European Review for Medical and Pharmacological Sciences 2015; 19: 247-255

Sorafenib combined with percutaneous radiofrequency ablation for the treatment of medium-sized hepatocellular carcinoma

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Abstract. – OBJECTIVE: Sorafenib, an oral multikinase inhibitor, is the proved therapy method for patients with advanced hepatocellular carcinoma (HCC). Based on heat delivery, Radiofrequency ablation (RFA) has been found to achieve complete neoplasm necrosis. It is the most widely performed percutaneous therapy for HCC. However, Study associated combined Sorafenib with RFA therapy for patients with advanced HCC has never been reported. The aim of present study is to explore the efficacy and safety of sorafenib combined with RFA therapy for the patients with medium-sized HCC.

PATIENTS AND METHODS: A total of 62 patients diagnosed as HCC were involved in this study. All patients were randomly assigned to sorafenib and RFA (n=30) or RFA-alone (n=32) treatment groups. Treatment outcomes, including recurrence rates, time to progression (TTP) and adverse reactions induced by sorafenib were observed and recorded to assess the efficacy and safety of the combination method.

RESULTS: During the overall follow-up period, the recurrence rate of the combination subgroup was 56.7% (17/30), and that of the RFA-alone subgroup was 87.5% (28/32) ($p < 0.01$). The median TTP was 17.0 months in the combination therapy vs. 6.1 months in the RFA-alone ($p < 0.05$). Hand-foot skin reactions were reported by 83.3% (25/30) of patients and 46.7% (14/30) reported diarrhea while the most adverse events (AEs) were mild to moderate in the combination subgroup.

CONCLUSIONS: Sorafenib combined with RFA significantly decreased recurrence rates and prolonged the survival time of medium-sized HCC patients. The combination therapy is safer and more effective than the control without unexpected side effects. Furthermore, the earlier application, the better results were.

Key Words:
Sorafenib, Radiofrequency ablation, Medium-sized, Hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly seen malignancy worldwide. The incidence of HCC is increasing in many countries[1]. In China, HCC is the second most common cause of cancer-related mortality[2] and it is most commonly caused by infection with the hepatitis B virus (HBV)[3]. The definitive treatment modality for HCC is surgical resection. But only approximately 30% of patients who present with early stage tumors undergo resection, due to various factors, such as multifocal tumor and poor liver function resulting from underlying cirrhosis[4,5]. Liver transplantation could solve the problems of both tumors and liver dysfunction simultaneously, but the shortage of donors restricted its application critically. It can be seen that both techniques were dangerous and time-consuming, so there is real need for an effective but less invasive alternative technique such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). Local ablation ther-

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apies such as percutaneous ethanol injection and RFA have been developed as alternatives to surgical treatment[6]. Clinical study demonstrated that RFA has the similar survival rates to resection[7], and can be conducted repeatedly with the same patient[8]. RFA has been found to achieve complete necrosis in 82-100% of small HCC[9]. For medium-sized HCCs, the combination of RFA with TACE provides better local control without increasing the procedure-related complication rate compared with RFA alone[10]. RFA has been shown safe and successful for local tumor control in patients with HCC and is increasingly used for HCC patients[11]. Clinical roles of RFA are actually more meaningful than those of surgery from the viewpoint that RFA could be applied to patients whose hepatic functional reserve is insufficient to endure surgery. Sorafenib is a newly developed molecular targeted agent. Sorafenib works by inhibiting several kinases in the MAPK pathway. The G-protein Ras is a key member of the MAPK pathway, and it helps regulate the Raf/Mek/Erk cascade. These kinases start a phosphorylation cascade that eventually leads to the transcription of genes that promote cell proliferation[12]. This multikinase inhibitor has been demonstrated significant survival benefits in phase III trials for patients with HCC[13]. The aim of this study was to assess the safety and efficacy of sorafenib combined with RFA for the treatment of medium-sized HCC.

