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Original Article

Multi-institutional phase II study on the safety and efficacy of dynamic tumor tracking-stereotactic body radiotherapy for lung tumors

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ABSTRACT

Background and purpose: This study aimed to evaluate the safety and efficacy of dynamic tumor tracking-stereotactic body radiotherapy (DTT-SBRT) for lung tumors.

Materials and methods: Patients with cStage I primary lung cancer or metastatic lung cancer with an expected range of respiratory motion of ≥10 mm were eligible for the study. The prescribed dose was 50 Gy in four fractions. A gimbal-mounted linac was used for DTT-SBRT delivery. The primary endpoint was local control at 2 years.

Results: Forty-eight patients from four institutions were enrolled in this study. Forty-two patients had primary non-small-cell lung cancer, and six had metastatic lung tumors. DTT-SBRT was delivered for 47 lesions in 47 patients with a median treatment time of 28 min per fraction. The median respiratory motion during the treatment was 13.7 mm (range: 4.5–28.1 mm). The motion-encompassing method was applied for the one remaining patient due to the poor correlation between the abdominal wall and tumor movement. The median follow-up period was 32.3 months, and the local control at 2 years was 95.2% (lower limit of the one-sided 85% confidence interval [CI]: 90.3%). The overall survival and progression-free survival at 2 years were 79.2% (95% CI: 64.7%–88.2%) and 75.0% (95% CI: 60.2%–85.0%), respectively. Grade 3 toxicity was observed in one patient (2.1%) with radiation pneumonitis. Grade 4 or 5 toxicity was not observed.

Conclusion: DTT-SBRT achieved excellent local control with low incidences of severe toxicities in lung tumors with respiratory motion.

Stereotactic body radiotherapy (SBRT) is important for treating early-stage non-small-cell lung cancer (NSCLC) and pulmonary oligometastases. After several prospective trials, including the RTOG 0236, JCOG 0403, and Nordic trials [1–3], SBRT has become the standard treatment for medically inoperable patients with early-stage NSCLC. The application of SBRT in oligometastases was established based on evidence from randomized phase II studies [4–6]. SBRT is most commonly used in the lungs for oligometastases.

Respiratory motion management is inevitable in the lungs for SBRT. Radiation pneumonitis is frequent in lower lobe lesions, and respiratory motion is suggested to be a contributing factor [7,8]. Without any respiratory motion management, a larger irradiated volume is needed to cover tumor motion, which potentially increases the risk of radiation pneumonitis. Various techniques have been developed for managing the respiratory motion of lung tumors, including breath-holding, gating, and dynamic tumor tracking (DTT).

Among these techniques, DTT is superior in patient compliance and treatment time. However, it is also the most challenging technique [9]. Several tracking techniques have been developed, including robotic, gimbaled, multileaf collimator, and couch track-

Abbreviations: DTT, dynamic tumor tracking; SBRT, stereotactic body radiotherapy.

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ing. The technical aspects of these DTT models have been evaluated, achieving high accuracy [10]. However, there is limited evidence for clinical outcomes for DTT-SBRT in prospective trials. Therefore, we conducted a multi-institutional phase II study to evaluate its safety and efficacy in lung tumors.

Materials and methods

Patients

The eligibility criteria for the study were as follows: presence of primary or metastatic lung cancer; inoperability assessed by thoracic surgeons or patient refused surgery; satisfying dose constraints for the surrounding organs; age of 20 years or above; Eastern Cooperative Oncology Group Performance Status of 0 to 2; ability of the patient to raise their arms for 30 min or more; and expected respiratory motion of 10 mm or more. For primary lung cancers, the tumor should meet the following two criteria: pathological or cytological diagnosis of NSCLC or clinical diagnosis of NSCLC with consensus from multiple doctors based on tumor markers and imaging studies, including computed tomography (CT) and 18F-fluoro-deoxy-glucose positron emission tomography; and tumor diameter of 5 cm or less and clinical stage of IA-IB (UICC 7th) diagnosed using imaging studies. For a metastatic lung tumor, the following two criteria were required: clinically diagnosed metastatic lung cancer and three or fewer tumors with diameters of 5 cm or less without any extrapulmonary lesions. The exclusion criteria were as follows: prior history of radiotherapy to the same site, active interstitial pneumonia or pulmonary fibrosis, severe diabetes mellitus or collagen disease, pregnancy or lactation, mental disease that prevents registration, and other issues considered inappropriate for the study. This study was conducted according to the Declaration of Helsinki. The institutional review boards of the participating institutions approved the study protocol. All patients provided written informed consent. The study was registered in the UMIN Clinical Trials Registry as UMIN000016547.

