Prognostic Impact of Transcatheter Arterial Chemoembolization (TACE) Combined with Radiofrequency Ablation in Patients with Unresectable Hepatocellular Carcinoma: A Comparison to TACE Alone using Decision-tree Analysis after Propensity Score Matching

Shigeo Shimose[1], Masatoshi Tanaka[2], Hideki Iwamoto[1], Takashi Niizeki[1], Tomotake Shirono[1], Hajime Aino[1], Yu Noda[1], Naoki Kamachi[1], Shusuke Okamuara[1], Masahito Nakano[1], Ryoko Kuromatsu[1], Takumi Kawaguchi[1], Atsushi Kawaguchi [3], Hironori, Koga[1], Yoshinori Yokokura[4], Takuji Torimura[1]

1. Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Kurume, Fukuoka 830-0011, Japan
2. Clinical Research Center, Yokokura Hospital, Miyama, Fukuoka 839-0295, Japan
3. Center for Comprehensive Community Medicine, Faculty of Medicine, Saga University, Nabeshima, Saga 849-8501, Japan
4. Department of Surgery, Yokokura Hospital, Miyama, Fukuoka, 839-0295, Japan

Short Title: Prognostic impact of TACE combined with RFA

Corresponding Author:

Masatoshi Tanaka, MD., Ph.D.

Yokokura Hospital, Miyama, Fukuoka 839-0295, Japan

480-2 Nose Takada-machi, Miyama City, Fukuoka 839-0295, Japan.

Tel. +81-944-22-5811, FAX, +81-944-22-2045

e-mail: mazzo6528@me.com

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; PS, performance status; TACE+RFA, TACE combined with RFA; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; ALBI, albumin-bilirubin; AEs, adverse events; SAEs, serious adverse events; CTCAE, common terminology criteria for adverse events.

Abstract

Aims: Prognosis of hepatocellular carcinoma (HCC) patients treated with transcatheter arterial chemoembolization (TACE) is still poor. We aimed to evaluate the impact of TACE combined with radiofrequency ablation (TACE+RFA) on the prognosis of HCC patients using decision-tree analysis after propensity score matching.

Methods: This was a retrospective study. We enrolled 420 patients with HCC treated with TACE alone (n=311) or TACE+RFA group (n=109) between 1998 and 2016 (age 72 years, male/female 272/148, The Barcelona Clinic Liver Cancer (BCLC) stage A/B 215/205). The prognosis of patients who underwent TACE+RFA was compared to patients who underwent TACE alone after propensity score matching. Decision-tree analysis was employed to investigate the profile for prognosis of the patients.

Results: After propensity score matching, there was no significant difference in age, sex, BCLC stage, or ALBI score between both groups. The survival rate of the TACE+RFA group was significantly higher than the TACE alone group (median survival time [MST] 57.9 months vs. 33.1 months, p<0.001). In a stratification analysis according to BCLC stage, the overall survival rate of the TACE+RFA group was significantly higher than the TACE alone group in BCLC stage A and B (MST 57.9 and 50.7 months vs. 39.8 and 24.5 months [p=0.007 and 0.001], respectively). Decision-tree analysis showed that TACE+RFA was the third distinguishable factor for survival in patients with alpha-fetoprotein level > 7 ng/mL and ALBI < -2.08.

Conclusion: Decision-tree analysis after propensity score matching

demonstrated that TACE+RFA may prolong the survival of HCC patients compared to TACE alone.

Introduction

Hepatocellular carcinoma is one of the most common causes of cancer-related deaths worldwide [1]. The survival of HCC patients depends on several prognostic factors that are either host related, such as liver function and general patient status or tumor related [2-6]. The Barcelona Clinic Liver Cancer (BCLC) classification is the most widely used classification to predict prognoses and determine treatment modalities [7]. Guidelines from the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases consider patients with stage 0 (very early stage BCLC) and stage A (early stage) suitable for curative treatment. However, palliative treatment is recommended in patients with intermediate stage HCC (BCLC B) and advanced stage HCC (BCLC C) and their prognosis is poor [7].

Transcatheter arterial chemoembolization (TACE) is a standard therapy for unresectable HCC [8], especially for patients with BCLC B [8]. Several studies have shown that TACE significantly improves patient survival compared to the best supportive care and can prolong survival in patients with multiple HCC tumors and no macro vascular invasion [9-12]. However, long-term prognosis of patients treated with TACE alone is unsatisfactory [13] and overall survival at 3 years remains low (< 30%) for intermediate HCC patients because of poor local control of HCC. On the other hand, radiofrequency ablation (RFA) is the main treatment method for patients with inoperable and small HCCs [14]. RFA shows excellent outcomes with 70-90% local control for small HCCs [15]. Thus, RFA may improve poor local control for HCC in patients treated with TACE alone.

Recently, TACE combined with RFA has been reported to yield better overall survival than TACE alone in HCC patients with BCLC stage B [16-21]. However, limitations of these previous studies are the small number of patients and different distributions of covariates between groups. Propensity score matching is generated using potential covariates and is able to overcome different distributions of covariates between groups. However, propensity score matching has not been applied to evaluate the impact of TACE combined with RFA. In addition, the significance of TACE combined with RFA on prognosis of patients with unresectable HCC has not been analyzed by using data mining analysis. Thus, the beneficial effects of TACE combined with RFA on prognosis of HCC patients remains unclear.

The aim of this study was to evaluate the impact of TACE combined with RFA on prognosis of patients with unresectable HCC by comparing them to patients treated with TACE alone and by decision-tree analysis after propensity score matching.

Subjects and Methods

Study design

This study was a retrospective cohort study carried out in two institutions. This protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected by the prior approval of the ethical committee of Kurume University School of Medicine, and Yokokura Hospital. An opt-out approach was used to obtain informed consent from the patients and personal information was protected during data collection.

Inclusion and exclusion criteria

The following patient inclusion criteria were used: (1) unresectable HCC diagnosed by biopsy or the diagnostic criteria according to American Association for the Study of Liver Diseases guidelines [22], (2) age >18 years, (3) no previous treatment for HCC except for hepatic resection or RFA alone, (4) World Health Organization performance status (PS) 0, and (5) complete follow-up from the initial treatment for HCC until death or the study censor time (May 31, 2018). The exclusion criteria were as follows: (1) a history of a malignant tumor other than HCC in the 5 years preceding the study (2) participation in any drug trial, (3) BCLC stage 0, C, and D, (4) PS > 1, (5) creatinine > 1.5 mg/dL, (6) infiltrative HCC, which was defined as represent true infiltrative of tumor cells into liver parenchyma, confluence of tiny nodules, or both in CT/MRI [23], (7) presence of portal vein thrombosis or extrahepatic metastasis, (8) presence of ascites, which was defined as uncontrollable ascites by treatment with 50 mg/day of spironolactone and 20 mg/day of furosemide), (9) F3 esophageal

varices, (10) a history of choledochojejunostomy, and (11) patients treated with liver transplantation.

