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Dynamic tumor-tracking stereotactic body radiotherapy with real-time monitoring of liver tumors using a gimbal-mounted linac: A multi-institutional phase II study

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ABSTRACT

Background and purpose: This prospective multicenter phase II study aimed to evaluate the safety and efficacy of dynamic tumor tracking (DTT) stereotactic body radiotherapy (SBRT) with real-time monitoring of liver tumors using a gimbal-mounted system.

Materials and methods: Patients with < 4 primary or metastatic liver tumors with diameters ≤ 50 mm and expected to have a respiratory motion of ≥ 10 mm were eligible. The prescribed dose was 40 Gy in five fractions. The primary endpoint was local control (LC) at 2 years. The secondary endpoints were overall survival (OS), progression-free survival (PFS), treatment-related toxicity, and tracking accuracy.

Results: Between September 2015 and March 2019, 48 patients (48 lesions) with a median age of 74 years were enrolled from four institutions. Of these, 39 were diagnosed with hepatocellular carcinoma and nine with metastatic liver cancer. The median tumor diameter was 17.5 mm. DTT-SBRT was successfully performed in all patients; the median treatment time was 28 min/fraction. The median follow-up period was 36.5 months. The 2-year LC, OS, and PFS rates were 98.0 %, 88.8 %, and 55.1 %, respectively. Disease progression was observed in 33 (68.8 %) patients. One patient (0.2 %) had local recurrence, 31 (64.6 %) developed new hepatic lesions outside the irradiation field, and nine (18.8 %) had distant metastases (including overlap). Grade 3 late adverse events were observed in seven patients (14.5 %). No grade 4 or 5 treatment-related toxicity was observed. The median tracking accuracy was 2.9 mm.

Conclusion: Employing DTT-SBRT to treat liver tumors results in excellent LC with acceptable adverse-event incidence.

1. Introduction

Primary liver tumors are classified as hepatocellular carcinomas (HCCs) or intrahepatic cholangiocarcinomas. HCC is the most common primary liver cancer, and liver metastases are observed with other primary cancers [1,2]. Localized HCC in patients with relatively preserved

Abbreviations: DTT, dynamic tumor tracking; SBRT, stereotactic body radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; CT, computed tomography; 4D, four-dimensional; TV, target volume; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; OAR, organs at risk; IR, infrared.

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hepatic function can be treated with surgical resection, liver transplantation, or radiofrequency ablation (RFA). Only 10–30 % of HCC or liver metastases are suitable for surgical resection because of unsuitable performance status and hepatic function. RFA cannot be used in tumors that are near blood vessels, intestines, or bile ducts [3,4].

Stereotactic body radiotherapy (SBRT) for liver tumors has been recognized as an alternative therapy for patients unsuitable for surgical resection or RFA and has exhibited excellent local control (LC) [5–10]. Management of respiration-associated movements of the liver is required when administering SBRT for liver cancer. Dynamic tumor tracking (DTT) is used to manage respiratory movement and is considered excellent in terms of treatment time and patient compliance [11]. Previously, we reported that we could perform DTT-SBRT for liver tumors and reduce the normal liver dose without sacrificing the tumor dose [12]. However, the evidence regarding the clinical usefulness of DTT-SBRT for liver tumors is limited. Thus, we conducted a prospective, multicenter phase II study to evaluate the safety and efficacy of DTT-SBRT.

2. Materials and methods

2.1. Ethics

This prospective phase II study was approved by our institutional review board (C1069) and conducted in accordance with the tenets of the Declaration of Helsinki and was registered on the University Hospital Medical Information Network (registration number: UMIN000017886). Written informed consent was obtained from all patients.

