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Sorafenib combined with transcatheter arterial chemoembolization and radiofrequency ablation in the treatment of postoperative recurrence of hepatocellular carcinoma

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Abstract: Objective Toexplorethetherapeuticeffectofsorafenibcombinedwithtranscatheterarterial chemoembolization （TACE） and radiofrequency ablation（RFA）in patients with postoperative recurrent hepatocellular carcinoma（HCC）, and to provide a reference for clinical selection of reasonable intervention plans. **Methods** A total of 107 patients with postoperative recurrent HCC diagnosed and treated in Hengshui Hospital of Traditional Chinese Medicine from January 2020 to March 2022 were selected as the research subjects. They were divided into the combination group（n=53）and the control group（n=54）by random number table method. The control group was treated with TACE combined with RFA, while the combination group was additionally given sorafenib tosylate tablets at a dose of 400 mg per time, twice a day, until the HCC progressed again. The clinical efficacy of the two groups was compared, as well as the serum levels of alpha-fetoprotein（AFP）, α-L-fucosidase（AFU）and abnormal prothrombin（APT）before and after treatment. The Kaplan-Meier method was used to draw survival curves for comparing the 2-year survival status of the two groups. **Results** The objective response rate of the combination group was significantly higher than that of the control group （83.02% *vs* 61.11%, χ^2=6.363, *P*=0.012）.There were no statistically significant differences in the levels of AFP, AFU and APT between the two groups before treatment（*P*>0.05）. At 2, 4 and 6 months after treatment, the levels of AFP, AFU and APT in the combination group were lower than those in the control group（*P*<0.05）. During the 2-year follow-up, the median follow-up time was 16 months. Up to the last follow-up, the median overall survival（OS）of the combination group and the control group was 20 months and 16 months, respectively, and the median progression-free survival（PFS）was 9.5 months and 6 months, respectively. The 2-year OS rate（log rank χ^2=4.863, *P*=0.027）and PFS rate（log rank χ^2=3.970, *P*=0.046）of the combination group were significantly higher than those of the control group. There was no statistically significant difference in the incidence of adverse reactions between the combination group and the control group（11.32% vs 3.70%, χ^2=1.277, *P*=0.258）. **Conclusion** Sorafenib combined with TACE and RFA has a significant effect in the treatment of postoperative recurrent HCC, which can further prolong the survival of patients, control complications, and effectively improve the prognosis of patients.
Keywords: Sorafenib; Transcatheter arterial chemoembolization; Radiofrequency ablation; Hepatocellular carcinoma; Postoperative recurrence; Survival analysis
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Sorafenib Combined with Transcatheter Arterial Chemoembolization and Radiofrequency Ablation for Postoperative Recurrence of Hepatocellular Carcinoma: A Prospective Controlled Study

China is a major country of hepatocellular carcinoma (HCC), with the incidence and mortality of HCC accounting for approximately half of the global total [1]. Surgical resection is the first-line treatment for HCC; however, the postoperative recurrence rate of HCC is high due to residual tumor cells and metastasis. Statistically, the postoperative recurrence and metastasis rate of early- and intermediate-stage liver cancer is as high as 70% [2]. Surgery remains the first choice for recurrent HCC; however, few patients can actually undergo reoperation due to insufficient postoperative liver reserve function, multiple recurrent lesions, and considerable surgical trauma. Transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are currently common non-surgical treatments [3-4]. Studies have shown that TACE combined with RFA can achieve favorable therapeutic effects [5]. As a targeted therapeutic agent for HCC, sorafenib inhibits tumor growth through multiple pathways, but the efficacy of sorafenib combined with TACE and RFA in the treatment of postoperative recurrence of HCC remains unclear. Therefore, the authors conducted a prospective controlled study, and the results are reported as follows.

1 Materials and Methods

1.1 Sample Size Calculation

A prospective randomized controlled study design was adopted. The overall response rate of HCC patients treated with conventional therapy was approximately 60% [6], and it was expected to increase to 85% in the experimental group. The clinical margin δ was set at 25%. A two-sided test was used with α = 0.05 and β = 0.20 (statistical power = 80%). According to the formula $n=\frac{[Z_{1-\alpha/2}\cdot\sqrt{2\cdot\bar{p}\cdot(1-\bar{p})}+Z_{1-\beta}\cdot\sqrt{p1(1-p1)+p2(1-p2)}]^2}{(p1-p2)^2}$, 49 patients were required per group. With a 10% dropout rate, a total of 107 patients were needed. Variable definitions: n, required sample size per group; p_1, expected response rate in the control group (0.60);p_2, expected overall response rate in the experimental group (0.85); p=(p1+p2)/2, Z(1-α/2)=1.96; Z(1-β)=0.84。

1.2 Inclusion and Exclusion Criteria

(1) Inclusion criteria:① Clear previous diagnosis of HCC with smooth surgery;② Confirmed HCC recurrence by clinical, imaging, serum alpha-fetoprotein (AFP), and pathological examinations;③ Ineligible for surgery after evaluation (e.g., single tumor diameter >10 cm, or tumor diameter >5 cm with >3 lesions; intrahepatic vascular invasion, lymph node metastasis, or distant metastasis; Child-Pugh class C liver function; portal hypertension).

(2) Exclusion criteria: ① Previous treatment with TACE, RFA, or other interventional therapies; ② Complicated with other tumors or infections;③ Severe cardiac, pulmonary, or mental disorders;④ Moderate or above ascites requiring drainage.

(3) Dropout criteria:① Failure to complete treatment per study protocol;② Participation in other clinical trials during the study interfering with efficacy evaluation;③ Voluntary withdrawal by the patient.

(4) Trial termination criteria:① Disease deterioration with potential risky events during the clinical trial, requiring discontinuation judged by the investigator;② Occurrence of serious adverse events related to the treatment regimen;③ Accidents;④ Death.

