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***Retrospective Study***

**Cyberknife treatment for advanced or terminal stage hepatocellular carcinoma**

Kato H *et al.* Cyberknife treatment for HCC

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**Abstract**

**AIM:** To investigate the safety and efficacy of the Cyberknife treatment for patients with advanced and terminal stage hepatocellular carcinoma.

**METHODS:** Patients with hepatocellular carcinoma and extrahepatic metastasis, vascular, or bile duct invasion were enrolled between May 2011 and June 2015. The Cyberknife was used to treat each lesion. Treatment response scores were based on Response Evaluation Criteria in Solid Tumors v1.1. Transition of tumor markers, including alpha fetoprotein (AFP) and proteins induced by vitamin K absence (PIVKA II) were assessed. Prognostic factors for tumor response and tumor markers were evaluated with Fisher's exact test and a logistic regression model. Survival was evaluated with the Kaplan-Meier method and multivariate analysis was performed using the Cox proportional hazards model.

**RESULTS:** Sixty-five patients with 95 lesions were enrolled. Based on the Barcelona Clinic Liver Cancer (BCLC) classification, all patients were either in advanced or terminal stage. The target lesions were as follows: 52 were bone metastasis; 9, lung metastasis; 7, brain metastasis; 9, portal vein invasion; 4, hepatic vein invasion; 4, bile duct invasion; and 10 were others. Response rate and disease control rate were 34% and 53%, respectively. None of the clinical factors was statistically significant for tumor response. Fiducial marker implantation was associated with better control of both AFP (HR = 0.152; 95%CI: 0.026-0.887; *P =* 0.036) and PIVKAⅡ(HR = 0.035; 95%CI: 0.003-0.342; *P =* 0.004). Median survival time was 9.0 mo (95%CI: 5.0 mo-15.0 mo). Terminal stage (HR = 9.809; 95%CI: 2.589-37.17, *P <* 0.001) and AFP more than 400 ng/mL (HR = 2.548; 95%CI: 1.070-6.068, *P =* 0.035) were associated with worse survival. Radiation dose higher than 30 Gy (HR = 0.274; 95%CI: 0.093-0.7541, *P =* 0.012) was associated with better survival. In the 52 cases of bone metastasis, 36 patients (69%) achieved pain relief. One patient had cerebral bleeding and another patient had esophageal ulcer after treatment.

**CONCLUSION:** The Cyberknife can safely be administered to patients with advanced and terminal stage hepatocellular carcinoma. High AFP levels were associated with worse survival, but a higher radiation dose improved the survival.

**Key words:** Hepatocellular carcinoma; Stereotactic body radiotherapy; Cyberknife; Neoplasm metastasis/therapy; Liver radiotherapy

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**Core tip:** Due to the aging of hepatocellular carcinoma (HCC) patients, a growing number of patients are ineligible for conventional therapy. The Cyberknife® system delivers stereotactic body radiation therapy (SBRT). It enables minimally invasive treatment with large radiation doses. Successful reports of SBRT against liver-confined HCC have been increasing. We found that the Cyberknife can safely be administered even in patients with advanced or terminal stage HCC. Our results revealed that SBRT might have the potential to increase the overall survival for advanced stage HCC patients. High alpha fetoprotein levels were associated with worse survival, but a higher radiation dose improved the survival.

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**INTRODUCTION**

***HCC treatment strategy***

Hepatocellular carcinoma (HCC) is the third cause of cancer related deaths worldwide[1] and is one of the leading causes of death in patients with hepatic cirrhosis[2]. The Barcelona Clinic Liver Cancer (BCLC) classification, which evaluates both tumor stage and patient condition, has been commonly used to determine the course of treatment[3,4]. Based on this staging system, patients with very early and early stage HCC are candidates to curative treatment such as surgery, percutaneous alcohol injection or radiofrequency ablation (RFA). However, less than 30% of patients are eligible for these radical treatments due to advanced disease stage, poor liver function, or other medical complications[5]. For patients with intermediate and advanced staged HCC, transarterial chemoembolization (TACE)[6,7], sorafenib[8], or best supportive care could be treatment options. However, patients remain incurable, and thus, have a poor prognosis. Therefore, less invasive and highly effective treatment options have been expected.

***History of the Cyberknife***

Although HCC is a radiosensitive tumor[9], the use of radiation therapy for HCC has been limited due to the poor tolerance of the whole liver to irradiation. Doses are required to be less than 30–35 Gy, and there is a risk of developing radiation induced liver disease (RILD)[10]. Originally, RILD was defined as having anicteric hepatomegaly, ascites, and elevation of alkaline phosphatase level typically occurring 2–12 mo after therapy[11]. In contrast to this “classic” RILD, “non-classic RILD” has been proposed as well. Patients with underlying chronic liver disease such as cirrhosis and viral hepatitis may present with liver dysfunction, including jaundice or markedly elevated serum transaminases (more than 5 times above the upper normal limit) within 3 mo after the radiation[12]. Over the past two decades, thanks to the advancements in computer and imaging technologies, this weakness has been overwhelmed, and radiation therapy has evolved to be a safe and feasible option for HCC, with RILD rates of less than 5%[13].

