Impact of local tumor lesion treatments and preoperative indicators on the survival of patients with small hepatocellular carcinomas

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Abstract. The prognosis for small hepatocellular carcinomas (SHCC) remains uncertain. The aim of the present study was to compare three local tumor lesion treatments and identify the prognostic factors in patients with SHCC by analyzing preoperative indicators. A retrospective study was performed using data from 206 patients with SHCC from 2006-2015. All of the patients had undergone transarterial chemoembolization (TACE) alone, TACE plus percutaneous microwave coagulation therapy (PMCT) or surgical resection (SR). The Kaplan-Meier method was used to calculate the survival rates. Multivariate analysis was conducted using Cox regression analysis. The median survival time of patients with SHCC was 27 (range, 14-49) months in the TACE group, 29.5 (range, 16-52) months in the TACE-PMCT group and 36.5 (range, 26-52) months in the SR group (P=0.091). The 1, 3 and 5-year survival rates for patients with SHCC were 82.4, 64.9 and 46.8% in the TACE group; 89.0, 72.6 and 58.3% in the TACE-PMCT group and 88.8, 72.3 and 58.6% in the SR group (P=0.181), respectively. Analysis from the Cox regression model demonstrated that preoperative α-fetoprotein (AFP; <400 ng/ml vs. ≥400 ng/ml; HR=0.548; P=0.036) was an independent predictor of the survival time of patients with SHCC. Analysis of patients with preoperative AFP levels of ≥400 ng/ml revealed that the median survival time in the SR group was 36 (range, 28.25-52) months, significantly longer than the TACE (17 months; range, 12-44 months) and TACE-PMCT group (27 months; range, 14-55 months; P=0.035). The 1, 2 and 3-year survival rates for patients with SHCC with ≥400 ng/ml AFP were: 70.8, 55.5 and 49.9% in the TACE group; 83.7, 68.0 and 60.8% in the TACE-PMCT group; and 90.9, 81.8 and 61.0% in SR group, respectively (P=0.664). However, there was no significant difference among the three groups in the survival time of patients with SHCC with <400 ng/ml preoperative AFP. The observations indicated that SR is not significantly different for overall survival time in the patients with SHCC between the two groups; this method can be employed for patients with SHCC. This was based on the median survival time of patients with ≥400 ng/ml AFP in the SR group who had a longer survival time and a higher survival rate than in the TACE and TACE-PMCT group.

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Introduction

Hepatocellular carcinoma (HCC) is one of the five most common cancer types globally and is an aggressive malignancy with poor prognosis (1). The majority of HCC cases occur in eastern Asia and sub-Saharan Africa, particularly in China, which accounts for >50% of HCC cases globally (2). The definition of small HCC (SHCC) is a single HCC nodule <5 cm or ≤3 nodules and a maximum diameter of each nodule <3 cm (3). A single HCC nodule of <3 cm is generally considered to be early stage HCC, according to the Barcelona Clinic Liver Cancer stage (BCLC) criteria (4).

Currently, several methods are used for the treatment of SHCC. Surgical resection (SR) is still regarded as the 'gold standard' treatment for HCC, particularly for SHCC (5). However, the long-term clinical outcomes remain frustrating due to a high recurrence rate (4,5). In addition, a number of patients cannot undergo the SR treatment by the time the diagnosis of SHCC is confirmed (6). A number of patients may worry about the high risk of hepatolobectomy and refuse surgical treatment (7). A number of alternative, local, mini-invasive therapies for SHCC have been produced and have become popular treatments with less surgical intervention and fewer complications (8-10). Several previous studies have reported that the local mini-invasive therapies (monotherapy or combined therapy) were safe and effective for patients with

SHCC in the short term (11,12). However, little attention has been paid to whether local mini-invasive therapies were effective for patients with SHCC in the long term (13). Furthermore, no data have been reported concerning the appropriate treatment for patients with SHCC, particularly for patients with SHCC and variousα-fetoprotein (AFP) levels (14,15).

A number of researchers have drawn different conclusions regarding the value of features, including tumor size and margin, in the prognosis of postoperative outcomes of patients with SHCC (16-19). Preoperative indicators were significantly important for the prognosis of patients with SHCC (20,21). However, to the best of our knowledge, there are still only scarce reports regarding the preoperative indicators in clinical and laboratory testing as predictive factors for patients with SHCC. Consequently, the present study sought to explore the influence predictive factors for patients with SHCC by comprehensively analyzing medical histories, imaging features and laboratory results.

