Original Article

Long-term outcome of stereotactic body radiotherapy for patients with small hepatocellular carcinoma

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Aim: To evaluate the long-term outcome of stereotactic body radiotherapy in patients with small hepatocellular carcinoma who were ineligible for resection or ablation therapies.

Methods: A total of 65 patients with 74 hepatocellular carcinomas (median tumor size 16 mm) were enrolled in the present study. They were treated with the prescribed dose of 48 Gy in four fractions at the isocenter. We extended the observation period and analyzed long-term outcomes, including overall survival, progression-free survival, local control, and various prognostic factors, in these patients.

Results: The median follow-up period was 41 months for all patients and 62 months for surviving patients. The 3- and 5-year overall survival rates were 56.3% (95% confidence interval, 44.1–68.5%) and 41.4% (95% confidence interval, 28.7–54.1%), respectively. The 3- and 5-year progression-free survival rates were 25.4% (95% confidence interval, 14.0–36.8%) and 10.6% (95% confidence interval, 1.5–19.8%), respectively. The 3- and 5-year local control rates were both 100% (95% confidence interval 100%). Liver toxicities exceeding grade 3 were observed in 15 patients (23.1%). The proportion of patients who had grade ≥3 toxicities did not increase. Adverse effects (grade ≤2) presented as significant prognostic factors of overall survival, while TNM stage (T1N0M0) was a significant prognostic factor of progression-free survival after multivariate analysis.

Conclusions: Stereotactic body radiotherapy was effective for patients with small hepatocellular carcinomas who were ineligible for resection or ablation therapies. The incidence of grade ≥3 adverse effects did not increase, even after longer follow-up times.

Key words: hepatocellular carcinoma, stereotactic body radiotherapy, treatment outcome

INTRODUCTION

Liver cancer, of which approximately 70–90% is hepatocellular carcinoma (HCC), is the fifth leading cause of Japanese cancer mortality.1,2 Patients with early-stage HCC are treated by resection, liver transplantation, or ablation, such as radiofrequency ablation (RFA). The treatment of HCC is dependent not only on the extent of the tumor, but also on the level of underlying hepatic dysfunction.3 In patients for whom these therapies are not suitable, transarterial chemoembolization (TACE) is recommended.3–5 TACE is widely used and is reported to be effective in patients with any type of HCC, regardless of tumor size, location, or number.6,7 However, in a meta-analysis of TACE alone in patients with inoperable HCC, Marelli et al. reported a median response rate of 38%, and median complete response and partial response rates of 0% (range, 0–35%) and 30% (range, 3–62%), respectively. These results indicate that local control after TACE is unsatisfactory.8

Stereotactic body radiotherapy (SBRT) uses highly conformal, multiple non-coplanar beams for precise delivery of high doses per fraction to focal HCC without increasing radiation-induced liver damage and can be applied to elderly patients with poor performance status. SBRT is practical even for lesions that are ineligible for resection or RFA; for example, lesions located near a central portal...
area, adjacent to great vessels, or to the biliary system.9 SBRT has become a treatment option for patients with small HCC who are ineligible for surgery, transplantation, or RFA.4 Several studies have reported good outcomes of SBRT for treatment of HCC with or without TACE.10–15 However, the follow-up duration of these studies was 17.0–31.4 months, and only a few studies have described the long-term outcome of SBRT for HCC;16,17 hence the long-term outcome of SBRT treatment remains unclear. According to the latest Barcelona Clinic Liver Cancer (BCLC) strategy, SBRT is not a first-line treatment, because the survival benefit has not been proven.18,19

We previously described the efficacy and safety of SBRT in 65 patients with 74 HCC who were ineligible for resection or ablation therapies and reported a median follow-up period of 26 months (29 months for survivors). The 2-year overall survival (OS), progression-free survival (PFS), and local control (LC) rates were 76.0% (95% confidence interval [CI], 65.4–86.7%), 40.0% (95% CI, 27.6–52.3%), and 100% (95% CI, 100%), respectively.20

In the present study, we aimed to extend the follow-up period and analyze the long-term outcomes, such as OS, PFS, LC, treatment-related toxicities, and various prognostic factors, in these same patients.

