Treatment of Gastrointestinal Tumor Liver Metastases with the Combination of Apatinib and Transarterial Chemoembolization

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Abstract

Background

There are no exact treatments been recommended for gastrointestinal tumor liver metastasis patients. This study intends to assess the safety and efficacy of transarterial chemoembolization (TACE) plus apatinib as a combination treatment for gastrointestinal tumor liver metastasis patients.

Methods

From January 2015 to December 2019, 53 patients with gastrointestinal tumor liver metastases were included in the analysis.

Results

The median progression-free survival (mPFS) and median overall survival (mOS) numbers were 7 months and 17 months, respectively. The mPFS of metastatic sites was 12 months. The disease control rate (DCR) and objective response rate (ORR) values were 86.8% (46/53) and 49.1% (26/53), respectively. The multivariate regression analysis showed that Child-Pugh and Eastern Cooperative Oncology Group (ECOG) were independent predictors for OS. The independent predictors for overall PFS include carbohydrate antigen 724 (CA 724), CA 199, TACE session, Child-Pugh, and ECOG; while for liver tumor PFS, the independent predictors are TACE session and ECOG scores. There were no changes of leukocyte, lymphocyte, carcinoemnryonicantigen (CEA), CA 724, CA 199, CA 125 of patients before receiving the treatments and one month after receiving the treatment (all P>0.05). Common adverse events at any grade were poor appetite (64.2%), hypertension (56.6%), and hand-foot syndrome (50.9%). Some patients had III or IV-grade adverse events after receiving the TACE-apatinib combination treatment. However, these adverse events alleviated after reducing apatinib administration or receiving symptomatic treatments.

Conclusions

The TACE-apatinib combination might be an effective treatment option against gastrointestinal tumors liver metastases with promising safety.

Introduction

Gastrointestinal tumor (GIT) is one of the most highly morbid malignant tumors with one of the greatest mortality rates. The 2018 global cancer statistics state that 18 million new cancer cases emerged across the world, and 9.6 million died from cancer-associated conditions. Besides, the incidences of gastrointestinal cancers (e.g. gastric, colon, and rectal cancers) were some of the highest.[1] Despite significant improvements in gastrointestinal tumor management, such as widespread screening programs, effective systemic therapies, and enhanced surgical and locoregional control, many patients still develop incurable metastatic gastrointestinal tumors. [2] The liver is an organ that is susceptible to

GIT metastasis, and secondary hepatic malignancies are 18–40 times more prevalent than primary ones. [3–5] About half of the liver metastasis patients have primary colorectal cancer (CRC), followed by gastric cancer (about 5-9%). [6] Besides, liver metastasis is a primary reason for morbidity, organ failure, and eventually mortality for gastrointestinal cancer patients[6, 7]. For these patients, there were no treatments recommended as the first-line choice. Thus, more treatments for these patients still needed to be explored.

Apatinib is an oral inhibitor of vascular endothelial growth factor (VEGF) receptor-2 [8] developed by Adrenchen Laboratories. It has been approved as a second-line novel agent to treat metastatic or advanced gastric cancer by FDA.[9] The literature has suggested that apatinib has promising antitumor activity against lung and colorectal cancers with tolerable toxicity.[10, 11] Besides, in a Phase III study, apatinib has been proved to improve PFS and OS of gastric cancer patients who have endured heavy pretreatments [9]. A pilot study also indicated that apatinib has the potential to be a third-line treatment agent for refractory metastatic colorectal cancer.[11]

Transarterial chemoembolization (TACE) is the first-line treatment option for medium-term liver cancer. [12] Recent studies have shown that TACE is also effective in the metastasis of liver cancer[13–15]. Studies showed that TACE is capable of bringing satisfactory tumor control and being used in palliative treatments for patients with either colorectal cancer liver metastases (CCLM) or gastric cancer liver metastases (GCLM) conditions.[16–18] The literature has suggested that TACE plus apatinib is potent to treat advanced liver cancer [19, 20], but in metastatic liver cancer, few studies have focused on the therapeutic efficacy of such combination. As the combination of TACE and apatinib has shown great therapeutic potential for GCLM and CCLM in previous research, this single-arm study aims to explore the safety and efficacy of the TACE-apatinib combination in treating metastatic liver cancer.