Patients

A total of 531 consecutive patients diagnosed with HCC between 1998 and 2016 were registered from Kurume University School of Medicine and Yokokura Hospital in Japan (Supplementary Figure 1). Patients with any of the exclusion criteria listed above were excluded from analysis (n=111). A total of 420 patients were enrolled and were classified into unresectable HCC underwent TACE alone (TACE alone group; n=311) or TACE combined with RFA (TACE+RFA group; n=109) (Subjects A in Supplementary Figure 1). In the TACE alone group, 204 HCC patients were treated with RFA or operation. There was no significant difference in survival between patients with and without the previous treatment in the TACE alone group (Supplementary figure 2). In the TACE+RFA group, no patients had previous treatment for HCC.

Propensity score matching

Propensity score matching overcomes different distributions of covariates among individuals allocated to specific interventions and was generated using potential covariates that could affect group allocation [6]. In this study, propensity scores for all patients were estimated by a logistic regression model using the following baseline characteristics as covariates: age, sex, etiology of chronic liver disease, BCLC stage, tumor number, tumor size, alpha-fetoprotein (AFP) level, des-γ-carboxy prothrombin (DCP) level, albumin-

bilirubin (ALBI) score [24] A one-to-one nearest-neighbor matching algorithm with an optimal caliper of 0.2 without replacement was used to generate 136 pairs of patients. Since P values could be biased by population size, the propensity score matching results were also reported as effect size: |value| < 0.2 indicated a negligible difference, |value| < 0.5 indicated a small difference, |value| < 0.8 indicated a moderate difference and any other value indicated a large difference. The c-statistics was 0.83 (Supplementary figure 3). Thus, 136 patients with BCLC stage A and B (TACE-RFA [n=68] and TACE alone [n=68]) were analyzed (Subjects B in Supplementary Figure 1).

Diagnosis and staging of HCC

HCC was diagnosed by a tumor biopsy or a combination of tests for serum tumor makers such as AFP and DCP, and imaging procedures such as ultrasonography, computed tomography, and magnetic resonance imaging. In this study, HCC was classified by BCLC staging system, which was based on the findings of dynamic CT or MRI, but not CT during hepatic arteriography, throughout the study period.

Treatment for HCC

TACE was selected based on the evidence-based clinical practice guidelines for HCC of The Japan Society of Hepatology [25] or BCLC staging and treatment strategy [7]. In addition, TACE alone was selected for patients that RFA was impossible to treat HCC, because there were some nodules which were not visible by the ultrasound examination.

The indication for TACE+RFA was based on the previously studies [16, 26, 27]. Briefly, the indication was HCC with 2 to 7 cm in maximum diameter, or HCC with fewer than 7 nodules, which can be detected by ultrasonography. In addition, we enrolled the HCC patients who refused hepatic resection, although the HCC was within the indication of hepatic resection according to the evidence-based clinical practice guidelines for HCC of The Japan Society of Hepatology [25] or BCLC staging and treatment strategy [7]. While, we excluded the HCC patients with portal vein thrombosis and extrahepatic metastasis.

TACE procedure

The hepatologist who performed TACE and RFA procedures had more than 10 years of experience in interventional therapy at the start of this study. TACE was performed for the celiac artery and common hepatic artery, which were catheterized with a 3 or 4 Fr catheter, and digital subtraction angiography was performed with nonionic iodine contrast agent. After evaluation of the tumor-located segment using imaging technique including cone-beam CT, a 1.7 or 1.9 Fr microcatheter (Piolax Inc., Kanagawa, Japan) was inserted into sub- or sub-sub- hepatic segment which locates the tumor using the adapted microwire (Piolax Inc.). The catheter was advanced toward the tumor-feeding artery. Then, epirubicin was manually emulsified with lipiodol (Guerbet Co., Ltd., Tokyo, Japan) depending on the size and number of tumors, and was administrated followed by embolization with absorbable gelatin sponge particles (NIPPON KAYAKU Co., Ltd., Tokyo, Japan) [28]. The amount of epirubicin used was 20-50 mg. In the other institutions, a cisplatin with 5 mg of lipiodol was prepared by

mixing 50 mg of cisplatin powder (IA-cal, NIPPON KAYAKU Co., Ltd.), resulting in a concentration of 10 mg/mL. The amount of cisplatin used was 20-50 mg.

TACE combined with RFA

The TACE procedure was same as in the TACE group. RFA was performed 4 days after the TACE procedure using a 17-gauge internally cooled electrode with a 2- or 3-cm exposed tip (Cool-tip RF Ablation System; Valleylab, Boulder, CO). Under general anesthesia, the electrode needles were introduced into the tumor under ultrasonographic guidance. RFA was performed percutaneously according to the technique described elsewhere [15, 29]. Track ablation was performed upon withdrawal of the RFA electrode to prevent bleeding and tumor seeding when necessary. Ablation for each HCC nodules were conducted in a single RFA session. In cases of multiple HCC nodules, more than 6 HCC nodules were treated with 2 sessions (n=2), and complete response was confirmed by contrast enhanced CT scanning 1 month after TACE+RFA in all cases. In this study, there was no AE greater than grade 3 AEs after TACE. Thus, after obtaining of informed consent, RFA was performed 4 days after TACE in all patients.

Follow-up schedule after treatment of HCC

The first follow-up visit was performed approximately 1 month after treatment of HCC to assess therapeutic efficacy, and the patients were followed up every 3 months until death or the study censor time (May 31, 2018). Each follow-up consisted of a physical examination, serum AFP and DCP analysis,

and at least one imaging examination (abdominal ultrasound, enhanced CT, or

MRI). When HCC recurred, additional treatment for HCC was selected based

on the evidence-based clinical practice guidelines for HCC of The Japan

Society of Hepatology [25] or BCLC staging and treatment strategy [7].

Safety evaluation

Adverse events (AEs) and serious adverse events (SAEs) were

monitored and recorded. AEs were assessed during treatment and the follow-up

period. AEs were assessed according to the National Cancer Institute Common

Terminology Criteria for Adverse Events (CTCAE) version 4.0. For this study,

adverse events were defined as those classified as greater than grade 3

according to CTCAE.

Clinical Outcomes

The primary endpoint of this study was the overall survival of the

patients.

Statistical Analysis

All data are expressed as the number or median (range). All statistical

analyses were carried out using a statistical analysis software (JMP Pro version

13, SAS Institute Inc., Cary, NC). To overcome possible selection bias between

the TACE+RFA and TACE groups, we performed one-to-one matching using

propensity score matching as previously described [6].Overall survival was

calculated by Kaplan-Meier method and analyzed by log-rank test.

To select the factors for multivariate analysis, stepwise procedure was employed as previously described [30, 31]. Although BCLB staging system consists with liver function and tumor size, both BCLC staging system and ALBI score were applied for stepwise procedure as previously described [32]. Factors associated with overall survival was evaluated multivariate analysis and decision tree analysis as previously described [30]. A two-tailed P-value of <0.05 was considered as statistically significant.

