Multicenter prospective study of stereotactic body radiotherapy for previously untreated solitary primary hepatocellular carcinoma: The STRSPH study

Tomoki Kimura | Tomohiro Yamaguchi | Naoko Sanuki | Keisuke Ariyoshi | Toshiyuki Imagembali | Norio Katoh | Takahisa Eriuchi | Yohei Oku | Shuichi Ozawa | Yuichiro Tsurugai | Masaki Kokubo | Shinichi Shimizu | Satoshi Ishikura

1Department of Radiation Oncology, Hiroshima University Hospital, Hiroshima, Japan
2Radiation Oncology Center, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan
3Department of Data Management, JORTC Data Center, Arakawa-ku, Tokyo, Japan
4Division of Biostatistics, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
5Department of Radiation Oncology, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
6Department of Radiation Oncology, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
7Department of Radiation Oncology, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Kanagawa, Japan
8Department of Radiation Medical Science and Engineering, Faculty of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan
9Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan

Correspondence
Satoshi Ishikura, Department of Radiology, Nagoya City University Graduate School of Medical Sciences 1, Kawasaki, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan. Email: sishikur@med.nagoya-cu.ac.jp

Abstract

Aim: To prospectively evaluate the efficacy and safety of stereotactic body radiotherapy (SBRT) for patients with previously untreated solitary primary hepatocellular carcinoma (HCC).

Methods: The main eligibility criteria included the following: (1) primary solitary HCC; (2) no prior treatment for HCC; (3) Child–Turcotte–Pugh score of seven or less; and (4) unsuitability for or refusal of surgery and radiofrequency ablation (RFA). The prescribed dose of SBRT was 40 Gy in five fractions. The primary endpoint was 3-year overall survival (OS); the secondary endpoints included local progression-free survival (LPFS), local control (LC), and adverse events. The accrual target was 60 patients, expecting a 3-year OS of 70% with a 50% threshold.

Results: Between 2014 and 2018, 36 patients were enrolled; enrollment was closed early because of slow accrual. The median tumor size was 2.3 cm. The median follow-up at the time of evaluation was 20.8 months. The 3-year OS was 78% (95% confidence interval [CI]: 53%–90%). The 3-year LPFS and LC proportion were 73% (95% CI: 48%–87%) and 90% (95% CI: 65%–97%), respectively. Grade 3 or higher SBRT-related toxicities were observed in four patients (11%), and grade five toxicities were not observed.

Conclusions: This study showed acceptably low incidence of SBRT-related toxicities. LC and OS after SBRT were comparable for previously untreated solitary HCC for patients unfit for resection and RFA. Although a definitive conclusion cannot be drawn by this study, the promising results indicate that SBRT may be an alternative option in the management of early HCC.

Abbreviations: ALT, alanine aminotransferase; AAA, analytical anisotropic algorithm; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CTP, Child–Turcotte–Pugh; CTV, clinical target volume; CTCAE, Common Terminology Criteria for Adverse Events; CT, computed tomography; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EASL, European Association for the Study of the Liver; GTV, gross tumor volume; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IRB, institutional review board; ITV, internal target volume; UICC, International Union Against Cancer; IHRF, intrahepatic recurrence-free proportion; LC, local control; LPFS, local progression-free survival; MRI, magnetic resonance imaging; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NASH, non-alcoholic steatohepatitis; OS, overall survival; PS, performance status; PTV, planning target volume; PSM, propensity score matching analyses; RFA, radiofrequency ablation; RFS, recurrence-free survival; SBRT, stereotactic body radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; TAE, transarterial embolization; TACE, transcatheter arterial chemoembolization; VMAT, volumetric modulated arc therapy.
INTRODUCTION

The Barcelona Clinic Liver Cancer (BCLC) algorithm recommends that resection, transplantation, and ablation, such as radiofrequency ablation (RFA), should be used first for patients with early hepatocellular carcinoma (HCC). However, according to a Japanese survey, approximately 38% of naïve patients with HCC were eligible for resection because of the multifocal nature of malignancies underlying cirrhosis and viral infections. RFA is also indicated as the first-line treatment for patients in early HCC. RFA has several advantages, such as less invasiveness and being more easily repeatable than resection, with comparable local control (LC). However, it is often not feasible because it is invisible by ultrasonography or because of the high risk of puncturing large vessels in the locality, either under the diaphragm or in the deep layers of liver tissue. In addition, LC for tumors smaller than 2 cm is excellent, while LC for tumors 2 cm or larger is more problematic; therefore, LC for tumors of 3 cm or larger are not attempted in most institutions. Many authors have reported a high LC proportion of 90%–100% at two to 3 years, and an overall survival (OS) proportion of 60%–70% for patients with early HCC who underwent stereotactic body radiotherapy (SBRT). Although these results are promising, radiotherapy has not been considered as a curative and first-line treatment for early HCC in the official guidelines because of the lack of evidence. In prospective studies exclusively focusing on HCC, the application of SBRT is broad, including large tumors over 10 cm, salvage treatment for residual disease or recurrence, and the presence of tumor vascular invasion. There are few prospective studies focusing on patients with newly diagnosed solitary HCC, as one of the definitive local treatments comparable to resection or ablation.