Stereotactic body radiotherapy (SBRT) is a technique that enables a delivery of high radiation doses (usually 8–12Gy/fraction) to the tumor with extreme accuracy, while minimizing the damage to normal surrounding tissue in 1–10 fractions. The major advantages are the promising radiobiological efficacy of the administration of such large radiation doses to tumor tissues, the short treatment course achieved by a small number of fractions, and minimally invasive therapy also given to patients with poor performance status. SBRT was initiated in the 1950s for the treatment of intracranial malignancies, and its treatment performance resulted in extremely high local control rates greater than 80%–90%[14]. However, its use in extracranial tumors has been limited because of the movement caused by the respiratory cycle. The Cyberknife® (Accuray Incorporated, Sunnyvale, California, USA) is a robotic image guided system that delivers SBRT, tracks tumors during respiration, and automatically adjusts treatment for any patient movement. The Cyberknife has been used to treat a broad range of tumors throughout the body, including prostate, lung, spine, liver, pancreas, kidney, and others. Nowadays, successful reports of SBRT studies against HCC and other liver tumors have been increasing. Four prospective studies and several retrospective studies have suggested that SBRT can be used safely and this method has been associated with high local control rates, mostly in the range of 70%–100% at 1–2 years[15-37]. However, the studies focusing on patients with advanced or terminal stage HCC are still scarce. We report treatment outcomes of therapy with the Cyberknife for patients with advanced or terminal stage HCC at our institution to clarify its safety and efficacy

**MATERIALS AND METHODS**

***Patients***

Patients with HCC unsuitable for surgery, TACE, RFA, or other therapies were eligible for Cyberknife treatment and were enrolled after careful discussion between the patients and treating physicians. We selected tumors eligible for Cyberknife as follows: intrahepatic tumors invading the hepatic vessels or bile duct without other viable lesions, single extrahepatic tumors, or bone metastases causing pain. In principle, patients with multiple metastases were eligible only for bone lesions.

All the patients submitted a written consent form before the treatment. This retrospective, single-institution study was approved by the institutional research ethics board.

The diagnosis of HCC was based on histological confirmation or a characteristic radiological appearance on dynamic computed tomography (CT) scan or dynamic contrast-enhanced magnetic resonance imaging (MRI) scan. The presence of risk factors, such as cirrhosis, HBV, or HCV infection was also taken into account. For metastatic lesions, we assumed that HCC was the primary tumor if the patient had previously been diagnosed with HCC and had metastasis.

***Treatment***

All patients were treated under hospitalization, except for 4 patients who chose strongly to be treated as outpatient. All patients were treated with the Cyberknife.

Real-time tracking of tumor movements was performed with MultiPlan® (Accuray) treatment planning software and Synchrony® (Accuray) respiratory tracking system. Gold marker was introduced beside the tumor for those who needed respiratory synchronization. For tumors invading the hepatic vessels or bile duct, Visicoil® (Sceti, Medical Labo K. K., Tokyo, Japan) a helical gold linear fiducial marker 0.75 mm in diameter by 5mm in length was implanted percutaneously under ultrasound-guidance near the tumor. For lung metastasis, a spherical fiducial marker 1.5 mm in diameter (Olympus, Tokyo, Japan) was inserted by bronchoscopy.

Patients were immobilized in a vacuum cushion or plastic shell in the treatment position to reduce the motion caused by breathing. A spiral CT scan with and without contrast and slice thickness of 1mm was obtained for planning. MRI was also used for spine or brain lesion planning. The gross tumor volume (GTV) for intrahepatic lesions was defined as the arterial enhancing site with washout on the venous and/or delayed phase CT. The GTV for extrahepatic lesions was defined depending on the characteristic radiologic aspect of metastases. The planned target volume (PTV) for intrahepatic lesions and lung metastases was defined as the GTV with a 2–5 mm margin in all directions. As the lesions inside the lung are especially subject to respiratory movement, margin for these lesions was estimated based on CT scans obtained during both inhale and exhale phases. For spine lesions, the PTV was defined as the GTV with 2 mm margin because these lesions are less subject to respiratory movement. For brain lesions, no margin was applied for the GTV because the surrounding brain tissue is considered critical. A total dose of 8–50 Gy in 1–10 fractions was prescribed to the 80% isodose line (95% PTV coverage) and delivered to the PTV in 1–7 consecutive working days. Dose constraints for organs at risk were applied based on a previous report[38]. .

***Evaluation***

Each patient had a clinical and biological evaluation during and after the completion of the treatment, every 1 to 3 mo afterwards unless they were lost to follow-up, or until death. Patients underwent CT scans 1-3 mo following the completion of SBRT, and radiological follow-up was performed by CT scan or MRI every 3 mo afterwards.

Tumor response was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[39] as follows: complete response (CR), complete disappearance of the irradiated tumor; partial response (PR), > 30% reduction in tumor size; stable disease (SD), < 30% reduction or < 20% increase in tumor size; and progressive disease (PD), > 20% increase in tumor size. Although mRECIST has recently taken place in evaluating treatment response of HCC, RECIST version still seems to be commonly used in terms of evaluating radiotherapy response as seen in previous reports[17,40]. Tumor markers, including alpha fetoprotein (AFP) and proteins induced by vitamin K absence (PIVKA II) were evaluated within in one week prior to the treatment and one month after the treatment. For bone metastases, the efficacy was also evaluated by symptom relief. Response was self-assessed by subjective pain score and was classified in either category: pain relief, exacerbation, or no symptomatic change. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[41]. Dose limiting toxicity (DLT) was any CTCAE grade 4 or 5 hepatic, thrombocytopenic, or GI toxicity occurring within 1 month of SBRT or RILD requiring treatment in the absence of disease progression within 3 months of SBRT.