Treatment planning

The treatment planning for DTT-SBRT of the lungs is detailed in our previous paper [11]. Before treatment planning, spherical gold markers (Disposable Gold Marker; Olympus Medical Systems, Tokyo, Japan) were placed around the tumor using a bronchoscope. CT images were acquired for treatment planning at the expiratory phase with a slice thickness of 3 mm or less. A correlation model (4D model) between the positions of the abdominal wall measured using an infrared camera, and the tumor positions obtained from kV X-ray pulsed fluoroscopy on the Vero4DRT system (Hitachi, Ltd., Tokyo, Japan) [12] was created. We estimated the 4D model errors for each patient using this model at the time of simulation.

In the treatment planning for DTT-SBRT, a clinical target volume (CTV) was defined as the gross tumor volume (GTV), which was delineated on exhaled CT images plus 3-mm margins [13]. The tracking internal target volume (ITV) was the CTV plus a margin for positional variations between the CTV and fiducials. The planning target volume (PTV) was determined using the tracking-ITV plus margins (5–8 mm for the craniocaudal direction and 5 mm for the other directions), compensating for the 4D model and mechanical errors. During planning, the lungs, spinal cord, esophagus, stomach, trachea, bronchus, and pulmonary artery were regarded as organs at risk. The planning organ-at-risk volume (PRV) for the lungs was defined as the bilateral lungs minus the GTV. The PRV for the spinal cord was defined as the spinal canal plus 3-mm margins. For the other organs, including the esophagus, stomach, trachea, bronchus, and pulmonary artery, PRV margins were set at 3–5 mm, and doses to the PRVs were extracted when the 20-Gy isodose line overlapped with the organs. The dose constraints for the PTVs and PRVs are listed in Table 1.

Multiple non-coplanar static beams with 6-MV X-rays from Vero4DRT were aligned to the tumor. The prescribed dose was 50 Gy in four fractions to the isodose, covering 95% of the PTV. The X-ray Voxel Monte Carlo (XVMC) algorithm in iPlan RT Dose (BrainLab AG, München, Germany) was used for dose calculations with a spatial resolution and deviation of $\leq$2 mm and $\leq$2%, respectively.

Delivery of the protocol treatment

A gimbal-mounted linac on the Vero4DRT system was used for DTT-SBRT delivery. Set-up error was corrected for bony structures using the ExacTrac X-ray system (BrainLab AG) before treatment beam delivery. Then, a 4D model was built to correlate abdominal motion with internal tumor motion. The treatment beams were delivered with tumor motion tracked according to the 4D model. Internal fiducials were monitored with kV imagers during treatment delivery. If the fiducial markers were displaced from the predicted positions by $\geq$3 mm, the treatment was interrupted and the 4D model was rebuilt. The patients were treated with one fraction per day and 2–4 fractions per week. Concurrent chemotherapy was not administered during treatment.

The treatment was discontinued in the following cases: if the patient was diagnosed unfit for DTT-SBRT after the daily check before each treatment fraction (*e.g.,* rapid exacerbation of comorbidities or complications); if a technical problem was found in the treatment processes, including the 4D-model and tracking; if a grade 4 or worse adverse event, or other adverse events occurred that required discontinuation of the treatment; and if the patient wished to discontinue the treatment.

Quality assurance (QA) program

The participating institutions were required to pass a dose delivery test using an anthropomorphic lung phantom provided by IROC Houston. All institutions passed the test using their system consisting of the Vero4DRT and iPlan RT Dose, with the XVMC algorithm before participating in the clinical trial.

After completing the treatment protocol for each case, the institutions reported the dose-volume indices for the PTVs and OARs, and log files regarding tracking accuracy during DTT-SBRT delivery were collected. Two types of target positions were calculated from the log files: the detected target positions, which were acquired through stereo fluoroscopic images every 1 s, and the tracked target positions where the treatment X-ray beams were delivered using the gimbal system. The range of respiratory motion was defined as the 95th percentile of the detected target position during the treatment fraction. The tracking accuracy was defined as the 95th percentile difference between the detected and tracked target positions [14].

Follow-up

Follow-up visits, including chest radiography or CT, were performed at least once every 2 months for the first 6 months after DTT-SBRT, at least once every 3 months between 6 months and 1 year, and at least once every 6 months after 1 year. Local tumor progression was determined based on radiological findings or pathological examinations according to the JCOG 0403 criteria [2]. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 4.0.

Endpoints

The primary endpoint was the 2-year local control rate for tumors treated with DTT-SBRT. Forty-eight samples were required

Table 1
Dose constraints and reported values for planning target volume and planning organ-at-risk volumes.

