ACTA ONCOLOGICA
2022, VOL. 61, NO. 1, 104–110
https://doi.org/10.1080/0284186X.2021.2001566

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Feasibility of marker-less stereotactic body radiotherapy for hepatocellular carcinoma

Yuichi Kibe[a,b], Atsuya Takeda[a], Yuichiro Tsurugai[a], Takahisa Eriguchi[a], Yohei Oku[a], Yuto Kimura[a] and Naoki Nakamura[b]

[a]Radiation Oncology Center, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan; [b]Radiation Oncology Division, St. Marianna University School of Medicine Hospital, Kawasaki, Kanagawa, Japan

ABSTRACT

Background: The feasibility of marker-less stereotactic body radiotherapy (SBRT) for hepatocellular carcinoma (HCC) has not yet been established, and, thus, was examined in the present study.

Material and methods: We retrospectively investigated patients who received marker-less SBRT for locally untreated HCC tumors between July 2005 and December 2018. Radiotherapy planning CT was performed under fixation with vacuum cushions and abdominal compression. The clinical target volume (CTV) was equivalent to the gross tumor volume (GTV). The internal target volume (ITV) margin to CTV was determined from calculations based on the motion of the diaphragm. The planning target volume (PTV) margin to ITV was 5–6 mm. In the set-up, radiotherapy planning CT and linac-integrated cone-beam CT performed in the same imaging and fixation settings were merged by referring to the anatomical components surrounding target tumors. The primary endpoint was the 3-year cumulative local tumor progression rate. The upper limit of the 95% confidence interval for the 3-year cumulative local tumor progression rate was less than 7.0%, which was interpreted as favorable local control and feasible for marker-less SBRT. Local tumor progression was assessed by mRECIST.

Results: We reviewed 180 patients treated with 35–40 Gy/5 fractions. The median follow-up time for the local tumor progression of censored tumors was 32.3 months (range, 0.3–104). The 3-year cumulative local tumor progression rate was 3.0% (95% CI, 1.1–6.5%). The 3-year overall survival rate was 71.6% (95% CI, 63.5–78.2%). Regarding acute hematologic toxicities, grade 3 hypoalbuminemia and thrombocytopenia were detected in 1 (0.6%) and 5 (2.9%) patients, respectively. Treatment-related death from SBRT was not observed. SBRT was initiated within 7 days after radiotherapy planning CT for 84% (152/180) of patients.

Conclusions: Marker-less SBRT for HCC achieved favorable local control that fulfilled the threshold. This result suggests that marker-less SBRT with appropriate settings is a feasible treatment strategy.

ARTICLE HISTORY
Received 20 August 2021
Accepted 28 October 2021

KEYWORDS
Hepatocellular carcinoma; stereotactic body radiotherapy; marker-less; local control; feasibility

Background

Hepatocellular carcinoma (HCC) is diagnosed as the seventh most common cancer in the world and the fourth most common cause of death from cancer [1]. The current definitive treatments for HCC are resection, ablation, and liver transplantation [2,3]. However, patients with HCC are often ineligible for the above definitive treatments due to an inability to tolerate surgery, a target lesion in a location that is difficult to ablate [4,5], and the limited supply of donors. Stereotactic body radiotherapy (SBRT) is an emerging treatment method that precisely irradiates high-dose radiation to targets in a limited number of fractions non-invasively and achieves favorable local control for HCC [6,7]. SBRT may be performed in cases in which other curative treatments are challenging, as described above. Therefore, SBRT is a promising curative treatment, particularly when other curative treatment options are not indicated [8].

HCC tumors are often invisible on non-contrast CT due to the surrounding liver parenchyma. Therefore, the implantation of fiducial markers close to target HCC tumors [9–11] or enhancing HCC tumors using lipiodol through transarterial chemoembolization (TACE) [9,12] is generally performed prior to radiotherapy planning CT for SBRT for HCC. Since both procedures generally necessitate hospitalization and labor, delays before marking may occur due to the availability of hospitalization and marking. They are also invasive and may cause complications. To overcome these issues, the establishment of a technique for marker-less SBRT for HCC is warranted; however, there is currently no information on marker-less SBRT for HCC.