The purpose of this multicenter study was to prospectively evaluate the efficacy and safety of SBRT aiming to investigate the OS for patients with previously untreated solitary primary HCC.

METHODS

Patient eligibility

This investigation was a multicenter, nonrandomized, single-arm study. The eligibility criteria included the following: (1) primary nodular HCC; pathologically proven or clinically diagnosed based on typical enhancement patterns on either dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI), or perflutane-enhanced ultrasound; (2) solitary tumor with a maximum diameter between 1 and 5 cm; (3) no previous treatment for HCC, such as surgery, RFA, or transcatheter arterial chemoembolization (TACE); (4) a Child–Turcotte–Pugh (CTP) score of seven or less (a CTP score of eight or more was allowed, if the patients took warfarin, and their CTP scores were six or less excluding the prothrombin activity); (5) an age of 20–85 years; (6) lack of suitability for or refusal of surgery and RFA (The suitability of surgery or RFA was decided by surgeons or hepatologists); (7) an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (8) appropriate organ function, a white blood cell count of 3000/mm³ or higher, a platelet count of 3 × 10⁹/mm³ or higher, hemoglobin of 8.0 g/dl or higher, total bilirubin of 2.0 mg/dl or lower, blood urea nitrogen of 35 mg/dl or lower, serum creatinine of 1.5 mg/dl or lower, and prothrombin activity of 50% or higher; and (9) written informed consent. The exclusion criteria included the following: (1) uncontrolled ascites; (2) a prior history of radiotherapy in the liver; (3) esophageal varices with a high risk of bleeding; (4) severe infection; (5) coexisting cancers; (6) interstitial pneumonitis, pulmonary fibrosis, and severe emphysema; (7) psychiatric disease; and (8) pregnancy. The study protocol was approved by each institutional review board (IRB). This study was registered at University hospital Medical Information Network (UMIN) (UMIM000013011).

SBRT planning

Three-dimensional conformal radiotherapy (3D-CRT) or volumetric modulated arc therapy (VMAT) with respiratory motion management and image guidance were used for SBRT. The set-up error must be verified to be 5 mm or less before each treatment delivery. The gross tumor volume (GTV) was delineated for the primary tumor on dynamic CT or MRI. The clinical target volume (CTV) was created by adding a 3–5 mm margin to the GTV. The internal target volume (ITV) was the CTV with an internal margin, which was mainly constituted of the respiratory motion. The margin was determined according to each institution’s method of respiratory control, such as shallow free breathing with abdominal compression, breath-hold technique and tumor tracking using fiducial markers. Cone-beam CT was used for verification. The planning target volume (PTV) was the ITV with an additional set-up margin of 5 mm. Dose constraints for the planning organ at risk volume were defined in Table 1. X-rays with a voltage of at least 6 MV were used. The prescribed dose was 40 Gy, delivered in five fractions over 5–10 days with three to five treatments per week. The dose was prescribed such that 95% of the PTV received 40 Gy and the maximum dose of the PTV was 143%–150% of the prescribed dose. The maximum dose at 5 cm outside the PTV should be less than 25 Gy. The conformity index was defined using the following equation, which was proposed by van’t Riet et al. for the calculation of the conformation number.
Table 1  Dose constraints of planning organ at risk volume (PRV)

| PRV       | Volume | Dose constraints | Max dose |
|-----------|--------|-----------------|----------|
| Spinal cord | <0.35 cc | 22 Gy | 28 Gy |
|           | <1.2 cc | 14.5 Gy |          |
| Skin      | <10 cc  | 36.5 Gy | 38.5 Gy |
| Esophagus | <5 cc   | 20 Gy  | 35 Gy   |
| Stomach   | <5 cc   | 20 Gy  | 35 Gy   |
| Duodenum  | <5 cc   | 20 Gy  | 26 Gy   |
| Small intestine | <5 cc  | 20 Gy  | 26 Gy   |
| Large intestine | <5 cc | 20 Gy  | 35 Gy   |
| Liver     | <20 %   | 20 Gy  |         |

Conformity Index = \( \frac{V_{PTV,ref}}{V_{PTV}} \times \frac{V_{PTV,ref}}{V_{ref}} \)

where, \( V_{PTV,ref} \) was the volume of the PTV that received at least the reference dose, \( V_{PTV} \) was the volume of the PTV, and \( V_{ref} \) was the volume that received at least the reference dose (treated volume). The reference dose was 40 Gy in this study, and the conformity index should have been 0.75 or higher. Superposition/convolution, analytical anisotropic algorithm (AAA) or Monte Carlo calculations with heterogeneity corrections were used to evaluate dose distributions. Figure 1 shows the typical dose distribution.