***Statistical analysis***

Prognostic factors for tumor response and tumor markers were evaluated with Fisher's exact test and a logistic regression model. Survival was evaluated with the Kaplan-Meier method and multivariate analysis with the Cox proportional hazards model. All statistical analyses were performed using the R statistical cmprsk in version 3.2.0. Differences were considered to be statistically significant at *P* < 0.05.

**RESULTS**

***Patients and treatment***

Between May 2011 and June 2015, a total of 65 patients with 95 lesions were treated with SBRT using the Cyberknife system. Fifty-one were male and 14 were female with a median age of 71 (range: 26–93) years. Underlying liver disease was hepatitis C in 35 patients (54%), hepatitis B in 9 patients (14%), and other causes in 21 patients. The patients included in the study had Eastern Cooperative Oncology Group performance score of less or equal to 2, except for 6 patients with a score of 3. Pre-treatment Child-Pugh score ranged from 5A to 8B, except for 2 patient who had 11C and 12C respectively. Based on the BCLC classification of HCC, 59 and 6 patients had advanced and terminal stage disease, respectively. All the patients had previously been treated for HCC. Twenty-four patients received surgery, 28 patients received RFA, 49 patients received TACE, 7 patients received radiation therapy other than SBRT previously. Seven patients with 15 lesions were treated along with sorafenib administration. Six patients had been previously treated with sorafenib but discontinued by its side effects. Other patients were not eligible for sorafenib due to contraindications such as poor liver function or brain metastasis. The composition of the target lesions were as follows: 52 were bone metastasis (mostly spine); 9, lung metastasis; 7, brain metastasis; 9, portal vein invasion; 4, hepatic vein invasion; 4, bile duct invasion; and 10 were others (pleura, cavernous sinus, and lymph node metastases).

For tumors invading the hepatic vessels or bile duct, the median tumor size was 29 (range: 12–54) mm and the median prescribed dose was 35 (range: 28–50) Gy in 3–10 fractions. For extrahepatic lesions, the median tumor size was 23 (range: 10–53) mm and the median prescribed dose was 25 (range: 6–48) Gy in 1–6 fractions.

The median follow-up period was 4.0 (range: 1–33) mo. Of the 65 patients, 35 patients were referred from other institution, and were followed up at the previous hospital after treatment, and 15 of them were lost to follow-up. Treatment was completed in all the patients. The characteristics of the patients are described in Table 1.

***Tumor response***

The efficacy of the therapy was as follows; CR was observed in 7 lesions, PR in 25, SD in 19, PD in 16, and 28 lesions were not evaluated because of patient death or lost to follow-up. Actual tumor responses are shown in Figure 1. The response rate (RR) and disease control rate (DCR) of all lesions were 34% and 53%, respectively. After excluding the unevaluated cases, RR and DCR were 48% and 76%, respectively. For tumors invading the hepatic vessels or bile duct, RR and DCR of evaluated cases were 50% and 80%, respectively. Lesions and treatment outcomes are summarized in Table 2.

Univariate analysis was performed but none of the clinical factors was statistically significant for tumor response (Table 3).

Transition of AFP and PIVKA II levels was available in 53 lesions. Thirty patients (57%) presented a decrease in AFP, and 28 patients (53%) presented a decrease in PIVKA II. In univariate analysis, radiation dose (≥ 30 Gy) and fiducial marker implantation were appeared to be factors associated with both AFP and PIVKAⅡreduction. In multivariate analysis, fiducial marker implantation remained to be associated with better control of both AFP [HR = 0.152; 95%CI: 0.026-0.887, *P =* 0.036) and PIVKAⅡ(HR = 0.035; 95%CI: 0.003- 0.342, *P =* 0.004). Results are shown in Tables 4 and 5.

For the 52 cases of bone metastases, the efficacy of treatment was also assessed in terms of pain control. Thirty-six patients (69%) achieved pain relief, 10 patients had no symptomatic change, 1 patient had worse pain, and 4 patients were not evaluated.

***Overall survival***

At the time of the analysis, 26 patients had died. All of them died of cancer. Overall 1-year survival rate was 49%. Median survival time for all the patients, advanced stage patients, terminal stage patients were 9.0 mo (95%CI: 5.0-15.0), 13.0 mo (95%CI: 7.0-15.0) and 1.0 mo (95%CI: 1.0-NA) respectively. The Kaplan-Meier curve for overall survival is presented in Figure 2. Univariate and multivariate analyses were performed to account for the factors associated with survival. In univariate analysis, AFP (≥ 400 ng/mL), BCLC terminal stage, Child-Pugh score (≥ 7) and radiation dose (< 30 Gy) were appeared to be factors associated with worse survival. In multivariate analysis, BCLC terminal stage (HR = 9.809; 95%CI: 2.589-37.17, *P <* 0.001) and AFP (≥ 400 ng/mL) (HR = 2.548; 95%CI: 1.070-6.068; *P =* 0.035) were associated with worse survival. Radiation dose (≥ 30 Gy) (HR = 0.274; 95%CI: 0.093-0.7541, *P =* 0.012) was associated with improved survival. Prognostic factors associated with overall survival are shown in Table 6.