Treatment programs for 206 patients with SHCC were determined through the BCLC proposal and patients' informed consent (22,23). By comparing three local tumor lesion treatments, the appropriate treatment for patients with SHCC was elucidated. In addition, preoperative indicators as predictors of HCC prognosis were determined.

Materials and methods

Patients. According to the inclusion and exclusion criteria for the present study, 206 patients were enrolled, including 159 males (77.18%) and 47 females (22.82%), aged 13-87 years with a mean age of 55.68±11.61 years. The inclusion criteria for the study population was as follows: i) Patients aged between 13-87 years; ii) single SHCC (≤3 cm) or multifocal HCC <3.0 cm in the greatest dimension; iii) diabetes mellitus (DM) and hypertension, if present, were controlled with medication; and iv) no multiple organ failure and no severe underlying diseases. Patients were excluded from the study if they: i) Received other treatments in another hospital; ii) were missing data; iii) were not tracked adequately; iv) received a liver transplant; v) received systemic chemotherapy; vi) received sorafenib; or vii) had another type of malignant tumor.

Collection of data and primary end-point assessment. Clinical data were collected from each patient at the time of SHCC diagnosis, including sex, age, other chronic diseases [including hypertension and type 2 DM (T_2DM)], Child-Pugh grade and BCLC stage. Imaging features were also collected, including tumor size, tumor number, cirrhosis, portal vein tumor thrombus (PVTT) and intrahepatic metastasis (IM). All laboratory indicators were collected in the week prior to surgery. Laboratory results determined the AFP, hepatitis B virus surface antigen and hepatitis C antibody (HCV-Ab) levels. The main endpoint was survival time, which was defined as the duration from the time of primary treatment for SHCC to mortality or August 2016, whichever was earlier. The secondary endpoint was outcomes during follow-up, including survival and mortality.

Treatments and follow-up. The SR was performed as a strictly standardized procedure for hepatobiliary surgery. A partial hepatectomy with 1-2 cm tumor-free margin was performed in these patients. Intra-operative ultrasonography was routinely used to estimate the number of tumors, and tumor size(s), location(s) and border.

Transarterial chemoembolization (TACE) was performed using the following procedures. Following using 5-French catheter selection to perform arteriography of the superior mesenteric, celiac and common hepatic arteries, the hepatic artery was catheterized with a coaxial microcatheter. The microcatheter was positioned into or as close as possible to the tumor feeding branch; then, an emulsion of doxorubicin hydrochloride (Adriamycin) and iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) was slowly infused through the catheter. Oily TACE was performed as selectively as possible and a microcatheter was routinely used. The doses of iodized oil and doxorubicin were determined according to the tumor size and tumor vascularity. The maximum doses of iodized oil and doxorubicin for a single session of TACE was 25 ml and 70 mg, respectively. Infusion of the Lipiodol® mixture was followed by particulate embolization with 1-2 mm diameter gelatin sponge pledgets (Cutanplast; Mascia Brunelli, Milan, Italy).

Percutaneous microwave coagulation therapy (PMCT) was performed using the KY-2000 microwave therapy instruments (Xuzhou Hengda Electronic Co., Ltd., Xuzhou, China). The PMCT procedure was performed by an experienced hepatobiliary surgeon following local anesthesia using 2% lidocaine. The entire procedure was guided and constantly monitored using real-time ultrasound (MyLab™ Twice; Esaote Co., Ltd., Genoa, Italy). Following anesthesia was achieved, a 15-cm 16-gauge cooling unipolar was inserted into the center of the nodule, and coagulation therapy was performed at 2,450 MHz with 60-80 W output for 8-10 min/ablation. The ablation was performed repeatedly until the tumors attained completed necrosis as monitored by real-time ultrasound, and the hyperechoic area overlapped the area of the tumor with a surrounding ≥1 cm safety margin.

Following TACE, PMCT or SR, patients were followed up every 1-3 months during the first 2 years, and at 3-6 months intervals thereafter. Following treatment, patients with SHCC were evaluated for treatment response by combining contrast-enhanced computer tomography with liver function. Patients who experienced recurrence were given subsequent treatment by physicians if clinically feasible.

Statistical analysis. The Kruskal-Wallis test was performed to analyze continuous variables; the results are expressed as the mean ± standard deviation for normal distributions and as median and interquartile range (Q1-Q3) for skewed distributions. For categorical variables, the χ^2 test and Fisher's exact test were utilized. Analyses regarding survival time were generated using the Kaplan-Meier method and COX regression analysis. For Fig. 1, the Spearman's rank correlation coefficient was used. All statistical tests were two-sided, and $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using the SPSS v.22.0 software (IBM Corp., Armonk, NY, USA).

