Liver Cancer

Research Article

Liver Cancer
DOI: 10.1159/000529635

Received: May 6, 2022
Accepted: January 17, 2023
Published online: February 10, 2023

Impact of Intrahepatic External Beam Radiotherapy in Advanced Hepatocellular Carcinoma Patients Treated with Tyrosine Kinase Inhibitors

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Keywords
Barcelona Clinic Liver Cancer stage C · Hepatocellular carcinoma · Tyrosine kinase inhibitor · Radiation therapy

Abstract

Introduction: We aimed to investigate whether concurrent use of intrahepatic external beam radiotherapy (EBRT) is a viable option for patients with advanced hepatocellular carcinoma (HCC) undergoing tyrosine kinase inhibitor (TKI) therapy. ***Methods:*** A total of 453 patients with Barcelona Clinic Liver Cancer stage C (BCLC C) HCC, who started first-line treatment with TKI with intrahepatic EBRT (TKI + RT, $n = 97$) or TKI without intrahepatic EBRT (TKI, $n = 356$) were analyzed. The overall survival (OS) and progression-free survival (PFS) were compared in the overall cohort, patients who received at least 8 weeks of TKI treatment and a propensity score-matched cohort. ***Results:*** OS and PFS were better in those treated with TKI + RT than TKI (8.6 vs. 4.4 months and 4.5 vs. 2.3 months, respectively, with $p < 0.001$). Of note, the TKI + RT group demonstrated significantly longer time to intrahepatic tumor progression. In subgroup analysis, TKI + RT led to better OS than TKI in all subgroups and PFS was significantly improved in patients without extrahepatic metastasis and those with portal vein invasion. There was no significant difference in treatment discontinuation due to adverse events between the TKI + RT and TKI groups (32.0% vs. 37.9%, $p = 0.34$). Furthermore, patients treated with TKI + RT showed better liver function preservation over time compared to TKI without intrahepatic EBRT. Comparable treatment outcomes were observed between patients who received at least 8 weeks of TKI treatment and the propensity score-matched cohort. ***Conclusion:*** Concurrent intrahepatic EBRT targeting the liver and/or macrovascular invasion can be a viable option to improve outcomes of BCLC stage C patients receiving TKI therapy with an aim to control intrahepatic progression and preserving the liver function.

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Introduction

For hepatocellular carcinoma (HCC) patients presenting with vascular invasion or extrahepatic spread, systemic treatment is first-line treatment option [1]. Currently, the recommended first-line systemic treatment regimen is a combination of atezolizumab and bevacizumab [2], which has shown superior survival benefit compared to sorafenib [3]. However, tyrosine kinase inhibitors (TKIs), such as sorafenib or lenvatinib, remain a valuable first-line systemic treatment option for advanced HCC [4], especially for those who are not candidates for an immunotherapy-based regimen [2]. Therefore, even in the era of immunotherapy, ways to improve treatment outcomes of TKI therapy for advanced-stage HCC remain an unmet clinical need.

With development of modern radiotherapy technologies, external beam radiotherapy (EBRT) has been increasingly used in HCC management, including advanced-stage HCC [5]. In a meta-analysis involving 512 patients from 11 studies, combined treatment with sorafenib and EBRT was associated with greater survival benefit than sorafenib alone for advanced-stage HCC [6]. In a nationwide cancer registry-based study involving 4,763 patients, combined treatment with sorafenib and EBRT showed better survival than sorafenib alone [7]. These studies suggest that the addition of EBRT to TKI therapy can be a viable strategy for improving treatment outcomes of TKI therapy for advanced HCC. However, no randomized controlled trials have evaluated the efficacy and safety of combined treatment with TKI and EBRT compared to TKI alone. In addition, worsening of liver function and significant dose-limiting toxicity were reported in patients receiving combined treatment with sorafenib and EBRT [8]. Grade ≥3 hepatologic and hematologic toxicity was higher when EBRT treatment targeted intrahepatic lesions [6]. Hence, the benefit of combined treatment with TKI and intrahepatic EBRT requires further evaluation in real-world clinical practice. Thus, we compared the outcomes of advanced HCC patients who received combined treatment with TKI and intrahepatic EBRT to outcomes of those treated with TKI alone to determine whether the addition of intrahepatic EBRT to TKI improves outcome in advanced HCC patients.

Materials and Methods

Study Design, Data Sources, and Patients

This was a retrospective cohort study performed at Samsung Medical Center, Seoul, Korea. We used the HCC registry, which is an electronic registry that records baseline clinical data, tumor factors, and initial treatment modality for each newly diagnosed HCC patient aged 18 years or older who received care at Samsung Medical Center in a prospective manner. The diagnosis of HCC was confirmed either histologically or clinically based on the Korean HCC guidelines during the study period [9, 10].

From the HCC registry, we identified 511 Barcelona Clinic Liver Cancer (BCLC) stage C HCC patients who received sorafenib or lenvatinib as a first-line systemic therapy between January 2010 and December 2020. Among them, we excluded 58 patients who met the following exclusion criteria: (i) Child-Pugh score 8 or higher ($n = 30$), (ii) combined use of transarterial therapy such as transarterial chemoembolization ($n = 12$), (iii) combined use of other clinical trial drugs (CS1001, resminostat) ($n = 5$), or (iv) use of intrahepatic EBRT as a rescue therapy (or salvage therapy) after disease progression (PD) during TKI treatment ($n = 11$). Finally, a total of 453 consecutive, treatment-naïve patients with BCLC stage C HCC who received sorafenib or lenvatinib therapy with or without EBRT as a first-line treatment were analyzed (Fig. 1). The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2022-02-099-001). As the study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed patient consent was waived.