Patients and Methods

Patients

A total of 62 inpatients with HBV-related medium-sized HCC (3.1-5.0 cm in diameter) were enrolled in this study during Jan 2010 and Apr 2014 in our hospital. All patients were diagnosed by histology, cytology, or persistently elevated serum alpha- fetoprotein (AFP ≥ 400 ng/ml) with typical imaging findings. AFP and the serological markers of HBV were measured with ARCHITECT Immunoassay Analyzers, ARCHITECT i2000SR, and its reagents (Abbott Park, Illinois, U.S.A). The inclusion criteria were as follows: (1) patients with a single HCC measuring 3.1-5.0 cm in diameter at CT scans (Philips Brilliance 16, Philips Healthcare, Franklin, PA, USA); (2); no history of previous treatment for HCC; (3) liver function classified as Child-Pugh class A or B; (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1 or 2; 5) prothrombin time no longer than 18 seconds; and 6) unwilling to underwent partial hepatectomy. Informed consent was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki and approved by Ethic Committee of our hospital.

The patients were randomly assigned to sorafenib and RFA (n=30) or RFA-alone (n=32) treatment groups. Patients with histologically or clinically diagnosed HCC were treated with percutaneous RFA under ultrasound guidance. For patients of the combination group, they took orally sorafenib (Bayer HealthCare AG, Leverkusen, Germany) 4 to 7 days after the first RFA. Treatment outcomes, including recurrence rates, time to progression (TTP), vascular endothelial growth factor (VEGF) (Yihan BioTechnologies, Shanghai, China), alpha fetoprotein (AFP) and adverse reactions induced by sorafenib were observed and recorded. Follow-up consisted of performing contrast-enhanced computed tomography (CT) examinations and serum biochemical index at both the first and third months following ablation as well as the same examinations obtained every two months.

Radiofrequency Ablation

All patients received RFA on an inpatient basis. Preoperative planning including evaluation of all imaging studies, and careful ultrasound examination was performed to identify the tumors and determine the access routes. RFA was performed with the RF 1500X generator system (RITA Medical System, Mountain View, CA, USA). After determining the best way to avoid large vessels, the electrode was inserted percutaneously into the center of the tumor under ultrasound guidance (Philips IU 22, Best, Netherlands). Radiofrequency current was maintained for 10-15 min. A successful case was defined as the ablated area was 0.5 cm wider than the tumor. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Jinan Infectious Disease Hospital. Written informed consent was obtained from all participants.

For patients with hypervascular tumors, TACE was performed 7-10 days before the RFA. TACE was performed by selective transarterial chemotherapy in the vessels feeding the tumor with an emulsion of lipiodol (10-20 ml) and doxorubicin (30-50 mg). Four to six weeks after the first RFA, a contrast-enhanced CT of the abdomen and a determination of the AFP and

VEGF were performed to assess the need of a consecutive treatment. When no vital tumor tissue is seen on the CT, RFA was discontinued but the patient remained on sorafenib 400 mg bid if tolerated and underwent contrast-enhanced CT and serum biochemical index determination at 2 month intervals. If the contrast-enhanced CT revealed new lesions, the patient was evaluated for feasibility of a new RFA treatment until tumor-free status to the greatest extent.

Sorafenib Administration

All patients of the combination group started receiving sorafenib at a dose of 400 mg twice daily on Day 4-7 after the 1st RFA. If patients show severe side effects or a severe deterioration of the quality of life (QoL) at the standard dosage, dose reductions or temporary interruptions were instituted. For adverse drug reactions (ADRs) of grade 3-4, the sorafenib dose was decreased to 200 mg twice daily until the ADRs improved to a grade of ≤2, then increased to 400 mg twice daily if well tolerated. Patients were treated with continuous sorafenib with no breaks before or after the new RFA procedure.

Study Objectives

This study was designed with the primary objectives to assess the safety and efficacy of using sorafenib combined with RFA to treat medium-sized HCC in a subcapsular location. Secondary objectives included: recurrence rates, time to progression (TTP), vascular endothelial growth factor (VEGF), alpha fetoprotein (AFP) and adverse reactions induced by sorafenib were observed and recorded.