2.2. Patients

The criteria for inclusion were: (1) $<$ 4 liver tumors diagnosed clinically or histologically, with diameters $\leq$ 50 mm, without extrahepatic lesions; (2) age $>$ 20 years and ability to consent to this prospective study; (3) ability to maintain a supine position with the arm up; (4) deemed medically unfit for surgical resection or percutaneous ablation or having refused these therapies; (5) Eastern Cooperative Oncology Group performance status of 0–2; (6) Child–Pugh score $\leq$ 8; and (7) expected respiratory motion $\geq$ 10 mm. The exclusion criteria were: (1) re-irradiation; (2) ascites difficult to control with medical treatment; (3) esophageal varices at high risk of bleeding; (4) either active pulmonary fibrosis or interstitial pneumonia; (5) any severe collagen diseases; (6) severe diabetes mellitus; (7) pregnant or lactating; (8) mental illnesses precluding registration; and (9) other situations deemed unsuitable for this study.

2.3. Treatment system and planning

A previous report presented the mechanical aspects of the Vero4DRT system (Hitachi, Co. ltd., Kashiwa, Japan), which was engineered at our institutes [13]. The system comprises an X-ray head that can rotate along two orthogonal gimbals, enabling rapid target pursuit and precise beam positioning. An on-board imaging subsystem consists of two sets of kV X-ray tubes and flat panel detectors, providing real-time fluoroscopic monitoring for pursuit irradiation, a pair of radiographs, and cone beam computed tomography (CT) images. The detailed method for DTT treatment planning and delivery has been previously reported [12,14]. Ahead of the procedures, a fiducial gold marker (VISICOIL, IBA dosimetry, Louvain-la-neuve, Belgium) was placed in the patients' livers. Using vacuum pillows, the patients were placed in a supine position with both arms raised.

Contrast-enhanced breath-hold CT and four-dimensional (4D) CT were used for planning with a 16-slice CT scanner with a $\leq$ 3 mm slice thickness. The target volume (TV) was set as follows: (1) Gross tumor volume (GTV), defined as the volume of the region where the tumor location was confirmed via diagnostic imaging. The area occupied by the tumor was determined after examining contrast-enhanced CT or magnetic resonance images. (2) Clinical TV (CTV), defined as GTV with 3 mm added three-dimensionally in consideration of invasion. (3) Tracking internal TV, defined considering the intra-fraction error between the CTV and the *in vivo* marker. (4) Planning TV (PTV), used to ensure daily setup margins and tracking accuracies, such as (i) the inter-fraction error between CTV and internal markers, (ii) 4D model error due to changes in the respiratory status during irradiation, and (iii) mechanical error. The required margin varies among patients but is generally set to at least 5 mm [15].

The prescription dose was defined as the dose to 95 % of PTV (D_{95}). The total dose was 40 Gy in five fractions, comprising 100 % of the dose. We ensured that the 100 % isodose line matched the outline of the PTV as much as possible. The dose received by the 2 % volume of PTV (D_2) was 133–143 %, and the dose distribution was steep. Table 1 shows the dose constraints for PTV and organs at risk (OAR).

2.4. Treatment delivery

Tumor tracking was performed based on a prebuilt 4D model that correlates an external respiratory signal with the internal tumor position. The respiratory signals were captured by an infrared (IR) camera using IR markers on the patient's abdominal wall. Tumor positions were calculated by detecting the inserted fiducial marker with kV X-ray imaging subsystems. The treatment beams were delivered and guided by the 4D model-based tumor tracking. During beam delivery, the detected target positions with stereo-fluoroscopic images were acquired every second, and the target positions where the treatment X-ray beams were delivered were tracked. When the fiducial marker (detected by kV imagers) moved 3 mm away from the predicted locations, the treatment beam was stopped, and the 4D model was corrected [15]. The 95th percentile difference between the detected and tracked target positions was used to measure tracking accuracy [16]. The irradiation was performed once daily, three to five times per week.

Table 1
Dose constraints and reported values of the PTV and planning OAR volumes.