Treatment Details and Follow-Up

All patients received oral TKI with or without EBRT within 3 months of being diagnosed with HCC. In general, sorafenib was started at a dose of 400 mg twice daily, and the initial dose of lenvatinib was determined by patient weight. Patients weighing <60 kg were administered 8 mg of lenvatinib daily, while those who weighed ≥60 kg were administered 12 mg of lenvatinib daily. During the follow-up period, the dose was reduced or treatment interrupted in patients who experienced grade ≥3 adverse events (AEs) or uncontrolled AEs despite symptom management. If the patient tolerated TKI, the therapy was continued until PD.

The decision to add EBRT to TKI therapy was made by the physician in charge of each patient. The target of EBRT was decided by a radiation oncologist. Usually, the target of EBRT is intended to treat vascular invasion and/or bile duct invasion, including the primary hepatic lesion as much as possible, but only vascular invasion was targeted when more than 60% of the normal liver was exposed to an EBRT dose ≥30 gray (Gy) [10]. If necessary, extrahepatic tumor lesions such as the adrenal gland, bone, or lymph node were also included in EBRT targeting. Modalities of EBRT included conventional EBRT, stereotactic body radiation therapy, and proton beam therapy. All EBRTs were conducted with pretreatment respiration control training accompanied by audiovisual guidance, four-dimensional computed tomography, and magnetic resonance imaging simulation, followed by image-guided and respiration-gated delivery. Additional details of EBRT during the study period have been described in previous articles [11–13].

Outcomes, Exposures, and Variables

The outcome variables were overall survival (OS), defined as time from the start date of primary treatment to death from any cause, and progression-free survival (PFS), defined as time from the start date of primary treatment to PD according to the modified response evaluation criteria in solid tumor [14] or death from any cause. For the evaluation of portal vein invasion (PVI), complete recanalization of the portal vein with full restoration of blood flow was considered complete remission (CR), any

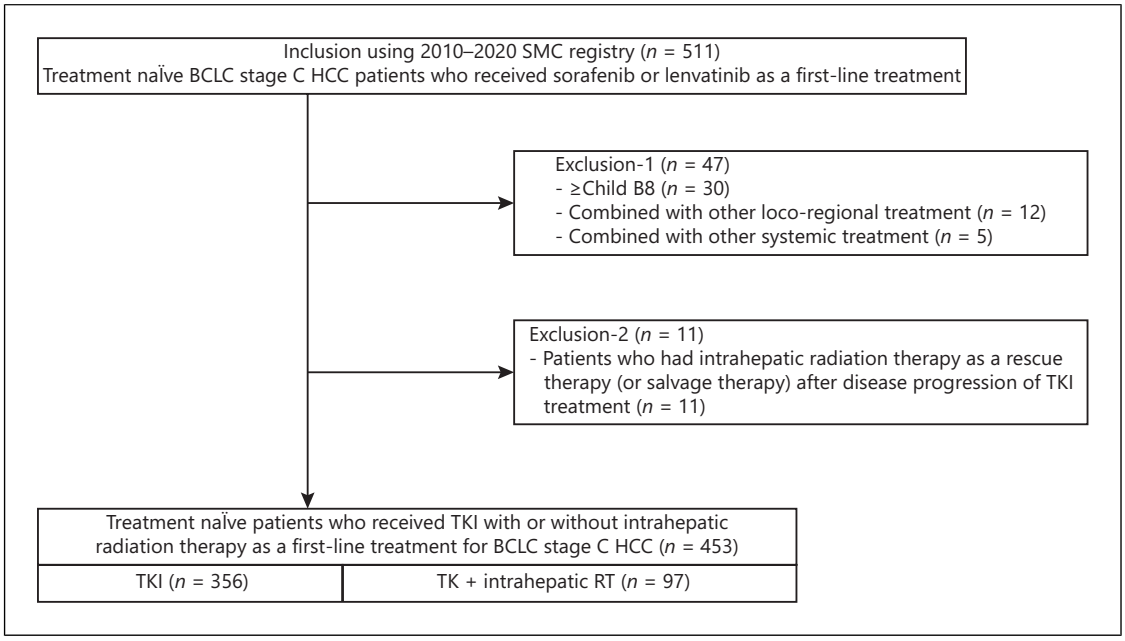


Fig. 1. Patient flow.

downstaging in Cheng's classification with partial recanalization as partial response (PR), and any upstaging as PD. Otherwise, the cases were classified as stable disease (SD) [15]. The referral date was September 30, 2021. For patients with PD, we analyzed patterns of intrahepatic versus extrahepatic PD.

Patients were divided into two groups: those who received TKI in combination with intrahepatic EBRT (TKI + RT) and those who received TKI without intrahepatic EBRT (TKI). Those who received extrahepatic EBRT only were classified into the TKI without intrahepatic EBRT group.