METHODS

Patients

From December 2008 to April 2013, 77 patients (93 tumors) who met the inclusion criteria received SBRT at Hiroshima University Hospital. The details of the criteria were previously reported.20 In principle, the patients’ Child–Turcotte–Pugh (CTP) class was A or B, they had <3 HCC nodules with the longest diameter <50 mm per lesion, they presented with comorbidities preventing them from tolerating surgery or RFA, or they were considered difficult or refused these therapies. We classified the tumor–node–metastasis (TNM) stage (UICC stage 7th edition; International Union Against Cancer) and BCLC stage at the time of initiating SBRT. The study protocol was approved by the Human Ethics Review Committee of Hiroshima University, and a signed consent form was obtained from each patient.

Treatment procedure

Before SBRT, patients underwent TACE with iodized oil (Lipiodol; Guerbet Japan, Tokyo, Japan), if they agreed. A coaxial microcatheter was selectively inserted into the hepatic feeding artery of a segment or subsegment containing the target tumor. Anticancer chemotherapies, such as cisplatin (Randa; Nippon Kayaku, Tokyo, Japan; 7–70 mg/bodyweight at a concentration of 10 mg/mL) or miriplatin (Miriplatin Hydrate; Dainippon Sumitomo Pharma, Tokyo, Japan; 20–80 mg/bodyweight at a concentration of 20 mg/mL) were mixed with iodized oil and administered by injecting the drug into the hepatic artery that fed a target tumor segment or subsegment. A small amount of gelatin sponge particles was used to induce embolization until the flow in the feeding artery was markedly decreased.

SBRT was carried out within 3 months after TACE. SBRT was administered even if complete response was accomplished by TACE, because the long-term accumulation of lipiodol was not enough even in these cases. Respiratory motion was coordinated by voluntary breath-holding at the end inspiratory phase with Absches (APEX Medical, Tokyo, Japan), a device that allows patients to control their chest and abdominal respiratory motion. For simulations, dynamic computed tomography (CT) scans (Lightspeed QX/I; GE Medical Systems, Waukesha, WI, USA), including the non-contrast enhancement, arterial, portal, and venous phases, were carried out by administering a bolus injection of non-ionic iodinated contrast material (100 mL at a rate of 3 mL/s). Arterial phase CT volume data were transferred to a 3-D treatment planning system (Pinnacle3 version 9.0; Phillips Medical Systems, Fitchburg, WI, USA). The gross tumor volume was defined as the tumor volume containing the remains of iodized oil from TACE and early enhancement in the arterial phase of dynamic CT. The clinical target volume margin was usually defined as 0–5 mm around the gross tumor volume. Typically, a planning target volume margin of 5–8 mm was added. A total dose of 48 Gy in four fractions at the isocenter was prescribed for peripherally located HCC. Photon beams of 6–10 MV were delivered from a linear accelerator (CLINAC 2300 C/D or iX; Varian Medical Systems, Palo Alto, CA, USA).

The SBRT dose and fractionation schedule were selected depending on tumor location. A total dose of 48 Gy in four fractions was selected for peripherally located HCC, and 60 Gy in eight fractions was selected for centrally located HCC that was within 5 mm of the major vessels, such as the aorta, portal vein, and inferior vena cava. For HCC that was adjacent to the gastrointestinal tract, a decreased dose/fractionation was selected to maintain dose constraints of the gastrointestinal tract (30 Gy in four fractions of 21 cc).

Evaluation

All patients were examined and underwent follow-up dynamic CT or magnetic resonance imaging every 3–6 months after SBRT completion. Tumor responses were...
assessed according to the modified Response Evaluation Criteria in Solid Tumors.21 Local tumor progression was defined as progressive disease on the modified Response Evaluation Criteria in Solid Tumors, and local control was defined as free of local progression. Treatment-related toxicities were evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0. Levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, platelets, and ascites were evaluated for 1 year after SBRT, because they were strongly affected by the progress of HCC, cirrhosis, and/or treatments for recurrent lesions after SBRT. Portal vein thrombosis, bile duct stenosis, gastrointestinal disorders, and ulcers were evaluated without limiting the period. After SBRT, we carefully checked the irradiated area and evaluated patients for the presence of SBRT-induced toxicities.