Statistical Analysis

Continuous variables were summarized as the means and ranges. The primary objective of the current study was recurrence rates. The treatment outcomes TTP, AFP, VEGF of the RFA group were compared with the RFA combined with sorafenib group. Associations between TTP and potential prognostic factors were assessed by the Kaplan-Meier method (log-rank test) in a univariable analysis. All statistical tests were two-sided, $p < 0.05$ was considered statistically significant. Statistical analysis was performed with Statistical Product and Service Solutions computer software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

A total of 62 patients, 43-64 years of age (average 53.2 years), were included in our study (30 patients in the combination subgroup and 32 patients in the RFA subgroup), of which, 82.3% were males. Table I lists the patients' characteristics, and there is no significant difference in any

Table I. Baseline characteristics of patients.

Variable	Combination therapy (n=30)	RFA (n=32)
Age (years)	53.7 ± 9.6	52.4 ± 8.9
Gender (%)		
Male	24 (80.0)	25 (78.1)
Female	6 (20.0)	7 (21.9)
ECOG performance status (%)		
0	5 (16.6)	6 (18.8)
1	23 (76.7)	21 (65.6)
2	2 (6.7)	5 (15.6)
BCLC stage B (%)	8 (26.7)	14 (43.6)
BCLC stage C (%)	22 (73.3)	18 (56.4)
Child-Pugh A	12 (40)	14 (43.8)
Child-Pugh B	18 (60)	18 (56.2)
Vascular invasion yes/no	4/26	5/27
Extrahepatic spread yes/no	6/24	8/24
ALT (U/L)	87 ± 43	89 ± 49
Serum bilirubin (umol/L)	37.6 ± 16.8	37.9 ± 17.2
Serum AFP (ng/mL)	742 ± 515	698 ± 523
VEGF (ng/L)	462 ± 238	471 ± 243

RFA: radiofrequency ablation; ECOG: Eastern Cooperative Oncology Group; BCLC: Barcelona Clinic Liver Cancer; ALT: alanine aminotransferase; AFP: alpha-fetoprotein; OS: overall survival; VEGF: vascular endothelial growth factor.

of the characteristics between the two groups of patients. Tumor ablation was complete in forty-nine (79.03%) in all patients for the first time. Thirteen (20.97%) patients with residual lesions received repeat RFA 1 month later. Most patients (71.0%) were ECOG (eastern cooperative oncology group, ECOG) Score 1 with the remainder Score 0 (17.7), 2 (11.3). The majority of patients were BCLC (Barcelona Clinic Liver Cancer) stage C (C-64.5% and B-35.5%), Child-Pugh Class B (58.1% B, 41.9% A). Chronic hepatitis B (CHB) was the most common etiology ascribed to patients HCC (90.3%) followed by chronic hepatitis C (CHC) (9.7%). The HBV DNA loads were low in 36 (60.0%), intermediate in 17 (28.3%) and high in 7 patients (11.7%). At the initiation of treatment with sorafenib, 43 had compensated cirrhosis (69.4%) and 19 had decompensated cirrhosis (30.6%). No significant differences were found in the distribution of these variables between those with compensated versus decompensated cirrhosis (data not shown).

Technical Success

Technical success of treatment was achieved in 62 patients (100%). No procedure-related deaths occurred in either group. RFA had a low rate of major complications and a short hospital stay.

Adverse Events

No patient experienced severe side effects during the RFA procedure. Major complications were requiring a higher level of care. No patients experienced tumor seeding or tumor bleeding. Issues related to radiofrequency treatment were negligible. Minor complications were fever > 38°C (37.1%), pain requiring analgesics (59.7%) and gastrointestinal reaction (33.9%).

Commonly observed adverse effects basing on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 in our study of patients received sorafenib included hand-foot skin reaction (83.3%), diarrhea (46.7%), fatigue (40.0%), alopecia (30.0%) and hypertension (13.3%). No Grade 4 or 5 AEs were deemed to be related to sorafenib. Laboratory data indicated the most common Grade 3 AEs were increases in ALT (alanine aminotransferase, ALT) and AST (aspartate aminotransferase, AST) for 8.1% and 6.5% of patients, respectively.

