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Treatment Outcomes of Stereotactic Body Radiation Therapy Using Real-time Tumor-tracking Radiotherapy System for Hepatocellular Carcinomas

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Running Head

Stereotactic Body Radiation Therapy for HCC

Abstract

Aim: To report the outcomes of stereotactic body radiotherapy (SBRT) using a real-time tumor-tracking radiotherapy (RTRT) system for hepatocellular carcinoma (HCC) patients.

Methods: From January 2005 to July 2018, 63 patients with 74 lesions with a maximum diameter ≤52 mm were treated by SBRT using the RTRT system. No patient with a Child-Pugh Score ≥9 was included and 85.6% had a score of 5 or 6. Using the biological effective dose (BED) with α/β ratio of 10 (BED_{10}), the median dose in BED_{10} at the reference point was 76.8 Gy (range: 60-122.5). Overall survival (OS) and local control (LC) rates were assessed using the Kaplan-Meier method.

Results: With a median follow up period of 24.6 months (range: 0.9-118.4), the 1-year and 2-year OS rates were 86.8% (95% confidence interval [95% CI]; 75.8-93.3) and 71.1% (57.8-81.6), respectively. The 2-year OS was 89.6% in patients with the baseline modified albumin-bilirubin (mALBI) grade =1 and 61.7% in patients with grade ≥2a. In the multivariate analysis, the mALBI grade (=1 vs ≥2a) was a significant factor for OS (p=0.028, 95%CI: 1.11-6.18). The 1-year and 2-year LC rates were 100% (100-100) and 92.0% (77.5-97.5). The LC rates were significantly higher in the BED_{10} ≥100 Gy group than in the BED_{10} <100 Gy (2-year 100% vs 86.5%, p=0.049) at the reference point.

Conclusion: This retrospective study of SBRT using RTRT for HCC showed favorable outcomes with lower incidence of toxicities, especially in patients treated with BED_{10} ≥100 Gy to the reference point.

Keywords

Stereotactic body radiotherapy, Real-time tumor-tracking radiotherapy, Hepatocellular carcinoma, Albumin-bilirubin grade

Introduction

Stereotactic body radiotherapy (SBRT) is a local treatment for hepatocellular carcinomas (HCC). Favorable long-term control and tolerable adverse events have been reported. Although SBRT is a promising strategy, issues of concern is the respiratory motion of tumors[1, 2]. As measures against respiratory motion during radiotherapy, several kinds of respiratory motion management have been attempted, including abdominal compression, breath holding (breath hold), end expiratory gating or tracking with or without using fiducial markers. Treatment results using each of these techniques have been published but no conclusion on which approach is most appropriate has been reached[3, 4].

Since 1999, we have started applying SBRT using a real-time tumor-tracking radiotherapy (RTRT) system to irradiate the target accurately. Details of RTRT have been published elsewhere[5, 6]. In brief, the radiation dose is delivered only when an inserted fiducial marker is within +/-2.0 mm of the planned coordinates relative to the isocenter. Until now, we have reported treatment outcomes for tumors in various organs using the RTRT system[7-12]. In respiratory motion management, a gating system using a fiducial marker enables a more accurate dose delivery than other methods[3], but only a few reports are available on the treatment results of HCC patients[7, 13]. The purpose of this study is to report treatment outcomes of SBRT using the RTRT system for HCC.

Methods

Patients

This study was approved by the institutional review board of Hokkaido University Hospital (IRB Number: 016-0307) and written informed consent was obtained from all patients. We retrospectively reviewed the medical records of patients who had received SBRT using the RTRT system for HCC from January 2005 to July 2018. Eligibility criteria were as follows: clinically diagnosed as HCC, not suitable for other local therapy including surgery, transarterial chemoembolization (TACE), or radiofrequency ablation (RFA), radical treatment in four or eight fractions. Exclusion criteria were Child-Pugh grade C, vascular or bile duct invasion, or extrahepatic metastasis at the time of the SBRT. No clear threshold regarding tumor size were made, but tumors of approximately less than 50 mm that can be treated in 4 or 8 fractions were included.

Planning

The fiducial marker was of gold, spherical, 2 mm diameter or a transarterial platinum coil. The gold markers were percutaneously inserted near the tumor[14], and the transarterial platinum coils were placed with catheter intervention by an interventional radiologists. After insertion or placement of the fiducial marker, treatment planning CT images were scanned. Basically, contrast-enhanced CT and/or MRI images were also obtained to contour the target accurately. In cases where the tumor and gastrointestinal tract were in close proximity, patients were instructed to eat nothing for at least six

106 hours before the planning CT scan and on every treatment day. Treatment planning was performed
107 using the XiO (Elekta AB, Stockholm, Sweden) or Pinnacle^3 (Philips, Amsterdam, Netherlands). We
108 contoured a tumor as a gross tumor volume (GTV) then added a 0-5 mm margin to create a clinical
109 target volume (CTV) depending on the tumor size and location. A 5 mm margin, including the internal
110 margin of 2 mm and the set-up margin of 3 mm, was added to the CTV to create the planning target
111 volume (PTV).