Results

Patient characteristics before propensity score matching

The characteristics of the enrolled patients were shown in Table 1. The median age was 72 years and 64.7% (272/420) patients were male. The etiology for HCC was hepatitis C virus in 80 % (336/420) of patients and the median ALBI was -2.1. About 50% of patients (205/420) were BCLC stage B, and 66.7% of patients had multiple tumors, and the median tumor size was 27 mm.

The median age and ALBI score were significantly higher in the TACE+RFA group compared to the TACE alone group; however, there was no significant difference in sex and cause of HCC between the two groups. The ratio of BCLC stage A was significantly higher in the TACE+RFA group compared to the TACE alone group; however, maximum tumor diameter was significantly higher in the TACE+RFA group compared to the TACE alone group.

Kaplan-Meier curves for overall survival before propensity score matching

Overall survival in the TACE+RFA group was significantly higher than in the TACE alone group (P<0.001, Figure 1 A). Overall survival rates for TACE+RFA were 96%,74%, and 46%, and for TACE were 88%,38%, and 13% in 1, 3, 5-years, respectively (Figure 1 A).

Patient characteristics after propensity score matching

To minimize the effect of confounding factors, we performed propensity score matching using the following factors: age, sex, cause of HCC, ALBI score,

BCLC stage, tumor number, maximum tumor diameter, AFP value, and DCP value. There was no significant difference between the TACE+RFA and TACE alone groups in any variable including age, ALBI score, BCLC stage, and maximum tumor diameter (Table 2).

Logistic regression analysis for survival after propensity score matching

Logistic regression analysis for overall survival was performed after propensity score matching. Treatment for HCC, BCLC stage, ALBI score, and cause of HCC were selected by stepwise procedure. In the logistic regression analysis, treatment for HCC, BCLC stage, and ALBI score were identified as independent factors for overall survival (Table 3).

Kaplan-Meier curves for overall survival after propensity score matching

Kaplan-Meier curves for overall survival were evaluated after propensity score matching. Overall survival period in the TACE+RFA group was significantly longer than the TACE alone group (P<0.001, Figure 1 B). Overall survival rates in the TACE+RFA group were 97%, 76%, and 46%, and the rates in the TACE group were 94%, 43%, 17% in 1, 3, 5-years, respectively (Figure 1 B).

Stratification analysis according to BCLC stage A and B for factors associated with overall survival after propensity score matching

Stratification analysis according to BCLC stage A and B for factors associated with overall survival was performed after propensity score matching.

Treatment of HCC (TACE+RFA) was identified as solo negative factor for survival in both BCLC stage A and B (Supplementary Table 1). Overall survival period in the TACE+RFA group was significantly longer than in the TACE alone group in both BCLC stage A and B (Figure. 2 A and 2 B).

Decision-tree analysis for overall survival after propensity score matching

After propensity score matching, 25.7% (35/136) of enrolled subjects were alive at the study censor time. AFP level was selected as the variable for the initial split, and 17.9% of patients with AFP level ≥ 7 ng/mL were alive (Figure 3). In patients with AFP level ≥ 7 ng/mL, ALBI score was selected as the second split, and 25.7% of patients with ALBI score < -2.08 were alive. In patients with ALBI score < -2.08, therapy was selected as the third split, 34.9% of patients treated with TACE+RFA were alive (Group 1 in Figure 3); while 15.4% of patients treated with TACE alone were alive (Group 2 in Figure 3).

AE and SAE

Among all patients, 6 (2%) experienced SAE that were assessed as greater than grade 3 AEs according to CTCAE. The complications that were noted included: hepatic failure in 2 (0.4%) in the TACE alone group, hepatic hemorrhage in 2 (0.4%), and bile duct injury in 2 (0.4%) in the TACE+RFA group. However, these patients recovered completely with no after effect.

Discussion

In this study, we demonstrated a beneficial impact of TACE combined with RFA on prognosis of patients with unresectable HCC by comparing to TACE alone. After propensity score matching, TACE combined with RFA was an independent factor associated with overall survival. In addition, decision-tree analysis showed, along with AFP level and ALBI score, TACE combined with RFA was selected as the third split factor for overall survival in patients with unresectable HCC.

In this study, overall survival period in the TACE+RFA group was significantly longer than in the TACE alone group. Although similar results have previously been reported, these studies were limited because of the small sample size (less than 100 patients) [33, 34]. A sample size of more than 100 patients is preferable for Kaplan-Meier analysis using the log-rank statistic [35]. In our study, 420 patients were enrolled and, therefore, our results are based on a sufficient number of patients and confirm the beneficial impact of TACE combined with RFA on prognosis. However, propensity score matching is required to further prove a prognostic impact of TACE combined with RFA to overcame different distributions of patients' characteristics including liver function and tumor factors.

In our study, 96% patients were classified as substages B1 or B2 in the TACE+RFA group. Hirooka et al. previously performed propensity matching using Child-Pugh scores and host/tumor factors and reported that the use of TACE+RFA for improves survival rates compared with TACE alone in patients with BCLC B1 and 2 [16]. Recently, ALBI score has been demonstrated to be a

better prognostic tool than the Child-Pugh score [24, 36, 37]. Therefore, ALBI score was employed in our study and we showed that overall survival in the treatment of TACE+RFA was significantly higher than the treatment of TACE alone after propensity matching using ALBI score [37]. Thus, our results further confirmed the results of previous reports. In addition, our study is the first to demonstrate that TACE+RFA improved survival rates compared to TACE alone in HCC patients with BCLC stage A. The reason for the improvement of prognosis remains unclear. However, in HCC patients with BCLC stage A, poor prognosis is seen in HCC patients with single tumor that is 3 cm to 5 cm in diameter and TACE alone is generally selected for such patients with unresectable HCC [25]. Thus, a possible reason is that TACE+RFA may be a better therapy than TACE alone for patients with a single tumor that is 3 cm to 5 cm in diameter.

In this study, we first analyzed the prognosis of patients with unresectable HCC using decision-tree analysis. Survival rate in patients treated with TACE combined with RFA was higher than that of patients treated with TACE alone, suggesting that TACE combined with RFA may contribute to a better prognosis for patients with unresectable HCC. However, treatment for HCC (TACE combined with RFA/TACE alone) was the third distinguishing factor. The first and second distinguishing factors were AFP level and ALBI score, respectively. Accordingly, tumor markers and liver function should be taken into consideration to improve prognosis in patients with unresectable HCC.