In our institution, we routinely performed TACE before SBRT for HCC to ensure the accumulation of lipiodol as a marker in the target tumor. In 2010, we examined the relationship between the respiration motion of lipiodol deposits

CONTACT Atsuya Takeda takeda@1994.jukuin.keio.ac.jp Department of Radiation Oncology, Ofuna Chuo Hospital, 6-2-24 Ofuna, Kamakura-Shi, 247-0056, Kanagawa, Japan

Supplemental data for this article can be accessed here.

in HCC tumors after TACE and that of the diaphragm. Based on the findings of this examination, we judged that SBRT for HCC may be performed without marking without missing the target by calculating the internal target volume (ITV) margins from the respiratory motion of the diaphragm and devising appropriate measures. Since then, preceding TACE is no longer routinely performed.

The purpose of the present study was to clarify the feasibility of marker-less SBRT for HCC by reviewing the clinical outcomes of marker-less SBRT for locally untreated HCC tumors.

Materials and methods

The present study was endorsed by the Institutional Ethics Committee (2020-006). Informed consent for the use of patient data in research was obtained from all patients in this study before treatment.

Patients

Five hundred and forty-two HCC patients who had received radiotherapy at our institution between July 2005 and December 2018 were identified. Of these, patients treated for locally untreated HCC tumors with marker-less SBRT without using any visual markers such as TACE-lipiodol or fiducial markers that met the following criteria were reviewed in this study: (1) no previous radiotherapy to the liver. (2) without previous histories of other cancers; (3) treated with radiotherapy by five or fewer fractions; (4) treated with radiotherapy with more than 7 Gy per fraction; (5) no prior local treatment (including TACE with the aim of assessing lipiodol deposition as a marker for SBRT) to the target tumor of SBRT. Cases with previous local treatment (such as resection, radiofrequency ablation (RFA), and TACE) to non-target lesions of SBRT were included in the present study if they met the above eligibility criteria.

The diagnosis of HCC was based on a diagnostic imaging test with multiphasic MRI or CT according to the international clinical practice guidelines for HCC [2,3]. Fundamental eligibility criteria for SBRT for HCC in our institution are as follows: (1) HCC patients who are unsuitable for resection and RFA or decline these treatments, (2) Child–Pugh Classification (CPC) A or CPC B, (3) maximum tumor diameter $\leq$5 cm, (4) number of tumors $\leq$3, and (5) normal liver V20 (the volume receiving $>$20 Gy) not exceeding 20%. After discussions on decision-making for treatment, several patients with deviations from these eligibility criteria received SBRT and were included in the study.

Treatment and follow-up

Until March 2010, TACE was performed to deposit lipiodol as a marker in targeted HCC tumors prior to treatment planning CT imaging for SBRT. Since then, preceding TACE has not been routinely performed.

As radiotherapy planning CT, time-averaged fast scan CT in which image data of all respiratory phases were reconstructed slice-by-slice from 6-8 images of the same slice captured at 1-second intervals was performed in free-breathing conditions under fixation with vacuum cushions and abdominal compression in the spinal position [13,14]. Abdominal compression was used to reduce diaphragmatic motion in the craniocaudal direction to less than 10 mm and to also reduce the respiratory motion of the liver and target tumor. After radiotherapy planning CT was performed, 3- or 4-phase spiral dynamic CT using nonionic contrast medium was performed using the same position and fixation as radiotherapy planning CT.

When target contouring was performed, radiotherapy planning CT and 3- or 4-phase spiral dynamic CT images were fused, and the gross tumor volume (GTV) was contoured on the radiotherapy planning CT image along with lesion enhancement on 3- or 4-phase contrast dynamic CT images in the clearer phase of the arterial (30 s) or portal (60 s) phase. The clinical target volume (CTV) was equivalent to GTV. ITV margins to CTV without visual markers were determined through the following process. In 2010, we examined the relationship between diaphragmatic motion and the motion of lipiodol deposited by TACE on the target tumor using time-averaged fast scan CT under fixation with vacuum cushions and abdominal compression in approximately 40 HCC patients who underwent SBRT after TACE to deposit lipiodol as a marker on the target tumor (unpublished data). As a result, the ITV margin was found to cover 95% of the motion of lipiodol, calculated from the length of the motion of the diaphragm in each axis (cranial-caudal; CC, right-left; RL, anterior-posterior; AP) as follows: cranial: CC/4 + 2 mm, caudal: CC*3/4 + 2 mm, right and left: RL/2 + 1 mm, anterior: AP/2 mm, posterior: AP/2 + 1 mm. Since abdominal compression is performed to restrict the diaphragm to less than 10 mm of motion in the cranial-caudal direction, the ITV margin in the cephalad-caudal direction, in which motion is greater than in the other axial directions, is basically 3–5 mm in the cranial direction and 5–10 mm in the caudal direction, respectively. ITV margins other than cephalocaudal were essentially in the following ranges: anterior: 2 mm, lateral and posterior: 3 mm. The planning target volume (PTV) margin to ITV was 5 mm (cranial and caudal: 6 mm).

