Original Article

Phase 2 Study of Stereotactic Body Radiotherapy and Optional Transarterial Chemoembolization for Solitary Hepatocellular Carcinoma Not Amenable to Resection and Radiofrequency Ablation

Atsuya Takeda, MD, PhD[1]; Naoko Sanuki, MD, PhD[1]; Yuichiro Tsurugai, MD[1]; Shogo Iwabuchi, MD, PhD[2]; Kotaro Matsunaga, MD, PhD[3]; Hirotoshi Ebinuma, MD, PhD[4]; Kento Imajo, MD, PhD[4]; Yousuke Aoki, BMSc[1]; Hidetsugu Saito, MD, PhD[5]; and Etsuo Kunieda, MD, PhD[6]

BACKGROUND: Curative treatment options for patients with early stage hepatocellular carcinoma (HCC) include resection, liver transplantation, and percutaneous ablation therapy. However, even patients with solitary HCC are not always amenable to these treatments. The authors prospectively investigated the clinical outcomes of patients who received stereotactic body radiotherapy (SBRT) for solitary HCC. **METHODS:** A phase 2 study involving SBRT and optional transarterial chemoembolization (TACE) was conducted in patients with Child-Pugh grade A or B and underlying, solitary HCC (greatest tumor dimension, ≤4 cm) who were unsuitable candidates for resection and radiofrequency ablation. The prescription dose was 35 to 40 grays in 5 fractions. The primary endpoint was 3-year local tumor control. **RESULTS:** From 2007 to 2012, 101 patients were enrolled, and 90 were evaluable with a median follow-up of 41.7 months (range, 6.8-96.2 months). Thirty-two patients were treatment-naïve, 20 were treated for newly diagnosed intrahepatic failure, and 38 were treated for residual or recurrent HCC as salvage therapy. Thirty-two patients did not receive TACE, 48 received insufficient TACE, and 10 attained full lipiodol accumulation. The 3-year local control rate was 96.3%, the 3-year liver-related cause-specific survival rate was 72.5%, and the overall survival rate was 66.7%. Grade 3 laboratory abnormalities were observed in 6 patients, and 8 patients had Child-Pugh scores that worsened by 2 points. **CONCLUSIONS:** SBRT achieved high local control and overall survival with feasible toxicities for patients with solitary HCC, despite rather stringent conditions. SBRT can be effective against solitary HCC in treatment-naive, intrahepatic failure, residual disease, and recurrent settings, taking advantage of its distinctive characteristics. ***Cancer*** **2016;122:2041-9**. © *2016 American Cancer Society.*

KEYWORDS: curative treatment, hepatocellular carcinoma (HCC), noninvasive treatment, stereotactic body radiotherapy (SBRT).

INTRODUCTION

Curative treatment options for patients with early stage hepatocellular carcinoma (HCC) are resection, liver transplantation (LT), and percutaneous ablation therapy.[1] However, <30% of patients are eligible for these treatments.[2] In addition, patients with solitary HCC are not always suitable for these treatments,[3] presumably because of poor liver function and/or tumor location. In such situations, the patient usually received transarterial chemoembolization (TACE)[1]; however, local control after TACE is unsatisfactory.[4,5]

Stereotactic body radiotherapy (SBRT) is a high-precision, conformal, external-beam radiation technique that ablates the target at extracranial sites using hypofractionated, high-dose radiation while sparing surrounding normal tissues. Currently, SBRT is considered a treatment option for patients with medically inoperable, early stage, nonsmall cell lung cancer.[6] Findings from retrospective series of patients with small HCC who received SBRT indicated high local control rates from 99% to 100%[7,8] with minimal blood vessel and bile duct toxicities.[9] In addition, phase 2 studies in HCC that included patients with large or locally advanced disease also demonstrated efficacy and safety.[10-12] However, to our knowledge, no prospective study of SBRT exclusively for early stage or small HCC with curative intent has been reported.

Corresponding author: Atsuya Takeda, MD, PhD, Radiation Oncology Center, Ofuna Chuo Hospital, 6-2-24 Ofuna, Kamakura, Kanagawa 247-0056 Japan; Fax: (011) 81-467-48-5877; takeda@1994.jukuin.keio.ac.jp

[1]Radiation Oncology Center, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan; [2]Hepato-Biliary-Pancreatic Center, Shonan Fujisawa Tokushukai Hospital, Fujisawa, Kanagawa, Japan; [3]Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Kanagawa, Japan; [4]Department of Gastroenterology and Hepatology, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan; [5]Department of Pharmacotherapeutics, Faculty of Pharmacy, Keio University, Tokyo, Japan; [6]Department of Radiation Oncology, Tokai University, Kanagawa, Japan

DOI: 10.1002/cncr.30008, **Received:** December 26, 2015; **Revised:** February 10, 2016; **Accepted:** February 22, 2016, **Published online** April 8, 2016 in Wiley Online Library (wileyonlinelibrary.com)