The present study has several limitations. First, the study design was a retrospective study. Second, in the TACE alone group, 65% of HCC patients

were previously treated with RFA or operation. While, in the TACE+RFA group, no patients had previous treatment for HCC. Although, there was no significant difference in survival between patients with and without the previous treatment in the TACE alone group, we could deny the possibility that history of previous treatment may affect overall survival. Third, treatment of the HCC recurrence and liver diseases including hepatitis C and hepatitis B virus might have affected prognosis of patients; however, we did not evaluate these treatment factors in this study. Thus, to prove a prognostic impact of TACE combined with RFA, it is necessary to perform a prospective study with treatment factors for the HCC recurrence and chronic liver diseases.

In conclusion, we demonstrated that TACE combined with RFA improved prognosis compared to TACE alone in patients with unresectable HCC. In addition, after propensity score matching, TACE combined with RFA was an independently associated with overall survival. Moreover, decision-tree analysis showed that TACE combined with RFA was selected as the third split factor for survival in patients with unresectable HCC.

Author Contributions

SS and MT participated in study conception and design, acquisition of data, interpretation of data, and drafting of manuscript. HI, TN, TS, HA, YN, NK, SO, MN, and RK participated in acquisition of data. TK participated in analysis, interpretation of data and drafting of manuscript. AK participated in analysis. HK, YY, and TT participated in critical revision.

Reference

1   Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015; **136**: E359-86.

2   Jin B, Wang D, Lewandowski RJ, et al. Chemoembolization endpoints: effect on survival among patients with hepatocellular carcinoma. *AJR Am J Roentgenol.* 2011; **196**: 919-28.

3   Hiraoka A, Horiike N, Yamashita Y, et al. Risk factors for death in 224 cases of hepatocellular carcinoma after transcatheter arterial chemoembolization. *Hepatogastroenterology.* 2009; **56**: 213-7.

4   Yasui Y, Tsuchiya K, Kurosaki M, et al. Up-to-seven criteria as a useful predictor for tumor downstaging to within Milan criteria and Child-Pugh grade deterioration after initial conventional transarterial chemoembolization. *Hepatol Res.* 2018; **48**: 442-50.

5   Hu HT, Kim JH, Lee LS, et al. Chemoembolization for hepatocellular carcinoma: multivariate analysis of predicting factors for tumor response and survival in a 362-patient cohort. *J Vasc Interv Radiol.* 2011; **22**: 917-23.

6   Kitai S, Kudo M, Nishida N, et al. Survival Benefit of Locoregional Treatment for Hepatocellular Carcinoma with Advanced Liver Cirrhosis. *Liver Cancer.* 2016; **5**: 175-89.

7   Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet.* 2018; **391**: 1301-14.

8   Ikeda K. Recent advances in medical management of hepatocellular carcinoma. *Hepatol Res.* 2019; **49**: 14-32.

9   Piscaglia F, Ogasawara S. Patient Selection for Transarterial Chemoembolization in Hepatocellular Carcinoma: Importance of Benefit/Risk Assessment. *Liver Cancer.* 2018; **7**: 104-19.

10 Hatanaka T, Arai H, Shibasaki M, et al. Factors predicting overall response and overall survival in hepatocellular carcinoma patients undergoing balloon-occluded transcatheter arterial chemoembolization: A retrospective cohort study. *Hepatol Res.* 2018; **48**: 165-75.

11 Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology.* 2006; **131**: 461-9.

12 Uraki J, Yamakado K, Nakatsuka A, Takeda K. Transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma invading the portal veins:

therapeutic effects and prognostic factors. *Eur J Radiol.* 2004; **51**: 12-8.

13 Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev.* 2011: CD004787.

14 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut.* 2005; **54**: 1151-6.

15 Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology.* 2005; **129**: 122-30.

16 Hirooka M, Hiraoka A, Ochi H, et al. Transcatheter Arterial Chemoembolization With or Without Radiofrequency Ablation: Outcomes in Patients With Barcelona Clinic Liver Cancer Stage B Hepatocellular Carcinoma. *AJR Am J Roentgenol.* 2018; **210**: 891-8.

17 Yin X, Zhang L, Wang YH, et al. Transcatheter arterial chemoembolization combined with radiofrequency ablation delays tumor progression and prolongs overall survival in patients with intermediate (BCLC B) hepatocellular carcinoma. *BMC Cancer.* 2014; **14**: 849.

18 Tanaka M, Ando E, Simose S, et al. Radiofrequency ablation combined with transarterial chemoembolization for intermediate hepatocellular carcinoma. *Hepatol Res.* 2014; **44**: 194-200.

19 Li L, Tian J, Liu P, Wang X, Zhu Z. Transarterial chemoembolization combination therapy vs monotherapy in unresectable hepatocellular carcinoma: a meta-analysis. *Tumori.* 2016; **2016**: 301-10.

20 Hyun D, Cho SK, Shin SW, et al. Early Stage Hepatocellular Carcinomas Not Feasible for Ultrasound-Guided Radiofrequency Ablation: Comparison of Transarterial Chemoembolization Alone and Combined Therapy with Transarterial Chemoembolization and Radiofrequency Ablation. *Cardiovasc Intervent Radiol.* 2016; **39**: 417-25.

21 Kong QF, Jiao JB, Chen QQ, Li L, Wang DG, Lv B. Comparative effectiveness of radiofrequency ablation with or without transarterial chemoembolization for hepatocellular carcinoma. *Tumour Biol.* 2014; **35**: 2655-9.

22 Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018; **67**: 358-80.

23 Chernyak V, Fowler KJ, Kamaya A, et al. Liver Imaging Reporting and Data

System (LI-RADS) Version 2018: Imaging of Hepatocellular Carcinoma in At-Risk Patients. *Radiology.* 2018; **289**: 816-30.

24 Ho CHM, Chiang CL, Lee FAS, et al. Comparison of platelet-albumin-bilirubin (PALBI), albumin-bilirubin (ALBI), and child-pugh (CP) score for predicting of survival in advanced hcc patients receiving radiotherapy (RT). *Oncotarget.* 2018; **9**: 28818-29.

25 Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). *Hepatol Res.* 2015; **45**.

26 Yan JY, Zhang JL, Wang MQ, et al. Combined transcatheter arterial chemoembolization and radiofrequency ablation in single-session for solitary hepatocellular carcinoma larger than 7 cm. *Asia Pac J Clin Oncol.* 2017.

27 Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol.* 2013; **31**: 426-32.

28 Horikawa M, Miyayama S, Irie T, Kaji T, Arai Y. Development of Conventional Transarterial Chemoembolization for Hepatocellular Carcinomas in Japan: Historical, Strategic, and Technical Review. *AJR Am J Roentgenol.* 2015; **205**: 764-73.

29 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology.* 2004; **127**: 1714-23.

30 Kawaguchi T, Tokushige K, Hyogo H, et al. A Data Mining-based Prognostic Algorithm for NAFLD-related Hepatoma Patients: A Nationwide Study by the Japan Study Group of NAFLD. *Sci Rep.* 2018; **8**: 10434.

31 Kawaguchi T, Inokuchi T, Honma T, et al. Factors associated with advanced hepatic fibrosis in patients with various internal diseases: A multicenter community-based survey. *Hepatol Res.* 2018; **48**: 882-92.