Materials And Methods

Patient Selection

The review board of the Union Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this retrospective study. Informed consent was waived since the study was retrospective. The principles of the Declaration of Helsinki were followed throughout the study. In this study, we selected 53 GCLM and CCLM patients who underwent consecutive TACE treatment in our medical center from January 2015 to December 2019. Before the initial TACE session, all patients were notified of all treatment options by the multidisciplinary tumor treatment board. TACE, a treatment capable to reduce tumor burden, was the last approach we could give to control disease progression.

Inclusion criteria were as follows: (1) Before TACE, the patients had their primary tumor(s) removed, and the chemoembolization indications were unresectable GCLM and CCLM with no disease progression, no response, and no toxicity after the administration of two systemic chemotherapy lines. (2) liver metastases as diagnosed by biopsy or imaging; (3) age > 18 years; (4) Child-Pugh A or B; (5) an Eastern

Cooperative Oncology Group (ECOG) performance status of 0 or 1 or 2; (6) patients did not receive TACE or apatinib. (7) patents with platelet count >50*109/L

Patients falling in either one of the following exclusion criteria were removed from the study: (1) main portal vein obstruction; (2) serious medical comorbidities, such as hepatic dysfunction (serum albumin level < 2.0 mg/dL, INR > 1.5, serum total bilirubin level > 3 mg/dL) and renal impairment (serum creatinine level >2 mg/dL) and ; (3) diffuse liver tumors which can not be evaluated;

TACE Procedure

TACE was performed following our previously-reported standard protocol. All operators had prior experience in performing TACE (≥5 years). At first, tumor-feeding arteries and tumor staining were observed and determined via angiography. Subsequently, a 2.6-Fr microcatheter (Terumo™, Japan) was inserted into the tumor-feeding arteries, through which an emulsion of 20–60 mg doxorubicin hydrochloride (Hisun Pharmaceutical Co., Ltd., Zhejiang, China) and 2–20 mL iodized oil (Lipiodol Ultra-Fluid; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) were administered inside the target blood vessels. The dosage of doxorubicin hydrochloride and lipiodol was decided based on the tumor vascularity/size and the patient's baseline liver function. Specifically, iodized oil was applied on a dosage of 1–3 mL per cm of tumor diameter, which varied based on the blood supply. For patients with poor liver function (Child-Pugh score ≥ 8) or a large tumor burden (tumor diameter > 10 cm), the initial TACE treatment was conducted with a smaller emulsion amount or via fractional embolization to avoid liver failure. Finally, the mixture of gelatine sponge particles (300–500 μm, Cook™, Bloomington, Indiana, USA) and a contrast material was administered into the tumor-feeding arteries until the arterial flow became stable.

Apatinib Administration

Patients in the TACE-apatinib group took 500 mg apatinib (Hengrui Pharmaceutical Co. Ltd, Jiangsu, China) orally at 3-5 days following TACE. Adjustment of apatinib doses was based on the patients' drug tolerance. Grading of apatinib-associated adverse events was given according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). If an apatinib-related adverse event was graded ≥3, then the apatinib dose would decrease to 250 mg. If the event continued to be ≥3 grade even after the dose reduction, the drug administration would be temporarily interrupted. Following the alleviation or elimination of the adverse event, the patient with temporary drug interruption would resume an apatinib dose of 250 mg/day.

Follow-up

All patients in this study were followed by CT or MRI and laboratory tests. The interval of follow-up was 1 month for the first three months after the initial TACE, and 2-3 months afterward. All treatment responses (based on the CT or MRI imaging) were evaluated by a diagnostic radiologist (experience >15 years) and an interventional radiologist (experience >10 years). Meanwhile, the patients were not blinded to their

treatment information because iodine could be found in the imaging. The decision of another TACE for patients was based on the tumor burden evaluated by the mRECIST criteria. When the tumor progressed during the follow-up or residual tumors were observed, the patients were recommended to undergo another TACE session on the condition of good liver function or physical condition. The end time of follow up for the study was June 2021.

Assessments

The study took PFS, OS, DCR, and ORR as the parameters for assessment. PFS, ORR, and DCR were evaluated according to the modified Response Evaluation Criteria for Solid Tumors (mRECIST) [21]. ORR was defined as the portion of patients whose liver tumor showed either partial response (PR) or complete response (CR). DCR was defined as ORR plus the portion of patients with stable disease (SD) in all patients, OS was defined as the time interval from the first TACE session to the last follow-up or death. Overall PFS was defined as the time interval from the first TACE session to any tumor progression or death. PFS of liver tumors was defined as the time interval from the first TACE session to liver tumor progression or death.