In the current study, we prospectively investigated the clinical outcomes of SBRT with or without TACE for solitary HCC in patients with a Child-Pugh grade of A or B.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients were diagnosed with a solitary HCC on pathologic confirmation or contrast uptake in the arterial phase and washout in the venous/late phase on dynamic computed tomography (CT) or magnetic resonance imaging (MRI) studies during follow-up of chronic hepatitis.[2] Solitary tumors invading portal or venous vessels (staged as T3 according to the International Union Against Cancer-Tumor, Lymph Node, Metastasis [TNM] classification) were permitted. The patients had tumors with a greatest dimension between 1.0 and 4.0 cm. Patients were not amenable to or had refused both surgery and percutaneous ablative therapies, had Child-Pugh grade A or B disease, were aged $\geq$20 years, and had an Eastern Cooperative Oncology Group performance status from 0 to 2. Prior treatments (TACE and percutaneous ablation therapy) were permitted for the targeted tumors themselves and for other previously detected HCC. All patients were required to sign informed consent forms before receiving the scheduled TACE and SBRT.

Treatment

Before SBRT, the scheduled TACE was performed. For TACE, from 0.5 to 5 mL of lipiodol mixed with anticancer drugs (doxorubicin or cisplatin) was injected into the hepatic artery that fed a segment or subsegments containing the target tumor for most patients. However, TACE could be omitted for patients who refused TACE or who had tumors that were difficult to embolize because of slight enhancement on arterial phase imaging, difficulty in selective catheterization, and a tendency to bleed and were expected to have a limited deposition of lipiodol. SBRT was conducted within 3 months after TACE.

For SBRT treatment planning, we used spiral, 4-phase, multidetector CT and/or dynamic contrast-enhanced MRI followed by a slow-scan CT (6-10 seconds per slice) during free breathing. These dynamic images were then fused with the slow-scan CT images, on which the gross tumor volume (GTV) was delineated. The GTV included enhanced tumor and whole lipiodol deposition. On plain CT images, we evaluated the effect of TACE: ie, the degree of lipiodol deposition. The clinical target volume (CTV) was equated to the GTV. For the internal target volume, an internal margin (4-6 mm) was created around the CTV according to the respiratory movement of the diaphragm or the lipiodol deposit observed during fluoroscopy. For the planning target volume (PTV), individualized margins of 2 mm were applied around the internal target volume as a setup margin.

Multiarc, dynamic conformal radiation was planned using a radiation treatment planning system (FOCUS XiO, version 4.2.0-4.3.3: Computerized Medical Systems, St Louis, Mo) and was performed using x-rays from a 6-MV linear accelerator (Clinac 2100C; Varian Medical Systems Inc, Palo Alto, Calif). The total dose was delivered in 5 fractions over 5 to 7 days, depending on liver function or the dose to the normal liver (liver volume minus GTV); 35 grays (Gy) in 2 patients with Child-Pugh grade B or A disease, with $>$20% of the normal liver receiving $>$20 Gy, and 40 Gy in the other patients. Treatment was planned to enclose the PTV using the 60% to 80% isodose line of maximal dose. The isodose was defined as the prescribed dose and covered at least 95% of the PTV. Additional normal tissue dose constraints were a maximum exposure limit to a 10-cc area of the stomach and bowels of $<$25 Gy and a maximal dose to the spinal cord of $<$25 Gy.

Follow-Up and Endpoints

Patients were followed monthly for 1 year after SBRT and every 3 months thereafter. Radiologic responses were evaluated using dynamic CT or MRI studies 1 month after treatment and every 3 months thereafter. Laboratory tests were performed at every visit, including measurement of transaminases, total bilirubin and albumin levels, platelet counts, α-fetoprotein levels, and protein induced by vitamin K absence or antagonists-II (PIVKA-II) levels. The presence of ascites and prothrombin time were also evaluated to calculate the Child-Pugh score.

The primary endpoint of the study was 3-year primary tumor local control. Local control was defined as freedom from primary tumor failure. Primary tumor failure was based on the definition of progressive disease according to the modified Response Evaluation Criteria in Solid Tumors. A new lesion within the PTV was regarded as primary tumor failure, and newly developed tumors outside the PTV were considered intrahepatic failure. Secondary endpoints included assessments of treatment-related toxicity, intrahepatic control, liver-related cause-specific survival (CSS), and overall survival (OS). Liver-related CSS was defined as death from progressive HCC or liver decompensation.

Toxicity was evaluated using the Common Terminology Criteria for Adverse Events, version 4.0. Acute

toxicities were defined as adverse events attributable to SBRT that occurred <3 months after treatment. To evaluate toxicities, newly developed toxicities or toxicities that had progressed to 1 grade higher than that at baseline were considered adverse events. Elevated liver transaminase levels grade ≥3 or a worsening of the Child-Pugh score by 2 points were defined as a deterioration in liver function.[13] Grade 5 hepatic failure caused by SBRT was defined as death from hepatic failure after the development of acute grade ≥3 liver toxicities in <6 months. Patients with new lesions or local recurrence were scheduled for further treatment: ie, radiofrequency ablation (RFA), SBRT, or TACE, depending on the individual presentation.

