Hepatic resection versus TILA-TACE in the treatment of Resectable Hepatocellular Carcinoma: study protocol for a randomized controlled trial

Yangyang Feng
Zhejiang University School of Medicine Second Affiliated Hospital https://orcid.org/0000-0003-0598-8727

Yun Jin
Zhejiang University School of Medicine Second Affiliated Hospital

Kai Jin
Zhejiang University School of Medicine Second Affiliated Hospital

Yuanquan Yu
Zhejiang University School of Medicine Second Affiliated Hospital

Donger Zhou
Zhejiang University School of Medicine Second Affiliated Hospital

Jianjun Wu
Zhejiang University School of Medicine Second Affiliated Hospital

Bin Li
Zhejiang University School of Medicine Second Affiliated Hospital

Guangqiang Zhang
Zhejiang University School of Medicine Second Affiliated Hospital

Shuyou Peng
Zhejiang University School of Medicine Second Affiliated Hospital

Xiaogang Qi
Zhejiang University School of Medicine Second Affiliated Hospital

Hao Geng
Zhejiang University School of Medicine Second Affiliated Hospital

Yinghao Guo
Zhejiang University School of Medicine Second Affiliated Hospital

Ming Chao
Zhejiang University School of Medicine Second Affiliated Hospital

Jiangtao Li (zrljt@zju.edu.cn)
https://orcid.org/0000-0001-7538-2910

Study protocol

Keywords: Hepatocellular carcinoma, Hepatic resection, TACE, TILA-TACE, Randomized-controlled study

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Abstract

Background: Hepatic resection and transcatheter arterial chemoembolization (TACE) are common treatments for hepatocellular carcinoma (HCC). Targeting intratumoral lactic acidosis TACE (TILA-TACE) is a new therapeutic approach developed by our team that has superior response rate and effective rate than conventional TACE (cTACE). In this randomized-controlled trial, we will compare the efficacy of hepatic resection and TILA-TACE in patients clinically diagnosed with HCC to provide reliable clinical data for the subsequent effective treatment of HCC patients. Methods: A total of 230 resectable HCC patients will be given hepatic resection or TILA-TACE using a parallel-controlled approach, and the efficacy of the treatments Page 4 of 24 will be compared. The primary endpoint is the post-treatment progression-free survival (PFS) of the patients, and the secondary endpoints are the post-treatment overall survival (OS), 1-year, 3-year and 5-year survival, and the quality of life of the patients at each corresponding stage. Discussion: The aim of this study is to compare the efficacy of hepatic resection and TILA-TACE in the treatment of resectable HCC. Trial registration: ClinicalTrials.gov,NCT03314532.Registered on 19 October 2017. Keywords: Hepatocellular carcinoma, Hepatic resection, TACE, TILA-TACE, Randomized-controlled study.

Background

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world with major occurrences in eastern Asian countries such as China[1-6].And its morbidity is still rising[7,8],more than 740,000 new cases are reported worldwide each year[9]. HCC is the third leading cause of cancer-related deaths in the world[10,11]. There are multiple treatment options for liver cancer including surgery, transcatheter arterial chemoembolization (TACE), liver transplantation, absolute ethanol injection, radiation therapy, and biological therapy[12]. Surgery is the primary radical treatment measure for HCC[13,14], but its indication is narrow and is only suitable for certain group of patients. Another common treatment for liver cancer, TACE, can not only block tumor blood supply, control tumor growth, or even cause necrosis and result in tumor shrinkage, it can also deliver target chemotherapy drugs to the tumor tissue.

The Barcelona Clinic Liver Cancer staging system (BCLC) is one of the more recognized staging criteria and has been recommended by the European Association for the Study of Liver and the American Association for the Study of Liver Diseases[15]. BCLC staging is based on patients' general condition, tumor condition, and liver function to identify the best treatment option and predict prognosis using evidence-based medicine. Surgical excision is recommended for BCLC stage 0, liver transplantation or radiofrequency ablation is recommended for BCLC stage A, and TACE treatment is recommended for BCLC stage B[12]. However, there are still some controversies on the efficacy of TACE treatment.