Statistical Analysis

SPSS 26.0 software (IBM, Armonk, New York) was used to perform all statistical analyses. Non-normally distributed data, categorical variables, and normally distributed data,were expressed as median (quartile range), frequency (percentage), and mean±standard deviation, respectively. OS and PFS of the study cohort were described by the Kaplan-Meier method. The survival and tumor progression of patients receiving TACE plus apatinib were predicted with the Cox regression risk model. Variables with $P<0.05$ in the univariable regression analysis were included in a multivariate regression analysis, and $P<0.05$ (two-tailed) was considered statistically significant.

Results

Patient demographic characteristics

In this study, 53 patients were included from January 2015 to December 2019. Patient selection was executed as described in Figure 1, and Table 1 summarizes the patients' clinical characteristics. The median follow-up time was 20 months (2–61 months). By the end of follow-up (September 20, 2021), 44 (81.48%) patients had died.

Table 1
Baseline characteristics of patients

Characteristics	Patients with TACE-Apatinib treatment (No, %; Mean±SD)
Age(years)	58.6±8.4
Gender	
Male	40
Female	13
ALT (IU/L)	32.7±26.7
AST (IU/L)	34.7±16.4
Neutrophils(10^9/L)	4.4±2.6
Lymphocytes(10^9/L)	1.3±0.4
Leukocyte(10^9/L)	5.8±2.8
CEA (ng/ml)	185.7±352.7
CA724 (ng/ml)	25.9±71.7
CA199 (ng/ml)	215.3±410.8
CA125 (ng/ml)	33.1±71.5
AFP (ng/ml)	5.8±7.5
Primary tumor	
Gastric cancer	17
Colorectal cancer	36
Tumor numbers in the liver	
1	1
≥2	48
Tumor size in the liver	
≤5 cm	35
>5 cm	17
Extrahepatic spread	
Yes	24
No	29

Characteristics	Patients with TACE-Apatinib treatment (No, %; Mean±SD)
TACE session	
1	7
≥2	46
Child-Pugh	
A	44
B	9
ECOG scores	
0	27
1	20
2	6

Tumor Response And Survival Outcomes

The mOS and overall mPFS of patients were 17 months (95% CI: 13.1-20.9 months) and 7 months (95% CI: 5.7-8.3 months), respectively. The mPFS of the liver tumors was 12 months (95% CI: 7.3-16.7 months) (Figure 2). For the liver tumors, 3 patients (5.7%) had CR, 23 patients (43.4%) had PR, 20 patients (37.7%) had SD and 7 patients (13.2%) had PD three months after receiving TACE combined with apatinib. Therefore, the ORR and DCR of patients for the liver tumors were 49.1% (26/53) and 86.8% (46/53), respectively.

Predictors for OS, overall PFS, and PFS of the liver tumors

For OS, univariable regression analysis showed that carbohydrate antigen 125 (CA 125) (HR: 1.006, 95%CI: 1.002-1.010, P=0.004), primary tumor (HR: 0.460, 95%CI: 0.240-0.880, P=0.019), extrahepatic spread (HR: 0.277, 95%CI: .0143-0.538, P<0.001), TACE session (HR: 0.122, 95%CI: 0.047-0.316, P<0.001), Child-Pugh (HR: 6.102, 95%CI: 2.674-13.928, P<0.001) and Eastern Cooperative Oncology Group (ECOG) scores (1 vs 0: HR: 3.876, 95%CI: 1.901-7.901, P<0.001; 2 vs 0: HR: 14.961, 95%CI: 5.049-44.332, P<0.001) were its independent predictors. However, only TACE session (HR: 0.183, 95%CI: 0.051-0.654, P=0.009), Child-Pugh (HR: 4.834, 95%CI: 1.816-12.868, P=0.002) and ECOG scores (1 vs 0: HR: 2.681, 95%CI: 1.111-6.472, P=0.028; 2 vs 0: HR: 6.385: HR: 1.459-27.934, P=0.014) were identified as the independent predictors of OS in the multivariable regression analysis (Table 2).