Statistical Design and Analysis

In the study design, we estimated that the 3-year primary tumor local control rate would be 90%. This estimated value was based on our previous preliminary result.[14] RFA is a treatment option for patients who have unresectable, early stage HCC, and RFA for HCCs ≤3 cm provides relatively satisfactory local control (3-year local control rate, 86%),[15] whereas the local control rate provided by RFA decreases for HCCs >3 cm.[16] The current study was supposed to include candidates who had intermediate sized tumors, and most of them were not amenable to either surgery or percutaneous ablative therapies. Therefore, we suspected that the local control rate in this study would be inferior to that achieved with RFA for small HCCs, and a rate of 80% was chosen as the lowest acceptable primary tumor control rate. For a 2-sided type I error rate of .05 with 90% statistical power to detect a difference in primary tumor control rates of at least 10%, a sample size of 90 with 3 years of follow-up was required. After adjusting for a potential ineligibility rate of 10% (based on pretreatment characteristics), the final sample size was determined as 100 patients.

Control and survival rates were calculated using Kaplan-Meier analysis. The durations of primary tumor local control and survival were measured from the start of treatment to the date of primary tumor failure, death, or the date of censoring. Liver-related cause-specific death included death directly caused by HCC progression, hepatic failure, and bleeding varices. Data were analyzed using JMP 11 software (SAS Institute Inc., Cary, NC). This phase 2 study received institutional review board approval (protocol no. 2007-2001). The trial was registered at the University Hospital Medical Information Network-Clinical Trial Registry (identification no. UMIN000000640). All authors had access to the study data and reviewed and approved the final article.

RESULTS

Between May 14, 2007, and June 25, 2012, 101 patients were enrolled in the study. Eleven of those patients were excluded from analysis, including 4 who had unidentified chronic hepatitis despite diagnosis by radiologic imaging and 7 who had tumors with a greatest dimension >4.0 cm. The pretreatment characteristics of the evaluable patients (n = 90) are detailed in Table 1. Figure 1 provides tumor location maps on CT image diagrams.

The median follow-up for all evaluable patients was 41.7 months (range, 6.8-96.2 months). Among the patients who remained alive (n = 41), the median follow-up was 55.9 months (range, 36.0-96.2 months). No patients were lost during follow-up. Among all evaluable patients, 32 were treatment-naive for HCC; and 20 and 38 patients had received treatment for newly diagnosed intrahepatic failure and residual or recurrent HCC, respectively, after additional salvage therapy. Eighteen patients had HCC tumors that measured ≥3 cm in greatest dimension. TACE was received as scheduled treatment by 58 patients who proceeded to SBRT. At treatment planning, lipiodol in the targeted HCC tumor was fully retained by only 10 patients (11%), who were expected to be controlled well with TACE alone. The median interval between TACE and SBRT was 1.0 months (range, 0.4-3.0 months).

Primary tumor failure occurred in 3 patients during follow-up (Table 2). All HCC tumors that measured ≥3 cm in greatest dimension were controlled. Intrahepatic failure and distant metastases occurred in 63 and 9 patients, respectively. The 3-year primary tumor local control rate was 96.3% (95% confidence interval [CI], 89%-98.8%) (Fig. 2, top left), and the 3-year intrahepatic control rate was 33.9% (95% CI, 24.6%-44.6%) (Fig. 2, top right). The 3-year liver-related CSS rate was 72.5% (95% CI, 62.3%-80.9%) (Fig. 2, bottom left), the median OS was 54.7 months (95% CI, 41.9-71.8 months), and the 3-year OS rate was 66.7% (95% CI, 56.3%-75.6%) (Fig. 2, bottom right). During the period of observation after treatment, 49 patients died. The causes of death were progressive HCC in 21 patients, liver failure in 20 patients, and nonspecific reasons in 8 patients.

Subgroup analyses were performed for OS and liver-related CSS. Patient outcomes are detailed in Table 3. The liver-related CSS rate in patients who had elevated levels of α-fetoprotein was significantly worse than the

TABLE 1. Patient and Tumor Characteristics (n = 90)

Characteristic	No. of Patients (%)
Age: Median [range], y	73 [48–85]
Sex	
Men	58 (64)
Women	32 (36)
ECOG PS	
0	85 (94)
1–2	5 (6)
Greatest tumor dimension: Median [range], cm	2.3 [1.0–4.0]
Patient type	
Treatment-naive	32 (36)
Intrahepatic	20 (22)
Residual or recurrent	38 (42)
Salvage SBRT for residual HCC	38 (42)
After TACE	25 (28)
RFA	3 (3)
PEI	1 (1)
TACE + RFA	7 (8)
TACE + PEI	2 (2)
Median no. of previous HCC treatments	
0	32 (36)
1	15 (17)
2	17 (19)
3	13 (14)
4	13 (14)
TACE before SBRT	
No	32 (36)
Yes	58 (64)
Lipiodol accumulation in HCC tumor, n = 58	
100%	10 (11)
≥50%	20 (22)
<50%	21 (23)
0%	7 (8)
UICC-TNM stage at treatment	
T1	81 (90)
T2	6 (7)
T3, N0M0	3 (3)
BCLC stage at treatment	
0	31 (34)
A	45 (50)
B	0 (0)
C	14 (16)
Child-Pugh score	
5	61 (68)
6	21 (23)
7	7 (8)
8	1 (1)
Type of chronic hepatitis	
HBV	12 (13)
HCV	68 (76)
Alcoholic	7 (8)
Other	3 (3)
Tumor marker	
AFP: Median [range], ng/mL[a]	12.1 [2.2–3780]
0–9.9	39 (44)
10–19.9	18 (20)
20–99.9	10 (11)
100–999	18 (20)
≥1000	4 (5)
PIVKA-II: Median [range], AU/mL[b]	22 [10–1620]
0–19.9	29 (34)
20–49.9	43 (51)
50–199	8 (9)
≥200	5 (6)
Total dose/fractions	
35 Gy in 5 fractions	10 (11)
40 Gy in 5 fractions	80 (89)