Efficacy

During the overall follow-up period, 17 patients (56.7%) in the combination subgroup (9 with local recurrence, 6 with recurrence distant in the liver, and 2 with extrahepatic recurrence) and 28 patients (87.5%) in the RFA subgroup (15 with local recurrence, 9 with recurrence distant in the liver, and 4 with extrahepatic recurrence) had tumor recurrence. The 1-, 2-, and 3- recurrence rates in the combination subgroup and the RFA subgroup were 36.7% (11/30), 43.3% (13/30), 56.7% (17/30) and 62.5% (20/32), 78.1% (25/32), 87.5% (28/32), respectively (Figure 1, $p < 0.01$). The recurrence rates were significantly associated with pretreatment serum AFP and VEGF level (Table II). 1 (3.3%) and 7 deaths (21.9%) happened in the combination and RFA-alone sub-

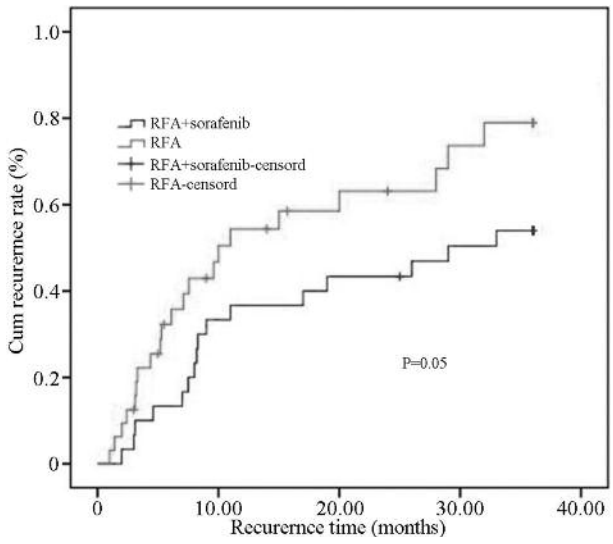

Figure 1. Kaplan-Meier survival curves displaying significant differences in local recurrence rates in patients between the combination group and RFA-alone group ($p < 0.05$).

Table II. Univariate analysis of patient demographics and clinical characteristics for predictive factors of local recurrence rates.

Variable	Sorafenib+RFA (n=30)	RFA (n=32)	p
Gender: men/women	26/4	27/5	> 0.05
Age	53.7 ± 9.6	52.4 ± 8.9	> 0.05
Distant metastasis	6	8	> 0.05
ECOG			> 0.05
1	5	6	
2			
3	23		
2	21		
5			
HBV-DNA (copies/ml) < 105/≥ 105	19/11	16/16	< 0.05
AFP (ng /ml): < 200/≥ 200	7/23	18/14	< 0.05
VEGF (ng/L): < 200/≥ 200	10/20	19/13	< 0.05
ALT (U/L): < 40/≥ 40	12/18	10/22	> 0.05
BCLC stage B/C	8/22	14/18	< 0.05
Family history of liver cancer yes/no	8/22	29/3	< 0.05
Neat tumor boundary yes/no	5/25	26/6	< 0.001
Tumor from the great vessels < 1 cm yes/no	18/12	8/24	< 0.001
Tumor location: left/right	7/23	6/26	> 0.05

RFA: Radiofrequency ablation; ECOG: Eastern Cooperative Oncology Group; HBVDNA: Hepatitis B virus deoxyribo nucleic acid; AFP: Alpha-fetoprotein; VEGF: Vascular endothelial growth factor; ALT: Alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer.

group, respectively ($p < 0.05$). Due to the majority of patients were alive, the data of the overall survival (OS, which refers to the time between first TACE or RFA to death by any cause) could not been obtained. The median TTP was 17.0 months in the combination therapy vs. 6.1 months in the RFA-alone ($p < 0.05$) group (Figure 2). The therapeutic procedure of a typical patient reflected by CT was displayed in Figure 3.