Table 2
Univariable regression analysis and multivariable regression analysis for overall survival

	Univariable analysis		Multivariable analysis	
Characteristics	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Age(years)	1.107 (0.983,1.052)	0.324		
Gender				
Male	Ref			
Female	0.808 (0.396,1.646)	0.557		
ALT (IU/L)	0.997 (0.984,1.09)	0.611		
AST (IU/L)	1.009 (0.991,1.027)	0.321		
Neutrophils(10^9/L)	1.027 (0.923,1.143)	0.624		
Lymphocytes(10^9/L)	1.272 (0.626,2.585)	0.505		
Leukocyte(10^9/L)	0.952 (0.845,1.072)	0.416		
CEA (ng/ml)	1.001 (1.000,1.001)	0.180		
CA724 (ng/ml)	1.004 (1.000,1.007)	0.051		
CA199 (ng/ml)	1.001 (1.000,1.001)	0.073		
CA125 (ng/ml)	1.006 (1.002,1.010)	0.004	0.998 (0.991,1.005)	0.568
AFP (ng/ml)	00.981 (0.938,1.025)	0.385		
Primary tumor				
Gastric cancer	Ref		Ref	
Colorectal cancer	0.460 (0.240,0.880)	0.019	0.659 (0.305,1.424)	0.289
Tumor numbers in the liver				
1	Ref			
≥2	1.309 (0.463,3.705)	0.612		
Tumor size in the liver				
≤5 cm	Ref			
>5 cm	1.273 (0.676,2.395)	0.455		
Extrahepatic spread				
Yes	Ref		Ref	

	Univariable analysis		Multivariable analysis	
No	0.277 (0.143,0.538)	<0.001	0.723 (0.282,1.856)	0.500
TACE session				
1	Ref		Ref	
≥2	0.122 (0.047,0.316)	<0.001	0.183 (0.051,0.654)	0.009
Child-Pugh				
A	Ref		Ref	
B	6.102 (2.674,13.928)	<0.001	4.834 (0.051,0.654)	0.009
ECOG scores				
0	Ref		Ref	
1	3.876 (1.901,7.901)	<0.001	2.681 (1.111,6.472)	0.028
2	14.961 (5.049,44.332)	<0.001	6.385 (1.459,27.934)	0.014

For overall PFS, univariable regression analysis showed that CA 724 (HR: 1.006, 95%CI: 1.002-1.010, P=0.050), CA 199 (HR: 1.001, 95%CI: 1.000-1.001, P=0.031), CA 125 (HR: 1.005, 95%CI: 1.001-1.009, P=0.009), TACE session (HR: 0.192, 95%CI: 0.081-0.563, P<0.001), Child-Pugh (HR: 4.568, 95%CI: 2.000-10.434, P<0.001) and ECOG scores (2 vs 0: HR: 9.106, 95%CI: 3.040-21.612, P<0.001) were its independent predictors. On the other hand, CA 724 (HR: 1.005, 95%CI: 1.001-1.010, P=0.017), CA 199 (HR: 1.000-1.002, P=0.007), TACE session (HR: 0.271, 95%CI: 0.089-0.825, P=0.021), Child-Pugh (HR: 4.137, 95%CI: 1.664-10.288, P=0.002) and ECOG scores (2 vs 0: HR: 4.405, 95%CI: 1.368-14.184, P=0.013) were identified as the independent predictors of overall PFS in the multivariable regression analysis (Table 3).

Table 3
Univariable regression analysis and multivariable regression analysis for progression-free survival

	Univariable analysis		Multivariable analysis	
Characteristics	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Age(years)	1.107 (0.985,1.050)	0.304		
Gender				
Male	Ref			
Female	0.949 (0.493,1.826)	0.875		
ALT (IU/L)	0.994 (0.982,1.006)	0.294		
AST (IU/L)	1.001 (0.984,1.019)	0.869		
Neutrophils(10^9/L)	0.998 (0.895,1.112)	0.965		
Lymphocytes(10^9/L)	1.351 (0.704,2.593)	0.366		
Leukocyte(10^9/L)	0.952 (0.860,1.054)	0.344		
CEA (ng/ml)	1.000 (1.000,1.001)	0.370		
CA724 (ng/ml)	1.006 (1.002,1.010)	0.005	1.005 (1.001,1.010)	0.017
CA199 (ng/ml)	1.001 (1.000,1.001)	0.031	1.001 (1.000,1.002)	0.007
CA125 (ng/ml)	1.005 (1.001,1.009)	0.009	1.002 (0.997,1.007)	0.547
AFP (ng/ml)	0.993 (0.955,1.032)	0.720		
Primary tumor				
Gastric cancer	Ref			
Colorectal cancer	0.552 (0.299,1.021)	0.058		
Tumor numbers in the liver				
1	Ref			
≥2	1.174 (0.464,2.972)	0.735		
Tumor size in the liver				
≤5 cm	Ref			
>5 cm				
Extrahepatic spread				
Yes	Ref			