112 The dose regimen was 40 Gy in 4 fractions in cases where the tumor was more than 2 cm away from
113 both the intestinal tract and hepatic hilum. In other cases, it was set to 40-48Gy in 8 fractions. Until
114 2014, prescription doses (40-48 Gy) were delivered to a reference point. From 2015, prescription doses
115 (40-48 Gy) were delivered to 95% of the volume of the PTV enclosed by the 67-83% isodose line of
116 the dose at the reference point. These dose variations were primarily caused by considering the
117 baseline liver function and dose to organs at risk such as the intestinal tract. Basically, the reference
118 point was set at the center of the PTV. Further, as the dose prescription method varied in this patient
119 cohort depending mainly on the time of treatment, we focused on the point dose at the reference point
120 using the biological effective dose (BED) with an α/β ratio of 10 (BED_{10}). In the dose constraints, a
121 normal liver volume (Liver minus GTV) irradiated with <15 Gy should be >700 cm^3 in 4 fractions or
122 with <17.5 Gy be >700 cm^3 in 8 fractions[15]. For cases where it was difficult to achieve these criteria
123 (mainly due to small liver volumes), we used a V22.9 (volume receiving 22.9 Gy) as <30% in 4

fractions for the Liver-GTV volume or V29.8 Gy as <30% in 8 fractions as previously reported[7]. For gastrointestinal organs, the maximum dose to 1 cm^3 < V26.7Gy in 4 fractions and 1 cm^3 < V35 Gy in 8 fractions was applied. To evaluate the doses of organs at risk, BED_3 (α/β ratio of 3) was used.

Radiotherapy

The SBRT was performed using a linear accelerator (LINAC) implementing the RTRT system. From February 2005 to February 2016, patients were treated with an MHCL-15SP (Mitsubishi Electronics Co., Ltd., Tokyo) LINAC. From October 2014, a new apparatus that combines a Varian CLINAC iX (Varian Medical Systems, Palo Alto, CA) and the RTRT system named SyncTraX (Shimadzu Co., Kyoto, Japan) was employed. Since July 2018, a TrueBeam (Varian Medical Systems, Palo Alto, CA) with a SyncTraX FX4 version (Shimadzu Co., Kyoto, Japan) has started treating patients. The day before start of the SBRT, we verify whether the marker can be tracked precisely in the treatment room. At first, the patient setup was performed based on the bone structure. Then the couch was moved so that the marker position at natural expiration coincided with that of the treatment planning CT. It has been reported elsewhere that the positional relationship between the tumor and an implanted marker in the liver is constant for more than one month[16]. Further, to ensure absence of marker migration, the three-dimensional position of the fiducial marker relative to bone structures was confirmed in the daily patient set-up. In the RTRT system, the marker position can be determined by two sets of fluoroscopic

X-ray cameras. To estimate the skin dose, imaging durations for each patient were extracted from the available log files. As for similar conditions with clinical practice, a pulsed X-ray fluoroscopy with a tube voltage of 100 kV, tube current of 80 mA, pulse width of 3 millisecond and image acquisition of 20 or 30 frames per second was assumed.

Evaluation and follow-up

Periodic examination was performed every 3 to 6 months after the SBRT. At the evaluation of treatment responses, we basically used dynamic CT or MRI images every 3 months until 1 year after the SBRT. After that, we used image evaluations every 3-6 months according to the individual patient situation. The treatment response was evaluated by the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[17]. According to these criteria, a progressive disease (PD) is defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions. Local control (LC) was defined as non-PD. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE ver5.0). Acute adverse events were defined as those occurring within 3 months of the treatment, and late adverse events were defined as events after that time. Classic and non-classic radiation-induced liver diseases (RILD) were also evaluated. Classic RILD includes anicteric hepatomegaly and ascites, or elevated alkaline phosphatase (≥2 times above the upper limit of the normal or baseline level)[15]. Non-classic RILD involves elevated levels of transaminases (≥5

160 times the upper limit of normal) or CTCAE grade 4 levels in patients with higher baseline values
161 within 3 months after treatments, or a worsening of the Child-Pugh score ≥2, in the absence of classic
162 RILD[15]. For the assessment of acute adverse events and RILD, we excluded patients who received
163 invasive treatment for HCC within 3 months of SBRT. The liver function was evaluated based on the
164 Child-Pugh grade and the modified ALBI (mALBI) grade[18]. In the evaluation of the coagulation
165 system, the international normalized ratio (INR) score was estimated because the study included cases
166 with warfarin or missing data. The INR score was estimated at 1 for the former and the most recent
167 INR score was used for the latter as previously reported[19].
168
169 Statistical analysis
170 The overall survival (OS) was calculated from the starting day of the SBRT to the date of the last
171 follow-up or death. The LC rates was to the date of local recurrence or the last image
172 evaluation. Kaplan-Meier methods was used for the analysis of the OS and LC rates with statistical
173 significance assessed by the log-rank test. Potentially important factors in the univariate analysis
174 were introduced in a multivariate Cox proportional hazards model. Fisher's exact test or chi-square
175 test was used to study the association between categorical variables. A p-value of less than 0.05 was
176 considered significant. The statistical analysis was performed with the JMP version 14 (SAS, Cary,
177 NC).