Baseline variables were obtained from the HCC registry including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, etiology of liver disease, tumor number, maximum tumor diameter, level of PVI, extrahepatic metastasis, type of TKI (sorafenib or lenvatinib), Child-Pugh score, modified albumin-bilirubin (ALBI) grade, serum alpha-fetoprotein, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels. Modified ALBI (mALBI) grades were calculated based on serum albumin and total bilirubin values using following formula: {ALBI score = ($\log_{10}$ bilirubin [μmol/L] × 0.66) + (albumin [g/L] × −0.085)} and were classified into following grade: ≤−2.6 (grade 1), >−2.60 to ≤−2.27 (grade 2a), >−2.27 to ≤−1.39 (grade 2b), >−1.39 (grade 3) [16]. We calculated ALBI score at baseline and after 1 month of TKI therapy or intrahepatic EBRT. Additionally, information about treatment discontinuation due to development of AEs was collected by medical record review.

Statistical Analyses

Baseline characteristics of patients treated with TKI with and without intrahepatic EBRT were compared using Mann-Whitney U test for continuous variables and χ^2 test or Fisher's exact test for categorical variables. Repeated measures ANOVA was used to investigate longitudinal change in ALBI score before and after treatment. Survival analyses were performed using the Kaplan-Meier method with differences in survival curves assessed using the log-rank test. To identify independent predictors of OS and PFS, univariable and multivariable analyses with $p < 0.10$ in univariable analysis were performed using the Cox proportional hazards regression model. Stratified analyses were performed using predefined subgroups. Subgroups were based on age, sex (female or male), etiology (hepatitis B virus [HBV] or non-HBV), mALBI grade (1-2a or 2b), tumor number (single or multiple), tumor size (<10 cm or ≥10 cm), extrahepatic metastasis (yes or no), and the presence of PVI (yes or no). All analyses were performed using the statistical program R (version 4.0.3; R Development Core Team, Vienna, Austria, http://www.R-project.org), with $p < 0.05$ indicating statistical significance.

Sensitivity Analysis

Given that different timing of intrahepatic EBRT during TKI therapy can lead to immortal time bias, we investigated the impact of the addition of EBRT to TKIs on OS and PFS from the start date of EBRT to death or PD for sensitivity analysis. In addition, we analyzed 265 patients who received at least 8 weeks of TKI with or without EBRT (185 patients receiving TKI and 80 patients receiving TKI + RT) and propensity score-matched patients ($n = 158$). For propensity score matching, we used propensity scores generated for age (<60 or ≥60 years), sex (female or male), ECOG performance status (0 or ≥1), etiology (HBV or non-HBV), tumor number (single or multiple), tumor size (<10 cm or ≥10 cm), level of PVI (none, Vp1/Vp2, or Vp3/Vp4), extrahepatic metastasis (yes or no), mALBI grade (1-2a or 2b), serum alpha-fetoprotein (<400 ng/mL or ≥400 ng/mL), and PIVKA-II (<1,000 mAU/mL or ≥1,000 mAU/mL). Propensity matching was paired 1:1 using the nearest neighbor matching method with a caliper of 0.02.

Table 1. Baseline characteristics of the study cohort (n = 453)

Characteristic	Total (n = 453)	TKI (n = 356)	TKI + RT (n = 97)	p value
Age, years	55 (49, 64)	55 (49, 64)	55 (48, 61)	0.12
Sex				
Female	63 (13.9)	46 (12.9)	17 (17.5)	0.25
Male	390 (86.1)	310 (87.1)	80 (82.5)	
ECOG performance status				
0	386 (85.2)	304 (85.4)	82 (84.5)	0.96
≥1	67 (14.8)	52 (14.6)	15 (15.5)	
Etiology				
HBV	335 (74.0)	260 (73.0)	75 (77.3)	0.69
HCV	20 (4.4)	16 (4.5)	4 (4.1)	
Nonviral	98 (21.6)	80 (22.5)	18 (18.6)	
Tumor number				
Single	126 (27.8)	89 (25.0)	37 (38.1)	0.02
Multiple	327 (72.2)	267 (75.0)	60 (61.9)	
Maximal tumor diameter				
<10 cm	142 (31.4)	108 (30.3)	34 (35.0)	0.45
≥10 cm	311 (68.7)	248 (69.7)	63 (65.0)	
Level of PVI	369 (81.5)	281 (78.9)	88 (90.7)	0.01
Sub/segmental (Vp1/Vp2)	75 (20.3)	64 (22.8)	11 (12.5)	
Lobar (Vp3)	90 (24.4)	68 (24.2)	22 (25.0)	
Main/bilateral (Vp4)	204 (55.3)	149 (53.0)	54 (62.5)	
Extrahepatic metastasis	298 (65.8)	248 (69.7)	50 (51.5)	0.001
Lymph node only	80 (26.9)	65 (26.2)	15 (30.0)	
Distant metastasis only	138 (46.3)	120 (48.4)	18 (36.0)	
Both	80 (26.9)	63 (25.4)	17 (34.0)	
Type of TKI				
Sorafenib	387 (85.4)	306 (86.0)	81 (83.5)	0.66
Lenvatinib	66 (14.6)	50 (14.0)	16 (16.5)	
Child-Pugh score				
A5	239 (52.8)	184 (51.7)	55 (56.7)	0.62
A6	157 (34.7)	125 (35.1)	32 (33.0)	
B7	57 (12.6)	47 (13.2)	10 (10.3)	
mALBI				
Grade 1	236 (52.1)	181 (50.8)	55 (56.7)	0.39
Grade 2a	120 (26.5)	94 (26.4)	26 (26.8)	
Grade 2b	97 (21.4)	81 (22.8)	16 (16.5)	
AFP, ng/mL	2,733 (96, 29,979)	2,788 (99, 31,444)	2,110 (92, 24,904)	0.42
<400 ng/mL	166 (36.6)	126 (35.4)	40 (41.2)	
≥400 ng/mL	287 (63.4)	230 (63.4)	57 (58.8)	
PIVKA-II, mAU/dL (missing: 22)	3,449 (861, 27,938)	3,485 (1,086, 28,623)	3,449 (414, 20,691)	0.28
<1,000 mAU/dL	116 (25.9)	82 (24.6)	34 (35.1)	
≥1,000 mAU/dL	315 (73.1)	252 (75.5)	63 (64.9)	