	Univariable analysis		Multivariable analysis	
No	1.204 (0.655,2.212)	0.550		
TACE session				
1	Ref		Ref	
≥2	0.192 (0.081,0.453)	<0.001	0.271 (0.089,0.825)	0.021
Child-Pugh				
A	Ref		Ref	
B	4.568 (2.000,10.434)	<0.001	4.137 (1.664,10.288)	0.002
ECOG scores				
0	Ref		Ref	
1	1.876 (0.998,3.524)	0.051	1.303 (0.644,2.637)	0.462
2	8.106 (3.040,21.612)	<0.001	4.405 (1.368,14.184)	0.013

For PFS of liver tumors, univariable regression analysis showed CA 125 (HR: 1.007, 95%CI: 1.003-1.011, P=0.001), primary tumor (HR: 0.525, 95%CI: 0.279-0.985, P=0.045), extrahepatic spread (HR: 0.354, 95%CI: 0.190-0.659, P=0.001), TACE session (HR: 0.129, 95%CI: 0.051-0.325, P<0.001), Child-Pugh (HR: 3.474, 95%CI: 3.474, 95%CI: 1.056-8.011, P=0.003) and ECOG scores (1 vs 0: 2.518, 95%CI: 1.296-4.890, P=0.006; 2 vs 0: HR: 14.407, 95%CI: 5.157-46.033, P<0.001) were its independent predictors. On the other hand, TACE session (HR: 0.197, 95%CI: 0.059-0.661, P=0.009) and ECOG scores (2 vs 0: HR: 6.608, 1.639-26.633, P=0.008) were identified as the independent predictors of PFS of liver tumors in the multivariable regression analysis (Table 4).

Table 4
Univariable regression analysis and multivariable regression analysis for progression-free survival of tumors in liver

	Univariable analysis		Multivariable analysis	
Characteristics	**HR (95%CI)**	**P value**	**HR (95%CI)**	**P value**
Age(years)	1.106 (0.984,1.049)	0.326		
Gender				
Male	Ref			
Female	0.845 (0.436,1.635)	0.616		
ALT (IU/L)	0.995 (0.984,1.007)	0.458		
AST (IU/L)	1.004 (0.987,1.022)	0.625		
Neutrophils(10^9/L)	1.011 (0.902,1.133)	0.854		
Lymphocytes(10^9/L)	1.271 (0.648,2.490)	0.485		
Leukocyte(10^9/L)	0.985 (0.885,1.096)	0.775		
CEA (ng/ml)	1.000 (0.999,1.001)	0.722		
CA724 (ng/ml)	1.004 (1.000,1.007)	0.053		
CA199 (ng/ml)	1.001 (1.000,1.001)	0.058		
CA125 (ng/ml)	1.007 (1.003,1.011)	0.001	0.999 (0.993,1.006)	0.794
AFP (ng/ml)	0.990 (0.951,1.031)	0.640		
Primary tumor				
Gastric cancer	Ref		Ref	
Colorectal cancer	0.525 (0.279,0.985)	0.045	0.795 (0.374,1.692)	0.552
Tumor numbers in the liver				
1	Ref			
≥2	1.041 (0.410,2.646)	0.932		
Tumor size in the liver				
≤5 cm	Ref			
>5 cm	1.137 (0.620,1.084)	0.678		
Extrahepatic spread				

	Univariable analysis		Multivariable analysis	
Yes	Ref		Ref	
No	0.354 (0.190,0.659)	0.001	0.668 (0.269,1.656)	0.384
TACE session				
1	Ref		Ref	
≥2	0.129 (0.051,0.325)	<0.001	0.197 (0.059,0.661)	0.009
Child-Pugh				
A	Ref		Ref	
B	3.474 (1.506,8.011)	0.003	1.911 (0.744,4.910)	0.179
ECOG scores				
0	Ref		Ref	
1	2.518 (1.296,4.890)	0.006	1.605 (0.689,3.737)	0.273
2	14.407 (5.157,46.033)	<0.001	6.608 (1.639,26.633)	0.008

The Changes Of Blood Examinations And Tumor Markers

The leukocyte, lymphocyte, neutrophils, CEA, CA 724, CA 199, CA 125 of patients before receiving the treatment and after receiving the treatment were reported. There was no significant statistically difference of the factors in patients before the treatment and after the treatment (all P>0.05) (Figure 3).