Volume	Constraints		Median	Range	
PTV	$D_{95\%}$	40 Gy	40 Gy	40–40.2 Gy	
	$D_{2\%}$	133 %–143 %	141.9 %	136.6–143.7 % *	
Liver-GTV	V_{20Gy}	20 %	8.4 %	2.0–19.9 %	
Spinal cord	D_{max}	28 Gy	6.0 Gy	0–19.2 Gy	
	V_{15Gy}	$\leq$1.2 cm^3	0 cm^3	0–1.2 cm^3	
Skin	D_{max}	38.5 Gy	17.1 Gy	4.2–13.9 Gy	n = 25
	V_{36Gy}	$\leq$10 cm^3	0 cm^3	0–3.7 cm^3	
Esophagus	D_{max}	35 Gy	16.5 Gy	6.4–26.0 Gy	n = 8
	V_{20Gy}	$\leq$5 cm^3	0 cm^3	0–4.7 cm^3	
Stomach	D_{max}	35 Gy	22.8 Gy	5.2–33.2 Gy	n = 11
	V_{20Gy}	$\leq$5 cm^3	0.2 cm^3	0–5 cm^3	
Small bowel	D_{max}	26 Gy	6.8 Gy	0.8–26.0 Gy	n = 17
	V_{20Gy}	$\leq$5 cm^3	0 cm^3	0–1.6 cm^3	
Large bowel	D_{max}	35 Gy	21.9 Gy	0.4–33.6 Gy	n = 15
	V_{20Gy}	$\leq$5 cm^3	0 cm^3	0–3.7 cm^3	
Kidneys	V_{20Gy}	33 %	1.6 %	0–13.9 %	n = 16

OARs (except for the spinal cord) were evaluated when the dose of OARs were expected to exceed 20 Gy. D_{max} was defined as the maximum dose displayed in the treatment planning system with spatial resolution and deviation set to $\leq$ 2 mm.
*PTV $D_{2\%}$ exceeded the constraints in one patient.
Abbreviations: PTV, planning target volume; OAR, organ at risk; GTV, gross tumor volume; $D_{x\%}$, dose covering *x*% of the volume; V_{xGy}, volume covered by the $\times$ Gy isodose; D_{max}, maximum dose.

2.5. Follow-up

Patients were examined every 2–3 months for 1 year after registration and every 2–6 months thereafter. Abdominal contrast-enhanced CT or abdominal magnetic resonance imaging with ethoxybenzyl diethylenetriamine pentaacetic acid contrast was performed at least once every 3 months until 1 year after registration and at least once every 6 months thereafter, until the end of follow-up. The last day of follow-up was the date of death or when survival was confirmed (mainly the date of outpatient visit). Additional treatment (local or systemic therapy) was not administered until disease progression.

2.6. Evaluation of effect and adverse events

The effect was judged using the modified Response Evaluation Criteria in Solid Tumors. Local progressions were defined as a diagnosis with progressive disease due to cancer by imaging or those diagnosed histopathologically by biopsy or surgical excision. The absence of local progression was considered LC, i.e., equivalent to complete response, partial response, or stable disease [17,18]. When a new lesion appeared outside the irradiation field, the disease progressions were divided into two groups: intrahepatic and other organs (including lymph-node metastases). Disease progression was defined as "exacerbation" if either local progressions or new lesions were identified. Progression-free survival (PFS) was defined as freedom from disease progression and all-cause mortality. Overall survival (OS) was defined as absence of death from any cause. All courses were initiated on the day SBRT was started. Adverse events related to SBRT were evaluated using the Common Terminology Criteria for Adverse Events, version 4.0. Acute and late toxicities were defined as adverse events occurring within 8 weeks of starting SBRT and thereafter, respectively.

2.7. Endpoints

The primary endpoint of this study was LC at 2 years. With a threshold value of 80 %, one-sided alpha of 0.15, and 80 % power, 45 samples were required to test for the expected value of 90 % LC. Therefore, 48 patients were registered to include a few cases of deviation or exclusion from the analysis. Secondary endpoints included OS, PFS, adverse events, and tracking accuracy.

2.8. Statistical analyses

All statistical analyses were performed using R version 3.5 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was defined as $p < 0.05$. The LC, PFS, and OS rates were estimated using Kaplan–Meier analysis. The participating institutions reported the dose-volume indices for PTVs, OARs, and log files were reported; the tracking accuracy data were collected for each case after treatment completion.