Preceding scheduled transarterial embolization (TAE) followed by SBRT, which involved lipiodol without chemotherapeutic agents, was allowed as a positioning marker, not as an antitumor effect.

Follow up and evaluation

All patients were followed up after the completion of patient accrual. A complete blood count, biochemical examinations, CTP score evaluation, and a prothrombin activity test were performed every month for the first 6 months, and every 3 months thereafter. Dynamic CT or MRI of the liver was performed every 3 months for the first 6 months, and every 6 months thereafter.

For the assessment of tumor responses, the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used, which accounted for tumor necrosis, recognized by nonenhanced areas. Only the response of the target lesion was evaluated using these criteria in this study. Local tumor progression was defined as progressive disease in mRECIST, and LC was defined as being free of local progression. Toxicities within and after 3 months from the completion of SBRT were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.
Statistical methods

The primary endpoint was the 3-year OS rate. The secondary endpoints included OS, local progression-free survival (LPFS), the 3-year LC proportions, intrahepatic recurrence-free proportion (IHRF), extrahepatic metastasis-free survival and liver failure-free survival, recurrence-free survival (RFS), salvage treatment for first recurrence, and rates of adverse events. We expected the 3-year OS proportion to be 70%, with a threshold of 50%. The accrual target was set to 60 patients, with an alpha of 0.05, beta of 0.1, a 3-year accrual period, and a 3-year follow-up period, using nonparametric confidence intervals for survival time.38

Monitoring

All data were collected at the JORCT Data Center, and central monitoring was performed each year. A central review of disease progression and LC was performed every year by our peers. Radiotherapy quality control and quality assurance were performed. Participating institutions were verified by the principal investigator and study coordinators before the start of the patient accrual. The validation process included (1) facility questionnaires, including a patient-specific quality assurance survey for VMAT; (2) an on-site audit of image-guided radiotherapy; and (3) a dummy run with delineation, and a planning exercise.19 Retrospective individual case reviews were performed for all registered cases.

RESULTS

Patients characteristics

Between January 2014 and July 2018, 36 patients were enrolled. The proportion of the cases refusal to surgery and RFA were 56 % and 14 %, respectively. The enrollment was closed early because of the slow accrual, although the target number of accruals was 60. Two patients were excluded from the analysis because they were unfit or unsuitable for the treatments. Specifically, one patient was not treated with SBRT because of difficulty in keeping the appropriate posture required for the treatment, and the other patient had another untreated HCC at diagnosis that was detected in the central review. The study flow chart was shown in Figure 2. Overall, 34 patients were analyzed in this study. For the analysis of the adverse events, 35 patients (including the patient in whom another untreated HCC was detected after the completion of SBRT) were included. Table 2 shows a summary of the patients’ clinical characteristics. The median age was 74 years. BCLC staging identified 12, 16 and eight patients who underwent SBRT with stage 0, A and C disease, respectively. The median tumor size was 2.3 cm.

FIGURE 2 Patient selection Two patients were excluded from the analysis because they were unsuitable for the treatment administration. Specifically, one patient had difficulty maintaining the appropriate posture required for the treatment, and another one had untreated hepatocellular carcinoma (HCC) as detected in central review

Treatment outcomes

The median follow-up at the time of evaluation was 21 months (range, 4–57). The two- and 3-year OS was 84% (95% confidence interval [CI]: 62%–94%) and 78% (95% CI: 53%–90%), respectively (Figure 3a). The 2-/3-year LPFS, LC, IHRF, and RFS rates were 79% (95% CI: 57%–91%)/73% (95% CI: 48%–87%), 90% (95% CI: 65%–97%)/90% (95% CI: 65%–97%), 63% (95% CI: 39%–80%)/63% (95% CI: 39%–80%), and 59% (95% CI: 36%–76%)/52% (95% CI: 28%–71%), respectively (Figure 3b–e). The 2-/3-year extrahepatic metastasis-free survival and liver failure-free survival were 100% (95% CI: 100%) and 95% (95% CI: 68%–99%)/88% (95% CI: 58%–97%), respectively. During the follow-up periods, six of the 34 patients died. The cause of death was cancer progression in two, hepatic failure in one, salvage treatment (resection)-related death in one and causes unrelated to the liver in two.