Volume	Constraints		Median	(range)
PTV	$D_{95\%}$	50 Gy		
	$D_{2\%}$	133%–143%	136%	(133–143)
Lungs minus GTV	D_{mean}	≤18 Gy	3.8 Gy	(1.6–13.6)
	V_{15Gy}	≤25%	7.2%	(2.1–17.0)
	V_{20Gy}	≤20%	5.0%	(1.0–10.7)
Spinal cord	D_{max}	≤25 Gy	7.5 Gy	(2.1–25.0)
Esophagus	V_{40Gy}	≤1 cm^3	0 cm^3	(0–0); *n* = 22
	V_{35Gy}	≤10 cm^3	0 cm^3	(0–0); *n* = 22
Pulmonary artery	V_{40Gy}	≤1 cm^3	0 cm^3	(0–0.2); *n* = 26
	V_{35Gy}	≤10 cm^3	0 cm^3	(0–0.5); *n* = 26
Stomach	V_{36Gy}	≤10 cm^3	0 cm^3	(0–1.7); *n* = 21
	V_{30Gy}	≤100 cm^3	0 cm^3	(0–3.2); *n* = 21
Bowels	V_{36Gy}	≤10 cm^3	0 cm^3	(0–0); *n* = 20
	V_{30Gy}	≤100 cm^3	0 cm^3	(0–0); *n* = 20
Trachea and main bronchus	V_{40Gy}	≤10 cm^3	0 cm^3	(0–0); *n* = 24
Other organs	V_{48Gy}	≤1 cm^3	0 cm^3	(0–0.9); *n* = 21
	V_{40Gy}	≤10 cm^3	0 cm^3	(0–4.2); *n* = 21

Abbreviations: PTV: planning target volume; GTV: gross tumor volume; $D_{x\%}$: dose covering *x*% of the volume; D_{mean}: mean dose; V_{xGy}: volume covered by the *x*-Gy isodose; D_{max}: maximum dose.

to be tested for the expected value of 90%, with a threshold value of 80%, one-sided alpha of 0.15, and power of 80%. Secondary endpoints included overall survival (OS), progression-free survival (PFS), adverse events, tracking accuracy, and dose-volume indices.

The local control rate was estimated using the Kaplan-Meier method, considering local progression as an event and censoring at the date of death or the last date of survival verification. OS and PFS were estimated using the Kaplan-Meier method considering death for OS (death and disease progression for PFS) as events and censoring at the last date of survival verification.

Results

In the study, 48 patients were enrolled from four institutions between July 2015 and January 2018 (Table 2). The patient cohort consisted of 38 men and 10 women with a median age of 80 years (range: 49–90 years). Forty-two patients had primary NSCLC, and six had metastatic lung tumors. Forty-eight tumors in 48 patients were intended for DTT-SBRT. No significant differences in patient or tumor characteristics were observed between the institutions (Supplementary Table 1).

DTT-SBRT was successfully delivered to 47 tumors in 47 patients. In the remaining patient, the abdominal wall motion was poorly correlated with internal tumor movement; therefore, DTT was abandoned. The motion-encompassing method (the ITV method) was applied to one tumor. The median treatment time per fraction for DTT-SBRT was 28 min (range: 14–77 min). In the treatment session that took 77 mins, the patient was very nervous about his first treatment fraction. His breathing rhythm was disturbed, and he moved his own body during the treatment. That led to interruptions in the treatment, and the 4D model had to be rebuilt three times.

The median follow-up period was 32.3 months (range: 3.0–53.8 months). The local control rate after 2 years was 95.2% (lower limit of the one-sided 85% confidence interval [CI]: 90.3%; Fig. 1a) for the 48 tumors intended for DTT-SBRT. No grade 4 or 5 toxicity was observed. Grade 3 toxicity was observed in one patient (2.1%; 95% CI: 0.1%–11.1%) with radiation pneumonitis at 3.0 months. Grade 2 toxicities were observed in seven patients, including radiation pneumonitis, dermatitis, rib fracture, and pleural effusion in three, one, two, and one patient, respectively. The incidence of radiation pneumonitis of grade 2 or worse was 8.3% (95% CI: 2.3%–20.0%). There was no significant difference in local control or in the incidence of grade 2–3 pneumonitis among the institutions (Supplementary Table 1).

Table 2
Characteristics of patients and tumors.