178

179 **Results**

180 Patient backgrounds

181 Detailed patient backgrounds are shown in Table.1. We identified 74 eligible lesions in 63 patients.

182 One patient had a total of two lesions irradiated at different times. The median age was 71 (range:

183 54-84) years. The median tumor size was 20 mm (range: 5–52) and the GTV volume was 4.6 cm^3

184 (range: 0.2-111.9). Fifty-six patients had some other treatment history for the HCC before the SBRT.

185 A total of 29 lesions were treated with SBRT due to the incomplete response or recurrences after

186 these other treatments. The median dose in BED_{10} at the reference point was 76.8 Gy (range: 60-

187 122.5). The data associated with X-ray fluoroscopy of fiducial marker tracking were available for 28

188 patients, who had been treated using the SyncTraX or SyncTraX FX4 version. Under the assumed X-

189 ray fluoroscopic conditions, we estimated the cumulative skin dose for each patient. The median

190 estimated skin dose was 0.68 Gy (range: 0.24-2.0 Gy) among these patients. There was no grade 2 or

191 higher radiation dermatitis in any of the patients.

192

193 Overall survival and local control

194 With a median follow up period of 24.6 months (range: 0.9-118.4), 1-year and 2-year OS in all patients

195 were 86.8% (95% confidence interval [95%CI]; 75.8-93.3) and 71.1% (57.8-81.6), respectively

196 (Figure 1A). With a median image follow up period of 18.9 months (range: 0 - 72.5), 1-year and 2-
197 year LC rates were 100% (100-100) and 92.0% (77.5-97.5), respectively (Figure 1B). An image
198 follow-up was not possible in two patients, one of whom died of a stroke soon after the SBRT. During
199 the follow-up period, local recurrences were confirmed in seven (9.5%) out of 74 lesions. We
200 performed univariate and multivariate analyses to identify factors associated with OS and LC (Table
201 2). Because the dose at the reference point (BED_{10}) was mainly distributed to <80 Gy or ≥100 Gy
202 depending on the method of dose prescription, we divided the patients into two groups: BED_{10} ≥100
203 Gy or <100Gy based on previous studies[20, 21] In the univariate analysis of OS, the baseline mALBI
204 grade and Barcelona Clinic Liver Cancer (BCLC) stage were significant factors. The 2-year OS was
205 89.6% in patients with the mALBI grade =1 and 61.7% in patients with grade ≥2a (Figure.2A). In the
206 multivariate analysis, the mALBI grade (=1 vs ≥2a) was a significant factor for OS (p=0.028, 95%CI:
207 1.11-6.18). Similarly, in the analysis of the LC, the prescribed dose to the reference point (≥100 Gy vs
208 <100Gy in BED_{10}) was significant in the univariate analysis (2-year 100% vs 86.5%, p=0.049, Figure
209 2B). There were no obvious differences in patient backgrounds between those with BED_{10} of ≥100 Gy
210 vs <100 Gy in terms of tumor size or liver functioning (Supplementary Table 1).
211
212 Adverse events
213 There was no ≥ Grade 3 adverse event related to marker placement. Acute grade 3 or higher SBRT-

related adverse events are shown in Table 3. No patients experienced late grade 3 or higher adverse events. The details of the mALBI grade at 3 months after SBRT are detailed in Supplementary Figure 1. Classic RILD was found in 2.1% (1/ 46) of patients. This patient was a 63 year old male with a tumor size of 30 mm and Child-Pugh score 5, mALBI grade of 1. Doses of 48 Gy in 8 fractions which is equal to 76.8 Gy in BED_{10} was delivered to the reference point. The mean normal liver (liver – GTV) dose was 9.59 Gy and the volume irradiated with <17.5 Gy was 947 cm^3 (>700 cm^3). No other dose-constraints were violated. At day 66 after the radiotherapy, grade 3 liver enzyme elevation was observed and the patient was hospitalized. At day 92, multiple lung, bone, and lymph node metastasis was confirmed in the CT scan. Finally, this patient died at day 117. Non-classic RILD was also found in 2.3% (1/ 42) of patients, a 54 year old male. In this patient, the tumor diameter was 19 mm and Child-Pugh score was 5, mALBI grade of 2b. A total of 48 Gy in 8 fractions (76.8 Gy in BED_{10}) was delivered here. The mean normal liver dose was 12.9 Gy and the volume irradiated was <17.5 Gy was 711 cm^3. This patient subsequently made a recovery with the standard therapy.