**Statistical analysis**

Univariate analyses using the Mantel–Haenszel χ2-test or Student’s t-test and multivariate analyses using logistic regression were carried out to determine the statistical significance of differences in responses. The Kaplan–Meier method was used to calculate the OS, PFS, and LC rates. OS was calculated from the starting date of SBRT until the date of the final follow-up or death. PFS was estimated from the starting date of SBRT until the date of extra- and/or intrahepatic disease progression or recurrence. Ekusen-Toukei 2015 (version 1.02; Social Survey Research Information Co., Ltd., Tokyo, Japan) was used to carry out all statistical analyses. Statistical significance was defined as P < 0.05.

**RESULTS**

**Patients**

OF THE 77 patients with 93 tumors who underwent SBRT, 65 patients with 74 lesions who received 48 Gy in four fractions at the isocenter were analyzed. A total of 12 patients with 19 lesions, including nine with 11 centrally located HCC and three with eight lesions who did not meet dose constraints for gastrointestinal tract exposure, were excluded from analysis because of differences in the prescribed dose. The details of patient characteristics were previously reported.20 A total of 44 men and 21 women, aged between 49 and 90 years (median 73 years), were included in this study. Tumor diameters ranged from 5 to 47 mm (median 16 mm); 56 cases were CTP class A and nine were CTP class B; 37 cases were BCLC stage 0 and 28 were BCLC stage A. A total of 52 patients (52/65; 80%) were treated previously. Of these 52 patients, 47 received TACE (24 patients; TACE alone), 29 underwent surgery, and 16 were treated with RFA.

Before SBRT, 60 patients with 68 HCC had undergone TACE with iodized oil. The median time interval between TACE and SBRT was 1 month. A total of 13 patients (13/65; 20%) underwent TACE after SBRT within 1–3 months without any other previous therapies, such as surgery or ablative therapies.

The median follow-up period at the time of evaluation was 41 months (range, 3–79 months). The median follow-up period for survivors was 62 months (range, 24–79 months). The follow-up period in survivors was extended by almost 3 years compared with the previous study.

**Treatment outcomes**

Figure 1 shows the OS, PFS, and LC rates compared with those in the previous study. During the follow-up period, 39 of the 65 patients died. The cause of death was cancer progression in 25 patients, hepatic failure in three, a ruptured esophageal varix in one, and liver-unrelated causes in 10.

The 3- and 5-year OS rates were 56.3% (95% CI, 44.1–68.5%) and 41.4% (95% CI, 28.7–54.1%), respectively. The 3- and 5-year PFS rates were 25.4% (95% CI, 14.0–36.8%) and 10.6% (95% CI, 1.5–19.8%), respectively. The 3- and 5-year LC rates were both 100% (95% CI, 100%).

In this study, all disease recurrence was recorded in 51 patients, and intrahepatic recurrence occurred in 48 patients (94.1%). A total of 33 patients who experienced first intrahepatic recurrence after SBRT received TACE (19 patients; TACE only); six patients underwent surgery, one patient underwent RFA, and 10 patients received SBRT after TACE.