Complications

Adverse event evaluations for patients after receiving the combination treatment are shown in Table 5, in which no treatment-related deaths were observed. There were 23 patients (43.4%) with any grades of fever, 25 patients (47.2%) with abdominal pain, 14 patients (26.4%) with nausea, 22 patients (41.5%) with vomiting, 34 patients (64.2%) with poor appetite, 20 patients (37.7%) with diarrhoea, 19 patients (35.8%) with headache, 14 patients (26.4%) with fatigue, 30 patients (56.6%) with hypertension, 27 patients (50.9%) with hand-foot syndrome and 13 patients (24.5%) with proteinuria. For severe adverse events (grade III and IV), there were 4 patients (7.5%) with fever, 8 patients (15.1) with abdominal pain, poor appetite, and hand-foot syndrome, 3 patients (5.7%) with nausea and diarrhea, 5 patients (9.4%) with vomiting and proteinuria, 2 patients (3.8%) with headache, 1 patient (1.9%) with fatigue and 11 patients (20.8%) with hypertension. All adverse events were relieved or eliminated after symptomatic treatments, dose reduction, or temporary dose interruption.

Table 5
Adverse events evaluation of patients after they receiving the treatment

Adverse events	TACE-A
Hand-foot skin reactions	34(64.2%)
Hypertension	22(41,5%)
Diarrhea	10(18.9%)
Headache	8(15.1%)
Gastrointestinal hemorrhage	2(3.8%)
scanty ascites	2(3.8%)
liver abscess	1(1.9%)

Discussion

TACE has been applied frequently to treat metastatic and intermediate primary liver cancer by combining the intratumoral cytotoxicity of antitumor agents and the ischemia induction effect of embolization agents for therapeutic outcomes.[22] Previous studies have suggested that the remaining tumor cells in lesions would proliferate rapidly in most patients treated by only TACE.[20, 23] The reason behind such a phenomenon is that the microenvironment is ischemic and hypoxic after TACE, which is favored for tumor angiogenesis, recurrence, and progression mediated by various factors, such as MMP-9 and VEGF.[24, 25]

On the other hand, apatinib is a strong inhibitor of VEGFR-2 and a promising anti-angiogenic agent with great anti-tumor activity.[26, 27] Specifically, it has been used to treat advanced gastrointestinal tumors and achieved good results.[9, 28] For primary liver tumors, such as hepatocellular carcinoma, a recent retrospective study [29] revealed that the TACE–apatinib combination could result in a significant increase of the median TTP and OS compared to TACE treatment alone. Therefore, TACE plus apatinib may be a favorable and effective treatment combination as a part of interdisciplinary palliative therapy management.

The median OS and PFS were 17 and 7 months, respectively, for the 53 refractory CRCLM patients treated with TACE plus apatinib in this study, both of which are longer than what another recent retrospective study has reported.[30] Therefore, the combination of TACE-apatinib may be an effective option to prolong the survival for patients with unresectable chemotherapy-refractory liver metastases. Apatinib also showed better survival results than other VEGFR-2 inhibitors, such as regofinib [32] and bevacizumab [33], when combined with TACE in treating liver metastases. Theoretical analyses have suggested that TACE-apatinib may be an effective and advantageous method to treat unresectable chemotherapy-refractory liver metastases. In addition, prior to this study, two lines of systemic

chemotherapy have been given to the patients without satisfactory outcomes. Even for these patients, TACE-apatinib demonstrated better survival data.

In the study, the multivariable regression analysis presented that ECOG and Child-Pugh scores were independent predictors for OS and overall PFS, while only ECOG scores were independent predictors for PFS of liver tumors. The result showed that the patients' physical conditions and liver function might influence the prognosis and tumor progression. Thus, boosting the liver function and physical health of the patients before receiving TACE plus apatinib might improve the patients' survival. In the study, the changes of blood examinations and tumor markers of patients before receiving the treatment and after receiving the treatment. There was no significant statistically difference of these factors, which might mean that the treatment did not influence blood test indicators and tumor markers. Even with 58 severe adverse events reported. The adverse events were relieved after symptomatic treatments, suggesting that TACE plus apatinib could still be a relatively safe treatment.

As a retrospective study, this study has certain limitations. The most critical limitation of this report is the small sample size. Secondly, no other treatments were involved as a reference for TACE plus apatinib to compare with. Therefore, further prospective studies in which other treatments are discussed are necessary to verify the therapeutic effects of the TACE-apatinib combination.

Conclusions

Patients with gastrointestinal liver metastases might get survival benefits from transarterial chemoembolization combined with apatinib. The results might provide new evidence for clinics to choose suitable treatment for these patients.

Declarations

Competing interests: All authors declared that there were no competing interests existing.