In recent years, development of technologies has led to improved methods including targeting-intratumoral-lactic-acidosis TACE (TILA-TACE). Early clinical practice has confirmed that compared with TACE, TILA-TACE has a relatively high response rate and efficiency[16]. After conventional TACE treatment,

the residual glucose in the tumor will increase the accumulation of lactic acid, making the tumor less prone to necrosis. However, after TILA-TACE treatment, the local injection of sodium bicarbonate neutralized lactic acid in the tumor and depleted the residual glucose in the tumor. Without lactic acid accumulation, the tumor will quickly died of necrosis..

Most studies believe that hepatic resection is more effective than TACE for resectable hepatocellular carcinoma. A RCT study from China showed that 1-year, 2-year and 3-year OS rates in the hepatectomy group were 76.1%, 63.5% and 51.5%, respectively, while those in the TACE group were 51.8%, 34.8% and 18.1%, respectively[20].According to our preliminary results, TILA-TACE can improve the therapeutic effect by 81.1% compared with cTACE[16]. Therefore in this study, we will conduct a randomized comparison study of the efficacy of surgical resection and TILA-TACE treatment.

Methods

Experimental design

A randomized controlled experimental design method will be adopted.

Grouping and sample size calculation

A parallel comparison design will be used. According to preliminary data, the disease progression-free periods were 67 weeks and 98 weeks after surgical resection and TILA-TACE treatment, respectively. An α value of 0.05 will be used to correspond to the statistical significance level. According to the 1:1 design, the degree of assurance will be set at 80%, the experimental inclusion time will be two years, and the follow-up missing rate will be controlled at 10%. Each group will require 115 cases for a total of 230 cases. Cases will be randomized by computer into the following groups:

(1) Surgery group: HCC resection.

(2) TILA-TACE group: TILA-TACE treatment.

Randomization

A total of 230 HCC patients who qualify the inclusion criteria will be randomized 1:1 into the hepatic resection group and TILA-TACE group (Fig. 1). Treatment will be assigned by the research coordinator based on the randomization table. Aside from the research coordinator, all other research personnel will be concealed from the treatments that the patients are receiving.

Case selection

Diagnostic criteria[17]

1. Evidence of cirrhosis and HBV/HCV infection

2. Classical imaging features of HCC: MRI/CT/CEUS/EOB-MRI shows arterial hypervascularity and venous or delayed phase washout of the hepatic space-occupying lesion (HSOL).
3. If the diameter of the HSOL is ≥2cm, one of the imaging tests must show the above classical features.
4. If the diameter of the HSOL is <2cm, at least two of the imaging tests must show the above classical features.
5. Serum AFP≥400ug/L for 1 month or ≥200ug/L for 2 months and other causes of AFP elevation including pregnancy, germline/embryonal cancer, active liver disease and secondary liver cancer are excluded.
6. Liver biopsy indicates HCC.

Patients are clinically diagnosed with HCC if (1) + (2)a or (1) + (2)b + (3) are met, or pathologically diagnosed with HCC if (4) is met.

Definition of resectable HCC:

1. Lesion can be completely resected with no residual tumor at the margin of resection.
2. Residual liver volume is sufficient to compensate for postoperative liver functions.
3. If HCC is complicated by portal vein tumor thrombus, the tumor thrombus should be grade I or grade II based on the Liver Cancer Study Group of Japan criteria[18].

Inclusion criteria

- Ages 18–75 with no gender, ethnicity, religion, or geographical restrictions.
- Diagnosed HCC patient.
- The following criteria will be used for the evaluation of tumor resectability and adequate remaining liver volume: ≥ 30% remaining liver volume/total liver volume for non-hepatitis patients; ≥ 40% remaining liver volume/total liver volume for hepatitis patients.
- Imaging examination with no cancer embolus above the secondary branch of the portal vein.
- New lesions found five years after liver cancer treatment.
- Child-Pugh A or B grade liver function.
- No concurrent malignancies in other systems.
- Informed subjects who fully understand and willingly cooperate with the test program with signed relevant documents.

Exclusion criteria

Patients with one or more of the following conditions will be excluded from the study:

- Suffer from other malignancies.

- Received radiofrequency ablation, traditional TACE, immunotherapy, chemotherapy and other treatments before enrollment.
- Pathological diagnosis as non-HCC.
- Experience large blood vessel invasion, distant metastases, or unresectable liver cancer.
- One or more organ failures.
- Child-Pugh C grade liver function.
- Incomplete removal of the tumor by resection or TILA-TACE.