1.3 General Data

A total of 107 patients with postoperative recurrence of HCC diagnosed and treated at Hengshui Hospital of Traditional Chinese Medicine from January 2020 to March 2022 were enrolled. They were randomly divided into two groups using a random number table: 53 patients in the combination group and 54 in the control group. There were no significant differences in baseline characteristics between the two groups ($P > 0.05$), as shown in **Table 1.** All patients were fully informed of the purpose, methods, risks, and other information of the study, and were promised confidentiality of their information. All patients voluntarily participated in the study. The study was approved by the Ethics Committee of Hengshui Hospital of Traditional Chinese Medicine (No. 20232201) and complied with the ethical principles of the Declaration of Helsinki.

1.4 Treatment Protocol

The control group received TACE and RFA, and the combination group received additional sorafenib on the basis of the control group.

1.4.1 TACE

The modified Seldinger technique was used for femoral artery catheterization. After angiography confirmed the tumor-feeding artery, chemotherapeutic agents and embolic agents were infused via the catheter. Chemotherapeutic agents included:0.75 g of 5-fluorouracil (Liaoning Xingao Pharmaceutical Co., Ltd., approval No. H21024236, specification 0.25 g),100-150 mg of oxaliplatin (Chengdu Changqing Pharmaceutical Co., Ltd., approval No. H20020648, specification 50 mg),10 mg of pirarubicin (Hanhui Pharmaceutical Co., Ltd., approval No. H20045983, specification 10 mg).Embolic agent: 10-30 mL of super-emulsified lipiodol (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., approval No. H31021603, specification 10 mL), with the dose adjusted according to the number, size, and blood supply of the lesions. After catheter removal, the puncture site was compressed for hemostasis and bandaged under pressure.

1.4.2 RFA

RFA was performed within 2 weeks after TACE. Patients fasted for 8 hours preoperatively and received intramuscular injections of diazepam 10 mg, pethidine 50 mg, and batroxobin 100 U.Under CT guidance, the ablation target was located, and the needle direction, angle, and depth were determined. After routine disinfection, draping, and local anesthesia with lidocaine, an RFA needle was inserted into the tumor. Ablation parameters: 15-gauge single electrode, frequency 480 kHz, temperature 90–110 °C, duration 20–30 minutes. The ablation range covered the entire tumor and a 5-mm peripheral margin. Postoperative care included hemostasis, infection prevention, and liver protection.

1.4.3 Sorafenib

Sorafenib tosylate tablets (Bayer HealthCare Pharmaceuticals, approval No. H20160201, 200 mg) were administered orally at 400 mg twice daily. In case of intolerable adverse reactions, the dose was reduced to 200 mg twice daily or temporarily interrupted until symptoms relieved. Treatment was continued until disease progression.

Tab.1 Comparison of baseline characteristics between two groups（case）

Item	Combined group (*n*=53)	Control group (*n*=54)	χ^2/Z *value*	*P value*
Age (years)	68.17±2.83	68.04±3.16	0.223	0.824
Sex (male/female)	42/11	46/8	0.646	0.421
BMI (kg/m²)	21.06±4.88	19.86±3.91	1.418	0.159
Albumin (g/L)	45.43±3.39	44.37±3.25	1.643	0.103
Total bilirubin (μmol/L)	1.96±0.38	2.11±0.42	1.944	0.055
AFP			1.124	0.289
>200 ng/mL	28	23		
≤200 ng/mL	25	31		
Tumor number			0.959	0.328
Single	39	44		
Multiple	14	10		
Maximum tumor diameter			0.524	0.469
≥3 cm	38	42		
<3 cm	15	12		
Portal vein tumor thrombus	4	7	0.365	0.546
Liver cirrhosis	46	50	0.448	0.503
Portal hypertension	5	3	0.156	0.693
Child-Pugh classification			0.311	0.756
A	49	49		
B	3	4		
C	1	1		
Complications				
Hemorrhage	3	2	0	0.983
Abscess	4	7	0.365	0.546
Effusion	9	10	0.043	0.835
Pneumonia	1	4	0.801	0.371

1.5 Observation Indicators

Clinical efficacy and serum tumor markers [AFP, α-L-fucosidase (AFU), abnormal prothrombin (APT)] were compared before and after treatment. Prognosis (overall survival (OS), progression-free survival (PFS) and safety were also evaluated.

1.5.1 Efficacy Evaluation

One month after treatment, efficacy was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [7], including complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) = (CR + PR)/total number × 100%.

1.5.2 Serum Tumor Markers

Fasting venous blood was collected before treatment and at 2, 4, and 6 months after treatment for detection of AFP, AFU, and APT.

1.5.3 Prognosis Evaluation

OS was defined as the time from treatment initiation to death or the last follow-up. PFS was defined as the time from treatment initiation to any event, including recurrence, death, fatal or intolerable adverse reactions.

1.5.4 Adverse Reactions

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [8]. Grade ≥3 treatment-related adverse events were compared between groups.

1.5.5 Follow-up

Patients were followed up monthly or irregularly for 2 years, with physical examination, blood routine, liver and kidney function, AFP, and contrast-enhanced CT if necessary. The follow-up cutoff date was March 31, 2024.

1.6 Statistical Methods

SPSS 19.0 was used for data analysis. Measurement data were expressed as $\bar{x}\pm s$ and compared using independent-samples t-test. Repeated-measures ANOVA and LSD-t test were used for multi-time point data. Enumeration data were expressed as cases (%) and compared using χ^2 test or Fisher's exact test. Rank sum test was used for ordinal data. Survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test. $P<0.05$ was considered statistically significant.

2 Results

2.1 Treatment Efficacy

The difference in efficacy between the two groups was statistically significant ($P<0.05$). The ORR was significantly higher in the combination group than in the control group (83.02% vs 61.11%, $\chi^2=6.363$, $P = 0.012$). Table 2.

Tab.2 Comparison of therapeutic effects between two groups [case(%)]

Group	n	CR	PR	SD	PD	ORR
Combined group	53	31(58.49)	13(24.53)	7(13.21)	2(3.77)	83.02%
Control group	54	14(25.93)	19(35.19)	14(25.93)	7(12.96)	61.11%
Z/χ^2value			13.027			6.363
***P*value**			0.005			0.012

2.2 Serum Markers at Different Time Points

There were no significant differences in AFP, AFU, and APT levels between the two groups before treatment ($P > 0.05$). Levels at 2, 4, and 6 months after treatment were lower than baseline in both groups ($P<0.05$), and were significantly lower in the combination group at each time point ($P<0.05$). Table 3 and Table 4.