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, grays; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PEI, percutaneous ethanol injection; PIVKA-II, protein induced by vitamin K absence or antagonists-II; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization. UICC-TNM, International Union Against Cancer Tumor, Lymph Node, Metastasis classification.

[a] There were 2 patients with missing values

[b] There were 5 patients with missing values (2 patients were receiving warfarin).

rate in those who had normal levels. There were no other significant differences in outcomes among any subgroups.

Table 4 details the toxicities after SBRT. All scheduled treatments were completed without manifestations of toxicity. There was no treatment-related gastrointestinal toxicity. Grade 3 treatment-related laboratory abnormalities included 2 patients (2.2%) with elevated transaminase levels and 4 patients (4.4%) with decreased platelet counts; elevated transaminase levels were transient, whereas the decreased platelet counts remained at grade 3 in 2 patients. Worsening of the Child-Pugh score by 2 points was observed in 8 patients (8.9%). Among these, the worse Child-Pugh score in 2 patients persisted, whereas the score in the remaining 6 patients improved in <6 months. No grade 4 or 5 liver failure caused by SBRT was observed.

DISCUSSION

Radiotherapy combined with surgery and chemotherapy is the mainstays of cancer therapy. However, radiotherapy was previously limited for the treatment of liver tumors because of the low radiation tolerance of the whole liver. Recent technologic advances in the planning and delivery of radiotherapy in a more focused manner, such as SBRT, allow for the safer and more effective treatment of liver tumors. In the current study, SBRT produced excellent local control with favorable toxicities and subsequently high OS for patients with solitary HCC. In addition, SBRT has its own distinguishing characteristics and may not have the limitations of other treatment modalities.

Curative Treatment Options for Stage 0 and A HCC

The Barcelona Clinic Liver Cancer (BCLC) staging system is intended for the prediction of prognosis and

TABLE 2. Primary Local Recurrent Tumor Characteristics (n = 3)

Segment Position	Greatest Tumor Dimension, cm	Patient Type	TACE Lipiodol Accumulation, %	Tumor Classification	Total Dose, Gy	Duration From SBRT to Recurrence, mo[a]	Recurrence Type
S8	1.5	Intrahepatic failure	<50	T1	40	12	New HCC in PTV
S8	2.5	Recurrent HCC after TACE	Not undertaken	T1	40	19	Primary tumor regrowth
S4	1.8	Treatment-naive	<50	T1	40	18	Primary tumor regrowth

Abbreviations: HCC, hepatocellular carcinoma; PTV, planning target volume; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization.
[a] The duration between the day SBRT was started and the day recurrence was detected is indicated.