3. Results

Between September 2015 and March 2019, 129 patients with liver tumors were referred to the participating institutions for indications of SBRT. Among them, 48 patients who met the inclusion criteria were registered in this study. Details of the non-registered cases are shown in Fig. 1. There was no trouble in inserting the fiducial marker; however, it dropped out from the liver in one patient. These patients (48 lesions) were successfully treated. The average treatment period per fraction was 28.6 (range, 12–90) minutes. The median patient age was 74 (range, 52–97) years. Thirty-five patients were men, and 13 were women. Thirty-nine cases had HCCs and nine had metastatic liver tumors. The median tumor diameter was 17.5 (range, 10–47) mm. The patient characteristics are summarized in Table 2.

The median follow-up period in all patients was 36.5 (range, 3.0–62.4) months, and the median follow-up period in surviving patients was 40.8 (range, 15.3–62.4) months. All surviving patients were evaluated by the primary endpoint of 2-year LC at the time of data cutoff on March 31, 2021.

The 2-year LC rate was 98.0 % (lower limit of the one-sided 85 % confidence interval [CI]: 86.1 %) (Fig. 2). The 2-year OS and PFS were 88.8 % and 55.1 %, respectively (Fig. 3). Disease progression was observed in 33 (68.8 %) patients. One patient (0.2 %) had local HCC

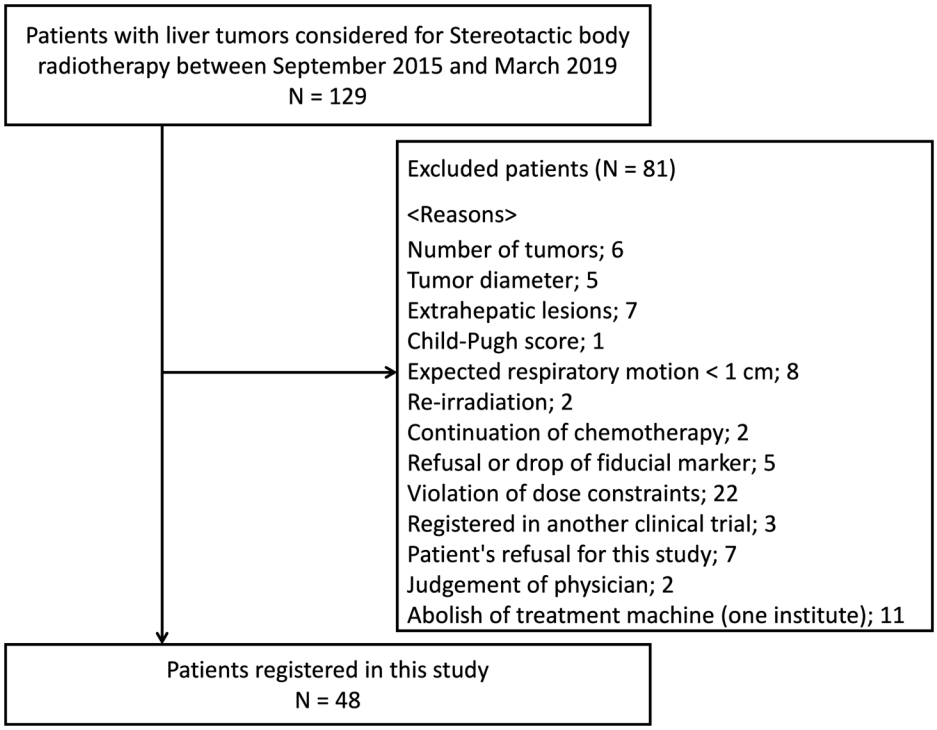

Fig. 1. Patient selection in this study.

Table 2
Patients' characteristics.