Tab.3 Comparison of AFP and AFU at different time points between two groups ($\bar{x}\pm s$)

Group	n	AFP(ng/mL)				AFU(U/L)			
		before treatment	2 month after treatment	4 month after treatment	6 month after treatment	before treatment	2 month after treatment	4 month after treatment	6 month after treatment
Combined group	**53**	885.13±68.56	237.03±47.46^{ab}	286.31±63.52^{abc}	314.75±57.61^{abcd}	39.12±1.71	18.65±0.97^{ab}	21.50±1.28^{abc}	23.20±1.53^{abcd}
Control group	**54**	882.94±74.77	388.46±85.62^{b}	422.96±74.59^{bc}	449.32±73.82^{bc}	40.07±10.64	25.36±9.35^{b}	28.56±11.34^{b}	31.47±14.21^{bc}
F/P_{group}		199.966/<0.001				26.995/<0.001			
F/P_{time}		2013.843/<0.001				48.408/<0.001			
$F/P_{interaction}$		24.742/<0.001				2.833/0.041			

Note: Compared with Control group, $^{a}P<0.05$; Compared with before treatment, $^{b}P<0.05$; Compared with 2 month after treatment, $^{c}P<0.05$; Compared with 4 month after treatment, $^{d}P<0.05$.

Tab.4 Comparison of APT at different time points between two groups ($\bar{x}\pm s$)

Group	n	APT(ng/mL)			
		before treatment	2 month after treatment	4 month after treatment	6 month after treatment
Combined group	**53**	74.46±36.80	35.51±14.11^{ab}	37.82±16.21^{ab}	39.12±19.89^{ab}
Control group	**54**	71.44±31.54	42.65±17.77^{b}	52.52±19.83^{bc}	55.26±21.64^{bc}
F/P_{group}		21.271/<0.001			
F/P_{time}		47.530/<0.001			
$F/P_{interaction}$		3.300/0.039			

Note: Compared with Control group, $^{a}P<0.05$; Compared with before treatment, $^{b}P<0.05$; Compared with 2 month after treatment, $^{c}P<0.05$; Compared with 4 month after treatment, $^{d}P<0.05$.

2.3 Survival

The follow-up duration was 4-24 months, with a median follow-up of 16 months. The median OS was 20 months in the combination group and 16 months in the control group. The median PFS was 9.5 months and 6 months, respectively. The 2-year OS (log-rank $\chi^2 = 4.863$, $P = 0.027$) and PFS (log-rank $\chi^2 = 3.970$, $P = 0.046$) were significantly higher in the combination group (Figure 1).

2.4 Adverse Reactions

Grade ⩾3 adverse events occurred in 6 patients (11.32%) in the combination group: hand-foot skin reaction (3 cases), myelosuppression (2 cases), diarrhea (1 case), all relieved after dose reduction and symptomatic treatment. In the control group, 2 patients (3.70%) had adverse events (liver function injury, myelosuppression), relieved after symptomatic treatment. There was no significant difference in the incidence of adverse reactions between the two groups ($\chi^2 = 1.277$, $P = 0.258$).

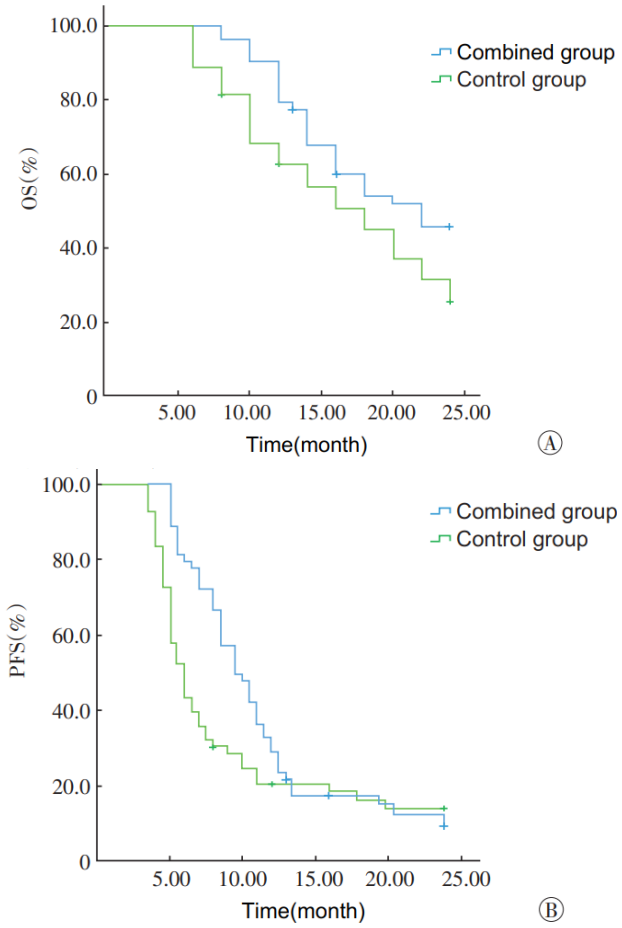

Fig.1 Survival curves of patients in the two groups

3 Discussion

Postoperative recurrence and metastasis are important factors affecting the prognosis of patients with HCC. The occurrence, development, invasion and metastasis of recurrent HCC are the result of combined effects of multiple factors [9]. For patients with recurrent HCC who have lost the opportunity for surgery, interventional therapy can improve symptoms and quality of life, and prolong survival to a certain extent [10]. TACE and RFA are the main non-surgical treatments at present. However, due to the dual blood supply system of the liver, the formation of tumor collateral circulation after TACE may lead to local recurrence and metastasis, thereby affecting long-term efficacy [11]. RFA is limited by its ablation range, which may result in incomplete tumor destruction and local recurrence [12]. Therefore, the combination of TACE and RFA is widely used to effectively compensate for the shortcomings of single therapy. Studies have shown that TACE combined with RFA can significantly prolong patient survival, with no significant difference compared with surgical treatment [13], but its long-term efficacy is still unsatisfactory. As a targeted drug that inhibits tumor cell growth, the efficacy of sorafenib combined with chemointerventional therapy for postoperative recurrent HCC remains unclear.