TKI, tyrosine kinase inhibitor; RT, intrahepatic external beam radiotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; mALBI, modified albumin-bilirubin; AFP, alpha-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II.

Results

Baseline Characteristics

The baseline characteristics of 453 patients (median age, 55 years; interquartile range, 49–64; 85.9% male) are listed in Table 1. The most common etiology was HBV (74.0%) and 396 (87.4%) patients had Child-Pugh A liver function. In terms of TKI type, 387 (85.4%) patients were treated with sorafenib, and 66 (14.6%) patients were treated with lenvatinib. There were 144 patients who received EBRT with TKI therapy. Among them, 97 patients were classified in the TKI + RT group, while 47

patients who received only extrahepatic EBRT were included in the TKI group. The target of intrahepatic EBRT was vascular invasion and/or bile duct invasion for 39 patients (40.2%), primary hepatic tumor mass for 11 patients (11.3%), and primary hepatic tumor mass and vascular invasion (and/or bile duct invasion) for 36 patients (37.1%). Conventional EBRT (n = 86, 88.7%) was the most commonly used modality, followed by proton beam therapy (n = 9, 9.3%). Two patients (2.0%) received stereotactic body radiation therapy. The dose of conventional EBRT mostly ranged from 30 to 50 Gy in 5–22 fractions, while approximately 15% of patients received palliative low doses ranging from 8 to 20 Gy in 1–5 fractions. Stereotactic body radiation therapy dose ranged from 36 to 45 Gy in 3–5 fractions, and proton beam therapy dose ranged from 20 to 72.6 Gy relative biological effectiveness in 5–22 fractions. All patients had planned combination of intrahepatic EBRT with a median time from TKI start to EBRT of 8 days (min–max: −40 to 56 days) except for four patients who received additional EBRT after 90 days of TKI therapy to control TKI-refractory lesions like liver mass or vascular/bile duct invasion (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000529635).

There was no significant difference in TKI type between groups treated with TKI with or without intrahepatic EBRT. However, patients treated with TKI without intrahepatic EBRT had a higher proportion of multiple intrahepatic lesions (75.0% vs. 61.9%, p = 0.02) and extrahepatic metastasis (69.7% vs. 51.5%, p = 0.001). In contrast, the TKI with intrahepatic EBRT group had a higher proportion of PVI (90.7% vs. 78.9%, p = 0.01).

Comparison of Treatment Outcomes

Efficacy

During a median follow-up of 4.8 months (min–max: 0.1–111.2 months), mortality was observed in 422 (93.1%) patients. Median OS and PFS were 8.6 months and 4.5 months, respectively, for the TKI with intrahepatic EBRT group and 4.4 months and 2.3 months, respectively, for the TKI without intrahepatic EBRT group (p < 0.001; Fig. 2a, b). Of the 453 patients, 344 (75.9%) underwent treatment response evaluation, whereas the other patients discontinued TKI or EBRT due to AE, death, or loss to follow-up prior to treatment response evaluation. In-field response to intrahepatic EBRT was CR/PR in 39 (40.2%) patients, SD in 42 (43.3%) patients, PD in 8 (8.3%) patients, and those without treatment response evaluation in 8 (8.2%) patients. The local control rate of EBRT was 73.5% at 24 months. Notably, the time to intrahepatic tumor progression was significantly prolonged in the TKI with intrahepatic EBRT group compared to the TKI without EBRT group (8.4 vs. 3.4 months, p < 0.001) (Fig. 3a), although the time to extrahepatic PD was not significantly different (Fig. 3b). Furthermore, patients treated with TKI and intrahepatic EBRT who developed in-field tumor progression after EBRT had worse OS than those without local tumor progression and similar to those with TKI alone (online suppl. Fig. 1). In multivariable Cox regression analysis, intrahepatic EBRT was an independent factor associated with OS (adjusted hazard ratio [aHR] 0.50; 95% confidence interval [CI] 0.39–0.64; p < 0.001) and PFS (aHR 0.50; 95% CI 0.39–0.65, p < 0.001) (Table 2).

Safety

There was no significant difference in treatment discontinuation due to AEs between the TKI + RT and TKI group (32.0% vs. 37.9%, p = 0.34, Table 3). Hepatic decompensation (hyperbilirubinemia, ascites, hepatic encephalopathy, or hepatorenal syndrome) was the most common reason for treatment discontinuation. Deterioration of performance status and death from any cause were the second most common reasons for treatment discontinuation in the TKI group, while gastrointestinal bleeding was the second most common reason in the TKI + RT group. When comparing ALBI score at baseline and 1 month after treatment, liver function decreased significantly with time. However, patients treated with TKI with intrahepatic EBRT showed less increase in ALBI score at 1 month (+0.38 [95% CI 0.27, 0.49] vs. +0.51 [95% CI 0.45, 0.57]; p = 0.03) than those with TKI without intrahepatic EBRT (online suppl. Fig. 2). Notably, patients with a CR/PR in-field response showed significantly better liver function preservation over time compared to patients with a SD/PD in-field response (online suppl. Fig. 3).