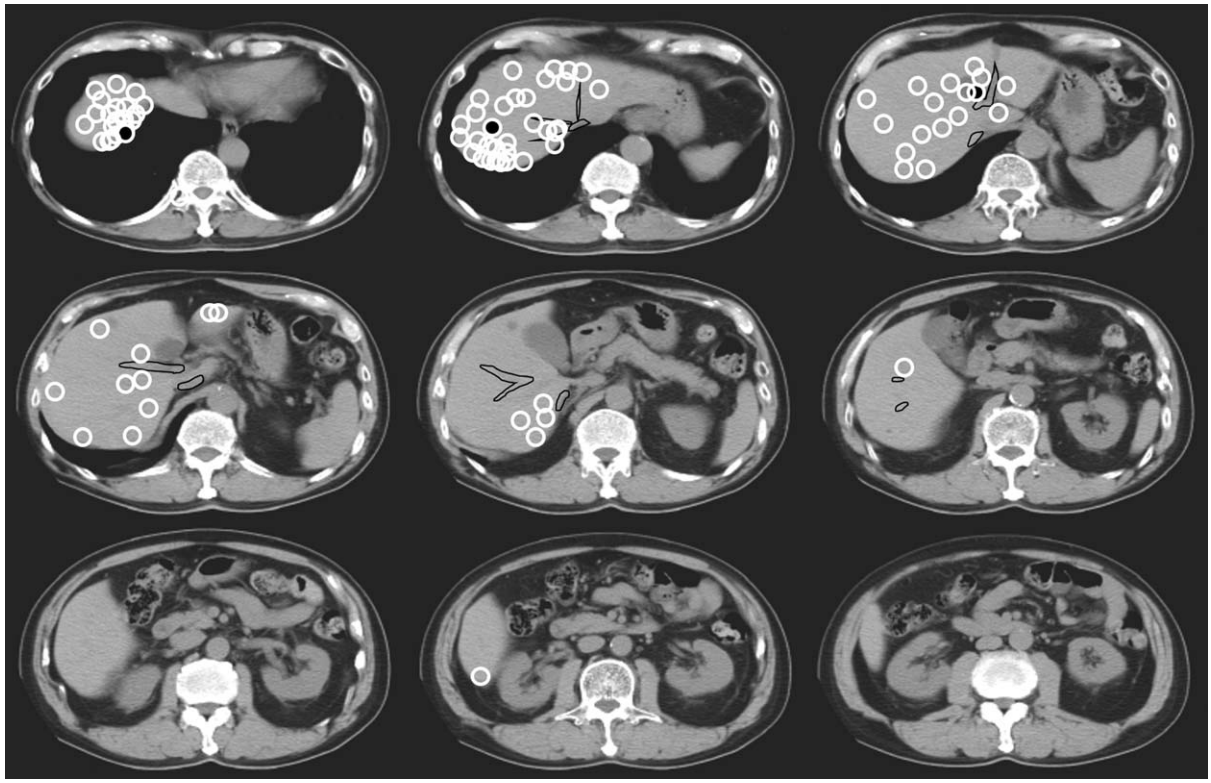

Figure 1. Treated tumor location maps on computed tomography image diagrams are shown. White circles indicate treated tumors; black circles, recurrent tumors after stereotactic body radiotherapy. Many tumors were located just below the diaphragm, suggesting that radiofrequency ablation is difficult to perform in that area.

selection of adequate treatment in patients with HCC.[1] According to this staging system, patients with BCLC stage 0 and A HCC are recommended for resection, liver transplantation, and percutaneous ablation therapy as curative treatment options. It has been estimated that the outcomes of these curative therapies achieve a median OS of >60 months or 5-year survival rates from 40% to 70%. However, such curative treatment is not always indicated for these patients. According to the Surveillance, Epidemiology, and End Results–Medicare-linked database, between 1998 and 2007, approximately 1/2 of patients with early stage HCC received curative treatment options (ablation therapy, 30%; resection, 16%; liver transplantation, 7%).[3] In addition, 3% of patients underwent TACE, 7% received systemic chemotherapy, and the remaining 36% received no therapy for HCC. Accordingly, the 5-year OS rates in patients who underwent liver transplantation, resection, ablation therapy, and no curative treatment were 63%, 33%, 20%, and 7%, respectively.[3]