Case elimination criteria

- Other drugs, surgery, or other treatment programs have been used without permission after inclusion in this study.
- Accidental death other than death caused by HCC, such as car crash, earthquake, or other unforeseeable disasters.

The data of the eliminated cases will be archived, labeled, and used for statistical analysis of relapse and survival rates in other studies.

Treatment plan

Control: HCC resection

Patients who are randomized to this group will receive hepatic resection. Principles of surgery: 1. Complete tumor resection by eye; 2. Absence of residual tumor at the margin of resection; 3. Regular/irregular hepatic segmentectomy, partial hepatic resection or extensive hepatic resection of liver tissues that are burdened by the tumor. After hepatic resection, >30% of residual liver volume should be spared in normal patients, and >40% of residual liver volume should be spared in cirrhosis patients[19].

Intervention:TILA-TACE treatment

After successful femoral artery catheterization, 5-Fr angiography catheters will be used for complete radiography of the celiac artery, the hepatic artery proper, left and right hepatic arteries and their branches, and 2.8-Fr micro-catheters will be used for complete radiography of the tumor's nutrient arteries and the extrahepatic blood supply such as the inferior phrenic arteries. After micro-catheter superselective catheterization, lipiodol-epirubicin emulsions and 5% sodium bicarbonate injection solutions will be used for perfusion of chemotherapy drugs. Different sizes of embolic microspheres will be used alternatively for chemoembolization. For nutrient arteries of relatively large tumors, different sizes of spring coils will be used to block the blood flow to eventually achieve total occlusion of the tumor's nutrient artery.

Conversion from HCC resection to TILA-TACE treatment

When the tumor cannot be completely removed by resection, patients in the HCC resection group will be converted to the TILA-TACE treatment group. Patients allocated to hepatic resection conversion to TILA-TACE treatment will still be analyzed in the hepatic resection group according to intention-to-treat principles. Reasons for conversion will be registered by our researchers.

Patients blindng

Patients will be blinded in this study, they will not know the treatment plan until the surgery is completed.

Clinical experimental procedures

For included cases, patient's disease history, symptoms, signs, and other situations will be examined and patients will sign the informed consent. The patient's age, height, weight, medical history, symptoms, signs, pathological test results, and TNM stages will be recorded. Patients will be grouped randomly using the digital method. According to test requirements, the study intends to be limited to five years. Day 0 will be set as the day when liver resection or the first TILA-TACE treatment is performed. Re-examinations will be conducted one-month post-treatment and every three months thereafter. The content of the re-examination will include symptoms and signs and adverse events. Routine blood tests, liver and renal functions, hepatobiliary-pancreatic-splenic B-ultrasonography, chest low dose high resolution CT, and liver MRI will be performed and the results will be recorded. Bone ECT will be checked every six months.

Disease-progression-free time will be used as the primary endpoint. The disease progression standards for surgical patients will be new intrahepatic or extrahepatic lesion images found during the re-examination. The progress of TILA-TACE patients will be evaluated using EASL guidelines mRECIST criteria on the treated lesions[28]. CR: disappearance of any intratumoral arterial enhancement in all target lesions. PR: at least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of targets. SD: any cases that do not qualify for either PR or PD. PD: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

For subsequent records until the secondary endpoint, all results will be recorded in the Case Report Form (CRF) for assessing the clinical efficacy and safety with any adverse events observed and recorded. If the patient is unable to come to the hospital for re-examination, the re-examination would be conducted by follow-up methods such as telephone or mail.

Efficacy and safety evaluation

Observation index

Index for diagnosis:

- The diagnostic indexes included cancer index, hepatobiliary-pancreatic-splenic B-ultrasonography, liver enhanced MRI, chest low dose high resolution CT, and bone ECT.

Index for therapeutic efficacy:

- Index for primary efficacy: The primary efficacy index will be the disease-progression-free survival time of patients in the two groups post-treatment.
- Index for secondary efficacy: The secondary efficacy index will be the overall survival period post-treatment, the 1-year, 3-year, and 5-year survival rates, and the assessment of quality-of-life of patients in the two groups at each stage.