The present study showed that the ORR in the combination group was significantly higher than that in the control group, indicating that the addition of sorafenib can effectively improve the therapeutic effect of TACE combined with RFA. The mechanism of TACE in the treatment of HCC is based on the vascular supply of HCC: most blood supply of HCC nodules originates from the hepatic artery. Therefore, blocking the hepatic artery can induce ischemic necrosis of tumor tissue without affecting normal liver tissue, thus effectively reducing tumor burden. Meanwhile, the infused chemotherapeutic drugs reach a high concentration in tumor tissue but a low concentration in other parts of the body, which effectively reduces toxic and side effects [6]. In addition, angiography during TACE can clearly demonstrate the scope and size of the tumor, providing a basis for subsequent RFA. As an emerging treatment for HCC, RFA mainly achieves complete destruction and thorough elimination of tumor cells through thermal ablation. Its principle is to generate high temperature via the oscillation and collision of charged ions and polar molecules in malignant tumor cells with poor heat tolerance, thereby achieving in-situ inactivation. RFA is characterized by high local control ability and minimal invasiveness [14], and is currently a radical treatment for tumors smaller than 3 cm in diameter. Therefore, TACE can reduce the heat-sink effect of subsequent ablation by blocking tumor blood supply, while the hyperthermia in the tumor area induced by ablation can enhance the efficacy of TACE. Although local combination therapy has achieved certain efficacy in intermediate and advanced HCC, only 10% of patients achieve CR after TACE combined with RFA. Regarding the low CR rate in HCC patients treated with TACE plus RFA, studies have reported that the expression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) may increase after incomplete embolization, leading to poor long-term survival in these patients [15]. Therefore, sorafenib, an inhibitor of VEGF and PDGF receptors, can exert a favorable

synergistic effect with TACE combined with RFA in the treatment of HCC.

AFP, AFU, and abnormal prothrombin (APT) are recommended HCC markers in the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2017 Edition). Their levels are of great significance for the diagnosis, progression and prognosis of HCC, and can also reflect the therapeutic effect to a certain extent [16]. The results of this study showed no significant differences in AFP, AFU and APT levels between the two groups before treatment, while these indicators in the combination group were significantly lower than those in the control group after treatment, indicating that the addition of sorafenib can better reduce tumor marker levels and enhance therapeutic efficacy. Studies have shown that HCC patients with serum AFP < 400 ng/mL after surgery have a longer median survival time [17]. AFP is also an important indicator in the Cancer of the Liver Italian Program (CLIP) scoring system. Studies have demonstrated that the combination of AFU, APT, and AFP can significantly improve the diagnostic sensitivity and detection rate of HCC [18]. Therefore, reducing serum levels of AFP, AFU, and APT is of great significance for improving the prognosis of HCC patients.

The survival results of this study showed that the median OS and median PFS in the combination group were significantly higher than those in the control group, indicating that the addition of sorafenib can effectively improve patient prognosis. For patients with postoperative recurrent HCC, prolonging survival and delaying disease progression are particularly important. TACE is effective for well-vascularized tumor tissue but less effective for poorly vascularized lesions. Moreover, the presence of peritumoral tissue, fibrous capsule, extracapsular invasive cancer tissue and portal vein tumor thrombus, which are mainly supplied by the portal vein, predisposes tumors to recurrence and metastasis [19]. Meanwhile, hypoxia of tumor tissue after treatment can promote the expression of VEGF, increasing the risk of recurrence and metastasis. RFA is less effective for large HCC due to its limited local ablation range [20]. As a multi-targeted molecular targeted drug, sorafenib can directly inhibit tumor growth by blocking the RAF/MEK/ERK signaling pathway, and also block the formation of neovascularization in HCC by inhibiting VEGF and PDGF [21], thereby compensating for the shortcomings of chemointerventional therapy. Studies have shown that continuous sorafenib treatment (continuous administration without interruption during chemotherapy and interventional therapy) and intermittent sorafenib treatment (administration before and after interventional therapy, with interruption during treatment) combined with TACE can effectively delay HCC progression and prolong patient survival, whereas sequential therapy (administration after completion of chemointerventional therapy) shows no significant improvement in prognosis [22]. The main adverse reactions of sorafenib are hand-foot skin reactions, which are mostly related to dose adjustment or treatment interruption. The incidence of grade $\geqslant$ 3 adverse reactions showed no significant difference between the two groups, confirming that sorafenib (continuous administration, 400 mg twice daily) does not increase the risk of TACE and RFA treatment, ensuring treatment safety.

Based on the above cohort study, we conclude that sorafenib combined with TACE and RFA has significant efficacy in the treatment of postoperative recurrent HCC and can effectively improve patient prognosis. However, this study has several limitations: it is a single-center study with a relatively small sample size, which is prone to type II statistical error, and the follow-up duration is relatively short. Although the sorafenib combination group showed a trend of prolonged OS, further in-depth investigations based on domestic multi-center and large-sample randomized controlled trials are still needed.