Ethical approval. All procedures in the current study were in accordance with the ethical standards of the Institutional

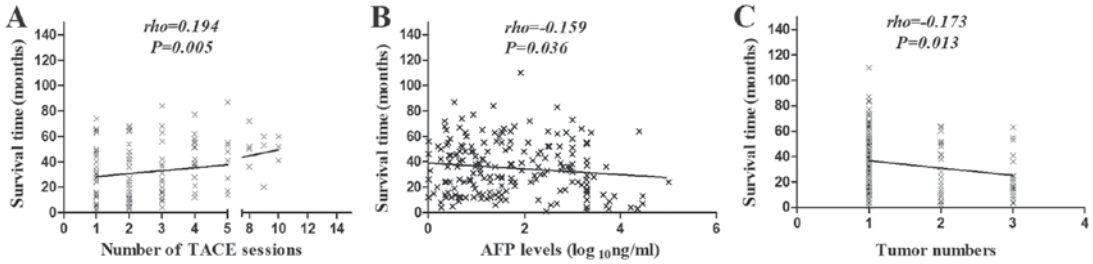

Figure 1. Correlation analysis for patients with small hepatocellular carcinomas. (A) Patients with multiple TACE sessions had longer survival times, compared with patients who underwent a single TACE treatment. (B) Patients with lower AFP levels had longer survival times, compared with those with higher AFP levels. (C) Patients with multiple tumor lesions had shorter survival times than patients with a single tumor lesion. AFP, α-fetoprotein; TACE, transarterial chemoembolization.

Research Committee and with The Declaration of Helsinki. This type of study was a retrospective data analysis, so formal consent was not required.

Results

Patient population. The sample was predominantly male (159/202, 77.2%), full-grown adults with a long period of HBV infection (189/202, 91.7%). As depicted in Table I, the majority of the patients had cirrhosis (88.8%). The majority of patients (154/202, 74.8%) had well-preserved liver function (Child-Pugh A), whereas 49 (23.8%) and 3 patients (1.5%) had Child-Pugh B and C functional status, respectively. The majority of patients (182/202, 88.3%) had an early-stage tumor (BCLC stage A); whilst, 9 (4.4%) and 15 patients (7.3%) had tumors classified as BCLC stage B and C, respectively. The mean number of tumors was 1.31±0.62 (range, 1-3), the mean tumor length was 2.07±0.63 cm (range, 0.5-3 cm) and the mean tumor width was 1.61±0.56 cm (range, 0.5-2.9 cm). Of these patients, 29 (14.1%) had IM, 19 (9.2%) had pathological vascular invasion and 51 (24.75%) had ≥400 ng/ml AFP.

General characteristics of subjects in the three groups. According to the BCLC proposal and with patients' informed consent, a total of 206 patients were included in the present study. A total of 68 patients were initially treated with TACE, 82 patients were treated with TACE-PMCT and 56 patients-were treated with SR. The demographic and clinicopathological characteristics of the three groups are summarized in Table II. The mean patient age in the SR group was younger than the other two groups (P=0.019), and the mean number of tumors was also less than in the other two groups (P=0.001). All patients in the SR group were BCLC stage A. The majority of patients (55/56) were infected with the hepatitis B virus. The proportion of patients with hypertension in the SR group was lower than that of the other two groups (P=0.032). Other laboratory and imaging parameters were not significantly different among three groups including AFP, HCV-Ab, tumor length, tumor width, cirrhosis, PVTT and IM (all of them, P>0.05). Sex, Child-Pugh grade and T_2DM were also not significantly different among the three groups (all, P>0.05).

Associations between survival time and local lesion treatment strategies. No fatal treatment-associated complications were recorded for these patients. This indicates that the local invasive treatments were safe and effective in the short term. The median survival time was 27 (range, 14-49) months in the TACE group, 29.5 (range, 16-52) months in the TACE-PMCT group and 36.5 (range, 26-52) months in the SR group. The results demonstrated that there were no significant differences in the survival time of patients with SHCC among the three groups (P=0.091). In addition, the 1, 3 and 5-year survival rates of patients with SHCC were 82.4, 64.9 and 46.8% in the TACE group; 89, 72.6 and 58.3% in the TACE-PMCT group; and 88.8, 72.3 and 58.6% in the SR group, respectively. This indicated that there were no significant differences among the three groups (P=0.181) for survival time.