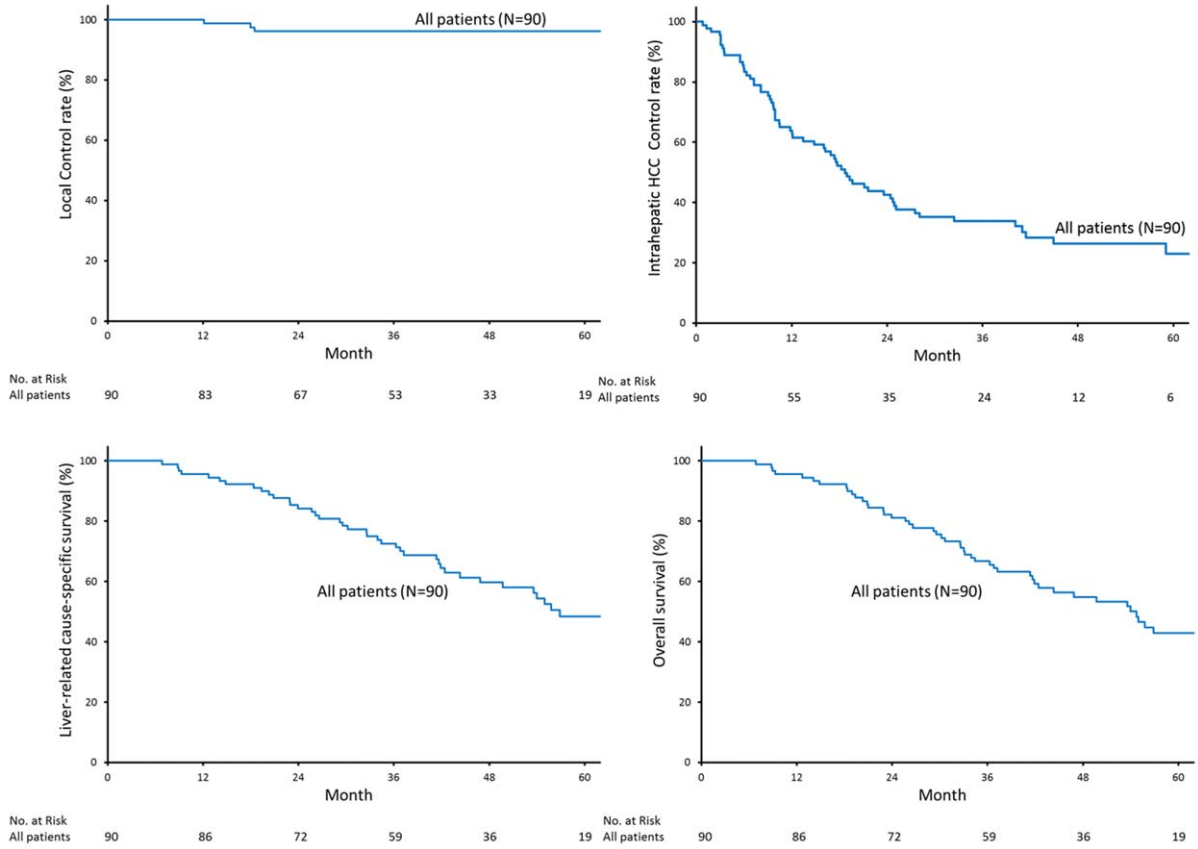

Figure 2. (*Top Left*) Primary tumor local control, (*Top Right*) the intrahepatic control rate, (*Bottom Left*) the liver-related cause-specific survival rate, and (*Bottom Right*) the overall survival rate are illustrated.

Among the curative treatment options, resection is the first-line option for patients who have a solitary tumor and a well preserved liver.[1] Anatomic resection can achieve high local control (90%) and high disease-free survival.[17] However, resectability requires certain conditions, including sufficient medical fitness to undergo a major operation, generally Child-Pugh grade A disease without portal hypertension, a solitary mass without major vascular invasion, a suitable tumor location, an adequate liver reserve, and a suitable liver remnant.[18] Consequently, candidates for resection are limited.

Liver transplantation is the best therapeutic option for unresectable HCC. For patients with a limited tumor load who satisfy the Milan criteria, 10-year OS rates as high as 70% have been reported.[19] Liver transplantation allows restored liver function and decreases the risk of developing new HCC.[2] However, the small number of available donor organs limits the indication for liver transplantation in patients with HCC. In the United States, liver transplantation is unlikely to be indicated for patients aged >70 years.[20] In Asia, the role of liver transplantation is much more limited because of ethical or religious considerations. Deceased donor liver transplantation is rarely performed in Japan, and living donor liver transplantation is performed annually in approximately 100 patients with HCC.[21]

Ablation therapy, such as RFA, is considered the first-line treatment option for patients with early stage disease who are not suitable for surgical therapies. RFA can achieve high local control while preserving liver function, with a 2-year local tumor control rate that ranges from 86 to 96%.[15,22] Especially among patients with stage 0 disease, OS was comparable to that reported for those who underwent resection.[23] In addition, RFA is less invasive and has fewer complications and lower costs.[24] One drawback is a high probability of incomplete ablation of lesions >3 cm[16] in greatest dimension. Wahl et al[25] compared outcomes between SBRT and RFA retrospectively. Their results indicated that, compared with SBRT, RFA was associated with significantly worse local control for tumors ≥2 cm. Another drawback is an inability to target some locations: incomplete ablation or major

TABLE 3. Subgroup Survival Analysis

Variable	No. of Patients	3-Year Liver-Related CSS (95% CI), %	*P*	3-Year OS (95% CI), %	*P*
Eligible patients	90	72.5 (62.3–80.9)		66.7 (56.3–75.6)	
Sex			.054		.20
Men	58	76.6 (63.7–85.9)		69 (56–79.5)	
Women	32	65.5 (47.7–79.8)		62.5 (44.9–77.3)	
ECOG PS			.64		.32
0–1	85	72.3 (61.7–80.9)		67.1 (56.4–76.2)	
2	5	80 (30.9–97.3)		60 (20–90)	
Treatment for HCC			.74		.75
Treatment-naive	32	80.7 (63.2–91.1)		71.9 (54.2–84.7)	
Second or more	58	68.1 (54.9–78.9)		63.8 (50.8–75.1)	
TACE before SBRT			.58		.44
No	32	74.4 (56.4–86.7)		65.6 (47.9–79.8)	
Yes	58	71.8 (58.8–82)		67.2 (54.3–78)	
UICC-TNM			.26		.19
T1	86	71.2 (60.6–79.9)		65.1 (54.5–74.4)	
T2-T3	4	100		100	
BCLC staging at treatment			.51		.64
0-A	81	70.9 (60–79.9)		65.4 (54.5–75)	
B-C	9	88.9 (50–98.5)		77.8 (421–94.4)	
Child-Pugh grade			.28		.49
A	82	74.8 (64.2–83.2)		68.3 (57.5–77.4)	
B	8	50 (20–80)		50 (20–80)	
AFP, ng/mL			< .01		.11
Normal: <9.9	40	83.9 (68.6–92.6)		72.5 (56.8–84.1)	
Increased: ≥10	49	63.1 (48.9–75.4)		61.2 (47.1–73.7)	
PIVKA-II, AU/mL			.11		.07
Normal, <40	68	77.6 (66.2–86.1)		72.1 (60.3–81.4)	
Increase, ≥40	17	54.1 (29.9–76.4)		47.1 (25.5–69.7)	
Dose prescription			.96		.76
35 Gy in 5fractions	10	60 (29.7–84.2)		60 (29.7–84.2)	
40 Gy in 5 fractions	80	74.2 (63.3–82.7)		67.5 (56.5–76.8)	