Characteristics	Value (N = 48)
Sex, male: female	35: 13
Median age (range)	74 years (range, 52–97 years)
Etiology, primary: metastases	39: 9 (primary site: colon cancer, 2; esophagus cancer, 2, nasopharyngeal cancer, 1; cholangiocarcinoma, 1; small cell lung cancer, 1; ovarian cancer, 1; prostate cancer; 1).
Median tumor diameter (range)	17.5 (range, 10–47) mm

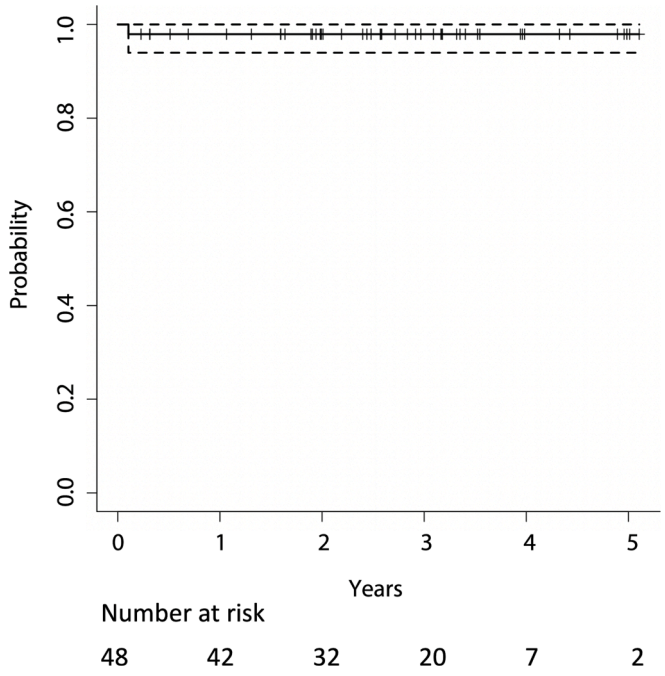

Fig. 2. Local control rates after starting stereotactic body radiotherapy. The dotted line indicates the 95 % confidence interval.

recurrence, 31 (64.6 %) developed new hepatic lesions outside the irradiation field, and nine (18.8 %) had distant metastases (including overlap). During the follow-up period, 15 patients succumbed, including eight from their primary diseases and seven from other causes. The 2-year LC, OS, and PFS in patients with HCC and metastatic liver tumors were 97.4 %, 86.4 %, and 50.7 % and 100 %, 88.9 %, and 66.7 %, respectively.

No patient experienced grade 4 or 5 adverse events. Seven patients (14.6 %) experienced grade 3 adverse events, such as elevation of hepatobiliary enzymes (five patients), hyponatremia (one patient), and thrombocytopenia (one patient) during the late course. The average time to grade 3 adverse events was 22.2 (range, 6.4–42.7) months. Among the seven patients, six underwent additional treatment for intrahepatic and/or distant recurrence and one developed intrahepatic recurrence and experienced adverse events during best supportive care.

Table 3
Adverse events of grades 2 and 3.

N = 48	Grade 2		Grade 3	
	Acute	Late	Acute	Late
Elevation of liver or biliary enzymes	0 (0 %)	4 (8.3 %)	0 (0 %)	5 (10.4 %)
Hypoalbuminemia	1 (2.1 %)	3 (6.3 %)	0 (0 %)	0 (0 %)
Anemia	1 (2.1 %)	3 (6.3 %)	0 (0 %)	0 (0 %)
Thrombocytopenia	1 (2.1 %)	2 (4.2 %)	0 (0 %)	1 (2.1 %)
Leukopenia	1 (2.1 %)	2 (4.2 %)	0 (0 %)	0 (0 %)
Hyponatremia	0 (0 %)	0 (0 %)	0 (0 %)	1 (2.1 %)
Ascites	0 (0 %)	1 (2.1 %)	0 (0 %)	0 (0 %)
Hyperglycemia	0 (0 %)	1 (2.1 %)	0 (0 %)	0 (0 %)
Chest wall pain	0 (0 %)	1 (2.1 %)	0 (0 %)	0 (0 %)
Melena	0 (0 %)	1 (2.1 %)	0 (0 %)	0 (0 %)
Fatigue	1 (2.1 %)	0 (0 %)	0 (0 %)	0 (0 %)