Linac-integrated cone-beam CT was performed before each treatment under free-breathing using the same fixation setting as radiotherapy planning CT. Cone-beam CT was imaged over 75 s in each round, and average processing was performed. Therefore, the images obtained from radiotherapy planning CT and linac-integrated cone-beam CT were similar averaged images. Regarding the set-up, radiotherapy planning CT and cone-beam CT were fused by referring to the anatomical components surrounding target tumors, including branches of the hepatic artery, branches of the hepatic vein, branches of the portal vein, and the liver surface.

Radiation treatment planning systems were used to plan non-coplanar volumetric-modulated arc therapy (Eclipse, version 10.0; Varian Medical Systems) or multi-arc dynamic conformal radiation (FOCUS XiO, version 4.2.0-4.3.3:

Computerized Medical Systems, St Louis, Mo, USA). Linear accelerators (Clinac 2100 C and iX, Varian Medical Systems, Inc., Palo Alto, CA, USA) were used to irradiate patients with 6- or 10-MV photons.

CPC-A patients were treated with 40 Gy/5 fractions (fr) over 5 to 9 days. Patients with CPC-B and those with normal liver V20 > 20% in the 40 Gy/5 fr plan were treated with 35 Gy/5 fr. The prescribed dose was defined as a 60–80% isodose of the maximum dose in PTV, and the prescribed dose covered 95% of PTV.

Patients were followed up 1 month after the completion of SBRT and every 3 months thereafter. In each follow-up, patients were evaluated with diagnostic dynamic MRI or CT and blood tests.

Endpoints and assessments

The primary endpoint was the 3-year cumulative local tumor progression rate. Local tumor progression was defined as the occurrence of progressive disease within the treated region assessed by mRECIST [15]. Local control was defined as the absence of local tumor progression. The time to local tumor progression was measured from the date of the start of SBRT to local tumor progression. The secondary endpoints were overall survival (OS), progression-free survival (PFS), toxicity, treatment after progression, and time to the start of SBRT. OS was defined as the time from the date of the start of SBRT to the date of death from any cause. PFS was defined as the time from the date of the start of SBRT to the date of disease progression or death from any cause. Acute hematological and non-hematological toxicities occurring within 3 months of the completion of SBRT were evaluated according to CTCAE Ver 4.0. Non-classic RT-induced liver disease (RILD) (an increase in liver enzymes of 5-fold or more above the upper limit of normal or the worsening of the Child-Pugh score by 2 points or more) within 3 months of the completion of SBRT was also evaluated [16]. The cause of death of all deceased patients was reviewed by two radiation oncologists to establish whether they were treatment-related deaths.

Statistical analysis

Local tumor progression was estimated by the cumulative incidence method, taking death without local tumor progression into account as a competing risk. We decided to interpret the local control of marker-less SBRT as favorable and feasible if the upper limit of the 95% confidence interval for the 3-year cumulative local tumor progression rate was less than 7.0%. This threshold of 7.0% was selected based on the findings of our previous study, in which the point estimate of the 3-year cumulative local tumor progression rate in the group that underwent SBRT for HCC tumors after TACE to accumulate lipiodol as a marker was 5.0% [17], as well as the advantages of marker-less SBRT, such as non-invasiveness and low labor requirements. A Fine-Gray analysis was performed for the univariate analysis to identify risk factors for local tumor progression. Regarding factors with $p<0.20$ in the univariate analysis, we decided to perform a multivariate analysis using the Fine-Gray model analysis if more than one factor was shown to be $p<0.20$ in the univariate analysis and the number of local tumor progression events was sufficient (10 events per factor). OS and PFS were estimated by the Kaplan- Meier method. Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [18].