Discussion

This study is the first to evaluate the safety and efficacy of the combination of sorafenib and conventional RFA in patients with medium-sized HCC. RFA techniques have developed very quickly in recent years. Clinical evidence indicates that RFA was a less invasive and effective procedure and it has emerged as one alternative

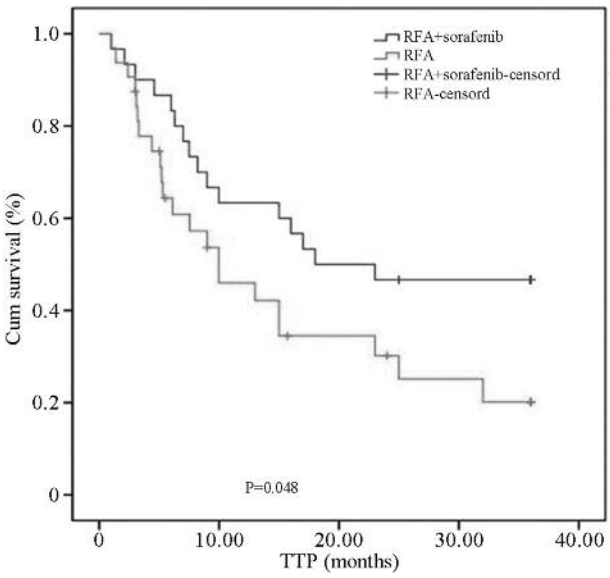

Figure 2. Kaplan-Meier survival curves displaying significant differences in TTP in patients between the combination group and RFA-alone group ($p < 0.05$).