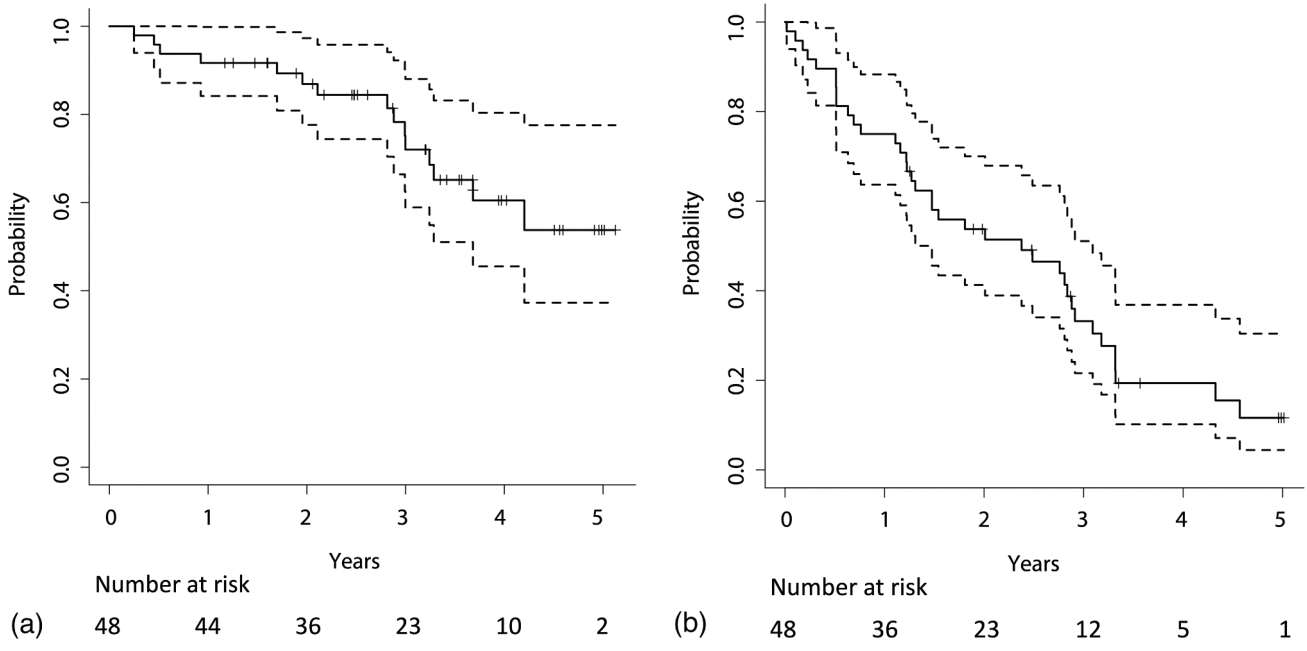

Fig. 3. Overall survival (a) and progression-free survival (b) after starting stereotactic body radiotherapy. The dotted line indicates the 95 % confidence interval.

Grade 2 adverse events were observed in 13 patients (27.1 %; Table 3).

The median PTV margin size was 5 (range, 5–8) mm and 33 tumors had a margin of 5 mm. The objectives of the dose-volume indices were met in 47 patients. In one case, the PTV D_2 dose was exceeded. A total of 225 fractions were logged during DTT-SBRT. The median tracking accuracy was 2.9 (range, 1.1–6.2) mm. The median respiratory motion was 14.0 (range, 7.1–40.0) mm. Only six patients had average respiratory motion < 10 mm (Fig. 4).

4. Discussion

This multicenter phase II trial was, to our knowledge, the first to evaluate the safety and efficacy of DTT-SBRT using real-time monitoring for liver tumors. The advantages of this study include the multi-institutional nature, using the same treatment protocol, and including patients with respiratory-moving tumors. DTT-SBRT was successfully performed for liver tumors and showed excellent LC (the primary endpoint was met with a 2-year LC of 98.0 %; the lower limit of the one-sided 85 % CI was 86.1 %). Grade 3 adverse events occurred in 14.6 % patients approximately 2 years after starting SBRT and after the recurrence of the primary disease; most patients received additional treatment. Grade 3 adverse events were reported since a causal relationship to DTT-SBRT could not be excluded; however, it could be attributed to disease progression or additional treatment. Therefore, DTT-SBRT is an effective and safe treatment option. This report described the longest observation period in DTT-SBRT for liver tumors using a gimbal-mounted linac.