**Treatment-related toxicities**

Liver toxicities exceeding grade 3 were observed in 15 patients (23.1%). Grade ≥3 adverse effects did not increase, even after longer follow-up times. Table 1 shows the baseline and post-SBRT liver toxicities that exceed those of grade 3. The most common event was thrombocytopenia (10 patients, 15.4%), but five patients presented with grade 3 thrombocytopenia before SBRT. Grade 3 elevated total bilirubin levels were observed in two patients (3.1%). Grade 3 elevated aspartate aminotransferase or alanine aminotransferase levels were observed in two patients (3.1%). Grade 3 ascites were observed in four patients (6.2%). Grade 3 portal vein thrombosis was observed in one patient (1.5%); it was diagnosed 7 months later and anticoagulation was initiated. Grade 1 portal vein...
thrombosis was observed in another patient (1.5%) and was diagnosed 11 months after SBRT. Bile duct stenosis was observed in two patients (3.1%), who progressed to grades 1 and 2. Grade 2 bile duct stenosis was diagnosed as cholangitis 8 months after SBRT and treated with an antibacterial agent. Grade 1 bile duct stenosis was observed 44 months after SBRT. No patients developed gastrointestinal disorders or ulcers.

Prognostic factors

Table 2 shows the univariate and multivariate analyses of OS and PFS. TNM stage (T1N0M0) and adverse effects (grade ≤2) were significant prognostic factors of OS in the univariate analysis, while adverse effects remained significant in multivariate analysis. TNM stage was not significant in multivariate analysis. Figure 2 shows the comparison between OS in 50 patients with grade ≤2 adverse effects after SBRT and 15 patients with grade ≥3 adverse effects. BCLC stage (stage 0) and TNM stage (T1N0M0) were significant prognostic factors of PFS in the univariate analysis, while TNM stage (T1N0M0) remained significant in multivariate analysis. BCLC stage was not significant in the multivariate analysis. Figure 3 shows the comparison between PFS in 51 patients with T1N0M0 disease and 14 patients with T2N0M0 disease. In our previous report, CTP (class A), TNM stage (T1N0M0), and adverse effects (grade ≤2) were the significant prognostic factors of OS, and no significant prognostic factor of PFS was identified in the multivariate analyses.20 In this study, CTP (class A) and TNM stage (T1N0M0) were not significant.

Discussion

In several reports on the results of HCC treatment with SBRT, the median follow-up duration was close to 30 months and the authors assessed the outcomes at 3 years.11–14,16,17 The LC rate was approximately 90% at 3 years, which was an excellent result. The OS rate was approximately 60–80% and the PFS rate was 30–50% at 3 years. However, radiation therapy is not considered an option for the treatment of HCC in the BCLC guidelines, and the reason might be the uncertainty of the long-term outcomes. To address this concern, we extended the follow-up period and analyzed the long-term outcomes at 5 years. To the best of our knowledge, this is the longest follow-up duration reported for SBRT treatment of small HCC.

First, we refer to the long-term LC, OS, and PFS rates. Even with long-term observation, the excellent LC rate did not change. In contrast, the 5-year OS rate was not as high compared with RFA or surgery, which provide excellent results for single lesions ≤2 cm and 5-year OS rates of 60–80%.22,23 We believe the most important reason for the unfavorable OS of SBRT when compared with other modalities including surgery and RFA, could be attributed to the fact that the majority of our patients (80%) had been treated with other therapies, such as surgery, RFA, and TACE, before their enrollment in this study. Thus,
the median duration of these prior treatments of 23 months (range, 0–144 months) might have influenced our results.

Second, we refer to the adverse effects. The proportion of patients who presented with grade ≥3 toxicities did not increase. However, it is difficult to distinguish SBRT-related toxicities from toxicities that are related to liver disease and cirrhosis or treatments for recurrent lesions after SBRT. In the present study, 48 patients experienced intrahepatic recurrence and underwent other treatments, such as TACE, resection, and RFA. Therefore, we evaluated levels of total bilirubin, alanine aminotransferase, aspartate

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 1 Grade 3 or 4 treatment-related toxicities

|                          | Baseline | 0–6 months | 6–12 months | After 1 year |
|--------------------------|----------|------------|-------------|--------------|
|                          | Grade 3  | Grade 4    | Grade 3     | Grade 4      | Grade 3     | Grade 4 |
| Elevated total bilirubin| 0        | 0          | 2           | 0            | -           | -       |
| Elevated AST/ALT         | 0        | 0          | 2           | 0            | -           | -       |
| Asites                   | 0        | 0          | 2           | 0            | -           | -       |
| Thrombocytopenia         | 5        | 0          | 9           | 0            | -           | -       |
| Bile duct stenosis       | 0        | 0          | 0           | 0            | 0           | 0       |
| Portal vein thrombosis   | 0        | 0          | 0           | 0            | (Grade 1: 1)| (Grade 1: 1, Grade 2: 1) |
| Gastrointestinal disorders| 0       | 0          | 0           | 0            | 0           | 0       |