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CSS, cause-specific survival; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, grays; HCC, hepatocellular carcinoma; OS, overall survival; PIVKA-II, protein induced by Vitamin K absence or antagonists-II; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; UICC-TNM, International Union Against Cancer-Tumor, Lymph Node, Metastasis classification.

complications are likely to occur for lesions located just below the diaphragm, on the liver surface, adjacent to a vessel or biliary duct, or near the hilum.[26,27] SBRT may be effective for such patients because most patients in this study were not amenable to RFA. The treated tumor maps in Figure 1 reflect the actual indications for SBRT.

Patients who are not candidates for curative treatment options usually undergo TACE.[1] However, local control after TACE is inferior to that achieved after curative treatment. In a study of TACE involving 265 patients with HCC, the 3-year local control rate for those who had tumors with complete and incomplete lipiodol accumulation was 41% and 9%, respectively.[4] In addition, it has been reported that noncompact lipiodol accumulation after TACE is a risk factor for early local recurrence.[5] In the current study, we suspected that most patients would achieve poor local control after TACE alone, including patients who had poor lipiodol accumulation (n = 48) and those who did not undergo TACE (n = 32). Therefore, we believe that the high local control rate achieved in this study can be attributed mainly to SBRT.

TABLE 4. Toxicities after SBRT.

Toxicity Parameters	Toxicity: No. of Patients (%)		
	Grade 3	Grade 4	Grade 5
Laboratory tests			
Elevated transaminases	2 (2.2)	0 (0)	0 (0)
Hyperbilirubinemia	0 (0)	0 (0)	0 (0)
Hypoalbuminemia	0 (0)	0 (0)	0 (0)
Decreased platelet counts	5 (5.6)	0 (0)	0 (0)
Elevated alkaline phosphatase	0 (0)	0 (0)	0 (0)
Worsening of CPS by 2 points	8 (8.9)	—	—

Abbreviation: CPS, Child-Pugh score.

Outcomes and Characteristics of SBRT

Each curative treatment option has its own limitation that restricts the indication for curative treatment, as

mentioned above. SBRT may compensate for the limitation of those treatment options. SBRT is a noninvasive therapy that is free of pain, bleeding, and needle-track seeding. Another advantage is its ablative characteristics: eradicative damage to both the HCC tumor and the normal liver parenchyma is induced in highly irradiated areas with minimal blood vessel and bile duct toxicities.[9] Lesions that are inaccessible to RFA and/or resection can be safely treated with SBRT, even if HCC has invaded major blood vessels or bile ducts or if the tumor measures $\geq$3 cm in greatest dimension. In addition, patients who are medically unfit to undergo these treatment options can receive SBRT. Consequently, the 3-year primary tumor local control rate was as high as 96.3% in this study, comparing favorably with that achieved with RFA.[15,22] OS in the current study was relatively high (median, 54.7 months) considering that the patients were treated under stringent conditions; they included elderly patients (median age, 73 years), who were likely to have comorbidities, and patients with T2 and T3 disease, who had been heavily pretreated with TACE and ablation therapies for local or intrahepatic failure. These outcomes are comparable to those reported in previous retrospective studies among patients who received treatment with SBRT alone; in those studies, the 2-year local control and OS rates after SBRT for small HCCs were from 99% to 100% and from 57% to 76%, respectively.[7,8] Therefore, SBRT alone may be sufficient to control such small HCCs. SBRT also plays a role in other situations, as a bridging therapy to liver transplantation[10,28] or as treatment for locally advanced HCC[11] and intrahepatic failure, which arise in 70% of patients at 5 years[1] and are treated after reassessment using BCLC staging. Although the indications for SBRT are generous, lesions near the gastrointestinal tract may be contraindicated or should be carefully treated, because the bowels are radiosensitive. In addition, patients with a decompensated liver may be contraindicated because of a high risk of radiation-induced liver disease. Andolino et al[10] reported that, of 4 patients who developed progressive liver dysfunction, 2 underwent liver transplantation, and 2 died. All 4 of those patients had Child-Pugh scores of 8 or 9. Huertas et al[7] also reported 2 fatal toxicities among 3 patients with Child-Pugh scores of 8 or 9. In the current study, only 1 patient had a Child-Pugh score of 8 by the time treatment was received. Consequently, elevation of transaminase levels (Common Terminology Criteria for Adverse Events grade 3) was observed in 2 patients, and worsening of the Child-Pugh score by $\geq$2 was observed in 8 patients.[13] No grade 4 or 5 liver failure was observed.

Our current prospective study had some limitations. Ours is a population of heterogeneous patients and may be inappropriate for evaluating outcomes regarding survival. Therefore, to accurately evaluate the results, other study settings with a homogeneous population should be performed in a multiinstitutional study. For example, patients with a solitary, macrovascular, invasive HCC (T2 and T3), elderly patients with HCC, and patients with centrally located HCC may be good candidates for future prospective studies. We are currently conducting a multicenter prospective study of SBRT for treatment-naive patients who have a solitary primary HCC with 3-year OS as the primary endpoint.