32 Sinn DH, Choi GS, Park HC, et al. Multidisciplinary approach is associated with improved survival of hepatocellular carcinoma patients. *PLoS One.* 2019; **14**: e0210730.

33 Azuma S, Asahina Y, Nishimura-Sakurai Y, et al. Efficacy of additional radiofrequency ablation after transcatheter arterial chemoembolization for intermediate hepatocellular carcinoma. *Hepatol Res.* 2016; **46**: 312-9.

34 Liu HC, Shan EB, Zhou L, et al. Combination of percutaneous radiofrequency ablation with transarterial chemoembolization for hepatocellular carcinoma:

observation of clinical effects. *Chin J Cancer Res.* 2014; **26**: 471-7.

35 Lakatos E, Lan KK. A comparison of sample size methods for the logrank statistic. *Stat Med.* 1992; **11**: 179-91.

36 Yan W, Zhu Z, Pan F, Huang A, Dai GH. Overexpression of c-kit(CD117), relevant with microvessel density, is an independent survival prognostic factor for patients with HBV-related hepatocellular carcinoma. *Onco Targets Ther.* 2018; **11**: 1285-92.

37 Hiraoka A, Kumada T, Hirooka M, et al. A better method for assessment of hepatic function in hepatocellular carcinoma patients treated with radiofrequency ablation: Usefulness of albumin-bilirubin grade. *Hepatol Res.* 2018; **48**: E61-E7.

Figure legends

Figure 1. (A) Kaplan-Meier curves for overall survival according to Barcelona Clinic Liver Cancer stage A and B. (B) Kaplan-Meier curves for overall survival according to Barcelona Clinic Liver Cancer stage A and B after propensity score matching. Red line indicates the TACE alone group. Blue line indicates the TACE combined with RFA group.

Figure 2. (A) Kaplan-Meier curves for overall survival according to Barcelona Clinic Liver Cancer stage A after propensity score matching. (B) Kaplan-Meier curves for overall survival according to Barcelona Clinic Liver Cancer stage B after propensity score matching. Red line indicates the TACE alone group. Blue line indicates the TACE combined with RFA group.

Figure 3. Decision-tree algorithm of survival predictive factors. The subjects were classified according to the indicated cut-off values of the variables. The pie graphs indicate the percentage of live patients (white)/deceased patients (black) in each group. AFP; α-fetoprotein, ALBI; albumin-bilirubin score, TACE; transcatheter arterial chemoembolization, RFA; radiofrequency ablation.

Supplementary Figure 1. Study design. A total of 531 HCC patients were enrolled from 1998 to 2016 and followed up until May 31, 2018. In the course of the study, 111 patients were excluded and 420 HCC patients (Subjects A) were used to evaluate the impact of TACE combined with RFA on prognosis by comparing them to patients treated with TACE alone. Then, the data from the 420 HCC patients were applied to propensity match scoring and 136 HCC patients (Subjects B) were used for the evaluation.

Supplementary Figure 2. Kaplan-Meier curves for overall survival according to with and without the previous treatment in the TACE alone group. Red line indicates patients with the pretreatment for HCC in the TACE alone group. Blue line indicates patients without pretreatment for HCC in the TACE alone group.

Supplementary Figure 3. C-statics by using ROC analysis. The c-statistics is 0.83, indicating good ability of the propensity score model to predict effect of treatment on patients' prognosis.

Table 1. Patient characteristics

Characteristic	All patients	TACE+RFA	TACE alone	p
n	420	109	311	
Age (years old)	72 (36-90)	70 (36-89)	73 (48-90)	<0.001
Sex (female/male)	148/272	40/69	108/203	0.710
Cause of HCC (HBV/HCV/Others)	27/336/57	92/9/8	244/18/49	0.069
ALBI score (mean (range))	-2.1 (-3.37– -0.72)	-2.4 (-3.37– -1.46)	-2.1 (-3.27– -0.72)	<0.001
ALBI grade (1/2/3)	98/308/14	41/68/0	57/240/14	<0.001
BCLC (stage A/B)	215/205	82/27	133/178	<0.001
Tumors number				
1	140	61	79	
2	80	17	63	
3	67	24	43	
4	47	4	43	
5	35	1	34	
>5	51	2	49	<0.001
Maximum tumor diameter (mm)	27 (10-127)	32 (21-64)	25 (10-127)	<0.001
AFP (ng/mL)	32.5 (1.3-91000)	31 (2-91000)	33.5 (1.3-62546)	0.866
DCP (mAU/mL)	71 (7-75000)	87 (9-10200)	68 (7-75000)	0.996
Ischemic heart	33/387	10/99	23/288	0.558

diseases with anti-coagulation medicine (Yes/No)				
Creatinine (mg/dL)	0.73 (0.3-1.42)	0.7 (0.3-1.4)	0.74 (0.3-1.42)	0.587
eGFR (mL/min/1.73m^2)	74.6 (30.2-162.6)	73.2 (30.2-162.6)	74.1 (30.6-160)	0.645
GFR classification	420			
G1	91	22	69	
G2	223	60	163	
G3a	68	15	53	
G3b	33	12	26	0.702

Note. Data are expressed as median (range), or number. Abbreviations: TACE+RFA, transcatheter arterial chemoembolization combined with radiofrequency ablation; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatis C virus; ALBI score, Albumin-bilirubin score; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin; eGFR, estimate glomerular filtration rate: GFR, glomerular filtration rate

Table 2. Patient characteristics after propensity score matching

Characteristic	All patients	TACE+RFA	TACE alone	p
n	136	68	68	
Age (years old)	71 (46-89)	70.5 (46-89)	71 (48-85)	0.969
Sex (female/male)	83/53	42/26	41/27	0.860
Cause of HCC (HBV/HCV/Others)	14/107/15	4/57/7	10/50/8	0.212
ALBI score (Median (rage))	-2.26 (-3.37– -1.46)	-2.04 (-3.37– -1.49)	-2.26 (-3.18– -1.46)	0.335
ALBI grade (1/2/3)	37/99/0	16/52/0	21/47/0	0.335
BCLC (A/B)	90/46	44/24	46/22	0.717
Tumor Number				
1	62	30	32	
2	25	12	13	
3	33	20	13	
4	7	4	3	
5	4	1	3	
>5	5	1	4	0.475
Maximum tumor diameter (mm)	32 (10-85)	32.7 (21-58)	31.4 (10-85)	0.540
AFP (ng/mL),	29.7 (1.8-27530)	31.5 (3.0-4622)	27.6 (1.8-27530)	0.221
DCP (mAU/mL)	60 (7-13933)	69 (9-10200)	60 (7-13933)	0.832

Note. Data are expressed as median (range), or number. P value are based on comparison between the TACE+RFA and TACE alone groups. Abbreviations: TACE+RFA, transcatheter arterial chemoembolization combined with

radiofrequency ablation; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatis C virus; ALBI score, Albumin-bilirubin score; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein; DCP, des-γ-carboxy prothrombin.