Discussion

In this study, the baseline mALBI grade (=1 or ≥2a) was a significant factor in the overall survival. The ALBI grade has been proposed as a new alternative to the Child-Pugh score and its usefulness has already been reported in the field of the SBRT[22-25]. Murray et al. investigated the relationships between

232 the ALBI score and prognosis in 102 patients with Child-Pugh A liver status treated with SBRT for
233 HCC. They concluded that the baseline ALBI score was better at discriminating in predictions of OS
234 and toxicities[22]. Several papers have also discussed the safety of SBRT using the ALBI grade as an
235 indicator[26, 27]. In addition, we used the mALBI grade to evaluate the baseline liver function in more
236 detail. Hiraoka et al. proposed that the mALBI grade, which divides the ALBI grade into 4 levels (1,
237 2a, 2b, and 3), can be used to evaluate the liver function in more detail[18]. In our analysis, we divided
238 the patients into two groups: mALBI grade =1 or ≥2a. The reference value for dividing the patients
239 into two groups by this grade (1 or ≥2a) is the same as that for ALBI grade (1 or ≥2). Therefore, as
240 with the above articles, the result of this present study also suggests that the mALBI grade was more
241 important in predictions of OS than the Child-Pugh score, which was not statistically significant in
242 this study. In the future, the ALBI grade or mALBI grade may become important as a predictor of the
243 prognosis for SBRT in HCC patients.

244 The advantage of using the RTRT system in SBRT is the highly accurate treatment regardless of
245 uncertainties in the breathing of the individuals. To date, no comparison of treatment outcomes or
246 adverse events has been made with the focus on respiratory motion management. Moreover, there are
247 some reports on the outcomes of SBRT in HCC using the RTRT system in respiratory motion
248 management. As far as the recent reports are reviewed, our study was comparable to the results using
249 other respiratory motion managements (Table 4)[21, 28-31]. Hanazawa et al. reported clinical advantages

250 of using coiled fiducial markers for HCC during SBRT and concluded that gated SBRT was well
251 tolerated and promising[13]. That study included only a small number of patients (n=17), but the 1-year
252 LC rate was shown to be 100%, which is comparable to our results. Assuming that the positional
253 relationship is constant between the tumor and the marker at the end of expiration[16], SBRT using the
254 RTRT can be performed with high reproducibility within a gating window +/-2 mm, regardless of
255 respiratory motion. This allows the internal target volume (ITV) margin only to take into account a
256 gating window of 2 mm because daily patient set-up is done using a fiducial marker. Due to these
257 advantages, the internal margin and the set-up margin was smaller in the present study while
258 maintaining comparable LC (Table 4). As for adverse events, no definitive statement can be made due
259 to differences in the assessment methods among studies. However, some studies have shown that doses
260 to the healthy parts of the liver can be decreased by reducing the ITV or PTV margin[32, 33]. Decreasing
261 the dose to the surrounding normal liver with a smaller margin could lead to preservation of the
262 residual liver function and be advantageous in the treatment of intrahepatic recurrence after the SBRT.
263 Although SBRT with a gating window of +/-1 mm is technically possible, the dose rate of conventional
264 LINAC would result in a longer time for the treatment. Therefore, we have used a gating window of
265 +/-2 mm in this study. If higher dose rates are realized, smaller gating windows (e.g., gating window
266 of +/-1 mm) will enable further reductions to the healthy liver dose without prolonging the treatment
267 time. In the present study, we have shown favorable results even with a smaller ITV or PTV margin

using the RTRT system, but it remains to be verified whether the reduction in healthy liver dose is clinically meaningful.

The patient group in the dose to the reference point with BED_{10} ≥100 Gy showed better LC in the univariate analysis. In a more detailed analysis, no significant differences were found in patient backgrounds, between the groups with BED_{10} ≥100 Gy vs <100 Gy (Supplementary Table 1). Bibault et al. analyzed 75 patients with 96 HCC lesions treated by SBRT and reported that a higher dose and lower alpha-fetoprotein levels were associated with better LC[34]. A study from a Korean group analyzed 108 patients with HCC treated by SBRT and also found a dose response relationship for LC and OS[35]. Meanwhile, Sun et al. reported that in an analysis of 108 small hepatocellular carcinoma patients, there were no significant differences in LC between the patient groups with a tumor dose (BED_{10}) of ≥100 Gy and <100 Gy. However, it should be noted that "BED_{10}" in their study means the prescription doses, not to the dose of the reference point as in our study. Therefore, in the Sun et al. study, an adequate dose to achieve a favorable LC could already have been given in most cases. In the present study, no significant difference was found in the incidence of adverse events between the BED_{10} ≥100 Gy and <100 Gy groups (Supplementary Table 1). Moreover, in current radiotherapy practice, the commonly applied method of dose prescription in SBRT is considered to be for the PTV volume. In our institution, when both the intestinal tract and hepatic hilum are more than 2 cm away from the tumor, a dose of 40 Gy (50 Gy to the reference point, BED_{10} =112.5 Gy) in four fractions are prescribed to the PTV

D95. In other cases, the dose to the PTV D95 is 48 Gy (60 Gy to the reference point, BED_{10} =105 Gy) in eight fractions. Although the doses to the organs at risk must be considered, we believe that the doses listed above are those necessary. In any case, an adequate dose prescription is certainly necessary (BED_{10} ≥100 Gy in this study) and consideration of the thresholds is a future issue. The normal liver dose increases in proportion to the dose given to the tumor, therefore, a very precise treatment (the RTRT system) with reduced margins is essential for an increased and safe dose delivery.