In conclusion, SBRT provides high local control and improved OS with feasible toxicities for patients with HCC who are not amenable both to resection and RFA, despite stringent treatment conditions. In the future, SBRT will play a role in the treatment of HCC in both curative and salvage treatment settings, taking advantage of its distinctive characteristics.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Atsuya Takeda: Study conception and design, acquisition of data, analysis and interpretation of data, and drafting the article. **Naoko Sanuki:** Acquisition and analysis of data, interpretation of data, and drafting the article. **Yuichiro Tsurugai:** Analysis of data. **Shogo Iwabuchi:** Acquisition and analysis of data and critical revision of the article for important intellectual content. **Kotaro Matsunaga:** Acquisition and analysis of data and critical revision of the article for important intellectual content. **Hirotoshi Ebinuma:** Acquisition and analysis of data and critical revision of the article for important intellectual content. **Kento Imajo:** Acquisition and analysis of data and critical revision of the article for important intellectual content. **Yousuke Aoki:** Acquisition and analysis of data and critical revision of the article for important intellectual content. **Hidetsugu Saito:** Study conception and design and critical revision of the article for important intellectual content. **Etsuo Kunieda:** Study conception and design and critical revision of the article for important intellectual content. All authors approved the final version of the article for publication and agreed to be accountable for all aspects of the work.

REFERENCES

1. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol.* 2012;56:908-943.

2. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology.* 2005;42:1208-1236.
3. Nathan H, Hyder O, Mayo SC, et al. Surgical therapy for early hepatocellular carcinoma in the modern era: a 10-year SEER-Medicare analysis. *Ann Surg.* 2013;258:1022-1027.
4. Hayashi K, Ina H, Tezuka M, Okad Y, Irie T. Local therapeutic results of computed tomography-guided transcatheter arterial chemoembolization for hepatocellular carcinoma: results of 265 tumors in 79 patients. *Cardiovasc Intervent Radiol.* 2007;30:1144-1155.
5. Rou WS, Lee BS, Moon HS, Lee ES, Kim SH, Lee HY. Risk factors and therapeutic results of early local recurrence after transcatheter arterial chemoembolization. *World J Gastroenterol.* 2014;20:6995-7004.
6. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010;303:1070-1076.
7. Huertas A, Baumann AS, Saunier-Kubs F, et al. Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. *Radiother Oncol.* 2015;115:211-216.
8. Kimura T, Aikata H, Takahashi S, et al. Stereotactic body radiotherapy for patients with small hepatocellular carcinoma ineligible for resection or ablation therapies. *Hepatol Res.* 2015;45:378-386.
9. Eriguchi T, Takeda A, Sanuki N, et al. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. *Int J Radiat Oncol Biol Phys.* 2013;85:1006-1011.
10. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2011;81:e447-e453.
11. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol.* 2013;31:1631-1639.
12. Kang JK, Kim MS, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer.* 2012;118:5424-5431.
13. Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3 suppl):S94-S100.
14. Takeda A, Takahashi M, Kunieda E, et al. Hypofractionated stereotactic radiotherapy with and without transarterial chemoembolization for small hepatocellular carcinoma not eligible for other ablation therapies: preliminary results for efficacy and toxicity. *Hepatol Res.* 2008;38:60-69.
15. Lin SM, Lin CJ, Lin CC, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut.* 2005;54:1151-1156.
16. Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. *Radiology.* 2005;234:954-960.
17. Regimbeau JM, Kianmanesh R, Farges O, Dondero F, Sauvanet A, Belghiti J. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. *Surgery.* 2002;131:311-317.
18. Benson AB 3rd, Abrams TA, Ben-Josef E, et al. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw.* 2009;7:350-391.
19. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693-699.
20. Schwartz JJ, Pappas L, Thiesset HF, et al. Liver transplantation in septuagenarians receiving model for end-stage liver disease exception points for hepatocellular carcinoma: the national experience. *Liver Transpl.* 2012;18:423-433.
21. The Japanese Liver Transplantation Society. Registry by the Japanese Liver Transplantation Society [in Japanese]. *Ishoku.* 2014;49:261-274.
22. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology.* 2003;228:235-240.
23. Wang JH, Wang CC, Hung CH, Chen CL, Lu SN. Survival comparison between surgical resection and radiofrequency ablation for patients in BCLC very early/early stage hepatocellular carcinoma. *J Hepatol.* 2012;56:412-418.
24. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology.* 2008;47:82-89.
25. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol.* 2016;34:452-459.
26. Komorizono Y, Oketani M, Sako K, et al. Risk factors for local recurrence of small hepatocellular carcinoma tumors after a single session, single application of percutaneous radiofrequency ablation. *Cancer.* 2003;97:1253-1262.
27. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology.* 2001;33:1124-1129.
28. Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT, Hezel AF. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. *Int J Radiat Oncol Biol Phys.* 2012;83:895-900.