Subgroup Analysis

Combined treatment with TKI and intrahepatic EBRT was associated with better OS than TKI without intrahepatic EBRT in all subgroups analyzed, without significant interaction (Fig. 4a). Combined treatment with TKI and intrahepatic EBRT was associated with better PFS than TKI without intrahepatic EBRT in all subgroups analyzed, and the association was stronger for those without extrahepatic metastasis (p for interaction = 0.02) and those with PVI (p for interaction 0.03) (Fig. 4b).

Sensitive Analysis

Considering that the majority of intrahepatic EBRTs were administered after TKI therapy, patients in the TKI with intrahepatic EBRT group may have a longer survival time. However, when the follow-up duration of TKI with

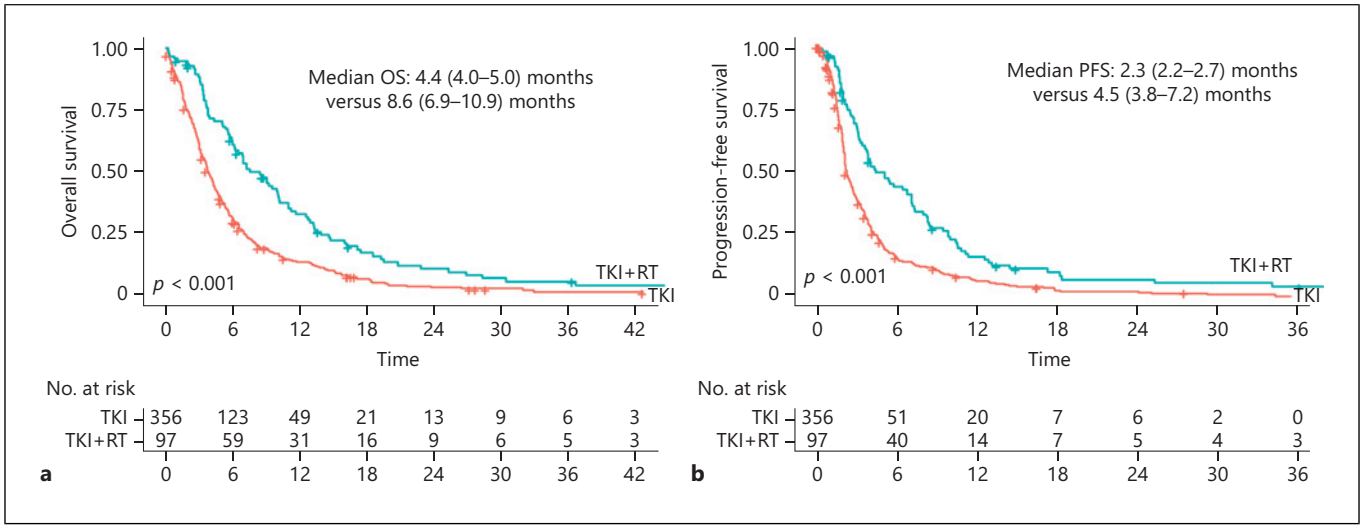


Fig. 2. OS (**a**) and PFS (**b**) in the overall cohort (n = 453).