***Adverse effects***

Overall, the treatments were well tolerated. No patient complained of changes in subjective symptoms, such as abdominal pain, nausea, fatigue, and joint pain, greater or equal to grade 2 toxicity. No hematologic complications, significant liver enzyme elevations, or classic RILD was observed during the treatment.

One patient had a grade 4 cerebral hemorrhage 2 h after radiation to brain metastasis. The patient recovered well after craniotomy and hematoma removal, but died of liver failure 45 d after therapy. This was the second case of hemorrhage that presented on the first day of the SBRT therapy experienced at our institution.

Another patient presented with a grade 2 esophageal ulcer following treatment that resulted in a digestive hemorrhage. For this patient, the treated target was in the hepatic vessels, and CR was achieved in that lesion. The maximum dose that had been irradiated to the esophagus was 31.2 Gy in 4 fractions and occurred 16 days after therapy. The patient recovered well with conservative management, such as proton pump inhibitor, mucoprotective agents, and 5-aminosalicylic acid administration.

**DISCUSSION**

To date, radiation therapy has not been established as a standard therapy for HCC[42]. This modality has not even been included as a treatment option in BCLC staging system. However, a growing number of patients who are not eligible for conventional therapy have been treated with radiation therapy with promising results. Furthermore, this therapy modality can be used not only as curative treatment but also for palliative care.

The treatment of advanced HCC with invasion of the major hepatic vessels or bile duct can be challenging. The majority of available liver-directed therapies are generally contraindicated for such cases. Additionally, these HCC lesions are associated with the worse prognosis for overall survival. Our results showed that RR and DCR for these lesions which were able to follow up were 50% and 80%, respectively. Kang *et al*[43] reported that RR for portal vein tumor thrombosis treated by SBRT alone was 66.7%, and could be improved up to 73.5% if combined with TACE. Compared with these results, our data are almost equivalent. We consider that little difference between them can be partly explained by the higher prescribed dose (median 40.2 Gy) in the previous study compared with our study (median 35 Gy). Previous reports underline a significant relationship between total prescribed dose and local tumor control[10,17,40]. Although our study couldn’t significantly certify the prognostic factors for tumor response, radiation dose (≥ 30 Gy) had a favorable tendency regarding tumor response (OR = 0.266; 95%CI: 0.027-1.370, *P =* 0.119). In terms of overall survival, radiation dose (≥ 30 Gy) and AFP (≥ 400 ng/mL) were significant prognostic factors as in previous reports. Because information regarding optimal treatment indication, doses, and methods remains limited, further studies are required to maximize the efficacy of SBRT.

In our study, all the patients had either advanced or terminal stage disease based on BCLC classification. Remarkably, all of our patients were able to complete the treatment although most of them had poor condition, poor performance status, or other medical complications. This was achieved because SBRT has the advantage of enabling a short treatment course while allowing the administration of a large radiation dose in a small number of fractions.

Furthermore, our patients were mainly composed of those who were not eligible for sorafenib due to its side effects or contraindications such as poor liver function or brain metastasis. Radu *et al*[44] reported that for advanced stage HCC patients, undertreatment results in a decreased survival (3 mo *vs* 4 mo) and overtreatment may increase survival (28 mo *vs* 4 mo) compared with standard therapy. Therefore, SBRT might be a hopeful option for those who are not eligible for other treatment.

To assess the overall disease control, transition of AFP and PIVKA II was evaluated. Thirty-five patients (57%) presented a decrease in AFP, and 28 patients (53%) presented a decrease in PIVKA II. In multivariate analysis, fiducial marker implantation remained to be associated with better control of both AFP and PIVKAⅡ. This was probably because fiducial marker implantation was performed against lesions that are largest burden for patients without other coexisting viable HCC. We assume that the reason why not all patients achieved tumor marker improvement is that there were patients who had other coexistent lesions which were left untreated (escpecially in bone metastases cases). We believe there was a therapeutic effect with respect to the lesions irradiated.

SBRT can also be used for palliative care. In terms of SBRT for bone metastases, 69% of the patients achieved pain relief without complications. We conclude that SBRT can be safely and successfully administered to palliate bone metastasis symptoms.

There are several limitations to this study. Its major limitation was the retrospective design and couldn’t produce the control group. Additionally, this study only involved one institution and our sample size was small. However, from the previous studies, median survival time of BCLC advanced stage and terminal stage are generally reported to be 4-7 mo and 1-3 mo respectively[44-46]. In our study, in spite of some lost to follow-up patients, median survival time for advanced stage and terminal stage were 13.0 mo and 1.0 mo respectively. This result suggests that SBRT might have the potential to increase the overall survival for advanced stage HCC patients, and compares favorably with best supportive care or even with sorafenib (4.2 to 7.9 mo and 6.5 to 10.7 mo, respectively[5,8]), the only other potentially available therapy for these patients. Further prospective studies are expected to define the role of Cyberknife in the management of this disease.

In conclusion, this report is pioneering because it focused on patients with advanced or terminal stage HCC. Our results suggest that the Cyberknife might be less invasive and useful for local tumor control, palliative care and increase survival for those who have no other treatment option.