Safety index:

- Adverse events occurring during study period, such as anaphylaxis, embolization syndrome, or other related adverse reactions after TILA-TACE treatment or surgery-related complications will be closely monitored.
- General physical examinations will include (temperature, resting heart rate, respiration, blood pressure), routine blood tests, liver functions (TBill, AST, ALT, Alb), cancer markers, chest high resolution CT plain scan, liver enhanced MRI, hepatobiliary-pancreatic-splenic B-ultrasonography, and bone ECT.
- The adverse event rate will be the main index for safety evaluation.

Effectiveness evaluation standard

Primary endpoint:

The disease-progression-free period of patients after treatment. This will be the time period from the beginning of treatment to the time that disease progression has been observed.

Secondary endpoint:

The overall survival period recorded from the beginning of the treatment, the follow-up, until the death of the patient or the end of the study period, as well as the 1-year, 3-year, and 5-year survival rates. In the meantime, the patient's quality-of-life will be recorded.

Safety assessment:

Changes in the physical examination and laboratory tests before and after treatments will be compared between the two groups. Additionally, the rates of the adverse events and adverse reactions occurring during the study will be compared between the two groups. Statistical analysis will be carried out after all data are collected and $p < 0.05$ will be considered statistically significant.

Adverse events recording and reporting

Information of non-serious and serious adverse events occurring during treatment will be recorded on the CRF and Adverse event registration form (Appendix file 2.4). In this study, adverse reactions and complications including severe hepatic renal failure, possible chemotherapy drug allergy reaction, or embolization syndrome may occur in a very small portion of patients after TILA-TACE treatment. In light of this, we will fully evaluate liver and kidney functions before operation. Intensive management with care and caution will be used during the perioperative period. Scientific and rational operation procedures will be adopted to reduce complications. Close connections will be strengthened with relevant departments so that adverse events can be reported to the head of the department and the hospital supervisor at once and to the hospital adverse event ethics committee within the time limit.

Data management and statistical analysis

Data recording and auditing:

Observation data will be recorded in the CRF by the attending doctor in black or blue-black pen to ensure the data will be recorded completely, accurately and truthfully in a timely manner. Any modifications made by relevant personnel will be signed and dated and amendments will not cover the originals. If possible, relevant laboratory testing sheets will be copied and pasted on the attached page at the end of the CRF.

Data entry:

A data entry program and database have been established for statistical analysis,data collection and entry was performed by two or more researchers.

Statistical analysis:

Primary and secondary endpoint data in the database will be collected and processed using the SPSS 17.0 statistical software. Patient survival (1-year, 3-year, 5-year OS and PFS) in the two groups will be calculated using the Kaplan-Meier method. A linear mixed model will be constructed to compare the quality of life between the two patient groups at each corresponding stage. $P<0.05$ is considered statistically significant.

Informed consent

Specific content related to the study should be known by the subject and written informed consent must be obtained from the subject before implementing the study procedures. The details are described in the consent form (Appendix file 5). The specific process to obtain informed consent is as follows: the doctor will inform the patient about his/her disease characteristics, treatment options, and related risks in detail and then the informed consent form is signed by the patient him/herself or by a legal guardian with capacity for civil conduct.

Discussion

This is a single-center randomized-controlled study aimed to compare the clinical efficacy of hepatic resection versus TILA-TACE in resectable HCC patients. Although both hepatic resection and TACE can be used as the clinical treatment for resectable HCC, the efficacy of these approaches is still debated. A randomized-controlled study by Lei Yin[20] found that patients who received hepatic resection and cTACE had a 3-year survival of 51.5% and 18.1% and a median survival time of 41 months and 18 months, respectively. Therefore, the authors concluded that the efficacy of hepatic resection is superior than cTACE. This finding was also supported by a retrospective non-randomized-controlled trial by Biao Yang et al[21-24]. who showed that hepatic resection provides significantly higher survival benefits to resectable HCC patients than TACE. In contrast, Lei Jianyong believe that hepatic resection should be used for patients with 1-3 intrahepatic nodules, whereas TACE is recommended for patients with >3 intrahepatic nodules[25].