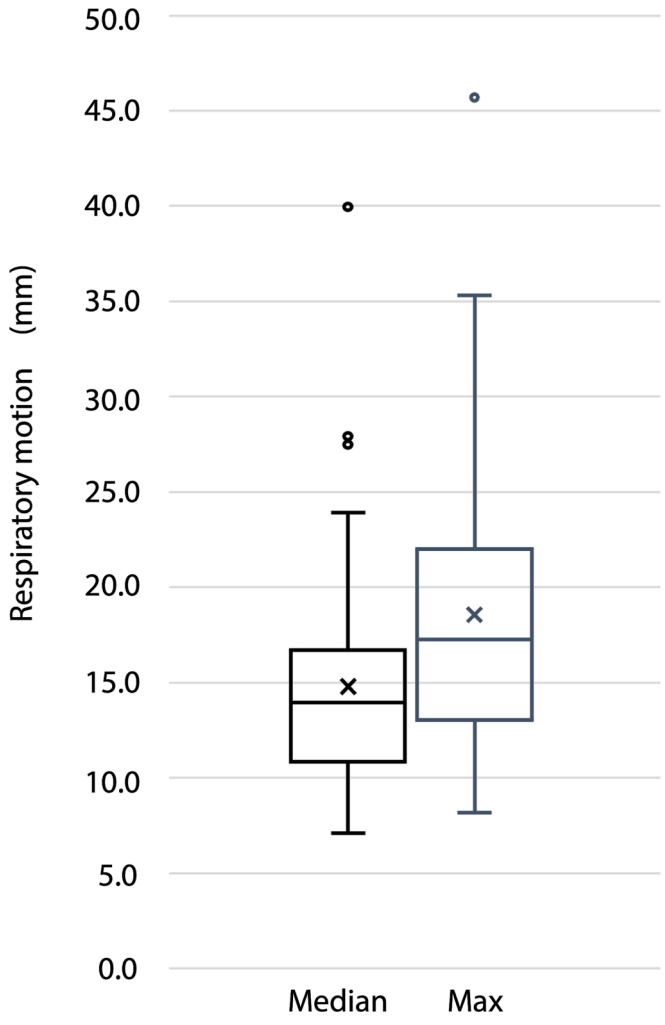

Fig. 4. Median and maximum respiratory motion characteristics of all patients.

DTT was successfully performed with a high tracking accuracy, with the median tracking error within the PTV margin (minimum: 5 mm). The tracking accuracy was reduced due to the decreased correlation between external and internal markers. There was no exact data regarding the frequency of beam stopping as the three patterns of beam stopping (during 4D model production, accuracy < 3 mm, and missing the fiducial marker in radiograph monitoring) on the log-files were indistinguishable.

Violations of dose constraints were observed in one patient, with D_2 0.7 % higher than the constraint (dose: 0.29 Gy). However, the results were not significantly affected. This patient showed no recurrence for 2 years by the end of follow-up.

LC was comparable to that reported by other studies on SBRT for liver tumors without DTT [5,6,10,19]. The DTT method could theoretically be a treatment with fewer side effects, as it can reduce the size of PTV and normal liver dose. However, there was no significant difference in this study. It seems that this depends on the differences in patient backgrounds.

Few reports have discussed the clinical outcomes of DTT and gating with the Vero4DRT system for liver tumors. Depuydt et al. reported the target size and normal tissue dose reduction using DTT-SBRT with Vero4DRT in 10 patients, including three patients with liver tumors [20]. However, the clinical results were not reported. We previously reported preliminary clinical results with a shorter observation period [12]. We treated 12 patients with liver tumors (seven with HCCs and five with metastases) using DTT-SBRT, with a median follow-up of 11 months and an LC rate of 90 % at 1 year. Uchinami et al. reported the clinical results of 63 patients with 74 HCCs treated with respiratory gating SBRT, with a median follow-up period of 24.6 months; the 1- and 2-year LC rates were 100 % and 92.0 %, respectively. The 1- and 2-year OS rates were 86.8 % and 71.1 %, respectively [21].