Confict of interest None

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·消化道肿瘤专题·论著·

索拉非尼联合经导管肝动脉化疗栓塞及射频消融治疗肝细胞癌术后复发的效果

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摘要：目的　探讨索拉非尼联合经导管肝动脉化疗栓塞(TACE)及射频消融(RFA)对术后复发的肝细胞癌(HCC)患者的治疗效果，为临床选择合理干预方案提供参考。**方法**　选取2020年1月至2022年3月间在衡水市中医医院诊断及治疗的术后复发的HCC患者107例为研究对象，以随机数表法分为联合组(n=53)与对照组(n=54)，对照组采用TACE联合RFA治疗，联合组在对照组治疗的基础上加用甲苯磺酸索拉非尼片400 mg/次，2次/d，直至HCC再次进展。比较两组患者临床疗效及治疗前后血清甲胎蛋白(AFP)、α-L-岩藻糖苷酶(AFU)及异常凝血酶原(APT)水平，采用Kaplan-Meier法绘制生存曲线比较两组患者2年生存情况。**结果**　联合组治疗客观缓解率显著高于对照组(83.02% *vs* 61.11%，χ^2=6.363，P=0.012)；治疗前两组AFP、AFU及APT水平差异无统计学意义(P>0.05)，治疗后2、4、6个月联合组AFP、AFU及APT均低于对照组(P<0.05)。随访2年，中位随访时间16个月，截至末次随访，联合组和对照组中位总生存(OS)时间分别为20、16个月，中位无进展生存(PFS)时间分别为9.5、6个月。联合组患者2年OS率(log rank χ^2=4.863，P=0.027)及PFS率(log rank χ^2=3.970，P=0.046)显著高于对照组。联合组和对照组不良反应发生率无差异无统计学意义(11.32% *vs* 3.70%，χ^2=1.277，P=0.258)。**结论**　索拉非尼联合TACE和RFA在治疗HCC术后复发的效果显著，进一步延长患者生存期，并发症可控，能有效提高患者预后。

关键词：索拉非尼；经导管肝动脉化疗栓塞；射频消融；肝细胞癌；术后复发；生存分析

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Sorafenib combined with transcatheter arterial chemoembolization and radiofrequency ablation in the treatment of postoperative recurrence of hepatocellular carcinoma

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Abstract: Objective　To explore the therapeutic effect of sorafenib combined with transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) in patients with postoperative recurrent hepatocellular carcinoma (HCC), and to provide a reference for clinical selection of reasonable intervention plans. **Methods**　A total of 107 patients with postoperative recurrent HCC diagnosed and treated in Hengshui Hospital of Traditional Chinese Medicine from January 2020 to March 2022 were selected as the research subjects. They were divided into the combination group (n=53) and the control group (n=54) by random number table method. The control group was treated with TACE combined with RFA, while the combination group was additionally given sorafenib tosylate tablets at a dose of 400 mg per time, twice a day, until the HCC progressed again. The clinical efficacy of the two groups was compared, as well as the serum levels of alpha-fetoprotein (AFP), α-L-fucosidase (AFU) and abnormal prothrombin (APT) before and after treatment. The

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Kaplan-Meier method was used to draw survival curves for comparing the 2-year survival status of the two groups. **Results** The objective response rate of the combination group was significantly higher than that of the control group (83.02% *vs* 61.11%, χ^2=6.363, *P*=0.012). There were no statistically significant differences in the levels of AFP, AFU and APT between the two groups before treatment (*P*>0.05). At 2, 4 and 6 months after treatment, the levels of AFP, AFU and APT in the combination group were lower than those in the control group (*P*<0.05). During the 2-year follow-up, the median follow-up time was 16 months. Up to the last follow-up, the median overall survival (OS) of the combination group and the control group was 20 months and 16 months, respectively, and the median progression-free survival (PFS) was 9.5 months and 6 months, respectively. The 2-year OS rate (log rank χ^2=4.863, *P*=0.027) and PFS rate (log rank χ^2=3.970, *P*=0.046) of the combination group were significantly higher than those of the control group. There was no statistically significant difference in the incidence of adverse reactions between the combination group and the control group (11.32% *vs* 3.70%, χ^2=1.277, *P*=0.258). **Conclusion** Sorafenib combined with TACE and RFA has a significant effect in the treatment of postoperative recurrent HCC, which can further prolong the survival of patients, control complications, and effectively improve the prognosis of patients.

Keywords: Sorafenib; Transcatheter arterial chemoembolization; Radiofrequency ablation; Hepatocellular carcinoma; Postoperative recurrence; Survival analysis

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我国是肝细胞癌(hepatocellular carcinoma, HCC)大国,HCC发病率及死亡率约占全球总数的一半[1],手术切除是治疗HCC的首选方法,但由于肿瘤细胞的残留、转移,HCC术后复发率较高,据统计早中期肝癌术后复发转移率高达70%[2]。对于复发HCC,手术仍是首选治疗方法,但因术后肝脏储备功能不足、复发病灶多发、手术本身创伤较大等原因,真正能够再次接受手术的患者较少,经导管肝动脉化疗栓塞(transcatheter arterial chemoembolization, TACE)及射频消融(radiofrequency ablation, RFA)是目前常用的非手术治疗方式[3-4]。研究显示,TACE联合RFA可以取得较好的治疗效果[5]。索拉非尼作为HCC靶向治疗药物,可通过多种途径抑制肿瘤生长,但索拉非尼联合TACE及RFA治疗HCC术后复发的效果尚不明确,为此,笔者开展一项前瞻性对照研究,结果报道如下。

1　资料与方法

1.1　样本量计算　采用前瞻性随机对照研究设计,HCC患者治疗总缓解率约为60%[6],预计提高至85%,临床界值δ= 25%,使用双侧检验,α= 0.05,β = 0.20,把握度设为80%。根据公式 $n=\frac{[Z_{1-\alpha/2}\cdot\sqrt{2\cdot\bar{p}\cdot(1-\bar{p})}+Z_{1-\beta}\cdot\sqrt{p1(1-p1)+p2(1-p2)}]^2}{(p1-p2)^2}$ 计算,需入组患者49例/组,脱落率10%,共需患者107例。变量说明:*n*,每组所需样本量;p1,对照组预期缓解率(0.60);p2,试验组预期总缓解率(0.85);$\bar{p}$=(p1 + p2)/2,*Z*(1-α/2)=1.96; *Z*(1-β)=0.84。

1.2　纳入与排除标准　(1) 纳入标准:①既往HCC诊断明确,且手术过程顺利;②经临床、影像、血清甲胎蛋白(alpha-fetoprotein, AFP)及病理检查确诊为HCC复发;③经评估已不适合接受手术治疗(如单个肿瘤直径>10 cm,或肿瘤直径>5 cm且数目超过3个;肝内血管侵犯、淋巴结转移或远处转移;肝功能Child-Pugh C级;门静脉高压)。(2) 排除标准:①既往接受过TACE、RFA及其他介入治疗;②合并其他肿瘤、感染;③严重心、肺功能或精神障碍;④需引流的中度及以上腹腔积液。(3) 脱落标准:①未按研究方案完成治疗;②研究期间参与其他临床试验,干扰疗效判定;③患者个人意愿中途退出。(4) 终止试验标准:①临床试验期间患者出现病情恶化,有可能发生危险事件,经操作者判断应该停止临床试验者;②发生与治疗方案有关的严重不良事件;③意外事故;④死亡。