Table 2 Prognostic factors; univariate analysis and multivariate analysis

|                          | n (%)  | 5-year OS (%) | UVA P | MVA P | 3-year PFS (%) | UVA P | MVA P |
|--------------------------|--------|---------------|-------|-------|----------------|-------|-------|
| Sex                      | Male   | 67.7          | 45.3  | 0.6963 | -              | 33.9  | 0.1885 |
|                          | Female | 32.3          | 34.0  | -      | -              | 20.3  | -      |
| Age (years)              | ≥70    | 61.5          | 36.8  | 0.9827 | -              | 27.0  | 0.8245 |
|                          | <70    | 38.5          | 47.7  | -      | -              | 24.2  | -      |
| CTP class                | A      | 86.2          | 44.8  | 0.0773 | -              | 27.7  | 0.3453 |
|                          | B      | 13.8          | 22.2  | -      | -              | 12.5  | -      |
| Viral infection          | HBV or HCV | 90.8       | 44.8  | 0.2238 | -              | 22.4  | 0.0533 |
|                          | NBNC   | 9.2           | 16.7  | -      | -              | 50.0  | -      |
| BCLC stage at treatment  | 0      | 56.9          | 51.0  | 0.0901 | -              | 30.2  | 0.0124 |
|                          | A      | 43.1          | 28.4  | -      | -              | 19.9  | -      |
| TNM stage at treatment   | T1N0M0 | 78.5          | 47.0  | 0.0362 | 0.1897         | 29.7  | 0.0003 |
|                          | T2N0M0 | 21.5          | 21.4  | -      | -              | 9.5   | 0.0008 |
| Greatest tumor dimensions| ≥20 mm | 38.5          | 26.9  | 0.1085 | -              | 21.8  | 0.2340 |
|                          | <20 mm | 61.5          | 50.7  | -      | -              | 28.1  | -      |
| GTV                      | ≥10 cc | 9.2           | 16.7  | 0.3668 | -              | 16.7  | 0.1199 |
|                          | <10 cc | 90.8          | 44.4  | -      | -              | 26.5  | -      |
| Adverse effects          | ≥Grade 3 | 23.1         | 13.3  | 0.0006 | 0.0049         | 23.8  | 0.6922 |
|                          | ≤Grade 2 | 76.9         | 50.6  | -      | -              | 26.5  | -      |
| Diagnosis history        | Initial| 20            | 26.6  | 0.7165 | -              | 16.8  | 0.3741 |
|                          | Recurrence | 80        | 44.2  | -      | -              | 25.7  | -      |

BCLC, Barcelona Clinic Liver Cancer; CTP, Child–Turcotte–Pugh; GTV, gross tumor volume; HBV, hepatitis B virus; HCV, hepatitis C virus; MVA, multivariate analysis; NBNC, non-hepatitis B/non-hepatitis C; OS, overall survival; PFS, progression-free survival; TACE, transcatheter arterial chemoembolization; UVA, univariate analysis.
aminotransferase, platelets, and ascites for 1 year after SBRT. Portal vein thrombosis, bile duct stenosis, gastrointestinal disorders, and ulcers were evaluated without limiting the period. In the long-term observation, no patients developed gastrointestinal disorders or ulcers, and only grade 1 bile duct stenosis was observed 44 months after SBRT. SBRT appeared to be relatively safe for patients with small HCC.