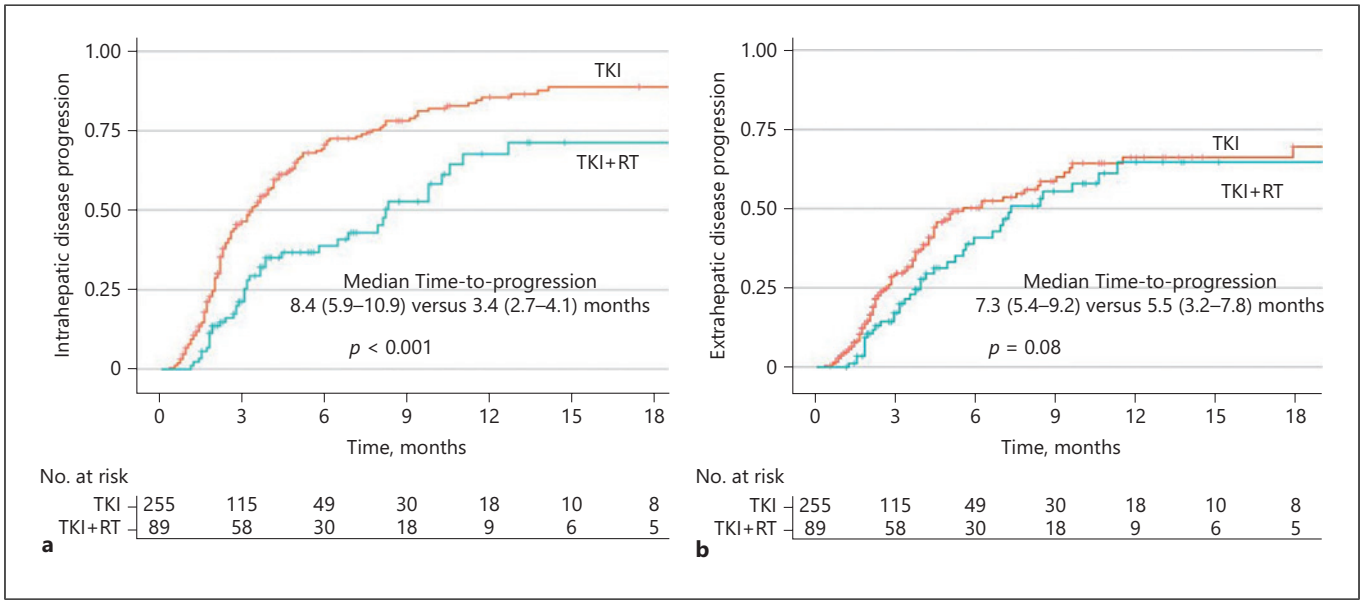


Fig. 3. a Time to intrahepatic PD during follow-up. **b** Time to extrahepatic PD during follow-up.

intrahepatic EBRT group was calculated from start date of EBRT, the comparable result was observed. Patients treated with TKI with intrahepatic EBRT showed significantly longer OS and PFS (OS, 8.2 vs. 4.4 months, $p < 0.001$; PFS, 3.7 vs. 2.3 months, $p = 0.001$) (online suppl. Fig. 4a, b).

In addition, survival analysis in patients who received at least 8 weeks of TKI treatment was performed. The baseline characteristics of patients who received at least 8 weeks of TKI treatment were similar to those of the entire cohort (online suppl. Table 2). Combination of TKI with intrahepatic EBRT led to a longer median OS (7.0 vs. 10.0 months, $p = 0.015$, online suppl. Fig. 5a) as well as a longer median PFS (3.9 vs. 6.9 months, $p = 0.004$, online suppl. Fig. 5b). Multivariable Cox regression analysis also confirmed the favorable impact of combination with intrahepatic EBRT to TKIs, with an aHR of 0.57 (95% CI 0.42–0.77) for OS and an aHR of 0.58 (95% CI 0.43–0.78) for PFS (online suppl. Table 3).

Table 2. Multivariable Cox regression analysis for OS and PFS in the entire cohort (n = 453)

	OS				PFS			
	univariable analysis		multivariable analysis		univariable analysis		multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age ≥60 (vs. <60) years	0.81 (0.66, 0.99)	0.04	0.84 (0.68, 1.04)	0.11	0.83 (0.68, 1.02)	0.07	0.83 (0.67, 1.03)	0.10
Male (vs. female)	1.09 (0.82, 1.46)	0.54			1.09 (0.82, 1.46)	0.55		
Etiology (HBV vs. non-HBV)	1.08 (0.87, 1.34)	0.50			1.03 (0.82, 1.29)	0.78		
ECOG ≥1 (vs. 0)	0.95 (0.72, 1.24)	0.70			1.08 (0.82, 1.41)	0.60		
mALBI grade 2b (vs. 1 or 2a)	1.75 (1.38, 2.22)	<0.001	1.64 (1.28, 2.11)	<0.001	1.58 (1.24, 2.02)	<0.001	1.57 (1.22, 2.04)	<0.001
Tumor number (multiple vs. single)	1.14 (0.92, 1.41)	0.24			1.29 (1.04, 1.61)	0.02	1.19 (0.94, 1.50)	0.15
Maximal tumor diameter ≥10 cm (vs. <10 cm)	1.17 (0.95, 1.44)	0.14			1.18 (0.96, 1.46)	0.12		
Level of PVI								
No/Vp1/Vp2	Reference				Reference			
Vp3/Vp4	1.55 (1.26, 1.90)	<0.001	1.76 (1.41, 2.20)	<0.001	1.33 (1.08, 1.64)	0.01	1.56 (1.24, 1.95)	<0.001
Extrahepatic metastases	0.97 (0.79, 1.18)	0.73			1.08 (0.88, 1.33)	0.47		
AFP ≥400 ng/mL (vs. <400 ng/mL)	1.32 (1.08, 1.61)	0.007	1.24 (1.01, 1.53)	0.04	1.43 (1.17, 1.76)	<0.001	1.29 (1.04, 1.61)	0.02
PIVKA-II ≥1,000 mAU/dL (vs. <1,000 mAU/dL)	1.24 (0.99, 1.56)	0.06	1.16 (0.92, 1.46)	0.22	1.33 (1.06, 1.67)	0.01	1.17 (0.93, 1.48)	0.18
TKI + RT (vs. TKI)	0.57 (0.45, 0.72)	<0.001	0.50 (0.39, 0.64)	<0.001	0.55 (0.43, 0.70)	<0.001	0.50 (0.39, 0.65)	<0.001

ECOG PS, Eastern Cooperative Oncology Group performance status; mALBI, modified albumin-bilirubin; Vp1, subsegmental portal vein; Vp2, segmental portal vein; Vp3, lobar portal vein; Vp4, main or bilateral portal vein; AFP, alpha-fetoprotein; PIVKA-II, vitamin K absence or antagonist-II; TKI, tyrosine kinase inhibitor; RT, intrahepatic external beam radiotherapy.