Results of the association between survival time and number of TACE sessions. The proportion of patients receiving TACE treatment was the highest in the present study, including the TACE and TACE-PMCT group. Fig. 1A depicts that the number of TACE sessions (r=0.194; P=0.005) was positively correlated with the survival time for patients with SHCC in the TACE and TACE-PMCT group. In addition, there were 24 patients in this group with BCLC stage B or C tumors. They could not undergo the SR treatment and so had received TACE or TACE-PMCT treatment. The median survival time was 13.5 (range, 4.25-27) months for these patients. Therefore, TACE treatment was one of alternative treatment therapies for patients with SHCC, particularly for unresectable patients with SHCC.

Results of the association between survival time and other factors. Fig. 1B and 1C depicted that AFP level (r=-0.159 and P=0.036) and tumor numbers were negatively correlated with survival time (r=-0.173 and P=0.013), which indicated that the patients with higher AFP level and multiple tumor lesions had reduced survival time, compared with patients with lower AFP level and a single tumor lesion.

Cumulative survival rate. Kaplan-Meier survival analyses were used to analyze the cumulative survival rate among the subgroups. The patients' age and preoperative AFP level were divided into two groups. Fig. 2A depicted that the cumulative survival rate of patients with SHCC >60 years of age was significantly lower than that of patients with SHCC <60 years of age (log-rank test P=0.005). Similarly, Fig. 2B demonstrates that the cumulative survival rate of patients with SHCC with preoperative AFP levels of ≥400 ng/ml was significantly lower

Table I. Demographic and clinical data of 206 patients with SHCC.

Variables	Value	Percentage (%)
Sex, male/female	159/47	77.2/22.8
Age, years	55.68±11.61	
Cirrhosis, negative/positive	29/177	14.1/85.9
Tumor length, cm	2.07±0.63	
Tumor width, cm	1.61±0.56	
Tumor number	1.31±0.62	
IM, negative/positive	177/29	85.9/14.1
PVTT, negative/positive	187/19	90.8/9.2
Child-Pugh, A/B/C	154/49/3	74.8/23.8/1.5
BCLC stage, A/B/C	182/9/15	88.3/4.4/7.3
Hypertension, negative/positive	168/24	87.5/12.5
Diabetes mellitus type 2, negative/positive	167/25	87/13
TACE/TACE-PMCT/SR	68/82/56	33/39.8/27.2
<400 ng/ml AFP/≥400 ng/ml AFP	117/89	56.8/43.2

Data are expressed as the mean ± standard deviation. BCLC stage, Barcelona Clinic Liver Cancer stage; IM, intrahepatic metastasis; PVTT, portal vein tumor thrombus; T_2DM, Diabetes mellitus type 2; AFP, α-fetoprotein; TACE, transarterial chemoembolization; TACE-PMCT, TACE plus percutaneous microwave coagulation therapy; SR, surgical resection.

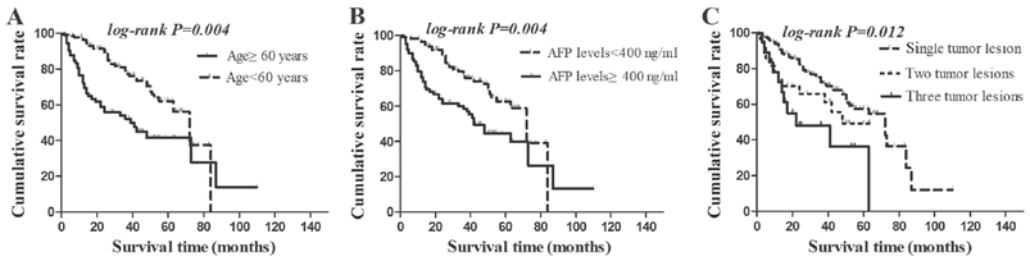

Figure 2. The Kaplan-Meier survival curves for patients with small hepatocellular carcinomas. (A) Significantly higher cumulative survival rate for patients <60 years, compared with those≥60 years. (B) Significantly higher cumulative survival rate for patients with AFP levels <400 ng/ml, compared with patients with AFP levels ≥400 ng/ml. (C) Significantly higher cumulative survival rate for patients with a single tumor lesion, compared with patients with two tumor lesions or three tumor lesions. AFP, α-fetoprotein.