Results

In the present study, 180 HCC patients were reviewed (Supplementary Figure 1). Patient characteristics are shown in Table 1. Ten patients were treated with SBRT without markers before April 2010 for the following reasons: poor renal function and inability to use iodine contrast media 4; severe arterial calcification and inability to perform TACE 1; a history of anaphylactic shock due to iodine contrast media 1; the patient refusal of TACE 1; inability to be admitted for TACE due to patient's schedule 1; reason unknown 2.

Local control

The median follow-up time for the local tumor progression of censored patients was 32.3 months (range, 0.3–104). During the follow-up period, local tumor progression was detected in 7 patients. The median time to local tumor

Table 1. Patient characteristics.

Characteristics	No. of patients (%)
Number of patients	180
Age: median [range], y	74 [46–93]
No. of females	54 (30)
Type of chronic hepatitis	
None	10 (5.6)
HBV	17 (9.4)
HCV	117 (75)
Alcoholic	20 (11)
NASH	8 (4.4)
Others	8 (4.4)
Child–Pugh score	
5	132 (73)
6	33 (18)
7	11 (6.1)
8	3 (1.6)
9	1 (0.6)
BCLC stage at treatment	
0	61 (34)
A	60 (33)
B	7 (3.7)
C	49 (27)
D	3 (1.6)
Tumor diameter: median, cm	1.9 [1.0–5.1]
Total dose/fraction	
35 Gy/5 fr	21 (12)
40 Gy/5 fr	159 (88)
Isodose	
60%	6 (3.3)
70%	153 (85)
80%	21 (11)
Year of treatment	
2006.3–2010.3	10 (5.5)
2010.4–2018.12	170 (94)

Abbreviations: BCLC: Barcelona clinic liver cancer staging system; HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: nonalcoholic steatohepatitis.

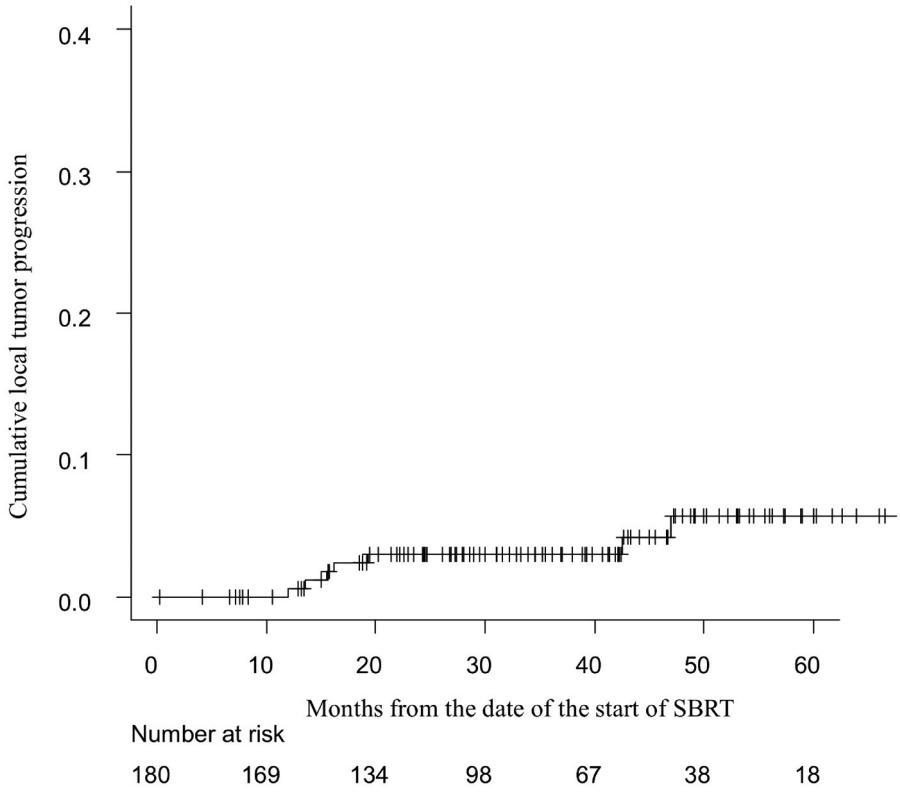

Figure 1. Cumulative local tumor progression curve.

progression was 15.5 months (range, 12.0–47.0). The 3-year cumulative local tumor progression rate was 3.0% (95% CI, 1.1–6.5%). (Figure 1). The upper limit of the 95% confidence interval for this 3-year cumulative local tumor progression rate met the threshold for interpreting the favorable local control and feasibility of marker-less SBRT. The tumor diameter was a significant risk factor for local tumor progression in the univariate analysis (Table 2). The multivariate analysis was not performed because of insufficient local tumor progression events.