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Research ethics and consent: This study was approved by ethics committee of Union Hospital of Huazhong University of Science and Technology. Written informed consent was waived by this institution.

Data deposition and data sharing: The data used in the study were available from the correspondence author on reasonable request.

Ethics approval and consent to participate: The study was approved by the Ethics Committee board of Tongji Medical College, Huazhong University of Science and Technology. The requirement of informed

consent was waived by the board of Tongji Medical College, Huazhong University of Science and Technology because the study utilized the SEER database.

Guidelines for Methods: This study was carried out in compliance with the Helsinki Declaration.

Consent for publication: All authors approve it for publication.

Data Availability: The data used in the study can be available from the correspondence authors upon reasonable request.

Competing interests: All authors declared that there were no conflicts of interest existing.

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Figures

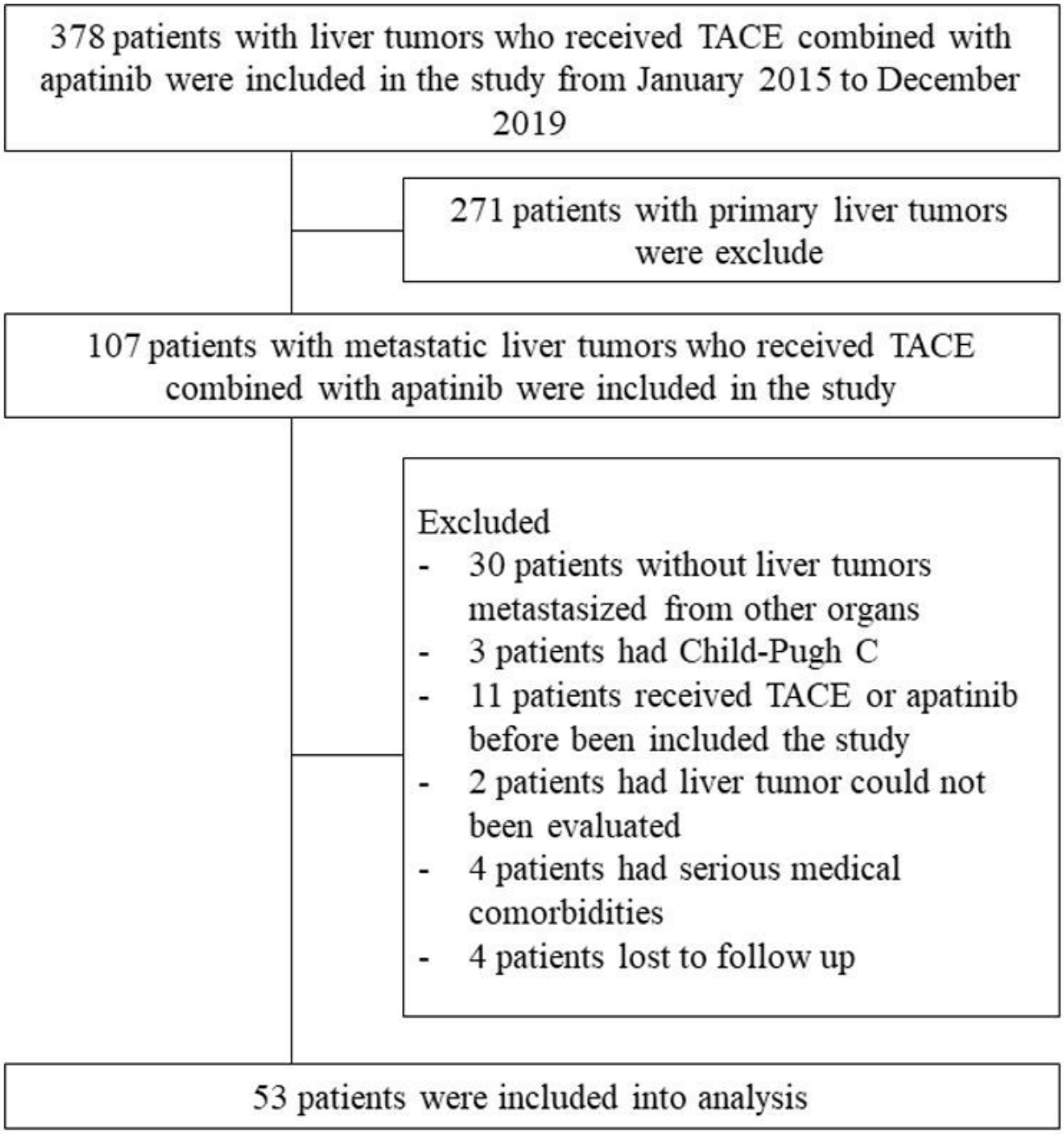

Figure 1

Patient selection flow chart.