Lastly, after PS matching, there were no significant differences in baseline characteristics including demographics, tumor extent, and hepatic reserve function between the groups treated with TKI and TKI + RT (both groups, n = 79), as shown in online supplementary Table 4. The median OS in TKI + RT group was 6.9 months (95% CI 5.9–10.0 months) and that of the TKI group was 4.1 months (95% CI 3.3–4.9 months) (online suppl. Fig. 6a). Median PFS was also longer in the TKI+ RT group compared to that of TKI group (4.1 vs. 2.2 months, p < 0.001) (online suppl. Fig. 6b).

Discussion

In this study, we observed better OS and better PFS with similar treatment discontinuation rates due to AEs for BCLC stage C patients who received a combination of intrahepatic EBRT and TKI therapy compared to patients who received TKI monotherapy. OS and PFS were better in the combination group for all subgroup analyzed. Of note, the PFS benefit associated with combination therapy was greater for those without extrahepatic metastasis compared to those with extrahepatic metastasis and in those with PVI compared to those without PVI. In sensitivity analysis with a different index date, comprising patients who completed at least 8 weeks of TKI treatment and in PS-matched patients, the findings were similar: OS and PFS were better in the combination group compared to the TKI group. These findings suggest potential synergistic effects between TKI and intrahepatic EBRT, indicating that adding intrahepatic EBRT can improve the outcomes of TKI

Table 3. AEs leading to treatment discontinuation

	N	TKI	TKI + RT	*p* value
Hepatic decompensation	68 (15.0)	57 (16.0)	11 (11.3)	0.33
Liver enzyme elevation	6 (1.3)	6 (1.7)	0 (0.0)	0.43
Bleeding*	15 (3.3)	10 (2.8)	5 (5.2)	0.41
Infection	11 (2.4)	8 (2.3)	3 (3.1)	0.91
Dermatologic symptoms**	9 (2.0)	7 (2.0)	2 (2.1)	1.00
Gastrointestinal symptoms[a]	10 (2.2)	7 (2.0)	3 (3.1)	0.78
Deterioration of performance status	17 (3.8)	15 (4.2)	2 (2.1)	0.49
Death from any cause	23 (5.3)	21 (5.9)	3 (3.1)	0.40
Other[b]	5 (1.1)	3 (0.8)	2 (2.1)	0.64
Total	166 (36.6)	135 (37.9)	31 (32.0)	0.34

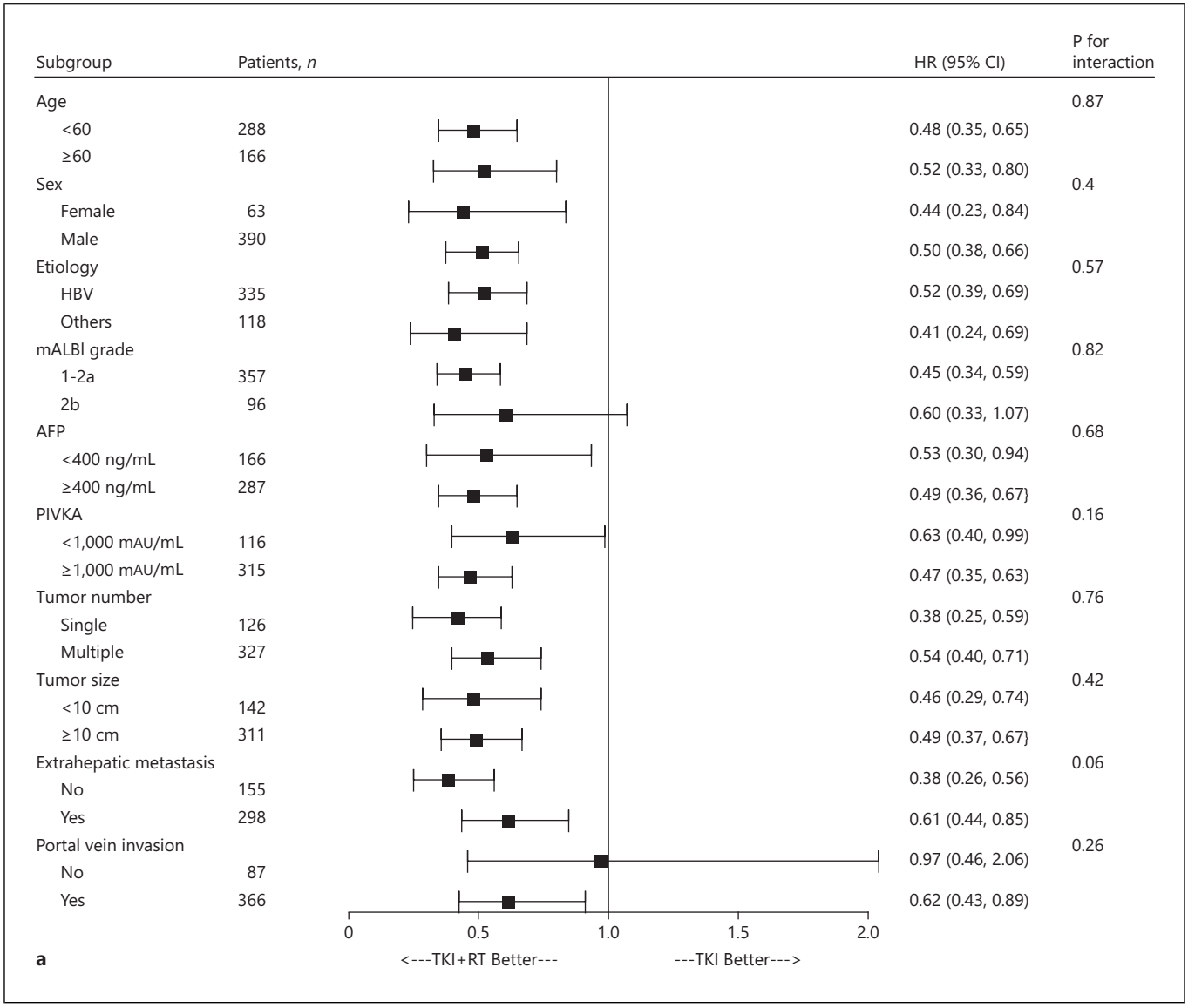
TKI, tyrosine kinase inhibitor; RT, intrahepatic external beam radiotherapy. *Gastrointestinal bleeding (n = 10), hemoperitoneum (n = 1). **Skin manifestations: hand-foot-skin reaction or skin rash. [a]Gastrointestinal symptoms: nausea, vomiting, diarrhea, abdominal pain. [b]Including hypotension, thrombocytopenia, proteinuria, pneumothorax, and acute pancreatitis.