Table 2. Univariate analysis of local tumor progression.

Variable	No. of tumors	HR (95%CI)	*p*-value
Age		1.00 (0.95–1.05)	0.97
Sex			
Male	126		
Female	54	0.38 (0.05–2.93)	0.35
Type of chronic hepatitis			
HCV	117		
Others	63	0.78 (0.16–3.90)	0.76
BCLC stage at treatment			
0, A, B	128		
C, D	52	1.09 (0.22–5.49)	0.92
Child–Pugh score			
5	132		
>5	48	1.24 (0.25–6.16)	0.79
Tumor diameter		1.08 (1.02–1.14)	0.011
Total dose/ fraction			
35 Gy/5 fr	21		
40 Gy/5 fr	159	0.28 (0.056–1.41)	0.12
Isodose			
<80%	159		
80%	21	1.09 (0.14–8.18)	0.94

Abbreviations: HCV: hepatitis C virus.

OS and PFS

The median follow-up time for the OS of censored patients was 39.1 months (range, 0.3–104). The 3-year OS rate was 71.6% (95% CI, 63.5–78.2%) (Figure 2(a)). The median follow-up time for the PFS of censored patients was 42.3 months (range, 0.3–82.7). During the follow-up period, disease progression occurred in 111 patients. The 3-year PFS rate was 31.2% (95% CI, 24.3–38.4%) (Figure 2(b)).

Toxicity

Acute toxicities were evaluated in patients with 173 patients because patients with 7 patients were not followed up for 3 months or had insufficient testing. Acute hematological toxicity is described in Table 3. Grade 3 hypoalbuminemia and thrombocytopenia were observed in 1 (0.6%) and 5 (2.9%) patients as acute hematologic toxicities and in 0 and 3 (1.7%) patients at baseline. No Grade 3 or higher non-hematological hepatic or gastrointestinal acute toxicities were observed. Non-classic RILD occurred in four patients (2.0%), all of which were caused by the worsening of the Child-Pugh score by 2 points or more from baseline (3 patients with 2 points, 1 patient with 3 points). Treatment-related death from SBRT was not observed.

Treatment after progression

After 111 patients had disease progression, 17 were untreated, 8 had no details, and 86 received at least one type of treatment, for a total of 116 types of treatment as