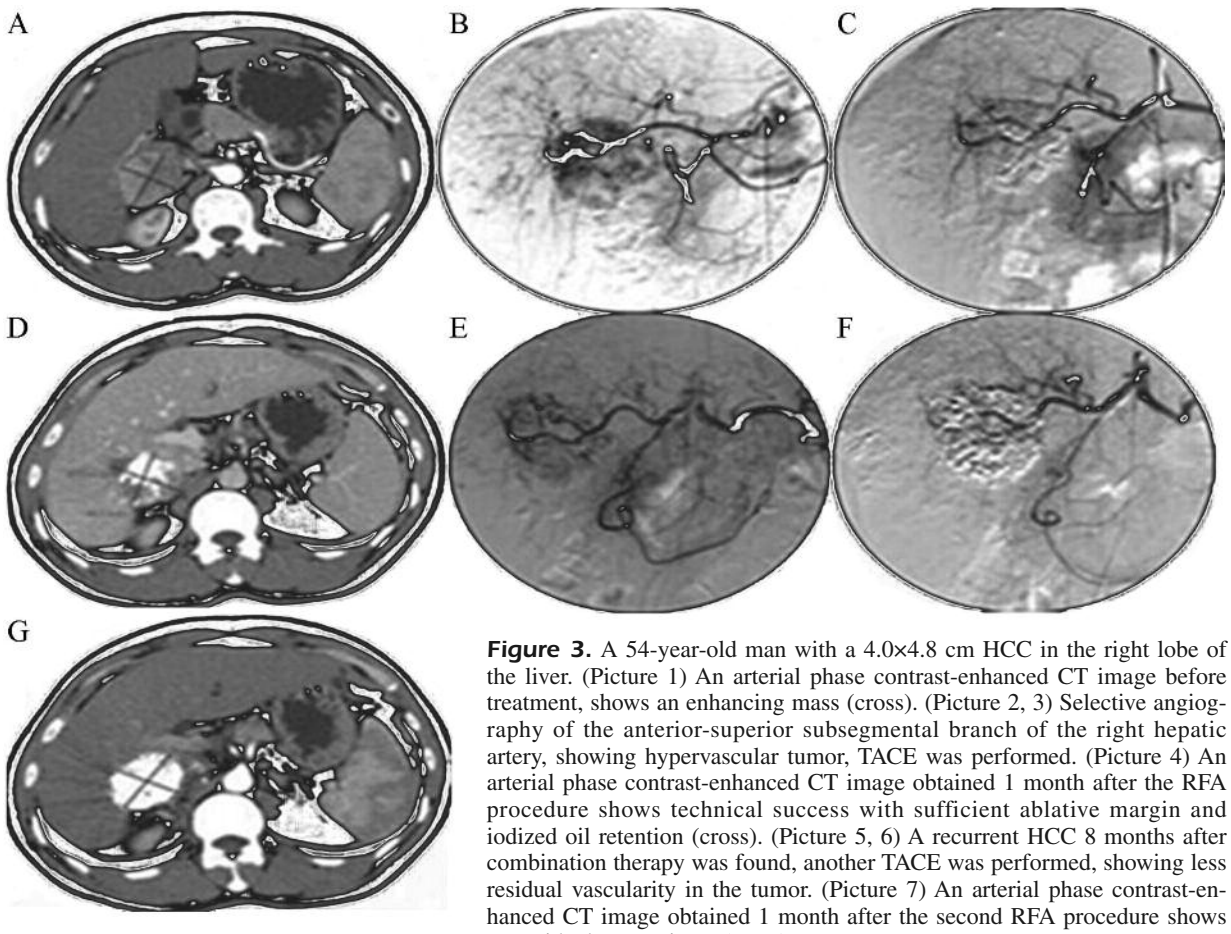

Figure 3. A 54-year-old man with a 4.0×4.8 cm HCC in the right lobe of the liver. (Picture 1) An arterial phase contrast-enhanced CT image before treatment, shows an enhancing mass (cross). (Picture 2, 3) Selective angiography of the anterior-superior subsegmental branch of the right hepatic artery, showing hypervascular tumor, TACE was performed. (Picture 4) An arterial phase contrast-enhanced CT image obtained 1 month after the RFA procedure shows technical success with sufficient ablative margin and iodized oil retention (cross). (Picture 5, 6) A recurrent HCC 8 months after combination therapy was found, another TACE was performed, showing less residual vascularity in the tumor. (Picture 7) An arterial phase contrast-enhanced CT image obtained 1 month after the second RFA procedure shows no residual tumor tissue (cross).

treatment for HCC. Chen et al[14] conducted a randomized controlled trial (RCT) involving 180 patients with small HCC (≤5 cm) to compare the survival rates and complications of RFA and PH (partial hepatectom, PH). Results show that there were no significant differences in survival rates between the two groups and the procedure-related complication rates were lower in the RFA group than the PH group. But Ng et al[15] demonstrated that different segment intrahepatic recurrence or distant metastasis after RFA significantly influenced the prognostic of patients. As such, the recurrence following RFA represents one of the major problems of this therapy, and limits its associated survival benefits. Sorafenib was a newly developed orally multi-targets antineoplastic drug. Clinical trials[13,16] have demonstrated the effectiveness and relative safety of sorafenib. Sorafenib is currently the only targeted therapy approved for the treatment of patients with advanced hepatocellular carcinoma. We found that sorafenib was capable of prolonging survival in HCC patients, however, in daily clinical practice, the efficacy of monotherapy with sorafenib in the treatment of advanced HCC was limited. High tumor burden may render patients refractory to sorafenib[17]. Two trials[13,16] also showed that the absolute benefit in survival time compared with placebo was not so prominent. So we consider sorafenib is used to reduce relapse prior to reduce tumor burden. The addition of sorafenib to RFA may overcome tumor burdens and reduce local recurrence, and improve significant survival benefits.

Several studies[18,19] have demonstrated that the use of local ablative therapy including RFA and TACE has increased in recent years. The survival benefits of TACE were better in patients with focal liver lesions, hypervascular tumors and without vascular invasion[20]. RFA was usually performed in the case of hypovascular tumor. The limitation of TACE was the incomplete target le-

sion necrosis. In addition, residue tumor proliferation, tumor recurrence and metastasis after TACE influenced long-term outcome[21]. So different from the previous studies[22-24], RFA rather than TACE was performed in our study to inactivate tumor completely. RFA may reduce the tumor burden, thus increasing the efficacy of sorafenib. Sorafenib mediated blockage of the Raf/mitogen-activated protein kinase and VEGFR pathways might enhance the efficacy of RFA. These possibilities are supported by the current data. The clinical benefits of the combination therapy may be largely due to the reduction of tumor burden by RFA, as well as reduction of tumor relapse by sorafenib. These encouraging results indicate that sorafenib combined with RFA may provide the best therapeutic benefit in patients suffering from medium-sized HCC.