The limitations of our present study include the following. This is a single-center retrospective study, in which there are differences in patient backgrounds. Moreover, the study included relatively small number of patients and with only a short observation period. Based on this, multicenter clinical trials are necessary to increase the number of cases and to have a study with a higher evidence level. We are planning to conduct a prospective clinical trial to further improve the treatment outcomes. Although the RTRT allows for high reproducibility using a fiducial marker, the skin dose associated with X-ray fluoroscopy can be a problem[36]. In the present study, we found no cases of grade 2 or higher radiation dermatitis, including in the patients treated with the MHCL-15SP, an early type of a LINAC equipped with an RTRT system. With advances in the tracking system, X-ray imaging durations are getting shorter due to the increased dose rate of the LINAC and reduced frame rate of the X-ray fluoroscopic system. As a result, these improvements decreased the irradiated skin dose compared to previously used treatment machines[13]. In fact, we estimate that the cumulative skin dose due to the X-ray

304 fluoroscopy has been up to 2.0 Gy (median 0.68 Gy) in a patient. Considering these findings, the skin
305 dose is at an acceptable level using an advanced RTRT system. Nevertheless, methods for further skin
306 dose reductions are required.
307
308 **Conclusions**
309 This retrospective study of SBRT using an RTRT system for HCC showed favorable outcomes with
310 lower incidence of toxicities, especially in patients treated with BED_{10} ≥100 Gy. Despite the smaller
311 internal and set-up margins employed in using the RTRT system, LC rates were comparable to those
312 using other motion management arrangements.
313
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316
317 **Conflict of Interest Statement**
318 All authors have no conflicts of interest to declare.
319

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Appendices

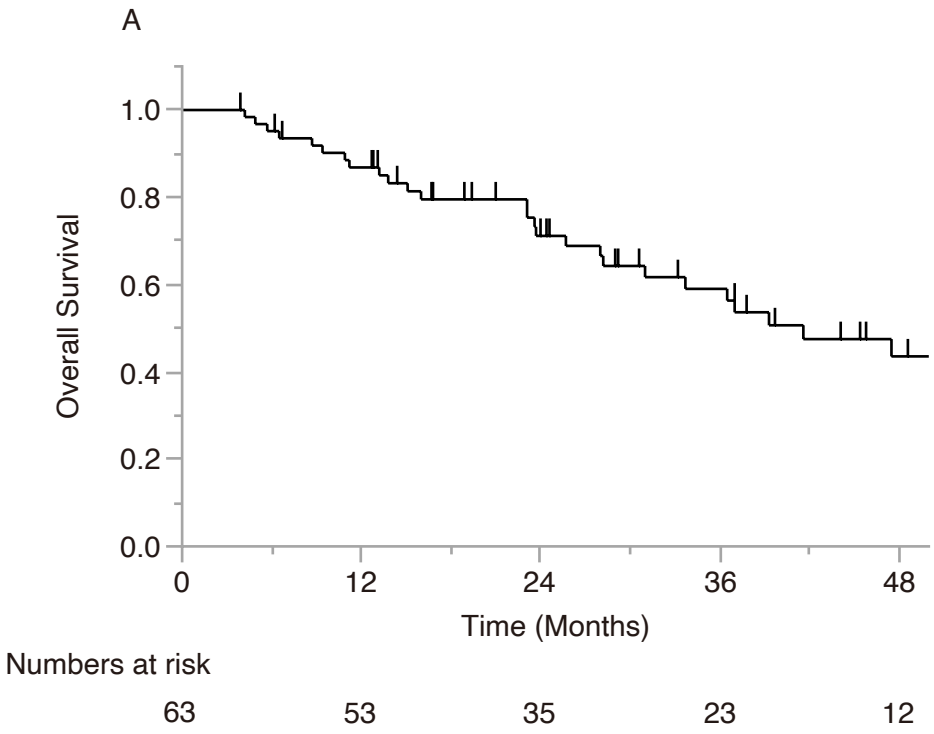
Supplementary Table 1. Patient backgrounds in the BED_{10} <100 Gy and BED_{10} ≥100 Gy groups.