Table 3. Multivariate analysis for overall survival

Factors	Unit	Odds ratio	95% Confidence interval	p
Treatment for HCC (TACE+RFA)	N/A	0.37	0.24–0.58	0.01
BCLC B	N/A	2.09	1.3–3.1	0.02
ALBI score	1	4.80	2.09–11.1	0.002

Abbreviations: TACE+RFA, transcatheter arterial chemoembolization combined with radiofrequency ablation; HCC, hepatocellular carcinoma; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer

Figure 1

A
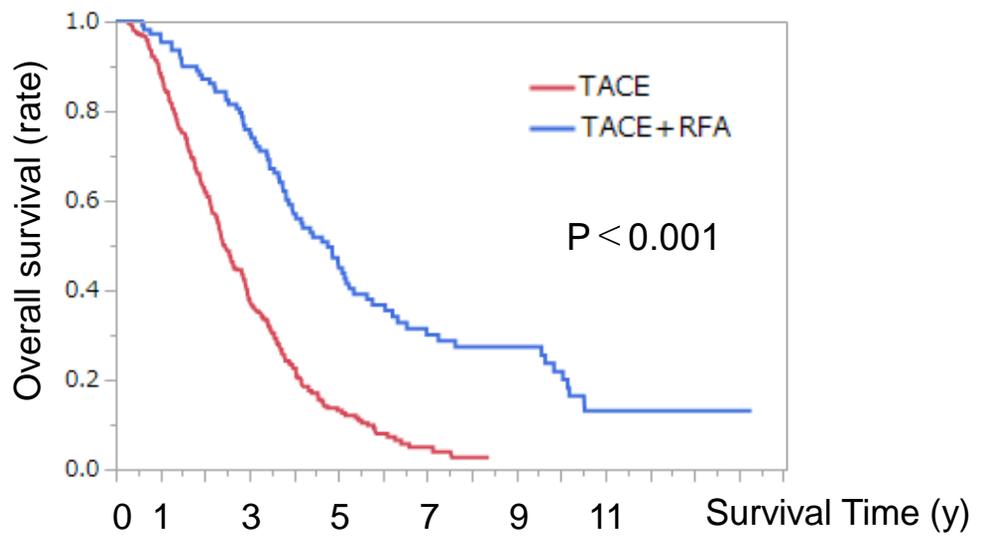
	0	1	3	5	7	9	11
TACE+RFA	109	107	94	41	23	18	10
TACE		311	275	194	26	5	

B
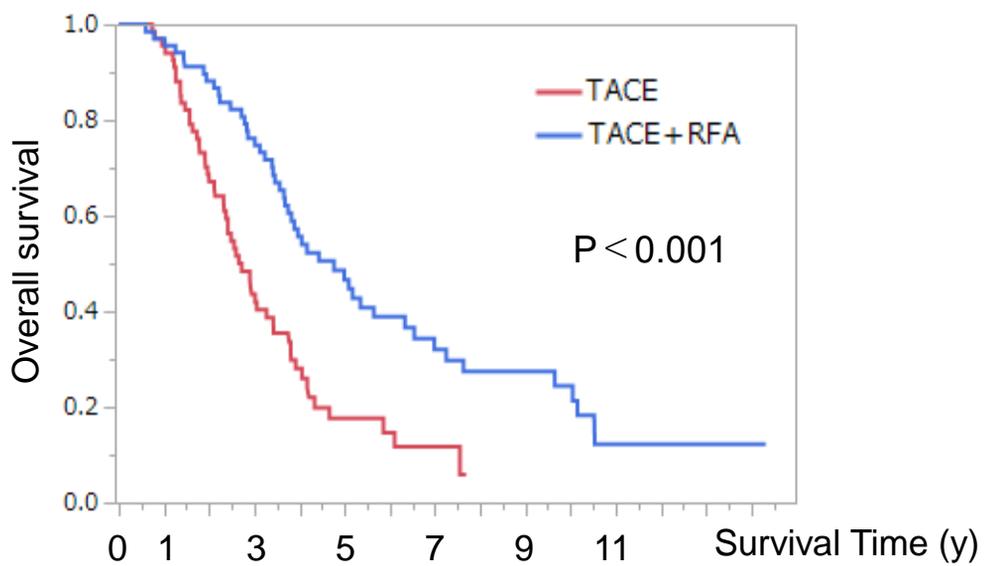
	0	1	3	5	7	9	11
TACE+RFA	68	67	52	25	15	11	3
TACE		68	64	28	8	2	

Figure 2

A — BCLC A
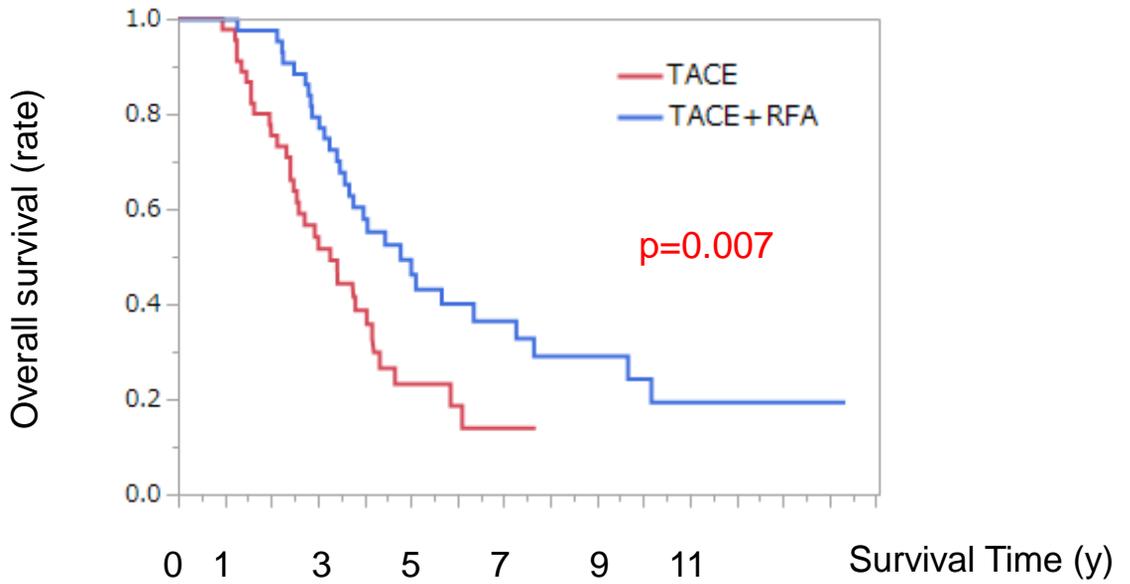
	0	1		3		5		7		9		11
TACE+RFA	44	44		36		16		11		7		2
TACE		46	45		23		7		2			