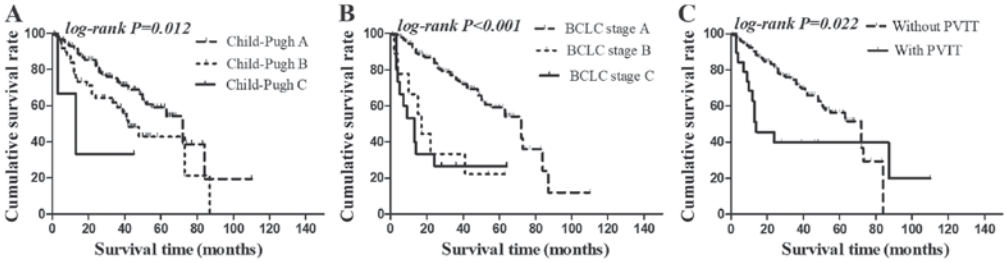

Figure 3. The Kaplan-Meier survival curves for patients with small hepatocellular carcinomas. (A) Significantly improved higher cumulative survival rate of patients with Child-Pugh A, compared with those with Child-Pugh B or Child-Pugh C. (B) Significantly higher cumulative survival rate for patients with BCLC stage A, compared with patients with BCLC stage B or C. (C) Significantly higher cumulative survival rate for patients without PVTT, compared with patients with PVTT. PVTT; portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer.

than that of patients with SHCC with preoperative AFP level of <400 ng/ml (log-rank test P=0.012). Fig. 2C depicts that the cumulative survival rate classifying by tumor numbers was also significantly different in patients with SHCC (log-rank test P=0.004). The data indicates that patients with SHCC, a single tumor lesion had higher cumulative survival rate than patients with multiple tumor lesions. In addition, Fig. 3A and B illustrated that the cumulative survival rates, considering Child-Pugh grade (log-rank test P=0.012) and BCLC stage, were significantly different in patients with SHCC (log-rank test, P<0.001). The Child-Pugh A and BCLC stage A patients had higher cumulative survival rate than patients classified as

Table II. Baseline character of TACE, TACE-PMCT and SR group.

Variables	TACE (n=68)	TACE-PMCT (n=82)	SR (n=56)	P-value
Age, years	56.96±9.20	57.15±13.00	51.99±11.45	0.019[a]
Sex, male/female	50/17	59/23	49/7	0.139
<400 ng/ml AFP	52	57	46	0.307
≥400 ng/ml AFP	16	18	17	
HCV-Ab, N/P	67/1	77/5	52/4	0.273
HBsAg, N/P	5/63	13/69	1/54	0.017[a]
Tumor length, cm	1.96±0.58	2.07±0.65	2.20±0.62	0.102
Tumor width, cm	1.59±0.55	1.68±0.57	1.56±0.54	0.427
Tumor number	1.32±0.66	1.46±0.72	1.05±0.23	0.001[a]
Cirrhosis, negative/positive	8/60	9/73	6/50	0.981
IM, negative/positive	57/11	71/11	49/7	0.822
PVTT, negative/positive	61/7	75/7	51/5	0.930
Child-Pugh A	45	64	45	0.281
Child-Pugh B	21	17	17	
Child-Pugh C	2	1	0	
BCLC stage A	57	69	56	0.022[a]
BCLC stage B	3	6	0	
BCLC stage C	8	7	0	
Hypertension, negative/positive	55/13	69/13	54/2	0.032[a]
T_2DM, negative/positive	57/11	69/13	51/5	0.430

Data are expressed as mean ± standard deviation. [a]P<0.05 was considered to indicate a statistically significant difference. N/P, Negative/Positive; BCLC stage, Barcelona Clinic Liver Cancer stage; IM, intrahepatic metastasis; PVTT, Portal Vein Tumor Thrombus; T_2DM, diabetes mellitus type 2; AFP, α-fetoprotein; HBsAg, hepatitis B virus surface antigen; HCV-Ab, hepatitis C antibody.

Table III. Risk factors for the mortality of patients with SHCC.

Factor	β	SE	Wald χ^2	HR	95% CI	P-values
Age (<60 vs. ≥60 years)	-0.602	0.258	5.452	0.548	0.331-0.908	0.020[a]
AFP (<400 vs. ≥400 ng/ml)	-0.612	0.292	4.394	0.542	0.306-0.961	0.036[a]
BCLC stage, A vs. C	-1.550	0.395	15.363	0.212	0.098-0.461	<0.001[a]
BCLC stage, B vs. C	-0.628	0.573	1.203	0.534	0.106-8.609	0.405

[a]P<0.05 was considered to indicate a statistically significant difference. β, regression coefficient; SE, Standard Error; HR, hazard ratio; CI, confidence interval; BCLC stage, Barcelona Clinic Liver Cancer stage; AFP, α-fetoprotein.