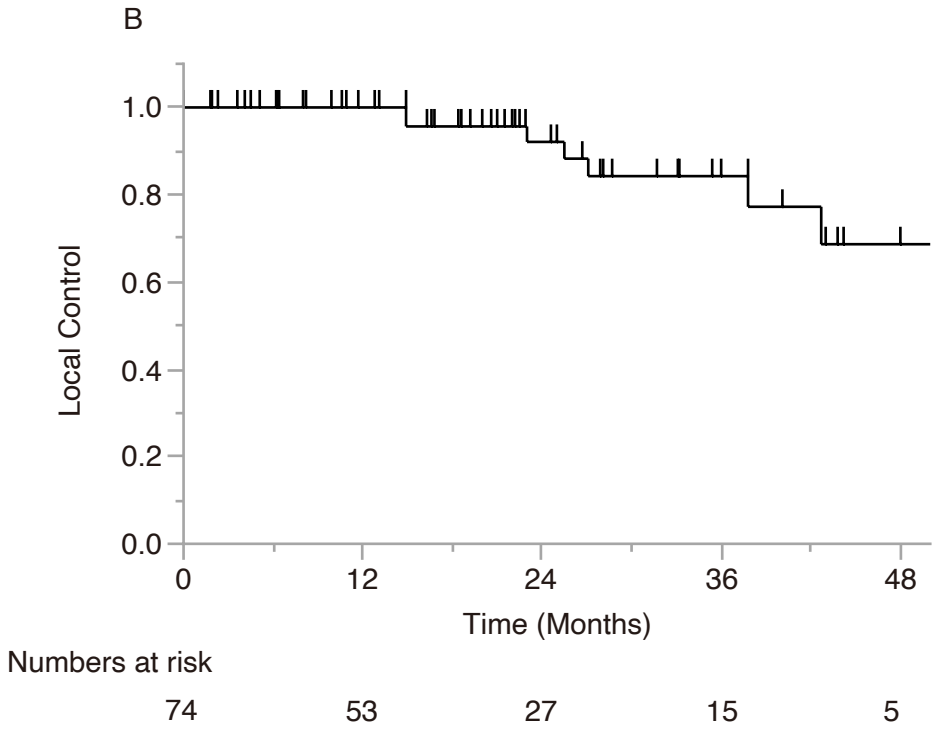
Supplementary Figure 1. The mALBI grade at 3 months after SBRT. Patients who received invasive treatment for HCC within 3 months of SBRT were excluded. mALBI grade: modified albumin-bilirubin grade.

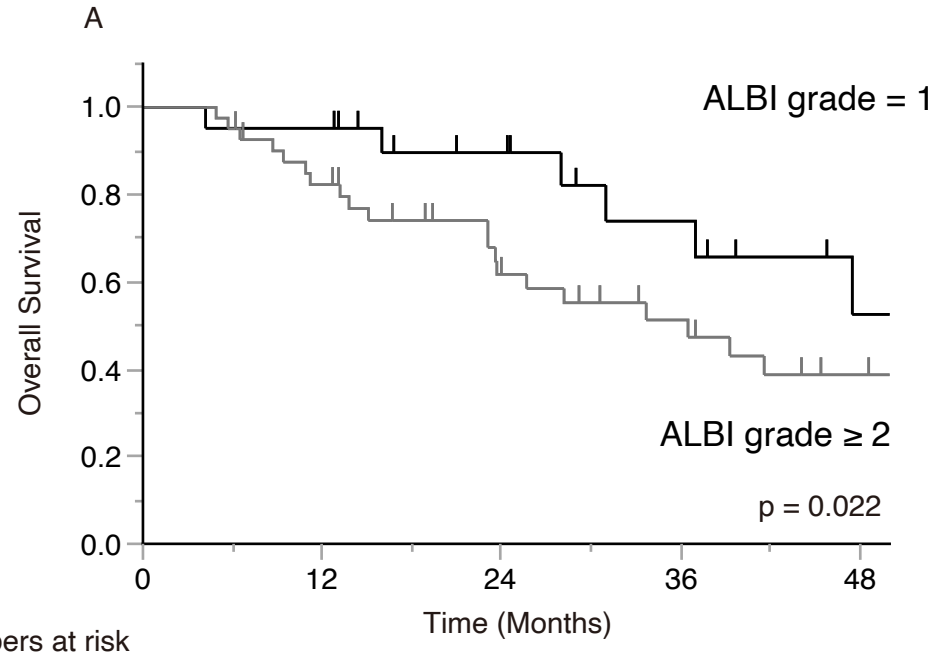
Figure legends

Figure 1. Overall survival (A) and local control rate (B) following the radiotherapy.

Figure 2. Overall survival in patients with an mALBI grade=1 vs ≥ 2a (A) and local control rate in BED_{10} <100 Gy vs BED_{10} ≥100 Gy (B) following the radiotherapy. mALBI grade: modified albumin-bilirubin grade.