1.3　一般资料　选取2020年1月至2022年3月间在衡水市中医医院诊断及治疗的HCC术后复发患者107例,采用随机数字表法随机分为两组,联合组53例,对照组54例,两组的基线特征差异无统计学意义(*P*>0.05),见表1。本研究已充分告知患者研究的目的、方法、风险等信息,承诺对患者的信息进行保密,所有患者均为自愿参加本研究。研究经衡水市中医医院伦理委员会审批通过(20232201),符合《赫尔辛基宣言》伦理准则。

1.4　治疗方案　对照组予以TACE和RFA治疗,联合组在对照组的基础上加用索拉非尼。

1.4.1　TACE　采用改良Seldinger法经股动脉插管,在造影明确肿瘤供血动脉后经导管动脉灌注注入化疗

药物与栓塞剂，化疗药物包括：5-氟尿嘧啶（辽宁新高制药有限公司，国药准字H21024236，规格0.25 g）0.75 g，奥沙利铂（成都长青制药有限公司，国药准字H20020648，规格50 mg）100~150 mg，吡柔比星（瀚晖制药有限公司，国药准字H20045983，规格10 mg）10 mg；栓塞剂采用超乳化碘油（上海旭东海普药业有限公司，国药准字H31021603，规格10 mL）10~30 mL，注入剂量视肿瘤病灶数、大小及供血情况而定，拔除导管后穿刺点压迫止血并加压包扎。

1.4.2 RFA 在TACE完成后2周内实施RFA，术前禁食禁水8 h，同时肌内注射地西泮10 mg，哌替啶50 mg，巴曲酶100 u，根据病灶位置协助患者以合适体位卧于CT机上，先行全肝扫描，定位消融靶灶并确定进针方向、角度、深度，常规消毒、铺巾，使用利多卡因局部麻醉后将RFA针刺入肿瘤内部，设定射频消融参数，15 G单电极消融针进行单针或多针组合消融，频率为480 kHz，温度90~110 ℃，时间20~30 min，消融范围尽量覆盖全部肿瘤组织及肿瘤周边5 mm的癌旁组织。术后观察有无并发症并予以止血、预防感染、护肝及术后护理等干预措施。

1.4.3 索拉非尼 患者入组后开始口服甲苯磺酸索拉非尼片（拜耳医药保健有限公司，批准文号H20160201，规格200 mg），400 mg/次，2次/日，若出现难以耐受的不良反应减为200 mg/次，2次/日，或停药等症状缓解后继续服用，疗程直至肝癌再次进展。

1.5 观察指标 比较两组患者临床疗效及治疗前后血清肿瘤标志物水平，包括：AFP、α-L-岩藻糖苷酶（α-L-fucosidase，AFU）、异常凝血酶原（abnormal prothrombin，APT）水平，同时对比两组的预后和治疗安全性。预后指标包括总生存期（overall survival，OS）和无进展生存期（progression-free survival，PFS），安全性指标主要分析治疗相关不良反应。

1.5.1 疗效判定 于治疗1个月后，根据改良实体瘤疗效评价标准[7]进行评定，包括完全缓解（complete remission，CR）、部分缓解（partial remission，PR）、疾病稳定（stable disease，SD）、疾病进展（progressive disease，PD）。客观缓解率（objective response rate，ORR）=（CR+PR）例数/总例数×100%

1.5.2 血清肿瘤标志物检测 于所有患者治疗前及治疗后2、4、6个月抽取清晨空腹静脉血，送至检验科进行AFP、AFU及APT检测。

1.5.3 预后判定 OS是指患者从开始治疗至死亡或随访截止的时间；PFS是指从开始治疗到发生任何事件的时间，包括复发、死亡、出现致死性或无法耐受的不良反应等各种事件。

1.5.4 不良反应 参照不良事件通用术语标准（Common Terminology Criteria for Adverse Events，CTCAE）4.0[8]评估和统计不良反应，主要比较研究治疗和随访期间3级及以上不良反应发生情况。

1.5.5 随访 患者出院后每月于门诊随访一次或不定期返院复查，检查患者生命体征、血常规、肝肾功能、血清AFP水平，必要时使用增强CT评估进展情况，随访2年，随访截止日期为2024年3月31日。

1.6 统计学方法 采用SPSS 19.0软件处理数据。计量资料以$\bar{x}\pm s$表示，比较采用独立样本t检验；多时间点数据的比较采用重复测量资料的方差分析及两两比较的LSD-t检验。计数资料以例（%）表示，采用χ^2检验或Fisher精确检验比较，等级资料比较采用秩和检验。应用Kaplan-Meier法绘制生存曲线，log rank检验比较组间差异。P<0.05为差异有统计学意义。

2 结 果

2.1 治疗效果比较 两组疗效比较差异有统计学意义（P<0.05），且联合组ORR显著高于对照组（83.02% *vs* 61.11%，χ^2=6.363，P=0.012），见表2。

2.2 不同时间点血清标志物比较 治疗前两组

表1 两组患者基线数据比较 （例）

Tab.1 Comparison of baseline characteristics between two groups （case）

项目	联合组（n=53）	对照组（n=54）	$t/\chi^2/Z$值	P值
年龄（岁）[a]	68.17±2.83	68.04±3.16	0.223	0.824
性别（男/女）	42/11	46/8	0.646	0.421
BMI（kg/m^2）[a]	21.06±4.88	19.86±3.91	1.418	0.159
白蛋白（g/L）[a]	45.43±3.39	44.37±3.25	1.643	0.103
总胆红素（μmol/L）[a]	1.96±0.38	2.11±0.42	1.944	0.055
AFP				
>200 ng/mL	28	23	1.124	0.289
≤200 ng/mL	25	31		
肿瘤数目				
单个	39	44	0.959	0.328
多个	14	10		
肿瘤最大直径				
≥3 cm	38	42	0.524	0.469
<3 cm	15	12		
门静脉癌栓	4	7	0.365	0.546
肝硬化	46	50	0.448	0.503
门静脉高压	5	3	0.156	0.693
Child-Pugh分级				
A	49	49		
B	3	4	0.311	0.756
C	1	1		
并发症				
出血	3	2	0	0.983
脓肿	4	7	0.365	0.546
积液	9	10	0.043	0.835
肺炎	1	4	0.801	0.371

