in 1 patient, and grade 2 chest wall pain in 1 patient [9]. Because the patient cohort in our study included

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patients with primary or metastatic lung cancer and our radiosurgery dose fractionation schedule was heterogeneous compared to that in Videtic *et al.*'s study, the toxicity outcomes are not directly comparable. However, overall, the toxicity outcomes of our study are worse than those of Videtic *et al.*'s study. We hypothesize that these differences are mainly owing to the varying dose fractionation schedules between these studies. We divided the total dose into 2-4 fractions, whereas Videtic *et al.* used 5 fractions. In most other studies on daily fractionated thoracic stereotactic radiotherapy that reported toxicity outcomes, >5 fractions were used [2, 19, 20]. Because stereotactic ablative body radiotherapy, also known as fractionated radiosurgery, is defined as a noninvasive treatment involving the precise delivery of ablative doses of ionizing radiation in 1-5 fractions [21], we could not gather comparable insights into safety of daily fractionated radiosurgery from these studies.

Our study has some limitations. Of the total of 94 treated masses, only 22 (23.4%) were located in the central lung. Several studies have reported that central lung tumor location is associated with worse toxicities after thoracic fractionated radiosurgery than the peripheral lung tumor location [7, 22-24]. Although patients in our study who received radiosurgery for central lung cancer experienced acceptable treatment-related toxicities (table 4), the reliability of our results is limited by the small sample size. Further studies with larger sample sizes are necessary to confirm whether daily fractionated radiosurgery is safe in patients with centrally located lung tumors. In addition, the results of this study were likely affected by biases inherent to retrospective design. However, we believe that this study provides valuable information regarding the safety of daily fractionated thoracic radiosurgery and hope that daily fractionated thoracic radiosurgery without interruption is widely adopted in clinical practice in the interest of patient convenience and better treatment outcome.

In conclusion, daily fractionated radiosurgery is safe and well-tolerated in patients with primary or metastatic lung cancer. For patient convenience and better treatment outcome, daily administration of radiosurgery fractions can be considered.

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***Data availability*:** The data that support the findings of this study are openly available in my data repository website at https://blog.naver.com/anjdixn/222415282441.

***Conflicts of interest*:** None.

***Ethical consideration*:** The Institutional Review Board of Kyung Hee University Medical Center approved this study and waived the need for written informed consent (KHUH-2021-07-018, date of approval: 20 July 2021). This study complied with the Helsinki Declaration.

***Author contribution*:** M.K.: conception and design, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, and final approval of the version to be submitted. Y.J.L: analysis and interpretation of data, drafting the article, and final approval of the version to be submitted.

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