Child-Pugh B and BCLC stage B or classified as Child-Pugh C and BCLC stage C. Similarly, Fig. 3C depicts that the cumulative survival rate classifying by PVTT were also significantly different in patients with SHCC (log-rank test, P=0.02). The data indicated that SHCC patients without PVTT had higher cumulative survival rate than patients with multiple tumor lesions and PVTT. However, there were no statistically significant differences in the cumulative survival rate of patients with SHCC when classifying by sex (log-rank test, P=0.227), age (log-rank test, P=0.87) or T_2DM (log-rank test, P=0.52).

Multivariate analyses. The Cox regression model was used to calculate hazard ratios (HRS). Table III demonstrated that patient age [<60 years vs. ≥60 years; HR=0.548; 95% confidence interval (CI): 0.331-0.908; P=0.020], preoperative AFP level (<400 ng/ml vs. ≥400 ng/ml; HR=0.548; 95% CI: 0.306-0.961; P=0.036) and BCLC stage (A vs. C; HR=0.212; 95% CI: 0.098-0.461; P<0.001) were independent prognostic factors for the survival time of patients with SHCC. Therefore, these results indicate that BCLC stage A was a protective factor, whist older age and higher preoperative AFP levels were risk factors for the survival time of patients with SHCC.

Subgroup analysis based on preoperative AFP level. Multivariate survival analysis revealed that preoperative AFP levels were an independent prognostic factor for patients with SHCC. Subsequently, subgroup survival analysis was

Table IV. Risk factors for mortality of patients with SHCC and ≥400 ng/ml AFP.

Factor	β	SE	Wald χ^2	HR	95% CI	P-values
Tumor number, single lesion vs. three tumor lesions	-1.587	0.628	6.387	0.205	0.606-0.701	0.011[a]
BCLC stage, A vs. C	-2.647	0.685	14.939	0.071	0.104-0.464	<0.001[a]
BCLC stage, B vs. C	-0.551	0.228	5.837	0.576	0.019-0.271	0.012[a]
Hypertension, no vs. yes	-1.263	0.640	3.897	0.283	0.081-0.991	0.048[a]

[a]P<0.05 was considered to indicate a statistically significant difference. SE, Standard Error; HR, hazard ratio; HR, hazardous ratios; CI, confidence interval; BCLC stage, Barcelona Clinic Liver Cancer stage.

performed based on preoperative AFP level. The analysis of the patients with ≥400 ng/ml AFP revealed that the median survival time was 17 (range, 12-44) months in the TACE group, 27 (range, 14-55) months in the TACE-PMCT group and 36 (range, 28.25-52) months in the SR group. Thus, the median survival time of the patients in the SR group was significantly longer than that of the patients in the TACE or TACE-PMCT groups (P=0.035). By contrast, in the analysis of the patients with <400 ng/ml preoperative AFP, the median survival time was 34.5 (range, 15.25-51.5), 38 (range, 22-52) and 38.5 (range, 24-52) months in the TACE group, TACE-PMCT group and SR group, respectively. Therefore, there was no significant difference in the survival time of patients with SHCC with <400 ng/ml preoperative AFP among the three groups (P=0.697). A multivariate analysis of the patients with ≥400 ng/ml preoperative AFP demonstrated that the number of tumors (HR=0.205; P=0.041), hypertension (HR=0.283; P=0.048) and BCLC stage (HR=1.96; P<0.001) were independent prognostic factors for patients with SHCC with preoperative AFP levels of ≥400 ng/ml. The results of the multivariate analysis are depicted in Table IV. Multivariate analysis of the patients with <400 ng/ml preoperative AFP demonstrated that age (HR=0.498; P=0.043) was an independent prognostic factor for those patients with SHCC.