Grade 3 or higher toxicities within 3 months after completion of SBRT were observed in 10 patients (28.6%), and all were laboratory toxicities. Grade 3 or higher toxicities after 3 months from the completion of SBRT (Table 3) were observed in 13 patients (37%), which included those before SBRT, and grade 5 toxicities were not observed. Grade 3 or higher toxicities which were related to SBRT were observed in four patients (11%). Grade 3 or higher nonlaboratory toxicities were observed in four patients (11%), including duodenal ulcer in one patient, dyspnea/hypoxia in one patient, ascites in two patients, liver failure in one patient (diagnosed at 26 months after SBRT, and CTP score before SBRT was 7), and portal vein thrombosis in one patient. A worsening CTP score 2 or more points were observed in 12 patients (34.3 %).

The recurrence was observed in eight patients (two patients: local recurrence, six patients: intrahepatic recurrence), and the salvage treatments for the local recurrence were TACE in one patient and percutaneous ethanol injection therapy in one patient, and those for intrahepatic recurrence were TACE in two patients, resection in one patient, RFA in one patient, radiotherapy in two patients.
DISCUSSION

In the European Association for the Study of the Liver (EASL) treatment algorithm, Japanese and Asian guidelines, radiation therapy is not presented as an option because of sparse evidence.\textsuperscript{1,20,21} In order to show that SBRT may be listed as one of the curative options, we defined our study populations as patients with previously untreated solitary primary HCC staged as “very early” or “early” in the EASL algorithm and set the OS as the primary endpoint. According to the 20th Nationwide Follow-up Survey of Primary Liver Cancer in Japan which was published in 2020, the 3-year OS for surgery and RFA to solitary 2–3 cm tumors, which population is close to the subjects in our study, is 79.8%–82.0% and 72.8%–78.9%, respectively and that for TACE to solitary HCC is 61.4%.\textsuperscript{5} TACE is currently the alternative treatment for patients who are unfit for surgery and RFA. However, treatment outcome of TACE is not optimal. In contrast, SBRT yielded 3-year OS rates of 58.7%–73.0%.\textsuperscript{6,7,9,10,22} Therefore, we expected the 3-year OS rate to be 70%, with a threshold of 50%. As a result, although the sample size of this study did not reach the target accrual, the 3-year OS was 78% which is equivalent to those of surgery and RFA.\textsuperscript{2,3,23–25} In addition, the lower limit of the 95% CI for 3-year OS was above 50% of the threshold survival rate, supporting the effectiveness of SBRT. In the EASL guidelines, 5-year survival rates of 40%–70% after curative treatment for very early to early stage are expected.\textsuperscript{26} As we cannot always have the best evidence based on randomized trials, the outcomes of SBRT seem to meet the expected values by EASL for the very early to early stage.

There are limited reports on the outcomes after SBRT as the first-line therapy aimed for early HCC.\textsuperscript{22,27} Most of the other reports
include large tumors and a wide range of recurrence cases, which are disadvantages in selecting SBRT, compared with surgery and RFA. One report with an intention similar to our study was conducted in France in 2020. Comparing the two studies, the median age (72 and 74 years) and size (28 and 23 mm) were similar, respectively, as well as the baseline liver function (CTP-A consisting of 86% and 91% of the cases). LC was also comparable to that of our study (the 18-month LC of 98% as their primary endpoint: 3 years LC of 90%). Toxicity was mild and acceptable in both studies. However, the 3-year OS of approximately 52%, read from the Kaplan-Meier
estimate of the OS curve, appears to be lower than that of our study and 3-year OS of 73% in the other retrospective study, although the reason is unknown. We will need to look carefully at the long-term results of our study.

TACE is often indicated for patients with HCC unfit for resection or RFA, regardless of tumor size, location, or number. For comparison between SBRT and TACE, three head-to-head comparison trials (NCT03338647, NCT02470533, and NCT02762266) are ongoing in patients with unresectable or recurrent HCC. However, it should be noted that large tumors (e.g., up to 10 cm) are allowed in these trials, so the results may not be applicable for small HCCs that are otherwise eligible for resection or RFA. With the already known good LC rate of SBRT, we planned a phase II trial targeting early HCC where surgery and RFA would be indicated. Results from prospective trials or large databases, surgery and RFA for newly diagnosed HCC are likely to achieve OS rates over 70% at 3 years, and 55% at 5 years (Table 3). In addition, OS rates of TACE are over 60% at 3 years and 40% at 5 years (Table 4). Notably, the median age of