Patient characteristics	*N* = 48
Sex	
Male	38
Female	10
Age [years]	
median (range)	80 (49–90)
Etiology	
Primary	42
Metastasis	6
Histology for primary	
Adenocarcinoma	8
Squamous cell carcinoma	8
Not otherwise specified	2
Unproven	24
Tumor characteristics	***N* = 48**
Tumor diameter [mm]	
median (range)	23.5 (5–47)
Laterality	
Left	14
Right	34
Lobe	
Upper or middle	4
Lower	44

The OS and PFS after 2 years were 79.2% (95% CI: 64.7%–88.2%) and 75.0% (95% CI: 60.2%–85.0%), respectively (Fig. 1b). At data cut-off, 11 patients died; the causes of death were cancer-specific in six patients and comorbidity in five (chronic obstructive pulmonary disease, renal failure, and other malignancies).

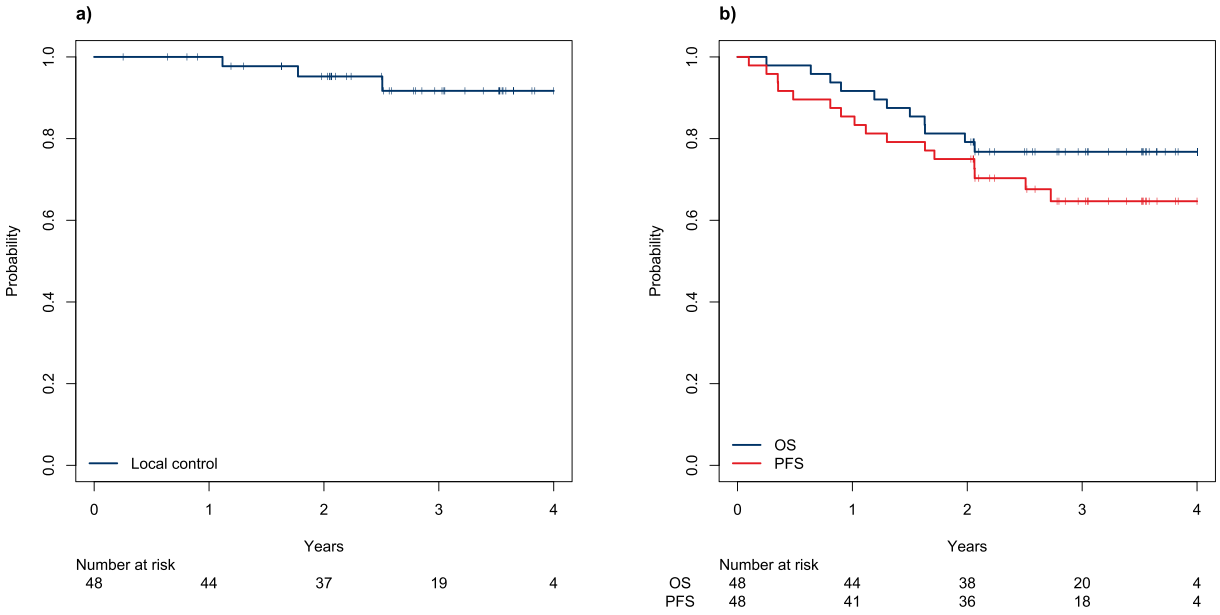

Fig. 1. a) Local control; b) overall survival (OS) and progression-free survival (PFS).

The goals for the dose-volume indices were satisfied in the 47 patients in whom DTT-SBRT was delivered (Table 1 and Supplementary Table 2). Median (range) values for GTV, CTV, tracking ITV, and PTV were 10 cm^3 (0.5–66 cm^3), 20 cm^3 (2.2–95 cm^3), 22 cm^3 (4.6–80 cm^3), and 51 cm^3 (16–148 cm^3), respectively. The logs during DTT-SBRT were obtained from 187 fractions from the 47 patients; however, the log file was missing for one fraction. The median range of respiratory motion during the DTT-SBRT was 13.7 mm (range: 4.5–28.1 mm). The motion range was <5, <8, and < 10 mm in two (1.1%), 19 (10.2%) and 41 fractions (21.9%), respectively. The median tracking accuracy was 3.6 mm (range: 1.7–6.9 mm). No significant difference was observed in the tracking accuracy among the institutions except a median difference of 1.7 mm between two institutions (Supplementary Table 2).

Discussion

To the best of our knowledge, this is the first multi-institutional phase II study to evaluate the efficacy and safety of DTT-SBRT in the lungs. The strengths of this study are the attendance of multiple institutions, the inclusion of patients with respiratory moving tumors, and the QA program. The local control rate was 95.2% after 2 years, which satisfied the predetermined primary endpoint. This indicates that the dose delivery of DTT was sufficiently accurate to control the tumor, which was supported by the high tracking accuracy of the QA program. Regarding safety, the incidence of severe toxicity (grade 3 or worse) was 2.1%. Radiation pneumonitis grade 2 or worse was observed in 8.4% of the patients, which is lower than would be expected from the proportion of lower lobe tumors (>90%). Motion management through DTT and compliance with dose constraints might contribute to a low incidence of toxicities.