注：[a]为数据以$\bar{x}\pm s$表示；BMI为身体质量指数。

AFP、AFU 及 APT 水平差异无统计学意义（P>0.05），治疗 2、4、6 个月两组均低于治疗前（P<0.05），且联合组各时点均显著低于对照组（P<0.05），见表 3、表 4。

2.3　生存情况对比　随访 4~24 个月，中位随访时间 16 个月，截至末次随访，联合组和对照组中位 OS 分别为 20、16 个月，中位 PFS 分别为 9.5、6 个月。联合组患者 2 年 OS（log rank χ^2=4.863，P=0.027）及 PFS（log rank χ^2=3.970，P=0.046）显著高于对照组，见图 1。

2.4　两组的不良反应　研究治疗及随访期间，联合组发生Ⅲ度以上不良反应共 6 例（11.32%），其中 3 例为手足不良反应，2 例为骨髓抑制，1 例为腹泻，经过索拉非尼减量及对症处理后缓解；对照组共发生 2 例（3.70%）不良反应，其中 1 例为肝功损害，1 例为骨髓抑制，均经对症处理后缓解。两组不良反应发生率差异无统计学意义（χ^2=1.277，P=0.258）。

表 2　两组治疗效果比较　［例（%）］

Tab.2　Comparison of therapeutic effects between two groups ［case（%）］

组别	例数	CR	PR	SD	PD	ORR（%）
联合组	53	31（58.49）	13（24.53）	7（13.21）	2（3.77）	83.02
对照组	54	14（25.93）	19（35.19）	14（25.93）	7（12.96）	61.11
Z/χ^2值			13.027			6.363
P值			0.005			0.012

表 3　两组不同时间点 AFP 和 AFU 比较　（$\bar{x}\pm s$）

Tab.3　Comparison of AFP and AFU at different time points between two groups　（$\bar{x}\pm s$）

组别	例数	AFP（ng/mL）				AFU（u/L）			
		治疗前	治疗后 2 个月	治疗后 4 个月	治疗后 6 个月	治疗前	治疗后 2 个月	治疗后 4 个月	治疗后 6 个月
联合组	53	885.13±68.56	237.03±47.46^{ab}	286.31±63.52^{abc}	314.75±57.61^{abcd}	39.12±1.71	18.65±0.97^{ab}	21.50±1.28^{abc}	23.20±1.53^{abcd}
对照组	54	882.94±74.77	388.46±85.62^{b}	422.96±74.59^{bc}	449.32±73.82^{bc}	40.07±10.64	25.36±9.35^{b}	28.56±11.34^{b}	31.47±14.21^{bc}
$F/P_{组间}$值		199.966/<0.001				26.995/<0.001			
$F/P_{时间}$值		2 013.843/<0.001				48.408/<0.001			
$F/P_{交互}$值		24.742/<0.001				2.833/0.041			

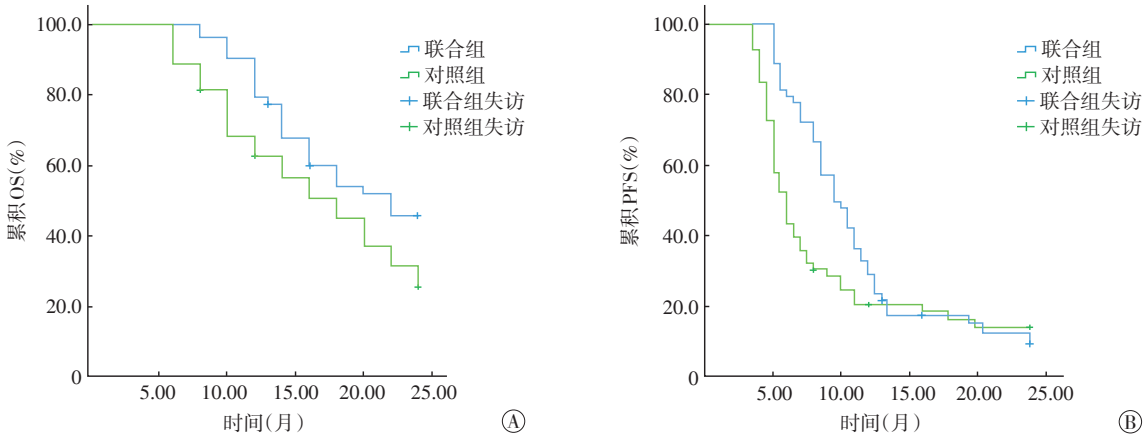
注：与对照组同期比较，^{a}P<0.05；与本组治疗前比较，^{b}P<0.05；与本组治疗后 2 个月比较，^{c}P<0.05；与本组治疗后 4 个月比较，^{d}P<0.05。

表 4　两组不同时间点 APT 比较　（ng/mL，$\bar{x}\pm s$）

Tab.4　Comparison of APT at different time points between two groups　（ng/mL，$\bar{x}\pm s$）

组别	例数	治疗前	治疗后 2 个月	治疗后 4 个月	治疗后 6 个月
联合组	53	74.46±36.80	35.51±14.11^{ab}	37.82±16.21^{abc}	39.12±19.89^{abcd}
对照组	54	71.44±31.54	42.65±17.77^{b}	52.52±19.83^{bc}	55.26±21.64^{bc}
$F/P_{组间}$值			21.271/<0.001		
$F/P_{时间}$值			47.530/<0.001		
$F/P_{交互}$值			3.300/0.039		