We evaluated the efficacy and safety of sorafenib treatment 30 patients combined with RFA in 62 medium-sized HCC patients. The present study demonstrated that the 1-, 2-, and 3-year recurrence rates for the combination and RFA-alone groups were 36.7%, 43.3%, 56.7% and 62.5%, 78.1%, 87.5%, respectively. The median TTP was 17.0 months in the combination therapy vs. 6.1 months in the RFA-alone ($p < 0.05$) group. The significant decrease in recurrence rate and improvements in TTP in the combination therapy group provide encouraging evidence that combination therapy may overcome the tumor burden and reduce tumor recurrence. In our study all patients received continuous oral antiviral treatment with 0.5 mg of entecavir once daily, so that HCC patients with antiviral therapy had the opportunity for maintenance therapy by improving liver function. Comprehensive therapy based on combination with antiviral therapy played an important role in improving the efficacy of therapy for medium- sized HCC. In comparison with the RFA-alone group, the medium serum AFP and VEGF in the combination group was significantly decreased ($p < 0.05$). Our findings were also relevant to serum AFP and VEGF level, which is a marker of HCC, a prognostic indicator after curative treatment of HCC. We speculate that in the current study, AFP level ≥200 ng/mL, VEGF level ≥ 200 ng/mL predicted a more aggressive tumor behavior than AFP and VEGF level < 200 ng/mL. AEs in the current study were mostly mild to moderate with skin and gastrointestinal. However, no patients developed permanent sequelae, tumor seeding, or tumor bleeding during treatment. The frequency and degree of sorafenib-related AEs were comparable to those from previous reports, and RFA did not increase the frequency and degree of sorafenib- related AEs. The current study confirms earlier reports that the combination of conventional RFA and sorafenib was well tolerated and safe. We, therefore; propose that this combination therapy is a safe and useful treatment option for patients with medium-sized HCC. Ng et al[15] demonstrated that different segment intrahepatic recurrence or distant metastasis after RFA carried significant poor prognostic influence on TTP outcome. So sorafenib was added to reduce tumor recurrence or distant metastasis. Furthermore, the application earlier, the better results were.

Three underlying mechanisms have been found to support sorafenib therapy. First, sorafenib blocks HCC cell proliferation by inhibiting BRaf and Raf1/c-Raf serine/threonine kinase phosphorylation in the mitogen-activated protein kinase pathway. Second, sorafenib induces apoptosis by reducing eIF4E phosphorylation and down- regulates anti-apoptosis protein Mc11[25,26] in tumor cells. Third, sorafenib prevents tumor-associated angiogenesis by inactivating vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor β (PDGFR); and RET receptor tyrosine kinases. Sorafenib inhibits MEK and ERK phosphorylation, down-regulates cyeline D1 level. Moreover, treatment with sorafenib was well tolerated and safe. Based on these data, sorafenib was recommended as the standard treatment for HCC.

Based on our results, sorafenib and RFA is an effective and safe method for the treatment of medium-sized HCC. The key to its success lies in achieving tumorfree status to the greatest extent for the appliance of RFA. Furthermore, sorafenib was added to prevent tumor recurrence, thus the recurrence rates of HCC patients were significantly decreased. The results of the current trial were consistent with our expectation. In addition, we observed that the more obvious the patients' AEs such as hand-foot skin reaction and diarrhea induced by sorafenib, the more ideal the patients' therapeutic effects.

Conclusions

The results of the present study showed that combination therapy of medium-sized HCC using RFA and sorafenib was effective and safe. It

can significantly decrease recurrence rates, prolong the survival time and provide better prognosis for patients with HCC. But a well-designed, randomized controlled trial with larger number of patients is necessary to validate our conclusion.

Acknowledgements

The authors would like to thank all the patients enrolled in this study for their kind understanding and support.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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