| TABLE 3 | Adverse events after 3 months |
|------------------|------------------|------------------|------------------|
| **Laboratory toxicities** | **Stereotactic body radiotherapy (SBRT; N = 35)** | **All grade/SBRT related, n (%)** | **Grade 3/SBRT related, n (%)** | **Grade 4/SBRT related, n (%)** |
| Increased alanine aminotransferase (ALT) | 14 (40)/2 (6) | 0 (0)/0 (0) | 1 (3)/0 (0) |
| Increased aspartate aminotransferase (AST) | 24 (69)/4 (11) | 3 (9)/1 (3) | 1 (3)/0 (0) |
| Increased blood bilirubin | 14 (40)/1 (3) | 1 (3)/0 (0) | 1 (3)/0 (0) |
| Increased γ-glutamyl transpeptidase | 21 (60)/3 (9) | 6 (17)/2 (6) | 1 (3)/0 (0) |
| Hypoalbuminemia | 22 (63)/6 (17) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Decreased platelet count | 31 (87)/4 (11) | 3 (9)/0 (0) | 1 (3)/0 (0) |
| Increased alkaline phosphatase | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Anemia | 13 (37)/0 (0) | 2 (6)/0 (0) | 2 (6)/0 (0) |
| Increased creatinine | 27 (77)/0 (0) | 2 (6)/0 (0) | 0 (0)/0 (0) |
| Increased hemoglobin | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Hyperglycemia | 25 (71)/0 (0) | 4 (11)/0 (0) | 0 (0)/0 (0) |
| Hyperkalemia | 7 (20)/0 (0) | 0 (0)/0 (0) | 1 (3)/0 (0) |
| Hypokalemia | 10 (29)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Hyponatremia | 14 (40)/0 (0) | 1 (3)/0 (0) | 1 (3)/0 (0) |
| Decreased white blood cell count | 15 (43)/1 (3) | 2 (6)/0 (0) | 1 (3)/1 (3) |
| **Nonlaboratory toxicities** | | | |
| Ascites | 6 (17)/1 (3) | 2 (6)/1 (3) | 0 (0)/0 (0) |
| Liver failure | 1 (3)/0 (0) | 1 (3)/0 (0) | 0 (0)/0 (0) |
| Portal vein thrombosis | 1 (3)/0 (0) | 1 (3)/0 (0) | 0 (0)/0 (0) |
| Duodenal ulcer | 1 (3)/0 (0) | 1 (3)/0 (0) | 0 (0)/0 (0) |
| Fever | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Dyspnea | 1 (3)/0 (0) | 1 (3)/0 (0) | 0 (0)/0 (0) |
| Pneumonitis | 3 (9)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Hypoxia | 1 (3)/0 (0) | 1 (3)/0 (0) | 0 (0)/0 (0) |
| Abdominal pain | 2 (6)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Disseminated intravascular coagulation | 1 (3)/0 (0) | 0 (0)/0 (0) | 1 (3)/0 (0) |
| Limb edema | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Pruritus | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Maculopapular rash | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
| Sepsis | 1 (3)/0 (0) | 0 (0)/0 (0) | 1 (3)/0 (0) |
| Sinusitis | 1 (3)/0 (0) | 0 (0)/0 (0) | 0 (0)/0 (0) |
TABLE 4 Comparison among the results of clinical outcomes of first-line treatment

| Treatment   | Author                                      | n   | Study design | Eligibility criteria                                      | Median/mean age | Three-/5-year OS (%) | Three-year RFS/IHRF (%) | Treatment-related adverse effects |
|-------------|---------------------------------------------|-----|--------------|----------------------------------------------------------|----------------|----------------------|-------------------------|----------------------------------|
| Resection   | 20th Follow-up survey in Japan²              | 7247| retrospective| Solitary 2–3 cm lesions                                   | -              | 79.8/68.3           | 82.0/69.5               | -                               |
| Izumi, et al³ | 150                                        | Prospective | ≤3 lesions, ≤3 cm                                       | 67.4           | -                   | 49.8/-                 | -                               |
| Huang, et al²³ | 115                                       | Prospective | One lesion ≤5 cm, or ≤3 lesions, ≤3 cm                  | 55.9           | 92.2/75.7           | 60.9/-                 | 27.8%²⁶                          |
| Feng, et al²⁴ | 84                                        | Prospective | ≤2 lesions, ≤2 cm                                       | 47             | 74.8/-              | 61.1/-                 | 21.4%²⁷                          |
| RFA         | 20th Follow-up survey in Japan²              | 7387| Retrospective| Solitary 2–3 cm lesions                                   | -              | 78.2/59.6           | 72.7/51.6               | -                               |
| Izumi, et al³ | 151                                        | Prospective | ≤3 lesions, ≤3 cm                                       | 67.1           | -                   | 47.7/-                 | -                               |
| Huang, et al²³ | 115                                       | Prospective | One lesion ≤5 cm, or ≤3 lesions, ≤3 cm                  | 56.6           | 69.6/54.8           | 46.1/-                 | 4.3%²⁸                          |
| Feng, et al²⁴ | 84                                        | Prospective | ≤2 lesions, ≤2 cm                                       | 51             | 67.2/-              | 49.6/-                 | 9.5%²⁹                          |
| Kim, et al²⁵ | 1305                                       | Retrospective | One lesion ≤5 cm, or ≤3 lesions, ≤3 cm                  | 58.4           | 77.9/59.7           | 29/40.5                | 8.3% (2.0%)                      |
| TACE        | 20th Follow-up survey in Japan²              | 9406| Retrospective| solitary                                                 | -              | 61.4/41.1           | -                       | -                               |
| Takayasu, et al²⁹ | 1475                                      | Retrospective | solitary, Child-Pugh A                                  | -              | 73/52               | -                       | -                               |
| SBRT        | Takeda, et al²³                             | 63  | Retrospective | ≤5 cm                                                    | 74             | 73/-                 | -/36                    | 15.9% (G5:0)²⁶                  |
| Durand-Labrunie, et al²⁷ | 43                                        | Prospective | Solitary, 1–6 cm                                       | 72             | 69 (2-year)/        | 48/- (2-year)           | 31% (G5: 0)                     |
| Current study | 34                                         | Prospective | Solitary, ≤5 cm                                        | 73.5           | 77.5/-              | 51.5/63.4              | 11.4% (G5:0)³¹                  |