Although higher doses of SBRT have been reported [22,23], 40 Gy in five fractions was used in this study since our treatment target was relatively small and previous studies from Japan used similar doses [10]. Moreover, dose escalation was deemed unnecessary due to the excellent LC and low adverse events. The incidence of grade 3 or higher side effects was similar to those in previous studies using the same dose fractionation [5,6,10]. We defined the prescribed dose as D_{95} for PTV. Since the treatment protocol in the previous planning study was the same as in this study and D_{98} values were similar [24], we decided that the collection of PTV D_{98} data was unnecessary. V_{20} was used for the liver and other organs based on a multi-institutional study [10]. The index of the volume of normal liver spared was not used owing to concerns that patients who underwent hepatectomy might not meet this criterion. We evaluated the peak dose of OAR as D_{max}, instead of D_2 or $D_{0.03\ mL}$, to evaluate the peak dose easily. D_{max} was defined as the maximum dose displayed in the treatment planning system with spatial resolution and deviation of ≤ 2 mm.

Although phase III clinical trials are desirable to confirm the evidence related to DTT-SBRT use, conducting phase III trials is challenging owing to limited recourse for motion management. Several studies have reported the clinical outcomes of DTT-SBRT with CyberKnife system. Louis et al. reported that the 1- and 2-year LC rates were 95 % with a median follow-up period of 12.7 months, and the 1- and 2-year OS rates were 79 % and 52 %, respectively, in 25 patients with HCCs. Two cases of grade 3 adverse events (pain and hepatic toxicity) were reported [22]. Vautravers–Dewas et al. treated 42 patients with 62 liver metastases. The LC rates for 1- and 2- years were 90 % and 86 %, respectively, with a median follow-up of 14 months; the OS rates for 1- and 2- years were 94 % and 48 %, respectively, with one case of grade 3 epidermitis [23]. Therefore, our results are roughly consistent with those of these previous reports. In this study, OS was better than those of previous studies, possibly due to the difference in patient populations or local and systemic therapy after recurrence.

This study had several limitations. First, we registered patients with

HCC and metastases. The LC rate for HCCs and metastatic liver cancer is similarly excellent [5,6,23,25]; therefore, we determined that the effect would be limited on the evaluation of the primary endpoint (LC), but this made it difficult to evaluate OS and PFS. Second, the observation period was short. We are currently conducting observational studies in this cohort. Lastly, the Vero4DRT system is not manufactured anymore, and eleven systems remain operating in the world. Notably, the development of a new gimbal-equipped linac based on the Vero4DRT concept was announced at the 2022 Japanese Society for Radiation Oncology annual meeting, with expected manufacturing and marketing approval in 2023. The results of this study are applicable for this successor as well as other systems.

5. Conclusions

DTT-SBRT achieved excellent LC in liver tumors with a low incidence of severe toxicity in this multi-institutional prospective phase II study.

Declaration of Competing Interest

Masaki Kokubo is in a speaker's bureau from AstraZeneca K.K.; Takashi Sakamoto is in a speaker's bureau from SCETI.K.K.; Mitsuhiro Nakamura receives research funding from Varian Medical Systems, Inc. and a scholarship donation from Hitachi, Ltd.; Yukinori Matsuo receives research funding from Varian Medical Systems, Inc.; Takashi Mizowaki has received honoraria from Varian Medical Systems, Inc., Elekta K.K., Hitachi, Ltd., and Brainlab AG; played a consulting or advisory role for Varian Medical Systems, Inc. Hitachi, Ltd.; has research funding from Hitachi, Ltd. and educational projects from Varian Medical Systems and Brainlab AG. Other authors have no conflicts of interest to declare.

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Data sharing statement

Clinical data and log files were anonymously collected. Data can be requested from the corresponding author.

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