Discussion

HCC affects millions of individuals globally (24). The observation of high-risk patients increases the early detection of SHCC but there are still a number of patients with SHCC who cannot undergo surgery by the time SHCC is diagnosed (25). To date, the treatment of SHCC remains a critical issue (26,27). Three aspects of this problem have been addressed in the present study. The first question involved the comparison of the TACE, TACE-PMCT and SR treatment modalities for patients with SHCC. The second question associated with the exploration of predictive factors for patients with SHCC. The third aspect was subgroup analysis based on preoperative AFP level. It was confirmed that there was no significant difference in the survival time of patients with SHCC receiving TACE, TACE-PMCT or SR treatments; however, it was determined that the number of TACE sessions was positively correlated with the survival time of patients with SHCC. Then, COX regression analysis indicated that age, BCLC stage and preoperative AFP levels were independent predictors for patients with SHCC. Additionally, according to the preoperative AFP level subgroup analysis, there was a significant difference in survival time for patients with SHCC with preoperative AFP ≥400 ng/ml among the three groups. Furthermore, tumor numbers, hypertension and BCLC stage were independent prognostic factors for patients with SHCC and ≥400 ng/ml preoperative AFP.

A 3 cm cutoff was selected to define SHCC in the present study as a result of this threshold being accepted for curative treatment by the Asian Pacific Association for the Study of the Liver (28,29). SR is regarded as the 'gold standard' in SHCC treatment (30). However, according to Ochiai *et al* (6), it appears that if there are preoperative risk factors for patients with SHCC, they should not receive SR and should be considered for other treatments as therapeutic options for SHCC. Good alternatives are available since the efficacy and safety of TACE have been demonstrated numerous times in patients with SHCC (9-11). Furthermore, TACE alone is an effective treatment option for patients with single HCC (31). However, it remains controversial whether SR or local mini-invasive therapies are the improved treatment option for patients with single nodules ≤3 cm or multifocal HCC <3.0 cm in the greatest dimension (32-34). Additionally, the impact of TACE, TACE-PMCT and SR treatments on the survival time of patients with SHCC had not been reported (12,33,35). In the present study, it was determined that TACE alone or TACE-PMCT treatment was safe and effective in the short-term and long-term observation. In addition, there was no significant difference in the survival time of the patients receiving the aforementioned treatment strategies. It was indicated that the survival time in the SR group had a notable tendency of being longer than that of the TACE group and TACE-PMCT group, although there was no significant difference (P=0.091), which might be caused by a number of potential factors, including: Although SR was a more radical therapy, as well as a higher risk therapy, it was prone to decrease postoperative residual liver function and increase serious postoperative complication, particularly for cirrhotic liver patients; PMCT with the cooling electrode can produce higher local temperature (36), However, it is difficult to accurately cover every melting zone in the three-dimensional liver under two-dimensional ultrasonography guidance, particularly for SHCC with irregular shapes (32); there were no evidence that indicated TACE treatment to be superior, in terms of survival time or survival rate, to SR treatment; there were no large-scale studies in the comparisons of survival time and survival rate for unresectable patients with SHCC receiving different tumor lesions treatments. Only a few

teams reported the comparison of treatment protocols and prognosis of SHCC (12,37). Tamai *et al* (37) reported that RFA-TACE should be considered for the treatment of single hypervascular HCC rather than RFA alone. Kim *et al* (35) reported that SR provided a survival benefit over TACE in intermediate-stage HCC. However, it was determined that TACE sessions were positively correlated with survival time of patients with SHCC in the TACE group and TACE-PMCT group (excluding SR group). The main reasons for TACE leading to the longer survival time of patients with SHCC were higher tumor necrosis rates and less hepatic function damage. Accordingly, although the data indicated that SR is not significantly different with regard to the overall survival time in the patients with SHCC between the two groups, this method can be employed for SHCC. This was based on the median survival time of patients in the SR group [36 (range, 28.25-52) months] that was significantly longer than the TACE [17 (range, 12-44) months] and TACE-PMCT groups [27 (range, 14-55) months] (P=0.035). Furthermore, the 1, 2 and 3-year survival rates for patients with SHCC and ≥400 ng/ml AFP in SR group (90.9, 81.8 and 61.0%) was mostly higher than in TACE group (70.8, 55.5 and 49.9%) and TACE-PMCT group (83.7, 68.0 and 60.8%) (log-rank test, P=0.664). In addition, the present study indicated that TACE treatment was one of alternative treatment therapies for the unresectable small tumor lesions.