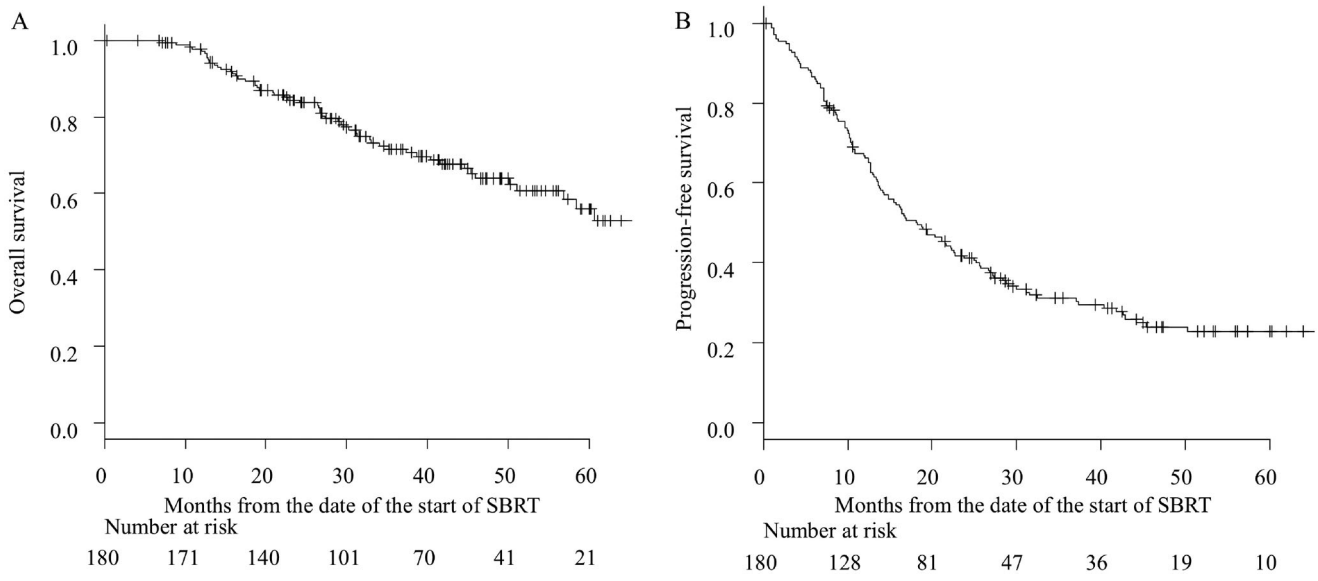

Figure 2. Kaplan–Meier curves of overall survival (A) and progression-free survival (B).

Table 3. Acute hematological toxicity.

	No. of patients (%)					
	Pre-SBRT (baseline) ($n = 180$)					
Grade	0	1	2	3	4	5
AST	114 (63%)	63 (35%)	3 (1.7%)	0	0	0
ALT	139 (77%)	38 (21%)	3 (1.7%)	0	0	0
Total bilirubin	144 (80%)	31 (17%)	5 (2.7%)	0	0	0
Albumin	132 (73%)	45 (25%)	3 (1.7%)	0	0	0
Platelets	86 (48%)	76 (42%)	15 (8.3%)	3 (1.7%)	0	0
	Post-SBRT ($n = 173$)					
Grade	0	1	2	3	4	5
AST	106 (61%)	63 (36%)	4 (2.3%)	0	0	0
ALT	137 (79%)	34 (20%)	2 (1.2%)	0	0	0
Total bilirubin	123 (71%)	35 (20%)	15 (8.7%)	0	0	0
Albumin	103 (60%)	62 (36%)	7 (4.0%)	1 (0.6%)	0	0
Platelets	65 (36%)	79 (46%)	24 (14%)	5 (2.9%)	0	0

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; SBRT: stereotactic body radiotherapy.

follows: RFA for 29 patients, TACE for 26, transarterial embolization for 2, transarterial infusion chemotherapy for 3, percutaneous ethanol injection therapy for 4, SBRT for 34, sorafenib for 8, lenvatinib for 7, regorafenib for 1, palliative radiotherapy for bone metastasis for 2. Salvage treatments for the seven tumors with local tumor progression after SBRT were as follows: RFA for 1 tumor, TACE for 1, salvage SBRT for 1, lenvatinib for 1, no treatment for 1, and no details for 2 because of transfer to another hospital after local tumor progression.

Time to the start of SBRT

The time to the start of SBRT and the reasons for delays are summarized in Supplementary Table 1. The median times from the first consultation to planning CT and from planning to the start of SBRT were 8 days (range, 0–44) and 6 days (range, 4–26), respectively. SBRT was initiated for 84% (152/180) of patients within 7 days after radiotherapy planning CT. There were more than 14 days from the first consultation to treatment planning CT for s 22% (40/180) of patients. However, in all cases, there were reasons other than preparation for radiotherapy. In 1.7% (3/180) of patients, the time from treatment planning CT to treatment initiation was longer than 14 days due to continuous national holidays.

Discussion

The present study showed that marker-less SBRT for HCC achieved favorable local control that fulfilled the threshold. To the best of our knowledge, this is the first study to evaluate the clinical outcomes of marker-less SBRT.

The favorable local control of marker-less SBRT for HCC in the present study suggests its feasibility. Although previous reports analyzed the intra- and interfraction motion of HCC tumors targeted for SBRT by evaluating the motion of fiducial markers [19–22], few investigated whether visual markers are absolutely necessary or whether marker-less SBRT may be performed. We performed marker-less SBRT and achieved favorable local control for HCC by the following measures: analyzing the relationship between the diaphragm and target tumor motion, abdominal compression, and the pretreatment fusion of treatment planning CT and cone-beam CT taken at the same imaging and fixation settings. Based on the good clinical outcomes of marker-less SBRT in the present study, we consider marker-less SBRT for HCC to be feasible under appropriate preparation and treatment settings.