In our previous study, we found that the geometric mean of residual live tumor was 6.4 times lower after TILA-TACE than after cTACE. Complete or partial response rate were significantly higher in the TILA-TACE group than in the cTACE group, and the objective response rate of the two groups were 100% and 44.4%, respectively. This indicates that TILA-TACE has superior treatment response rate and effective rate than cTACE. In addition, the 1-year, 2-year, and 3-year survival rates and median survival time were higher in the TILA-TACE group (82.8%, 67.7% , 61.8% and 41 months, respectively) than the cTACE group (66.7%, 40.7%, 25.9% and 14 months, respectively), demonstrating that TILA-TACE provides superior post-treatment survival than cTACE[16].

There is currently a lack of solid evidence on the efficacy of TILA-TACE versus hepatic resection in the treatment of resectable HCC, and we did not find any literature that compares the efficacy of the two treatment approaches. Further clinical studies, especially randomized-controlled studies, will be needed to provide insights to treatments that are more suitable for HCC patients.

In summary, we will conduct a prospective randomized-controlled study to compare the efficacy of hepatic resection and TILA-TACE in the treatment of resectable HCC in the hopes of providing reliable evidence for the clinical treatment of resectable HCC.

Trial status

The first patient was recruited at 2 May 2018, and we will complete the recruitment of all patients by 31 Dec 2021. Protocol version 2 dated 23 August 2017 has been approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

Abbreviations

HCC：hepatocellular carcinoma

TACE：transcatheter arterial chemoembolization

TILA-TACE:Targeting-intratumoral-lactic-acidosis transcatheter arterial chemoembolization

BCLC：Barcelona Clinic Liver Cancer　TNM：Tumor, Node, Metastases

OS：overall survival　PFS：progression-free survival

CT： Computed tomography　MRI：Magnetic Resonance Imaging

CEUS：Contrast-enhanced ultrasound　ECT：Emission Computed Tomography

ALT：alanine aminotransferase　AST：aspartate transaminase

CRF：Case Report Form　AFP：alpha fetoprotein

TBill：total bilirubin　Alb：albumin

HBV：hepatitis B virus　HCV：hepatitis C virus

EASL：European Association for the Study of the Liver

CR：complete response　PR：partial response

SD：stable disease　PD：progressive disease

Declarations

Ethics approval and consent to participate

The study will be conducted according to the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of the second affiliated hospital of Zhejiang university.The trial is registered in the US Trial Register (http://clinicaltrials.com.gov/) with identification number NCT03314532. Patients can only participate if written informed consent has been provided.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yangyang Feng and Yun Jin drafted the manuscript. Jiangtao Li and Ming Chao are the main coordinators of the trial.Yangyang Feng, Yun Jin, Kai Jin, Yuanquan Yu, Donger Zhou, Jianjun Wu, Bin Li, Guangqiang Zhang, Xiaogang Qi, Hao Geng, Yinghao Guo, Shuyou Peng, Jiangtao Li and Ming Chao participated in the design of the trial. Shuyou Peng and Ming Chao provided advice, support and assistance. All authors critically revised the manuscript and have approved the final version.

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Authors' information

1. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 2. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 3. Department of Radiology and interventiona, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 4. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 5. Department of Surgery, Second Affiliated Hospital,Zhejiang University School of Medicine,Hangzhou,China; 6. Department of Radiology and interventional, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 7. Department of Radiology and interventional, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 8. Department of Radiology and interventional, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 9.Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 10. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 11. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 12. Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 13.Department of Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 14. Department of Radiology and interventional, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