**COMMENTS**

***Background***

The Cyberknife® system delivers stereotactic body radiation therapy (SBRT). SBRT is a technique that enables a delivery of high radiation doses (usually 8–12 Gy/fraction) to the tumor with extreme accuracy, while minimizing the damage to normal surrounding tissue in 1–10 fractions. The major advantages are the promising radiobiological efficacy of the administration of such large radiation doses to tumor tissues, the short treatment course achieved by a small number of fractions, and minimally invasive therapy also given to patients with poor performance status. Nowadays, successful reports of SBRT studies against hepatocellular carcinoma (HCC) and other liver tumors have suggested that SBRT can be used safely and this method has been associated with high local control rates, mostly in the range of 70%–100% at 1–2 years. The authors report treatment outcomes of therapy with the Cyberknife for patients with advanced or terminal stage HCC at our institution to clarify its safety and efficacy

***Research frontiers***

Most studies published about SBRT for HCC focused only on liver confined tumors. Articles about SBRT for extrahepatic HCC are scarce. The authors present the largest study about Cyberknife treatment for patients with advanced and terminal stage HCC.

***Innovations and breakthroughs***

In this study, the authors found that the Cyberknife can safely be administered even in patients with advanced or terminal stage HCC. Median survival time was 9.0 mo (95%CI: 5.0-15.0 mo). Terminal stage (HR = 9.809; 95%CI: 2.589-37.17, *P <* 0.001) and AFP more than 400 ng/ml (HR = 2.548; 95%CI: 1.070-6.068, *P =* 0.035) were associated with worse survival. Radiation dose higher than 30 Gy (HR = 0.274; 95%CI: 0.093-0.7541, *P =* 0.012) was associated with better survival.

***Applications***

Present results revealed that SBRT might have the potential to increase the overall survival for advanced stage HCC patients. High AFP levels were associated with worse survival, but a higher radiation dose improved the survival.

***Terminology***

Cyberknife system: A non-invasive alternative to surgery for the treatment of both cancerous and non-cancerous tumors anywhere in the body. It delivers beams of high dose radiation to tumors with extreme accuracy. SBRT: A technique that enables a delivery of high radiation doses (usually 8–12 Gy/fraction) to the tumor with extreme accuracy, while minimizing the damage to normal surrounding tissue in 1–10 fractions.

***Peer-review***

This is a study describing the treatment outcome of CyberKnife SBRT to primary or metastatic lesions in patients with advanced or terminal hepatocellular carcinoma according to Barcelona Clinic Liver Cancer classification.

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**Figure 1 Tumor responses treated with Cyberknife.** A1: CT scan of 59 year-old male with portal vein tumor thrombosis. Tumor is invading portal vein from main trunk to 1st branch. Tumor diameter was 46 mm. Fiducial marker was implanted nearby;A2: Three months after irradiation of 35 Gy/5 fractions. Portal vein tumor thrombosis disappeared completely and achieved CR;B1: CT scan of 85 year-old male with pleural HCC metastasis. Tumor diameter was 53 mm. Fiducial marker was implanted nearby;B2: Three months after irradiation of 30 Gy/5 fractions. The tumor disappeared completely and achieved CR;C1: CT scan of 72 year-old male with thoracic spine HCC metastasis. Tumor is invading left side of the thoracic spine 2-3 causing bone destruction. Tumor diameter was 52 mm;C2: Three months after irradiation of 30 Gy/5 fractions. The tumor decreased to 33 mm (37% reduction in size) and achieved PR;D1: T1-weighted MRI of 83 year-old female with brain HCC metastasis. There is a right frontal lobe lesion with gadolinium enhancement. Tumor diameter was 19 mm;D2: One month after irradiation of 20 Gy/1 fraction. The tumor disappeared completely and achieved CR.



**Figure 2 Kaplan Meier curves for overall survival.** Median survival time for advanced stage patients and terminal stage patients were 13.0 mo and 1.0 mo respectively.

**Table 1 Patient characteristics *n* (%)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 |
|  | **Characteristics** |  |  | **Parameter** |  |  |  **Patients** |
|  |  |  |  |  |  | 65 (100)51 (78)1(22)7126-9335 (54)9 (14)21 (32)38 (58)24 (37)2 (3)1 (2)16 (25)43 (66)6 (9)24 (37)28 (43)49 (75)13 (20)7 (11)59 (91)6 (9)2561-24070014318-316400 |
| 　 | No. of patients |  |  |  |  |
| 　 | Sex |  |  | Male |  |  |
| 　 |  |  |  | Female |  |  |
| 　 | Age, years |  | Median |  |  |
| 　 |  |  |  | Minimum-Maximum |  |  |
| 　 | Viral hepatitis |  | HCV |  |  |
| 　 |  |  |  | HBV |  |  |
| 　 |  |  |  | None |  |  |
| 　 | Child-Pugh classification | A |  |  |
| 　 |  |  |  | B |  |  |
| 　 |  |  |  | C |  |  |
| 　 |  |  |  | NA |  |  |
| 　 | ECOG perfomance status | 0 |  |  |
| 　 |  |  |  | 1-2 |  |  |
| 　 |  |  |  | 3 |  |  |
| 　 | Previous treatments | Surgery |  |  |
| 　 |  |  |  | RFA |  |  |
| 　 |  |  |  | TACE |  |  |
| 　 |  |  |  | Sorafenib |  |  |
| 　 |  |  |  | Radiation |  |  |
| 　 | BCLC stage |  | C |  |  |
| 　 |  |  |  | D |  |  |
| 　 | AFP(ng/ml) |  | Median |  |  |
| 　 |  |  |  | Minimum-Maximum |  |  |
| 　 | PIVKAⅡ(mAU/mL) |  | Median |  |  |
| 　 |  |  |  | Minimum-Maximum |  |  |

ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer staging system; AFP: Alpha fetoprotein; PIVKAⅡ: Proteins induced by vitamin K absence; HCV: Hepatitis C virus; HBV: Hepatitis B virus; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization. NA: Not available.