注：与对照组同期比较，^{a}P<0.05；与本组治疗前比较，^{b}P<0.05；与本组治疗后 2 个月比较，^{c}P<0.05；与本组治疗后 4 个月比较，^{d}P<0.05。



注：A 为 OS；B 为 PFS。

图 1　两组患者的生存曲线

Fig.1　Survival curves of patients in the two groups

3　讨　论

HCC 术后复发与转移是影响 HCC 患者预后的重要因素，复发的发生、发展、侵袭和转移是多因素共同作用的结果[9]，对于已丧失手术机会的复发性 HCC 患者，介入治疗可一定程度改善患者症状、生活质量

并延长生存期[10]。TACE及RFA是当前主要的非手术治疗手段，但由于肝脏的双供血系统，TACE术后肿瘤侧支循环的形成可能导致局部再次复发、转移，进而影响远期疗效[11]，而RFA由于本身消融范围限制，可能存在肿瘤破坏不完全、局部复发等不足[12]。因此目前多使用TACE联合RFA，能够有效弥补单一方式的不足。研究显示联合TACE及RFA治疗能显著提高患者生存时间，且与手术治疗差异无统计学意义[13]，但其远期疗效仍不够理想。索拉非尼作为抑制肿瘤细胞生长的靶向药物，其联合化学介入治疗对于HCC术后复发的效果尚不明确。

本研究显示，联合组治疗后ORR显著高于对照组，证明加用索拉非尼可有效提高TACE联合RFA的治疗效果。TACE治疗HCC的主要原理是基于HCC的血管构成，HCC结节的血供大多数来源于肝动脉，因此阻断肝动脉供血可使肿瘤组织缺血坏死同时不影响正常肝组织，有效减轻肿瘤负荷，同时注入的化疗药物在肿瘤组织的浓度较高，而身体其他部位浓度较低，有效减轻毒副反应[6]；此外TACE操作中的血管造影也可清晰显示肿瘤组织的范围及大小，为RFA的治疗做好基础。RFA作为新兴的HCC治疗手段，主要是利用热消融完全毁损并彻底杀灭肿瘤细胞，其原理为在高温耐受力较差的恶性肿瘤细胞范围内通过带电离子及极性分子的震荡和碰撞产生高温进而达到原位灭活作用，具有较高的局部控制能力及微创的特点[14]，是目前直径<3 cm肿瘤的根治方法。因此，TACE可以通过阻断肿瘤的供血来减少后续消融的热吸收效应，而消融引起的肿瘤区域的高热可以加强TACE的效果，尽管局部联合治疗在中晚期HCC中取得了一定的疗效，但仅有10%的HCC患者通过TACE联合RFA治疗后能获得CR。对于接受TACE联合RFA治疗的HCC患者的低CR率，研究报道血管内皮生长因子和血小板源性生长因子的表达可能会随着不完全栓塞而增高，导致这些患者的长期生存结果较差[15]。因此，同时使用血管内皮生长因子和血小板源性生长因子受体抑制剂索拉非尼，对TACE联合RFA治疗HCC患者可产生良好的协同作用。

AFP、AFU及APT作为《原发性肝癌诊疗规范（2017年版）》推荐的HCC标志物，其水平对于HCC的诊断、进展及预后均具有重要意义，也可一定程度反映治疗效果[16]。本研究结果显示，治疗前两组AFP、AFU、APT水平差异无统计学意义，治疗后联合组的上述指标均显著低于对照组，表明加用索拉非尼可更好地改善肿瘤标志物水平并增强治疗效果。有研究表明血清AFP<400 ng/mL的HCC术后患者具有较长的中位生存期[17]，同时也是意大利肝癌项目（Cancer of the Liver Italian Program，CLIP）评分系统的重要指标。有研究显示AFU、APT联合AFP可显著提高HCC的诊断敏感性及检出率[18]，因此降低血清AFP、AFU、APT水平对于改善HCC患者预后具有重要意义。

本研究生存情况结果显示，联合组中位OS及中位PFS均显著高于对照组，表明加用索拉非尼能有效改善患者预后。对于HCC术后复发患者，延长生存时间及延缓病情进展的意义更为重大。TACE治疗对于血供丰富的肿瘤组织效果较好，而对于供血贫乏的肿瘤组织效果不够理想，且由于存在肿瘤组织周边、纤维包膜、包膜外浸润癌组织及门静脉癌栓等由门静脉供血的肿瘤组织，使得肿瘤容易发生复发和转移[19]，同时由于治疗后肿瘤组织缺氧状态会促进血管内皮生长因子的表达，增加了复发及转移风险。RFA则由于局部治疗范围有限，因此对于较大HCC的治疗效果不够理想[20]。索拉非尼作为多靶点分子靶向药物，可通过抑制RAF/MEK/ERK等信号通路直接抑制肿瘤生长，同时也可通过抑制血管内皮生长因子和血小板衍生生长因子阻断肝癌新生血管的形成[21]，进而弥补化学介入治疗的不足。研究显示索拉非尼连续治疗（即患者连续服用，在化疗及介入治疗过程中不停药）及间断治疗（在化疗及介入治疗前后服用，治疗中停用）联合TACE可有效延缓HCC进展并延长患者生存期，但序贯治疗（在化疗及介入治疗完成后开始服用）对患者预后并无有效改善[22]。索拉非尼的主要不良反应为手足及皮肤反应，其发生的原因多与治疗过程中剂量改变或用药中断有关。本研究不良反应发生情况显示，两组3级及以上不良反应发生率差异无统计学意义，证实使用索拉非尼（连续治疗，400 mg/次，2次/日）不会增加TACE及RFA治疗的风险，治疗安全性得以保障。

通过上述队列研究，笔者认为：索拉非尼联合TACE和RFA治疗HCC术后复发的效果显著，可有效改善患者预后。但局限性在于本研究为单中心研究且入组样本较小，易发生统计学第Ⅱ类错误，观察时间也较短，虽索拉非尼联合组表现出能延长OS的趋势，但仍需国内有多中心、大样本的随机对照研究进行更深入的探讨和报道。

利益冲突　无

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