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Figures

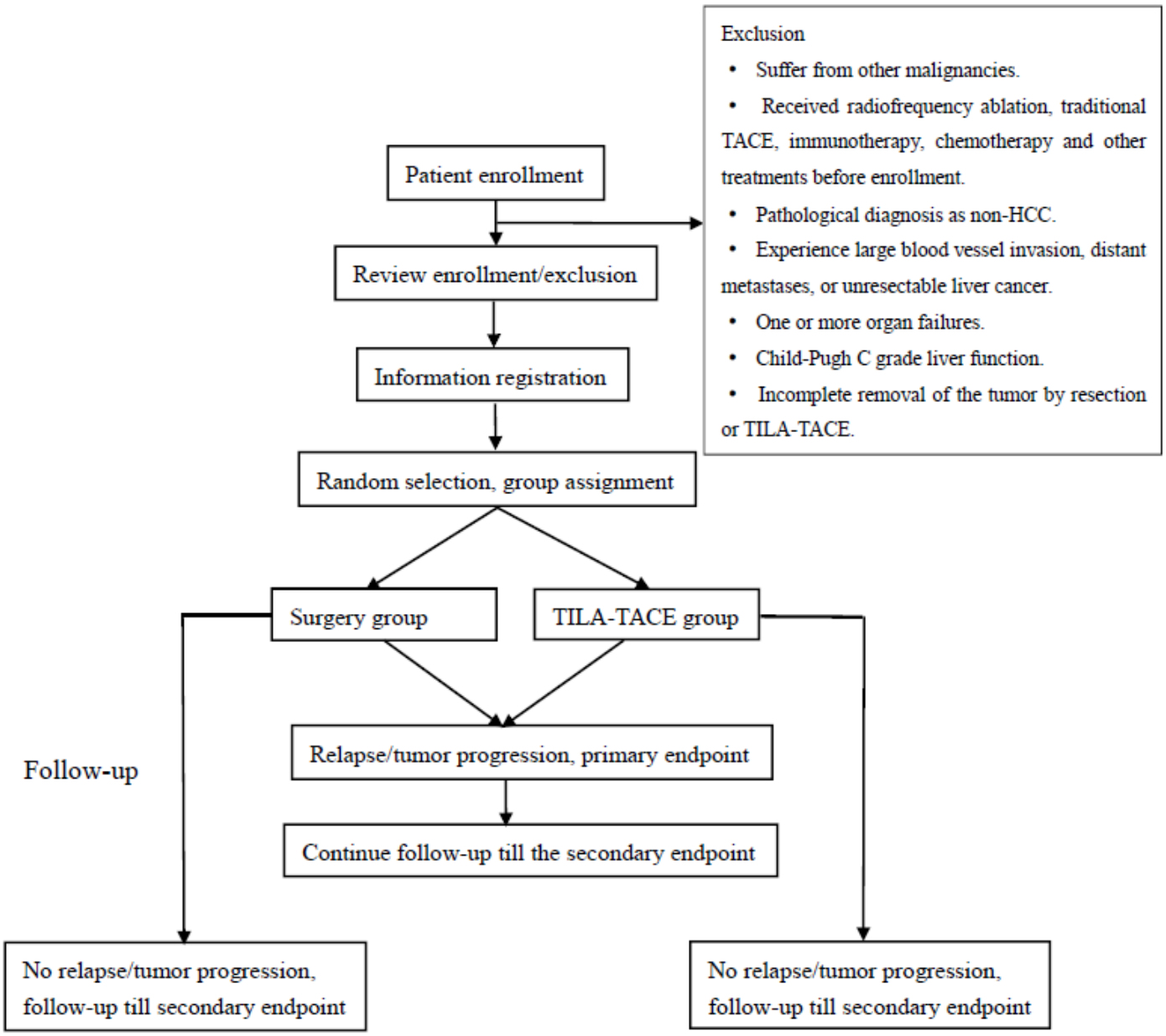

Figure 1

Trial flow diagram for randomized comparison study of the therapeutic effectiveness of hepatic resection or TILA-TACE in patients with resectable hepatocellular carcinoma.

	STUDY PERIOD								
	Enrolment	Allocation Treatment	Treatment	Post-allocation					Close-out
TIMEPOINT	Inpatient	Before treatment	On the day of treatment	*1 month*	*4 months*	*7 months*	...	*5 years*	Study endpoint
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
INTERVENTIONS:									
[Surgery]			X						
[TILA-TACE]			X						
ASSESSMENTS:									
[Baseline characteristics]	X								
[Advent forms registration]			X	X	X	X	X	X	X
[SF-36 questionnaire]	X			X	X	X	X	X	X

Figure 2

Schedule of enrolment, interventions, and assessments according to standard protocol items: recommendations for interventional trials (SPIRIT).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendixfile4ADVERSEEVENTSLogform.pdf
- Appendixfile3SF36QUESTIONNAIRE.pdf
- Appendixfile1SPIRITChecklist.pdf
- Appendixfile5Informedconsent.pdf
- Appendixfile2Casereportform.pdf