**Table 2 Lesions and treatment outcomes**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Total lesions (*n* = 95)** |  | **Size (mm)** |  | **Radiation (Gy)** |  | **Response** |
| 　 | Variables | 　 | 　 | *n* | 　 | Median | Range | 　 | Dose | Range | Fraction | 　 | CR | PR | SD | PD | NA |
| 　 | Liver | Portal vein | 9 |  | 34.5 | (15-54) |  | 36 | (28-50) | (3-6) |  | 2 |  | 2 | 1 | 4 |
| 　 | Hepatic vein | 4 |  | 38 | (20-54) |  | 32.1 | (28-36) | (4-10) |  | 1 | 1 |  | 1 | 1 |
| 　 | Bile duct |  | 4 |  | 19.5 | (12-29) |  | 38.5 | (28-45) | (5-7) |  |  | 1 | 1 |  | 2 |
| 　 | Bone |  |  |  | 52 |  | 24.5 | (10-52) |  | 21.5 | (8-33) | (1-6) |  | 1 | 13 | 16 | 11 | 11 |
| 　 | Lung |  |  |  | 9 |  | 19 | (18-48) |  | 40 | (27-48) | (3-4) |  |  | 4 |  | 1 | 4 |
| 　 | Brain |  |  |  | *7* |  | *23.5* | *(12-38)* |  | *22* | *(14-30)* | *(1-3)* |  | *2* |  |  | *2* | *3* |
| 　 | Others |  |  |  | *10* |  | *31* | *(15-53)* |  | *30* | *(16-48* | *(1-6)* |  | *1* | *6* |  |  | *3* |

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease. NA: Not available.

**Table 3 Prognostic factors for tumor response *n* (%)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Prognostic** |  | **Response (+)** |  | **Response (-)** |  | ***P* value** |
|  | **foctors** |  | **CR, PR, SD** |  | **PD** |  |  |
|  |  |  |  |  |  |  |  |
|  | Gender |  |  |  |  |  | 0.716  |
|  | Female |  | 8 (73) |  | 3 (27) |  |  |
|  | Male |  | 43 (77) |  | 13 (23) |  |  |
|  |  |  |  |  |  |  |  |
|  | Age (yr) |  |  |  |  |  | 1.000  |
|  | < 70 |  | 23 (77) |  | 7 (23) |  |  |
|  | ≥ 70 |  | 28 (76) |  | 9 (24) |  |  |
|  |  |  |  |  |  |  |  |
|  | AFP (ng/mL) |  |  |  |  |  | 0.123  |
|  | < 400 |  | 25 (69) |  | 11 (31) |  |  |
|  | ≥ 400 |  | 23 (88) |  | 3 (12) |  |  |
|  |  |  |  |  |  |  |  |
|  | BCLC |  |  |  |  |  | 1.000  |
|  | Advanced |  | 46 (75) |  | 15 (25) |  |  |
|  | Terminal |  | 5 (83) |  | 1 (17) |  |  |
|  |  |  |  |  |  |  |  |
|  | Child-Pugh |  |  |  |  |  | 0.363  |
|  | < 7 |  | 36 (80) |  | 9 (20) |  |  |
|  | ≥ 7 |  | 15 (68) |  | 7 (32) |  |  |
|  |  |  |  |  |  |  |  |
|  | Diameter (mm) |  |  |  |  |  | 0.401  |
|  | < 30 |  | 29 (81) |  | 7 (19) |  |  |
|  | ≥ 30 |  | 22 (71) |  | 9 (29) |  |  |
|  |  |  |  |  |  |  |  |
|  | Dose (Gy) |  |  |  |  |  | 0.119  |
|  | < 30 |  | 33 (70) |  | 14 (30) |  |  |
|  | ≥ 30 |  | 18 (90) |  | 2 (10) |  |  |
|  |  |  |  |  |  |  |  |
|  | Dose/Fraction (Gy) |  |  |  |  |  | 0.137  |
|  | < 8 |  | 22 (88) |  | 3 (12) |  |  |
|  | ≥ 8 |  | 29 (69) |  | 13 (31) |  |  |
|  |  |  |  |  |  |  |  |
|  | Lesion |  |  |  |  |  | 0.274  |
|  | Intrahepatic |  | 10 (91) |  | 1 (9) |  |  |
|  | Extrahepatic |  | 41 (73) |  | 15 (27) |  |  |
|  |  |  |  |  |  |  |  |
|  | Fiducial |  |  |  |  |  | 0.126  |
|  | (-) |  | 34 (71) |  | 14 (29) |  |  |
|  | (+) |  | 17 (89) |  | 2 (11) |  |  |
|  |  |  |  |  |  |  |  |
|  | Sorafenib |  |  |  |  |  | 0.460  |
|  | (-) |  | 43 (78) |  | 12 (22) |  |  |
|  | (+) |  | 8 (67) |  | 4 (33) |  |  |
| 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 |

Fisher's exact test was used to evaluate prognostic factors for tumor response. Complete response (CR), Partial response (PR) and stable disease (SD) were categorized into response (+), progressive disease (PD) was categorized into response (-).