Third, we refer to prognostic factors. Adverse effects (grade $\leq 2$) were significant prognostic factors of OS in the multivariate analysis. Several prognostic factors were suggested as possibly influencing the survival, performance status, alpha fetoprotein levels, tumor volume, and CTP class. In this study, CTP (class A) was not a significant prognostic factor. However, the incidence of grade $\geq 3$ toxicity was higher in CTP class B than in class A ($P = 0.0127$), and an association between pretreatment CTP scores and the development of toxicity has been observed by several other studies. Therefore, liver function before SBRT was an important factor for longer OS. There were few prognostic factors for PFS after SBRT. In this study, TNM stage (T1N0M0) was a significant prognostic factor for PFS in the multivariate analysis, and intrahepatic recurrence was more frequent in patients with T2N0M0 disease ($P = 0.0020$). Poon et al. evaluated the long-term results of treatment and prognostic factors in patients with intrahepatic recurrence after curative resection of HCC. They found that intrahepatic recurrence was significantly associated with advanced TNM staging. In the case of SBRT for HCC, vascular invasion or multiple tumors may increase intrahepatic recurrence rates.

The present study will help to show the long-term efficacy of SBRT. However, this study has several limitations, including a retrospective single-center study and patients’ backgrounds excluding centrally located HCC. This may cause a selection bias, especially in the frequency of gastrointestinal disorder and portal vein thrombosis. In addition, most patients in this study underwent resection and RFA as initial therapies, which may have confused the results, including the OS and PFS rates. To compare with surgery or RFA, a prospective study of SBRT in HCC is necessary. In Japan, the STRSPH study, a multicenter prospective study of SBRT for untreated solitary primary HCC, is ongoing. If the efficacy and safety of SBRT are proved, it will be added as a treatment option that is comparable with resection or RFA for patients who were considered unfit or refused these other therapies.

In conclusion, the clinical results reported from these same patients demonstrate that SBRT appears to be effective and relatively safe, even after longer follow-up times, for patients with small HCC who were ineligible for resection or ablation therapies.

ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (grant no. 17 K10478).

REFERENCES

1 National Cancer Center, Center for Cancer Control and Information Services. Latest cancer statistics 2014. Available from URL: http://ganjoho.jp/reg_stat/statistics/stat/summary.html.
2 Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87–108.
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Thomas MB, Jaffe D, Choti MM et al. Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol 2010; 28: 3994–4005.

National Comprehensive Cancer Network Inc NCCN clinical practice guidelines in Oncology. Hepatobiliary Cancers version 2. 2016. Available from URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#hepatobiliary.

European Association for the Study of the Liver and National Comprehensive Cancer Network Inc NCCN clinical practice guidelines in Oncology. Hepatobiliary Cancers version 2. 2016. Available from URL: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#hepatobiliary.

Miyayama S, Matsui O, Yamashiro M et al. Ultraselctive transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of portal vein with iodized oil. J Vasc Interv Radiol 2007; 18: 365–76.

Takayasu K, Arii S, Kudo M et al. Superselective transcatheter chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. J Hepatol 2012; 56: 886–92.

Marelli L, Stigliano R, Triantos C et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007; 30: 6–25.

Sanuki N, Takeda A, Kunieda E. Role of stereotactic body radiation therapy for hepatocellular carcinoma. World J Gastroenterol 2014; 20: 3100–11.

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

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.

Kwon JH, Bae SH, Kim JY et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. BMC Cancer 2010; 10: 475. Cited 3 Sep 2010 Available from URL: https://www.ncbi.nlm.nih.gov/pubmed/20813065.

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: 5424–31.

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

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

Takeda A, Sanuki N, Tsurugai Y et al. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. Cancer 2016; 122: 2041–9.

Su TS, Liang P, Lu HZ 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. https://doi.org/10.1016/j.ijrobp.2017.02.095.

Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379: 1245–55.

Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016; 150: 835–53.

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: 378–86.

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

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: 82–9.

Roayaie S, Obeidat K, Sposito C et al. Resection of hepatocellular cancer ≤2 cm: results from two western centers. Hepatology 2013; 57: 1426–35.

Poon RT, Fan ST, Lo CM et al. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999; 229: 216–22.