Serum AFP was an important tumor biomarker of HCC. Nomura *et al* (38) analyzed 606 patients with HCC and indicated that that serum AFP levels could be used as an indicator to assess the clinical features and prognosis of HCC (28). Additionally, Choi *et al* (39) further demonstrated that serum AFP levels and tumor size prior to RFA were important predictors of long-term outcomes in HCC. In addition, Carr *et al* (40) reported that elevated AFP levels are associated with reduced survival time of patients with large tumors. More recent studies by Blank *et al* (41), and Terentiev and Moldogazievain (42), reported that preoperative serum AFP was an independent predictive factor among patients with HBV-HCC following surgical resection (41,42); however, the literature contained only scarce research about the impact of the preoperative AFP level on the survival time of patients with SHCC. In the present study, higher preoperative AFP level was identified as an independent risk factor for the survival time of patients with SHCC. This result was comparative with a 2012 study by Giannini *et al* (43), in which they collected a large amount of sample data and failed to indicate a prognostic value of AFP on the survival time of patients with compensated cirrhosis and SHCC. The reason for the different results may be due to different treatment modalities and the setting of AFP subgroup boundaries.

In the present study, it was demonstrated that preoperative AFP levels have a prognostic relevance for patients with SHCC. Then, considering patients with ≥400 ng/ml preoperative AFP, the analysis demonstrated that patients receiving SR treatment had significantly longer survival time than TACE and TACE-PMCT groups. Further analysis determined that tumor numbers, hypertension and BCLC stage were independent predictive factors for patients with SHCC, while the treatment strategies were not predictive factors for the survival time of patients with SHCC with preoperative AFP levels of <400 ng/ml. To the best of our knowledge, the current study is the first to identify hypertension as an independent predictive factor for patients with SHCC with ≥400 ng/ml AFP, but a larger sample is desirable to confirm this correlation. A number of other results of the present study are inconsistent with the results of previous studies (34). Nagashima *et al* (30) reported that AFP level was not significantly associated with survival rate in treating patients with SHCC by surgical resection. Then, Graham *et al* (44) reported that patients with single HCC using the Milan criteria and AFP-positive status should not undergo resection but rather receive orthotropic liver transplantation. In combination, the differences in results may be due to a lack of subgroup analysis based on preoperative AFP levels in the study by Nagashima *et al* (30). In addition, due to the lack of liver donors, SR treatment is a preferable option for patients with SHCC with AFP levels of ≥400 ng/ml.

Kaplan Meier survival analysis demonstrated that Child-Pugh grade and BCLC stage are beneficial factors for the survival time of patients with SHCC. Conversely, age, preoperative AFP levels, tumor size and PVTT were identified as adverse factors. Those results were similar to other associated HCC types (45-47). Cox regression analysis demonstrated that BCLC stage was a protective factor for survivaltime and patients with SHCC who classified as BCLC stage A have higher survival rates than those grouped in BCLC stage B or C. For older patients with higher preoperative AFP levels, a poor prognosis was predicted. Previous publications have reported that T_2DM and impaired glucose tolerance are predictors of poor prognosis for patients with SHCC (≤5 cm) (48,49). However, it was not determined in the present study that there was any association between T_2DM and the prognosis of SHCC (≤3 cm).

In conclusion, although the present study indicated that SR is not significantly different with regard to the overall survival time in the patients with SHCC between the 2 groups, this treatment therapy can be employed for patients with SHCC. This was based on the patients with SHCC with ≥400 ng/ml AFP in the SR group had longer survival time and a higher survival rate than the TACE and TACE-PMCT group. In addition, the present study indicated that TACE treatment was one of alternative treatment therapies for the unresectable small tumor lesions. However, the results of this retrospective study need to amplify the sample to identify the benefits from TACE treatments and be validated by prospective clinical trial.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YW collected and analyzed the patient data, contributed to the discussion, wrote the manuscript, reviewed and edited the manuscript. YY, FD, WY and WZ collected and analyzed the patient data, contributed to the discussion, and reviewed and edited the manuscript. YW is the guarantor of this work and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures in the current study were in accordance with the ethical standards of the Institutional Research Committee and with The Declaration of Helsinki. The study was approved by the Ethics Committee of the Second Hospital of Nanjing and written informed consent for participation was obtained. This study had no influence on the subsequent management of patients.

Patient consent for publication

All patients, patients' parents or next of kin (if patients have deceased) have provided written informed consent for the publication of any associated data.

Competing interests

The authors declare that they have no competing interests.

Authors' information

YW, WY and WZ have extensive experience in the treatment of liver diseases. WZ is an academic leader of department of the liver disease in The Second Hospital of Nanjing. YY is the leader of the department of hepatobiliary surgery in The Second Hospital of Nanjing. FD is experienced at interventional therapy for hepatocellular carcinoma in The Second Hospital of Nanjing.

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