Feasible marker-less SBRT may allow patients to avoid the complications induced by the implantation of fiducial markers and TACE. These procedures for marking are invasive and may cause minor and major complications (fiducial marker implantation: e.g., pneumothorax, bleeding, subcapsular hematoma, and fiducial marker migration to the inferior vena cava [23–27], TACE: e.g., non-target embolization, aortic dissection, and infection [28]). The present study showed that marker-less SBRT is feasible and may avoid these

complications from invasive marking procedures without impairing local control.

The marker-less strategy may enable the prompt preparation of SBRT for HCC and improve treatment outcomes. The delay from the diagnosis to treatment of HCC has been suggested to worsen clinical outcomes due to tumor progression [29,30]. Both marking procedures, implanting fiducial markers and TACE, generally necessitate hospitalization and labor; therefore, delays before marking may occur due to the availability of hospitalization and marking. Radiotherapy planning CT may be postponed for approximately one week from the implantation of markers to 'settle' the markers in order to decrease the risk of their migration and alleviate inflammation [31–33]. Comparisons of the promptness of preparing SBRT for HCC are difficult because limited information is currently available on the time needed to prepare for SBRT for HCC. However, in the present study, the median times from the first consultation to planning CT and from planning CT to the start of SBRT were 8 and 6 days, respectively, and SBRT was started within 7 days from planning CT for 83% of tumors. Therefore, we assume that marker-less SBRT allows for a shorter preparation time for SBRT, which may improve outcomes by minimizing tumor growth.

The present study had several limitations. There might be biases due to the retrospective nature of the study. In addition, we used time-averaged fast scan CT as radiotherapy planning CT, not 4-dimensional computed tomography (4D-CT), which is generally used for SBRT radiotherapy planning for HCC [9]. However, time-averaged fast scan CT and 4D-CT provide similar averaged imaging and we consider marker-less SBRT using 4D-CT to also be feasible under appropriate treatment settings with respiratory motion management, margin settings, and set-up.

In summary, the present results suggest that marker-less SBRT for HCC with appropriate settings is feasible due to its favorable local control. Marker-less SBRT for HCC is a promising strategy that allows patients to avoid the complications induced by marking as well as prompt preparation without impairing local control.

Disclosure statement

Dr. Takeda reports the following grants outside of the submitted work. None of the other authors have any conflicts of interest to declare.

Funding

Dr. Takeda reports a grant from Varian and a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science outside of the submitted work.

ORCID

Yuichi Kibe http://orcid.org/0000-0001-6588-3703
Atsuya Takeda http://orcid.org/0000-0003-2820-0760
Yuichiro Tsurugai http://orcid.org/0000-0003-0872-2000
Takahisa Eriguchi http://orcid.org/0000-0001-6818-2240