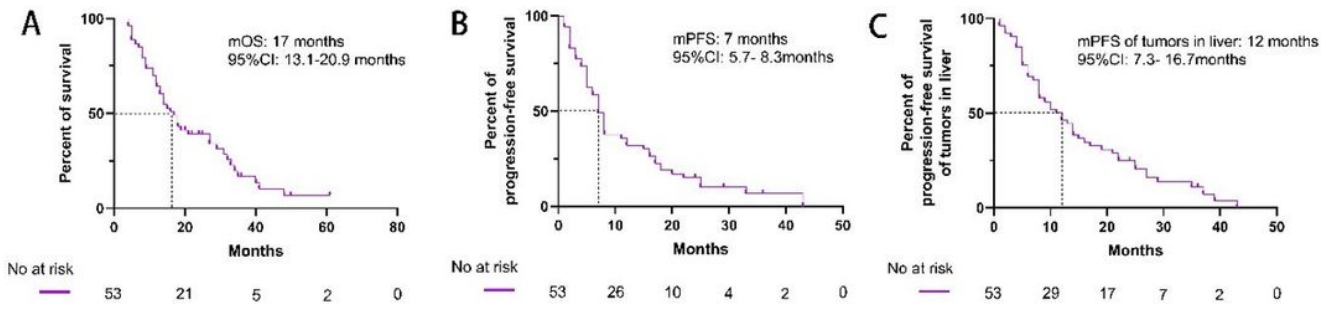

Figure 2

Kaplan-Meier curves for OS, overall PFS, and PFS of liver tumors. (A) OS; (B) overall PFS; (C) PFS of liver tumors.

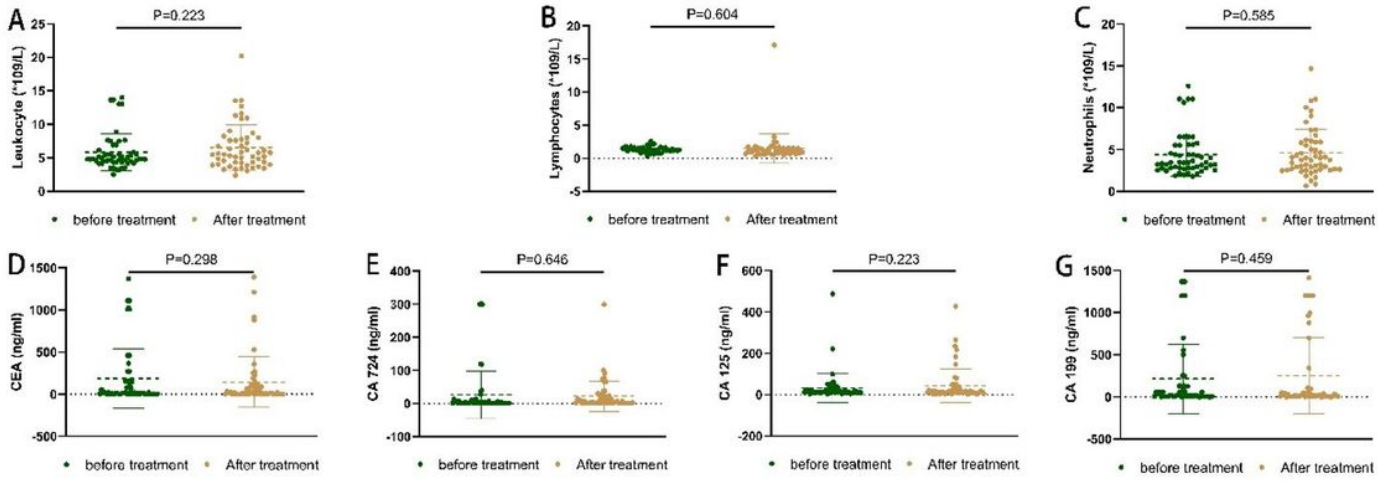

Figure 3

The changes of blood examination and tumor markers of patients before receiving the treatment and after receiving the treatment. (A) the changes of leukocyte; (B) the changes of lymphocytes; (C) the changes of neutrophils; (D) the changes of CEA; the changes of CA 724; (E) the changes of CA 125; (F) the changes of CA 199.