p=0.007

Overall survival (rate) · Survival Time (y)
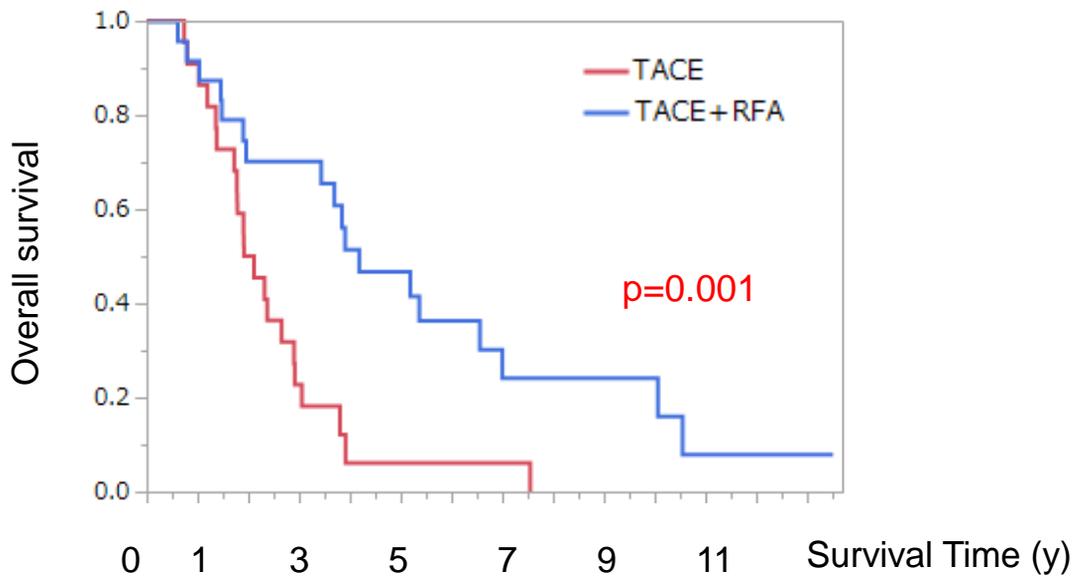
B — BCLC B

	0	1		3		5		7		9		11
TACE+RFA	24	22		16		9		5		5		2
TACE		22	20		6		2		2			

p=0.001

Overall survival · Survival Time (y)

Figure 3

Model building
n = 136

25.7%

Decease
Alive

< 7 ng/mL   AFP   ≥ 7 ng/mL

n = 24   n = 112
                                          17.9%
61.0%   95.0%

< -2.08   ALBI   ≥ -2.08

n = 70   n = 42   5.2%
25.7%
                               79.5%

TACE+RFA   Treatment   TACE

n = 37   n = 33
34.9%   15.4%
                               79.5%

Group 1   Group 2
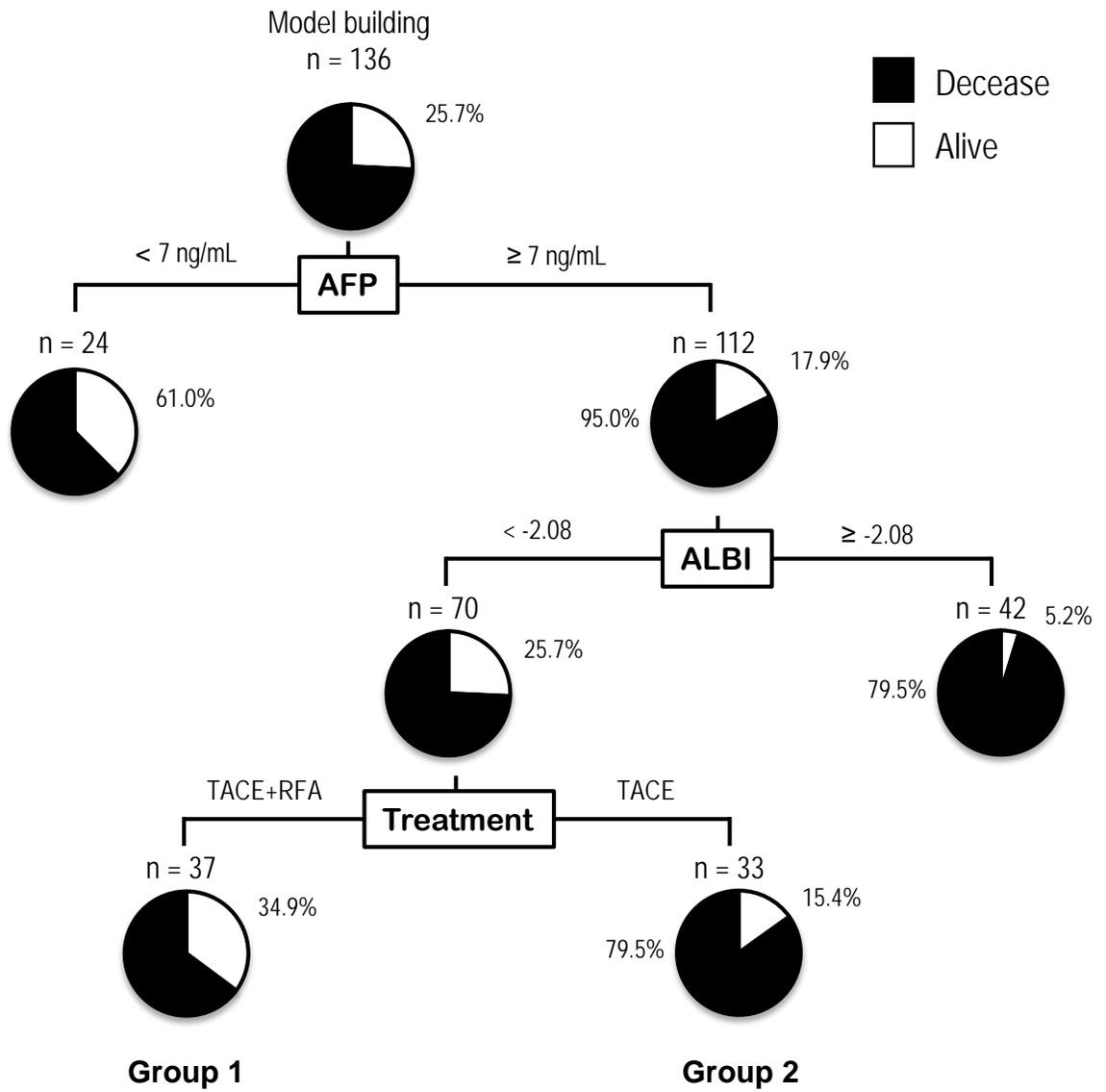
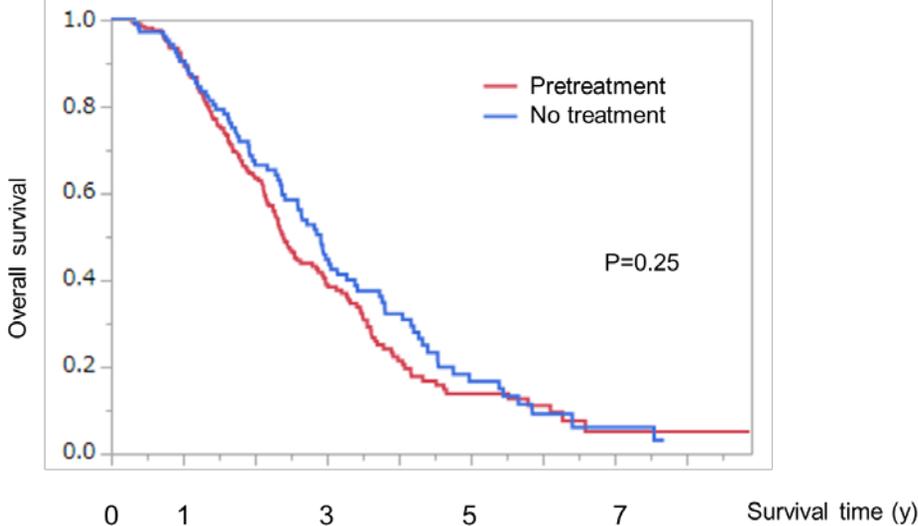Supplementary Table 1. Multivariate analysis for overall survival in BCLC A B