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
[2] Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology. 2018;68(2):723–750.
[3] Galle PR, Forner A, Llovet JM, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
[4] Bruix J, Sherman M. Practice guidelines committee AAftSoLD. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–1236.
[5] Liu JH, Chen PW, Asch SM, et al. Surgery for hepatocellular carcinoma: does it improve survival? Ann Surg Oncol. 2004;11(3):298–303.
[6] Rim CH, Kim HJ, Seong J. Clinical feasibility and efficacy of stereotactic body radiotherapy for hepatocellular carcinoma: a systematic review and meta-analysis of observational studies. Radiother Oncol. 2019;131:135–144.
[7] Ohri N, Tome WA, Mendez Romero A, et al. Local control after stereotactic body radiation therapy for liver tumors. Int J Radiat Oncol Biol Phys. 2021;110(1):188–195.
[8] Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, version 1.2017: featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2017;15(5):563–573.
[9] Murray LJ, Dawson LA. Advances in stereotactic body radiation therapy for hepatocellular carcinoma. Semin Radiat Oncol. 2017;27(3):247–255.
[10] Bibault JE, Dewas S, Vautravers-Dewas C, et al. Stereotactic body radiation therapy for hepatocellular carcinoma: prognostic factors of local control, overall survival, and toxicity. PLOS One. 2013;8(10):e77472.
[11] Huertas A, Baumann A-S, Saunier-Kubs F, et al. Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. Radiother Oncol. 2015;115(2):211–216.
[12] Gerum S, Heinz C, Belka C, et al. Stereotactic body radiation therapy (SBRT) in patients with hepatocellular carcinoma and oligometastatic liver disease. Radiat Oncol. 2018;13(1):100.
[13] Mori S, Kanematsu N, Mizuno H, et al. Physical evaluation of CT scan methods for radiation therapy planning: comparison of fast, slow and gating scan using the 256-detector row CT scanner. Phys Med Biol. 2006;51(3):587–600.
[14] Takeda A, Kunieda E, Shigematsu N, et al. Small lung tumors: long-scan-time CT for planning of hypofractionated stereotactic radiation therapy–initial findings. Radiology. 2005;237(1):295–300.
[15] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(01):052–060.
[16] Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S94–S100.
[17] Kibe Y, Takeda A, Tsurugai Y, et al. Local control by salvage stereotactic body radiotherapy for recurrent/residual hepatocellular carcinoma after other local therapies. Acta Oncol. 2020;59(8):888–887.
[18] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452–458.
[19] Nakayama M, Uehara K, Nishimura H, et al. Retrospective assessment of a single fiducial marker tracking regimen with robotic stereotactic body radiation therapy for liver tumours. Rep Pract Oncol Radiother. 2019;24(4):383–391.
[20] Liang Z, Liu H, Xue J, et al. Evaluation of the intra- and interfractional tumor motion and variability by fiducial-based real-time tracking in liver stereotactic body radiation therapy. J Appl Clin Med Phys. 2018;19(3):94–100.

[21] Hanazawa H, Takahashi S, Shiinoki T, et al. Clinical assessment of coiled fiducial markers as internal surrogates for hepatocellular carcinomas during gated stereotactic body radiotherapy with a real-time tumor-tracking system. Radiother Oncol. 2017;123(1): 43–48.

[22] Worm ES, Bertholet J, Hoyer M, et al. Fiducial marker guided stereotactic liver radiotherapy: is a time delay between marker implantation and planning CT needed? Radiother Oncol. 2016; 121(1):75–78.

[23] Scher N, Bollet M, Bouilhol G, et al. Safety and efficacy of fiducial marker implantation for robotic stereotactic body radiation therapy with fiducial tracking. Radiat Oncol. 2019;14(1):167.

[24] Ohta K, Shimohira M, Murai T, et al. Percutaneous fiducial marker placement prior to stereotactic body radiotherapy for malignant liver tumors: an initial experience. J Radiat Res. 2016;57(2): 174–177.

[25] Ohta K, Shimohira M, Sasaki S, et al. Transarterial fiducial marker placement for image-guided proton therapy for malignant liver tumors. Cardiovasc Intervent Radiol. 2015;38(5):1288–1293.

[26] Park SH, Won HJ, Kim SY, et al. Efficacy and safety of ultrasound-guided implantation of fiducial markers in the liver for stereotactic body radiation therapy. PLOS One. 2017;12(6):e0179676.

[27] Jarraya H, Chalayer C, Tresch E, et al. Novel technique for hepatic fiducial marker placement for stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2014;90(1):119–125.

[28] Clark TW. Complications of hepatic chemoembolization. Semin Intervent Radiol. 2006;23(2):119–125.

[29] Tsai WC, Kung PT, Wang YH, et al. Influence of the time interval from diagnosis to treatment on survival for early-stage liver cancer. PLOS One. 2018;13(6):e0199532.

[30] Singal AG, Waljee AK, Patel N, et al. Therapeutic delays lead to worse survival among patients with hepatocellular carcinoma. J Natl Compr Canc Netw. 2013;11(9):1101–1108.

[31] Valentine K, Cabrera T, Roberge D. Implanting metal fiducials to guide stereotactic liver radiation: McGill experience and review of current devices, techniques and complications. Technol Cancer Res Treat. 2014;13(3):253–258.

[32] Seppenwoolde Y, Wunderink W, Wunderink-van Veen SR, et al. Treatment precision of image-guided liver SBRT using implanted fiducial markers depends on marker-tumour distance. Phys Med Biol. 2011;56(17):5445–5468.

[33] Kothary N, Heit JJ, Louie JD, et al. Safety and efficacy of percutaneous fiducial marker implantation for image-guided radiation therapy. J Vasc Interv Radiol. 2009;20(2):235–239.