There are several methods to manage respiratory motion in radiotherapy for the lung [15]. Among them, those that allow irradiation with 100% duty cycles (*i.e.,* no beam gating) under free-breathing are the ITV method, the mid-ventilation method, and the DTT method. The ITV method covers the entire tumor motion, which ensures dose coverage to the target, but leads to a larger target volume. The mid-ventilation method potentially reduces PTV margins by using a CT image of the time-weighted mean tumor position and a margin recipe based on the tumor motion amplitude. Peulen et al. applied the mid-ventilation method to SBRT for 297 patients with NSCLC [16]. The method reduced PTV in 47% of the patients compared to the ITV method. With the median motion amplitude of 6.5 mm (range: 0–39 mm), median GTV (=CTV) and PTV were 5.6 cm^3 (range: 0.3–63 cm^3) and 34.8 cm^3 (2.3–183 cm^3), respectively. In our study using DTT, the corresponding values were 13.7 mm (range: 4.5–28.1 mm), 20 cm^3 (2.2–95 cm^3), and 51 cm^3 (16–148 cm^3), respectively. Although a direct comparison between the two methods is difficult, our DTT method seems to be able to reduce PTV as much as or more than the mid-ventilation method.

Evidence of the clinical outcomes of DTT-SBRT in prospective trials is limited. Van den Begin et al. conducted a prospective phase II trial at a single institution (UZ Brussel, Brussels, Belgium) [17], which evaluated the local control of SBRT for oligometastatic disease using the DTT or ITV method. Respiratory motion during the planning 4D-CT was 11.2 and 6.9 mm for tumors treated with DTT and ITV methods, respectively. The 1-year local control rate was 89%, with no difference found between the motion management methods (88% and 90% for DTT and ITV methods, respectively). Grade 3 or worse toxicities were observed in three patients (7%), including grade 3 nausea, grade 3 RP, and fatal cholangitis. Iwata et al. conducted a phase I/II trial of DTT-SBRT for lung tumors at a single institution (Yokohama CyberKnife Center, Yokohama, Japan) [18]. The patients were treated using CyberKnife with fiducial-based or markerless DTT. Forty patients were enrolled, grade 3 RP was observed in one patient (2.5%), and the 2-year local control was 98%. Detailed information on respiratory motion or tracking errors during treatment was not available in this study. The results from this multi-institutional study are consistent with those of these two reports.

Although phase III trials are desirable to obtain a high level of evidence for respiratory motion management in radiotherapy, they are difficult to conduct because of limited equipment available at each institution for motion management. A comparison of outcomes from different institutions with appropriate adjustment for confounding factors could be a solution to overcome this limitation. Claude et al. conducted an observational prospective study comparing two models (CyberKnife and non-robotic standard linacs) of SBRT for peripheral NSCLC [19]. In this study, 106

patients were enrolled from 11 institutions in France. They found no significant difference in recurrence, survival, or toxicities between the two models after adjusting for potential bias with inverse probability treatment weighting. Their study did not intend to evaluate respiratory motion management. However, this type of clinical trial could be applied to compare clinical outcomes between different radiotherapy models.

This study has several limitations. One is the range of respiratory motion. The study did not collect data on respiratory motion during treatment planning. The recorded range of respiratory motion during treatment was under 8 mm in 10% of the treatment fractions; however, an inclusion criterion for the study was expected respiratory motion of 10 mm or more. Our pretreatment estimation of the respiratory motion might be excessive for some patients, considering that the motion range would be smaller than the peak-to-peak range because it was defined as the 95th percentile of the detected target positions during a treatment fraction. Dhont et al. evaluated the long-term and short-term variability of respiratory motion in the lungs and liver [20]. They suggested difficulty in the pretreatment estimation of respiratory motion because of significant variabilities. Another limitation is the short follow-up period. The median follow-up period of 32.3 months was sufficient to evaluate local control; however, it was insufficient to evaluate OS. To confirm the long-term safety and survival, we decided to extend the follow-up period to 5 years for the study cohort. The other limitation is that the development and sales of the Vero4DRT system were already finished in 2016 [12]. Therefore, it is impossible to newly install this system and start DTT-SBRT. However, we believe that this study is of importance in that it demonstrates the translation of this novel irradiation technique to clinical outcomes.

In conclusion, DTT-SBRT achieved excellent local control and low incidence of severe toxicity in lung tumors with respiratory motion.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.04.028.

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