**Table 4 Prognostic factors for** **alpha fetoprotein response**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Univariate analysis** |  |  |  |  |  | **Multivariate analysis** |  |  | 　 |
|  | **Prognostic** |  | **AFP** |  | **AFP** |  | ***P* value** |  | **Odds ratio** |  | **95%CI** |  | ***P* value** |  |
|  | **foctors** |  | **decrease** |  | **increase** |  |  |  |  |  |  |  |  | 　 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Gender |  |  |  |  |  | 0.478 |  |  |  |  |  |  |  |
|  |  Female |  | 4 (44) |  | 5 (56) |  |  |  |  |  |  |  |  |  |
|  | Male |  | 26 (59) |  | 18 (41) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Age (yr) |  |  |  |  |  | < 0.001 |  |  |  |  |  |  |  |
|  | < 70 |  | 11 (37) |  | 19 (63) |  |  |  |  |  |  |  |  |  |
|  | ≥ 70 |  | 19 (83) |  | 4 (17) |  |  |  | 0.116 |  | 0.029-0.460 |  | 0.002 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | AFP (ng/ml) |  |  |  |  |  | 0.570 |  |  |  |  |  |  |  |
|  | < 400 |  | 20 (61) |  | 13 (39) |  |  |  |  |  |  |  |  |  |
|  | ≥ 400 |  | 10 (50) |  | 10 (50) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | BCLC |  |  |  |  |  | 1.000 |  |  |  |  |  |  |  |
|  | Advanced |  | 27 (57) |  | 20 (43) |  |  |  |  |  |  |  |  |  |
|  | Terminal |  | 3 (50) |  | 3 (50) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Child-Pugh |  |  |  |  |  | 0.151 |  |  |  |  |  |  |  |
|  | < 7 |  | 22 (65) |  | 12 (35) |  |  |  |  |  |  |  |  |  |
|  | ≥ 7 |  | 8 (42) |  | 11 (58) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Diameter (mm) |  |  |  |  |  | 0.054 |  |  |  |  |  |  |  |
|  | < 30 |  | 11 (42) |  | 15 (58) |  |  |  |  |  |  |  |  |  |
|  | ≥ 30 |  | 19 (70) |  | 8 (30) |  |  |  | 0.286 |  | 0.073-1.120 |  | 0.072 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose (Gy) |  |  |  |  |  | 0.013 |  |  |  |  |  |  |  |
|  | < 30 |  | 18 (46) |  | 21 (54) |  |  |  |  |  |  |  |  |  |
|  | ≥ 30 |  | 12 (86) |  | 2 (14) |  |  |  | 0.992 |  | 0.093-10.50 |  | 0.995 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose/Fraction (Gy) |  |  |  |  |  | 0.555 |  |  |  |  |  |  |  |
|  | < 8 |  | 11 (65) |  | 6 (35) |  |  |  |  |  |  |  |  |  |
|  | ≥ 8 |  | 19 (53) |  | 17 (47) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Lesion |  |  |  |  |  | 0.270 |  |  |  |  |  |  |  |
|  | Intrahepatic |  | 7 (78) |  | 2 (22) |  |  |  |  |  |  |  |  |  |
|  | Extrahepatic |  | 23 (52) |  | 21 (48) |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Fiducial |  |  |  |  |  | 0.025 |  |  |  |  |  |  |  |
|  | (-) |  | 19 (48) |  | 21 (52) |  |  |  |  |  |  |  |  |  |
|  | (+) |  | 11 (85) |  | 2 (15) |  |  |  | 0.152 |  | 0.026-0.887 |  | 0.036 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Sorafenib |  |  |  |  |  | 0.738 |  |  |  |  |  |  |  |
|  | (-) |  | 23 (55) |  | 19 (45) |  |  |  |  |  |  |  |  |  |
|  | (+) |  | 7 (64) |  | 4 (36) |  |  |  |  |  |  |  |  |  |
| 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 |

Fisher's exact test and a logistic regression model were used to evaluate prognostic factors for AFP response. AFP: Alpha fetoprotein.