Abbreviations: OS: overall survival; RFA: radiofrequency ablation; SBRT: stereotactic body radiotherapy; TACE: transcatheter arterial chemoembolization.

²Cumulative OS of local therapy (RFA was included in 89.2%). RFS/IHRF: recurrence-free survival/intrahepatic recurrence-free rate.

²⁵Hepatic failure (1), refractory ascites (13), encapsulated effusion needing percutaneous drainage (5), bile leakage (9), postoperative bleeding (2), and gastrointestinal bleeding (2).

²⁶Pleural effusion (7), pneumonia (3), liver section effusion plus infection (1), wound infection or dehiscence (3), biliary fistula (1), abdominal bleeding (2), pneumothorax or hemothorax (1).

²⁷Gastric perforation (1), procedure-related hemorrhage (2), malignant seeding (1), and hepatic infarction (1).

²⁸Pleural effusion (5), liver abscess (1), and abdominal bleeding (2).

²⁹A total of 8.3% complications were encountered, of these, 20% major complications were identified.

³¹The incidence of grade 3 (CTCAE ver 3.0 or 4.0) or higher toxicities were related with SBRT.
patients receiving surgery or RFA are younger than that if patients receiving SBRT. Because SBRT is essentially an alternative therapy in practice, many patients are elderly and often have comorbidities for which the standard of care is not applicable. Nonetheless, the excellent OS associated with SBRT noted in this study seems to be attributed to good outcomes such as the LC of 90%, and mild toxicities.

There is one notable ongoing phase III trial being conducted in China (NCT03898921). Starting in 2019, they are aiming to compare RFA and SBRT for previously untreated small HCC (solitary tumor ≤ 5.0 cm without vascular invasion), expecting to accrue 270 participants with a primary endpoint of 3-year OS rate. If the study could be successfully completed, the results may add an important evidence to be considered in the clinical guidelines for HCC.

In addition to the treatment outcomes, many factors, such as the degree of invasiveness, quality of life, or cost, influence the decision making. It is ideal to have multiple options for the patient. For the very early stage cases in the BCLC staging system, surgery or ablation is recommended as a curative local therapy, without a clear evidence of superiority for either therapies. To prospectively compare the efficacy of both modalities as the first-line approach to primary HCC, a multicenter randomized controlled trial comparing surgery with RFA was conducted between 2006 and 2015 (SURF trial) in Japan. A total of 301 patients were analyzed with a median follow-up of 5 years. According to the result reported in 2019, the 3-year RFS was comparable to each other: 49.8% versus 47.7%, respectively (p = 0.793). If OS rates were also comparable, RFA might be preferred because of it being less invasive, sustaining a better quality of life, or costing less. Likewise, if the outcome of SBRT is comparable to that of other curative treatments, it may be an advantageous treatment for the same reasons.

Without existing data comparing SBRT with other treatments directly, there are few papers that attempted propensity score matching analyses (PSM). Regarding resection and SBRT, Su et al. compared the clinical outcomes of patients who underwent resection (n = 35) and SBRT (n = 82) for one or two HCCs ≤ 5 cm. The 5-year OS rates of resection (69.2%) and SBRT (74.3%) were comparable after PSM (p = 0.405). With respect to TACE and SBRT, Sapir et al. compared outcomes in patients with one to two tumors who underwent TACE to 114 tumors (in 84 patients) or SBRT to 173 tumors (in 125 patients) with PSM. The 2-year LC proportion favored SBRT (91%) compared to TACE (23%) (P < 0.001). A meta-analysis also showed better OS with SBRT compared to TACE alone. Although the result of our study did not meet the primary endpoint due to early study closure, the present study, which showed good LC and OS of SBRT, may also support these reports. Regarding comparisons between RFA and SBRT, four studies reported that SBRT revealed equivalent or superior LC compared to that of RFA among five studies. Among them, three studies with closely matching baseline liver function scores, showed that the OS was similar between RFA and SBRT.