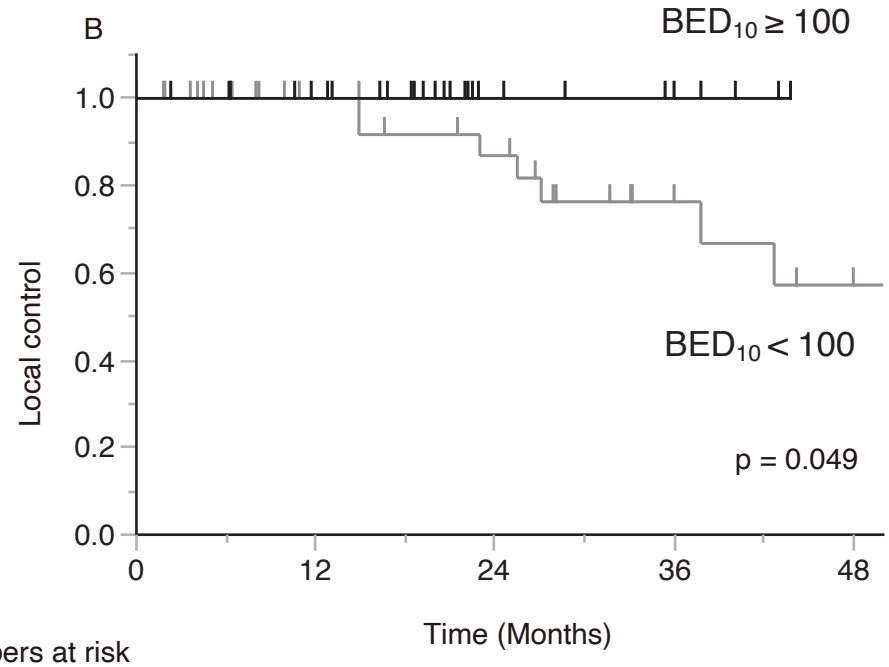

A
1.0
0.8
0.6
0.4
0.2
0.0
Overall Survival
0
12
24
36
48
Time (Months)
Numbers at risk
63
53
35
23
12


B
1.0
0.8
0.6
0.4
0.2
0.0
Local Control
0
12
24
36
48
Time (Months)
Numbers at risk
74
53
27
15
5



Numbers at risk

ALBI grade = 1	21	21	15	10	6
ALBI grade ≥ 2	41	33	22	14	8



Numbers at risk

$BED_{10} \geq 100$	41	25	19	9	5
$BED_{10} < 100$	33	29	10	5	1

Table 1. Patient backgrounds

Patient and lesion numbers	n=63, lesions=74
Sex	
Male	47 (74.6%)
Female	16 (25.3%)
Age (years)	71 (range: 54-84)
Follow-up period (median, months)	24.6 (range: 3.9 – 118.4)
Image follow-up period (median, months)	18.9 (range: 0 – 72.5)
Performance status	
0	56 (88.9%)
1	5 (7.9%)
2	2 (3.2%)
TNM (UICC 8th) stage	
1a	19 (30.2%)
1b	20 (31.7%)
2	24 (38.0%)
BCLC stage	
0	19 (30.2%)

A	37 (58.7%)
B	7 (11.1%)
Baseline liver disease	
HBV	24 (38.1%)
HCV	26 (41.3%)
Alcohol	7 (11.1%)
NASH	3 (4.8%)
Non-B non-C	4 (6.3%)
Baseline Child-Pugh grade	
A	54 † (85.7%)
B	8 (12.6%)
Unavailable	1 (1.6%)
Baseline modified ALBI grade	
1	21 (33.3%)
2a	15 (23.8%)
2b	24 (38.1)
3	2 (3.2%)
Unavailable	1 (1.6%)

Previous treatment for any HCC	
Yes (total)	56 (88.9%)
Surgical Operation	16 (25.4%)
RFA	38 (60.3%)
TACE/ TAE	44 (69.8%)
None	7 (11.1%)
Tumor size (median, mm)	20 (range: 5 – 52)
Treatments	
Treatment days (median, days)	12 (range: 4-16)
Fiducial Marker	
Coil	6 (9.5%)
Gold-marker	57 (90.5%)
Dose prescription	
Reference point	36
48 Gy in 8 fractions	32 (88.9%)
35 Gy in 4 fractions	2 (5.56%)
40 Gy in 4 fractions	1 (2.8%)
40 Gy in 8 fractions	1 (2.8%)

PTV D95	38
48 Gy in 8 fractions (Reference point dose = 60 Gy)	23 (60.5%)
40 Gy in 8 fractions (Reference point dose = 60 Gy)	6 (15.8%)
40 Gy in 8 fractions (Reference point dose = 48 Gy)	5 (13.1%)
40 Gy in 4 fractions (Reference point dose = 50 Gy)	3 (7.9%)
40 Gy in 4 fractions (Reference point dose = 52.8 Gy)	1 (2.6%)
Fraction numbers	
four	7 (9.5%)
eight	67 (90.5%)
BED10 of the reference point (median, Gy)	76.8 (range: 60-122.5)
Until 2014	76.8 (65.6-105.0)
From 2015-	105 (60.0-122.5)
GTV volume (median, cm^3)	4.6 (range: 0.2-111.9)
PTV volume (median, cm^3)	43.7 (range: 12.7-381.3)
Normal Liver volume (median, cm^3)	921.6 (range 515.2-1594.4)
Mean GTV dose (median, Gy)	48.3 (range: 35.0-60.7)
Mean GTV dose of BED_{10} (median, Gy)	77.8 (range: 50.9-121.3)
Mean PTV dose (median, Gy)	47.4 (range: 34.2-56.9)

Mean PTV dose of BED_{10} (median, Gy)	75.6 (range: 48.8-97.4)
Mean (Liver-GTV) dose (median, Gy)	9.3 (range: 1.7-17.0)
Mean (Liver-GTV) dose of BED_3 (median, Gy)	12.9 (range: 1.8-29.1)

ALBI grade: albumin-bilirubin grade, BCLC: Barcelona Clinic Liver Cancer, BED: biological equivalent dose, GTV: gross tumor volume, HBV: hepatits B virus, HCC: hepatocellular carcinoma, HCV: Hepatitis C virus, NASH: non-alcoholic steatohepatitis, PTV: planning target volume, RFA: radiofrequency ablation, SBRT: stereotactic body radiation therapy, TACE: transarterial chemoembolization. TAE: transarterial embolization. UICC: Union for International Cancer Control. † One patient received two courses of SBRT for different lesions in two years