**Table 5 Prognostic factors for PIVKAⅡ response *n* (%)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Univariate analysis** |  |  |  |  |  | **Multivariate analysis** | 　 | 　 | 　 |  |
|  | **Prognostic** |  | **PIVKAⅡ** |  | **PIVKAⅡ** |  | ***P* value** |  | **Odds ratio** |  | **95%CI** |  | *P* value |  |  |
|  | **foctors** |  | **decrease** |  | **increase** |  |  |  |  |  |  | 　 | 　 | 　 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Gender |  |  |  |  |  | 0.278  |  |  |  |  |  |  |  |  |
|  | Female |  | 3 (33) |  | 6 (67) |  |  |  |  |  |  |  |  |  |  |
|  | Male |  | 25 (57) |  | 19 (43) |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Age (yr) |  |  |  |  |  | 0.052  |  |  |  |  |  |  |  |  |
|  | < 70 |  | 12 (40) |  | 18 (60) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 70 |  | 16 (70) |  | 7 (30) |  |  |  | 0.359 |  | 0.093-1.390 |  | 0.139 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | AFP (ng/mL) |  |  |  |  |  | 0.738  |  |  |  |  |  |  |  |  |
|  | <400 |  | 18 (55) |  | 15 (45) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 400 |  | 10 (50) |  | 10 (50) |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | BCLC |  |  |  |  |  | 0.404  |  |  |  |  |  |  |  |  |
|  | Advanced |  | 26 (55) |  | 21 (45) |  |  |  |  |  |  |  |  |  |  |
|  | Terminal |  | 2 (33) |  | 4 (67) |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Child-Pugh |  |  |  |  |  | 0.267  |  |  |  |  |  |  |  |  |
|  | < 7 |  | 20 (59) |  | 14 (41) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 7 |  | 8 (42) |  | 11 (58) |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Diameter (mm) |  |  |  |  |  | 0.056  |  |  |  |  |  |  |  |  |
|  | < 30 |  | 10 (38) |  | 16 (62) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 30 |  | 18 (67) |  | 9 (33) |  |  |  | 0.185 |  | 0.047-0.730 |  | 0.016 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose (Gy) |  |  |  |  |  | <0.001 |  |  |  |  |  |  |  |  |
|  | < 30 |  | 15 (38) |  | 24 (62) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 30 |  | 13 (93) |  | 1 (7) |  |  |  | 0.270  |  | 0.021-3.40 |  | 0.312 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose/Fraction (Gy) |  |  |  |  |  | 0.769  |  |  |  |  |  |  |  |  |
|  | < 8 |  | 8 (47) |  | 9 (53) |  |  |  |  |  |  |  |  |  |  |
|  | ≥ 8 |  | 20 (56) |  | 16 (44) |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Lesion |  |  |  |  |  | 0.026  |  |  |  |  |  |  |  |  |
|  | Intrahepatic |  | 8 (89) |  | 1 (11) |  |  |  |  |  |  |  |  |  |  |
|  | Extrahepatic |  | 20 (45) |  | 24 (55) |  |  |  | 0.000  |  | 0.00-∞ |  | 0.994 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Fiducial |  |  |  |  |  | 0.001  |  |  |  |  |  |  |  |  |
|  | (-) |  | 16 (40) |  | 24 (60) |  |  |  |  |  |  |  |  |  |  |
|  | (+) |  | 12 (92) |  | 1 (8) |  |  |  | 0.035 |  | 0.003-0.342 |  | 0.004 |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Sorafenib |  |  |  |  |  | 1.000  |  |  |  |  |  |  |  |  |
|  | (-) |  | 22 (52) |  | 20 (48) |  |  |  |  |  |  |  |  |  |  |
|  | (+) |  | 6 (55) |  | 5 (45) |  |  |  |  |  |  |  |  |  |  |
| 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 |  |

Fisher's exact test and a logistic regression model were used to evaluate prognostic factors for PIVKAⅡ response.

**Table 6 Univariate and multivariate analysis for overall survival**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Univariate analysis** |  |  |  |  |  | **Multivariate analysis** | 　 | 　 | 　 |
|  | **Prognostic** |  | **Hazard ratio** |  | **95%CI** |  | ***P* value** |  | **Hazard ratio** |  | **95%CI** |  | *P value* |  |
|  | **foctors** |  |  |  |  |  |  |  |  |  |  | 　 | 　 | 　 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Gender (Male) |  | 0.968  |  | 0.387-2.419 |  | 0.945  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Age (≥ 70 yr) |  | 0.770  |  | 0.355-1.670 |  | 0.508  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | AFP (≥ 400 ng/mL) |  | 2.662  |  | 1.181-6.001 |  | 0.018  |  | 2.548  |  | 1.070-6.068 |  | 0.035  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | BCLC (Terminal) |  | 7.022  |  | 2.442-20.19 |  | < 0.001 |  | 9.809  |  | 2.589 -37.17 |  | < 0.001 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Child-Pugh (≥ 7) |  | 3.031  |  | 1.258-7.301 |  | 0.013  |  | 1.364  |  | 0.510-3.645 |  | 0.536  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Diameter (≥ 30 mm) |  | 0.654  |  | 0.285-1.500 |  | 0.316  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose (≥ 30 Gy) |  | 0.302  |  | 0.114-0.804 |  | 0.017  |  | 0.274  |  | 0.093-0.7541 |  | 0.012  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Dose/Fraction (≥ 8 Gy) |  | 1.889  |  | 0.790-4.516 |  | 0.153  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Lesion (Extrahepatic) |  | 1.789  |  | 0.665-4.817 |  | 0.250  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Fiducial (+) |  | 0.491  |  | 0.195-1.238 |  | 0.132  |  | 0.783  |  | 0.264-2.321 |  | 0.659  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | Sorafenib (+) |  | 1.068  |  | 0.247-4.618 |  | 0.930  |  |  |  |  |  |  |  |
| 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 | 　 |

Cox proportional hazards model was used to evaluate the prognostic factors for overall survival.