Since SBRT is commonly indicated for those who are not eligible for percutaneous ablation, patients and tumor characteristics cannot be inevitably well-matched. Patients treated with salvage therapy or those with larger tumors or tumors located close to the vessels, are not balanced in PSM studies, and are often treated with SBRT. Factors that cannot be matched by PSM are the reasons why randomized trials are difficult to complete yet they are the very areas where SBRT will have greater significance in clinical practice. Other SBRT-preferable (ablation-unpreferable) features may include those near the surface of the liver, invisible on ultrasound, bleeding tendency, low platelet counts, patients taking anticoagulant agent, patients requiring dialysis, or those who are not responding TACE. For those patients, SBRT will have greater significance in clinical practice. In other words, RFA, surgery, and SBRT are not a matter of superiority or inferiority, but rather complement each other. Just as if patients with early stage lung cancer had many effective options which improved the overall outcome of patients, the same might be true for HCC. Without existing data comparing SBRT with other treatments directly, there are few papers that attempted propensity score matching analyses (PSM). Regarding resection and SBRT, Su et al. compared the clinical outcomes of patients who underwent resection (n = 35) and SBRT (n = 82) for one or two HCCs ≤ 5 cm. The 5-year OS rates of resection (69.2%) and SBRT (74.3%) were comparable after PSM (p = 0.405). With respect to TACE and SBRT, Sapir et al. compared outcomes in patients with one to two tumors who underwent TACE to 114 tumors (in 84 patients) or SBRT to 173 tumors (in 125 patients) with PSM. The 2-year LC proportion favored SBRT (91%) compared to TACE (23%) (P < 0.001). A meta-analysis also showed better OS with SBRT compared to TACE alone. Although the result of our study did not meet the primary endpoint due to early study closure, the present study, which showed good LC and OS of SBRT, may also support these reports. Regarding comparisons between RFA and SBRT, four studies reported that SBRT revealed equivalent or superior LC compared to that of RFA among five studies. Among them, three studies with closely matching baseline liver function scores, showed that the OS was similar between RFA and SBRT.

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Limitations of the current study include early study closure and small number of patients enrolled and short follow-up period. Although the accrual target was set to 60 patients, the limited accrual was attributed to the fact that SBRT was not the first-line treatment for patients with untreated HCC. Nonetheless, the good OS, exceeding the expectation in the current study, compensates for the poor patient accrual. In this study, TAE with only lipiodol was allowed as a target maker, but its therapeutic effect cannot be completely ignored. Nevertheless, the small number of patients using TAE (four patients) may have little impact on OS as primary endpoint. Another strength of this study is a well-monitored and multiinstitutional design with detailed data on adverse events. The current trial will meanwhile play a significant role because it provided solid data that SBRT can serve as a less invasive and effective treatment alternative for patients unfit for surgery or RFA.

CONCLUSIONS

This study showed acceptably low incidence of SBRT-related toxicities. Although definitive conclusions cannot be drawn because of early study closure, the OS values comparable to other local therapies were very promising. Further studies to define patients who are eligible for each curative local modality are needed in order for radiotherapy to be listed as one of the recommended local treatment modalities for early HCC in the guidelines.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest related to this manuscript.

ORCID

Noria Katoh  https://orcid.org/0000-0003-3959-2114
Satoshi Ishikura  https://orcid.org/0000-0002-6480-8418

REFERENCES

1. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.

2. Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shinya S, et al. Report of the 20th Nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res. 2020;50:15–46.

3. Izumi N, Hasegawa K, Nishioka Y, Takayama T, Yamanaka N, Kudo M, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial). ASCO 2019 annual meeting abstract #4022.

4. Wahl DR, Stenmark MH, Tao Y, Poliom EL, Caoli EM, Lawrence TS, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol. 2016;34:452–9.

5. NCCN clinical practice guidelines in Oncology [NCCN Guidelines®] hepatobiliary cancers ver. 3. 2019 [homepage on the internet]. Fort Washington: National Comprehensive Cancer Network®; [updated 2019 Aug 1; cited 2019 Oct 28]. https://www.nccn.orgprofessionals/physician_gls/pdf/hepatobiliary.pdf

6. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tecto AJ, Zook J, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011;81:e447–53.

7. Kang JK, Kim MS, Cho CK, Yang AM, Yoo HJ, Kim JH, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete trans arterial chemoembolization. Cancer. 2012;118:5424–31.

8. Takeda A, Sanuki N, Tsurugai Y, Iwabuchi S, Matsunaga K, Ebinuma H, et al. Phase 2 study of stereotactic body radiotherapy and optional trans arterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. Cancer. 2016;122:2041–9.