Table 2. Univariate and multivariate analysis for prognostic factors

Variable		Overall Survival				Local Control			
		n	2y OS (%)	p-value UVA	p-value MVA (95%CI)	n	2y LC (%)	p-value UVA	p-value MVA (95%CI)
Age	<70	28	72.4	0.862		33	88.0	0.095	0.283 (0.37-2.61)
	≥70	35	70.1			41	96.0		
Sex	Male	47	70.8	0.702		57	89.6	0.412	
	Female	16	73.3			17	100		
Child-Pugh grade	A	53	74.3	0.838		63	90.8	0.189	
	B	8	50.0			9	100		
mALBI grade	1	21	89.6	0.022	0.017 (1.11-6.18)	27	84.0	0.645	
	≥2a	41	61.8			46	96.7		
Previous treatments	Yes	57	76.6	0.102		65	91.4	0.538	
	No	6	33.3			9	100		
Liver	Viral	50	68.5	0.701		59	92.0	0.936	
	others	13	81.8			15	92.3		
Tumor size	<20 mm	28	79.3	0.139		36	88.4	0.593	

	≥20 mm	35	64.0			38	95.4		
Dose in BED_{10}	<100 Gy	36	72.6	0.806		41	86.8	0.049	0.947 (0-inf)
	≥100 Gy	27	67.0			33	100		
GTV volume	<5 cc	29	77.5	0.198		39	85.2	0.053	0.084 (0.18-1.28)
	≥5 cc	34	65.3			35	100		
BCLC stage	0 or A	56	75.7	0.043	0.148 (0.78-5.06)	64	91.6	0.726	
	B or C	7	34.3			10	100		
TNM(UICC 8^{th}) stage	1a or 1b	39	80.5	0.232		40	91.9	0.825	
	2	24	54.1			34	93.3		

95%CI: 95% confidence interval, mALBI grade: modified albumin-bilirubin grade, BCLC stage: Barcelona Clinic Liver Cancer stage, BED: biological equivalent dose, GTV: gross tumor volume, HCC: Hepatocellular carcinoma, MVA: multivariate analysis, LC: local control, NASH: non-alcoholic steatohepatitis, OS: overall survival, PTV: planning target volume, UICC: Union for International Cancer Control, UVA: univariate analysis.

Table 3 Details of adverse events

	Adverse Events	Rate
RILD	Classic	2.1% (1/ 46)
	Non-classic	2.3% (1/ 42)
Acute adverse events†	AST elevation	2.1% (1/ 47)
(≥ grade 3, within 3 months)	ALT elevation	2.2% (1/ 47)
	γGT elevation	2.6% (1/ 39)
	ALP elevation	0% (0/ 43)
	Thrombocytopenia	2.7% (1/ 37)
	Hypoalbuminemia	2.2% (1/ 44)
	Hyperbilirubinemia	0% (0/ 47)
	Ascites / Encephalopathy	0% (0/ 46)

ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, BED: biological equivalent dose, γGT: gamma-glutamyl transferase, RILD: radiation-induced liver disease.

† Pre-treatment ≥grade 3 levels were excluded

Table 4. Summary of results of previous studies

Study, Year	n	Tumor size (mm)	Motion management	Margin		Prescription point	Dose in BED_{10} (Gy)	1-year/ 2-year		RILD
		median (range)		ITV (mm)	PTV (mm)		median (range)	OS (%)	LC (%)	(%)
Jeong[28], 2018	119	17 (8-60)	Respiratory gating	Sum of the individual GTVs on 30-70% phases CT	5	PTV	113	99.2/ 83.8 (3y)	98.5/ 97.0 (3y)	1.7
Feng[29], 2018	90	30 (0-130)	Breath holding Free breathing	0 Encompassing the range of the motion	Radial: 5 Craniocaudal: 8	PTV D99.5	132	67/ 36	99/ 95	-
Teraoka[30], 2018	117	16 (10-30)	Breath holding	0	5 – 8	Isocenter, PTV D95	80-105.6	96.2-96.8 (1y)	100/ 100	-

Sun[21], 2019	108	23 (0.7-49)	Respiratory tracking	0	3 – 5	-	100 (76.8–102.6)	96.3/ 89.8	98.1/ 96.2	3.7
Liu[31], 2020	96	38 (15-170)	Breath holding	0	Radial: 5	PTV D95	45-112.5	71-95 (1y)	94/ 88 (1.5y)	-
					Craniocaudal: 8					
			Abdominal compression	Encompassing the range of the motion	5					
This study, 2020	63	20 (5-52)	RTRT	2	3	Isocenter, PTV D95	76.8 (60-122.5)	86.8/ 71.1	100/ 92.0	2.1-2.3

BED: biologically equivalent dose, ITV: internal target volume, LC: local control, OS: overall survival, PTV: planning target volume, RILD: radiation-induced liver disease, RTRT: real-time tumor-tracking radiotherapy