BCLC A				
Factors	Unit	Odds ratio	95% Confidence interval	p
Treatment for HCC (TACE+RFA)	N/A	0.40	0.22–0.72	0.002
Number tumors	1	1.36	0.90–2.01	0.124
Maximum tumor diameter (mm)	1	1.01	0.97–1.05	0.479
ALBI score	1	2.71	1.35–5.52	0.005
BCLC B				
Factors	Unit	Odds ratio	95% Confidence interval	p
Treatment for HCC (TACE+RFA)	N/A	0.27	0.11–0.60	0.001
Number tumors	1	1.08	0.97–1.21	0.130
Maximum tumor diameter (mm)	1	1.00	0.97–1.03	0.802
ALBI score	1	2.24	1.05–5.01	0.003

Abbreviations: TACE+RFA, transcatheter arterial chemoembolization combined with radiofrequency ablation; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatis C virus; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer

Supplementary Figure 1

Consecutive patients with HCC
from 1998 to 2016 (n=531)

111 patients were excluded

Subjects A
Patients with BCLC stage A and B (n=420)
　TACE-RFA　(n=109)
　TACE　alone (n=311)

Propensity score matching

Subjects B
Patients with BCLC stage A and B (n=136)
　TACE-RFA (n=68)
　TACE alone (n=68)

Supplementary Figure 2

A Kaplan-Meier overall survival curve comparing Pretreatment (red) and No treatment (blue) groups, with P=0.25.
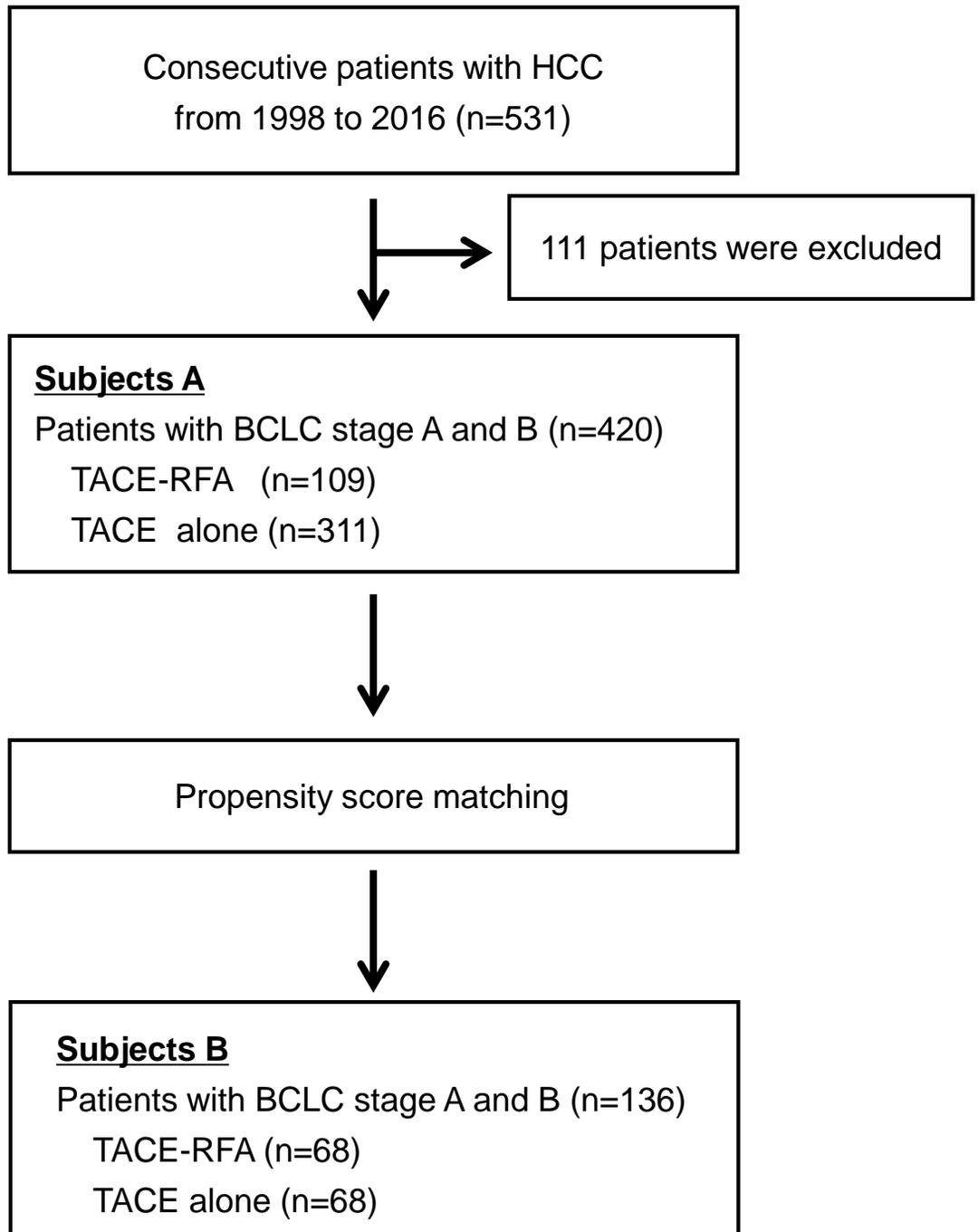
	0	1	3	5	7
Pre-treatment	204	174	57	14	3
No pre-treatment	107	92	41	11	3

Supplementary Figure 3

AUC:0.83

Sensitivity
True-positive

1-specificity
(false-positive)