9. Sanuki N, Takeda A, Oku Y, Mizuno T, Aoki Y, Eriguchi Y, et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. Acta Oncol. 2014;53:399–404.

10. Kubo K, Kimura T, Aikata H, Takahashi S, Takeuchi Y, Takahashi I, et al. Long-term outcome of stereotactic body radiotherapy for patients with small hepatocellular carcinoma. Hepatol Res. 2018;48:701–7.

11. Marrero JA, Kell LM, Sirlin C, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology. 2018;68:723–50.

12. Lasley FD, Mannina EM, Johnson CS, Perkins SM, Althouse S, Maluccio M, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. Pract Radiat Oncol. 2015;5:e443–449.

13. Kim JW, Kim DY, Han HK, Seong J. Phase I/II trial of helical IMRT-based stereotactic body radiotherapy for hepatocellular carcinoma. Dig Liver Dis. 2019;51:445–51.

14. Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RKS, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31:1631–9.

15. Jang W, Bae SH, Kim MS, Han CJ, Park SC, Kim SB, et al. A phase 2 multicenter study of stereotactic body radiotherapy for hepatocellular carcinoma: safety and efficacy. Cancer. 2020;126:363–72.

16. van’t Riet A, Mak AC, Moerland MA, Elders LH, van der Zee WA. Conformal number to quantify the degree of conformality in brachytherapy and external beam irradiation: application to the prostate. Int J Radiat Oncol Biol Phys. 1997;37:731–6.

17. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.

18. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29–41.

19. Eriguchi T, Takeda A, Oku Y, Ishikura S, Kimura T, Ozawa S, et al. Multi-institutional comparison of treatment planning using stereotactic ablative body radiotherapy for hepatocellular carcinoma – benchmark for a prospective multi-institutional study. Radiat Oncol. 2013;8:113.

20. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res. 2019;49:1109–13.

21. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;31:317–70.

22. Takeda A, Sanuki N, Eriguchi T, Kobayashi T, Iwabuchi S, Matsunaga K, et al. Stereotactic ablative body radiotherapy for previously untreated solitary hepatocellular carcinoma. J Gastroenterol Hepatol. 2014;29:372–9.

23. Huang J, Lvnan Y, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252:903–12.

24. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57:794–802.

25. Kim YS, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. J Hepatol. 2013;58:89–97.

26. European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56:908–43.

27. Durand-Labrunie J, Baumann AS, Ayav A, Laurent V, Boleslawski E, Cattan S, et al. Curative irradiation treatment of hepatocellular carcinoma: a multicenter Phase 2 trial. Int J Radiat Oncol Biol Phys. 2020;107:116–25.

28. Miyayama S, Matsui O, Yamashiro M, Ryu Y, Kaito K, Ozaki K, et al. Ultrasound-selective transcatheter arterial chemoembolization with a 2-F tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol. 2007;18:365–76.

29. Takayasu K, Arii S, Kudo M, Ichida T, Matsui O, Izumi N, et al. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol. 2012;56:886–92.

30. Su TS, Liang P, Liang J, Lu HZ, Jiang HY, Cheng T, et al. Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2017;98:639–46.

31. Spair E, Tao Y, Schipper MJ, Bazzi L, Novelli PM, Devlin P, et al. Stereotactic body radiation therapy as an alternative to trans arterial chemoembolization for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2018;100:122–30.
32. Huo RY, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma. A systematic review and meta-analysis. *JAMA Oncol.* 2015;6:756–65.

33. Hara K, Takeda A, Tsurugai Y, Saigusa Y, Sanuki N, Eriguchi T, et al. Radiotherapy for Hepatocellular carcinoma results in comparable survival to radiofrequency ablation: a propensity score analysis. *Hepatology.* 2019:0:1–13.

34. Rajyaguru DJ, Borgert AJ, Smith AL, Thomes RM, Conway PD, Halfdanarson TR, et al. Radiofrequency ablation versus stereotactic body radiotherapy for localized hepatocellular carcinoma in nonsurgically managed patients: analysis of the National Cancer Database. *J Clin Oncol.* 2018;36:600–8.

35. Kim N, Cheng J, Jung I, Liang JD, Shih YL, Huang WY, et al. Stereotactic body radiation therapy vs. radiofrequency ablation in Asian patients with hepatocellular carcinoma. *J Hepatol.* 2020;73:121-129.

36. Brunelli A. It is not just about surgery versus stereotactic ablative radiotherapy, it is about curing as many patients with lung cancer as possible. *J Thorac Cardiovasc Surg.* 2018;156:1247-8.

37. Bertolaccini L, Spaggiari L. Should we use the Olympic spirit in the controversy between surgery and stereotactic ablative radiotherapy in operable early stage not small cell lung cancer? *Ann Thorac Surg.* 2020;110:235.

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