therapy in BCLC stage C patients, especially for those without extrahepatic metastasis, and those with PVI.

Consistent with this study, several previous publications have reported a favorable response and promising treatment outcomes of combination therapy in patients with advanced HCC with macrovascular invasion or extrahepatic metastasis [17, 18]. Combined treatment with sorafenib and EBRT showed better survival than sorafenib alone in a nationwide cancer registry-based study involving 4,763 patients [7]. Recently, in a meta-analysis involving 512 patients from 11 studies, combination treatment with sorafenib and EBRT was associated with greater survival benefit than sorafenib alone for advanced-stage HCC [6]. The clinical rationale for EBRT targeting of vascular invasion with or without encompassing the primary liver tumor in BCLC stage C patients is to prevent further tumor growth and intravascular spread [19]. In the current study, we demonstrated that combining EBRT with TKI notably reduced intrahepatic disease, whereas patients treated who developed in-field tumor progression after intrahepatic EBRT showed worse OS than those without local tumor progression and similar OS to those treated with TKI alone. These findings are in line with our previous finding, suggesting local control via intrahepatic EBRT is important for the management of advanced HCC [20].

Several preclinical studies focused on the potential synergistic anticancer effect of combination therapy of TKI and EBRT. Sorafenib enhanced radiation-induced apoptosis in HCC cells and a xenograft model by inhibiting tumor proliferation and DNA repair and angiogenesis [21]. *LRRK2* mutation was suggested to have a role in promoting sorafenib and radiation sensitivity via an ROS-dependent mechanism [22]. Upregulation of P-gp activity had a dynamic effect on the pharmacokinetics of sorafenib, increasing efflux and intensifying the recycling and enterohepatic circulation of sorafenib, resulting in an increase in the area under the plasma concentration-time curve of sorafenib [23].

Safety is a concern when adding intrahepatic EBRT to TKI therapy. Worsening of liver function and significant dose-limiting toxicity were reported in patients receiving combined treatment with sorafenib and EBRT [8]. The single-arm clinical trial of sorafenib and radiation therapy reported that the proportions of grade ≥3 hepatotoxicity and hematotoxicity were as high as 25% and 33.3% [8, 17]. Moreover, the rates of grade ≥3 hepatotoxicity and gastrointestinal toxicity were higher in EBRT targeting intrahepatic lesions than EBRT targeting non-intrahepatic lesions [6]. However, in this real-life cohort study, we could not observe increased drug discontinuation rates due to AEs in the combination group compared to the TKI alone group. Patients treated with TKI with intrahepatic EBRT had better liver function preservation over time compared to those treated with TKI without intrahepatic EBRT. Given that the majority (75%) of patients in this study had major PVI (Vp3 or Vp4), which causes particular susceptibility to liver function deterioration due to decreased liver blood flow [24], it may be important to prevent progression of major PVI during systemic therapy in order to preserve liver function. This hypothesis is supported by the fact that patients with a CR/PR in-field response preserved liver function better than those with an SD/PD in-field response (online suppl. Fig. 3).



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(Figure continued on next page.)

Although this study suggests that adding intrahepatic EBRT can be an option to improve the outcomes of TKI therapy, there are several limitations to this study. As it was not a randomized controlled trial, whether to add intrahepatic EBRT was decided at the discretion of the physician in charge of the patient. Confounding by indication may exist. The median survival of the TKI alone group was 4.4 months, which is lower than the survival of patients enrolled in previous clinical trials (10.7–13.6 months) [25, 26]. BCLC stage C comprises a heterogeneous population [27], and in East Asian countries, BCLC stage C patients receive very heterogeneous treatment including TACE with/without EBRT [28]. TKI therapy is usually only considered in more advanced cases within BCLC stage C [28]. In this study, 81.5% had PVI and 65.8% had extrahepatic metastasis, while these percentages were 36% and 53% in the SHARP trial [25] and 23% and 61% in the REFLECT trial [26]. In this study, we used treatment discontinuation due to AEs as a surrogate of safety. Due to retrospective analysis of medical records, safety assessment could not be done according to common terminology criteria for AEs. For the combination treatment group, treatment protocols were not standardized, in terms of mode, dose, and timing of intrahepatic EBRT before or after TKI therapy. Therefore, it is difficult to identify the specific

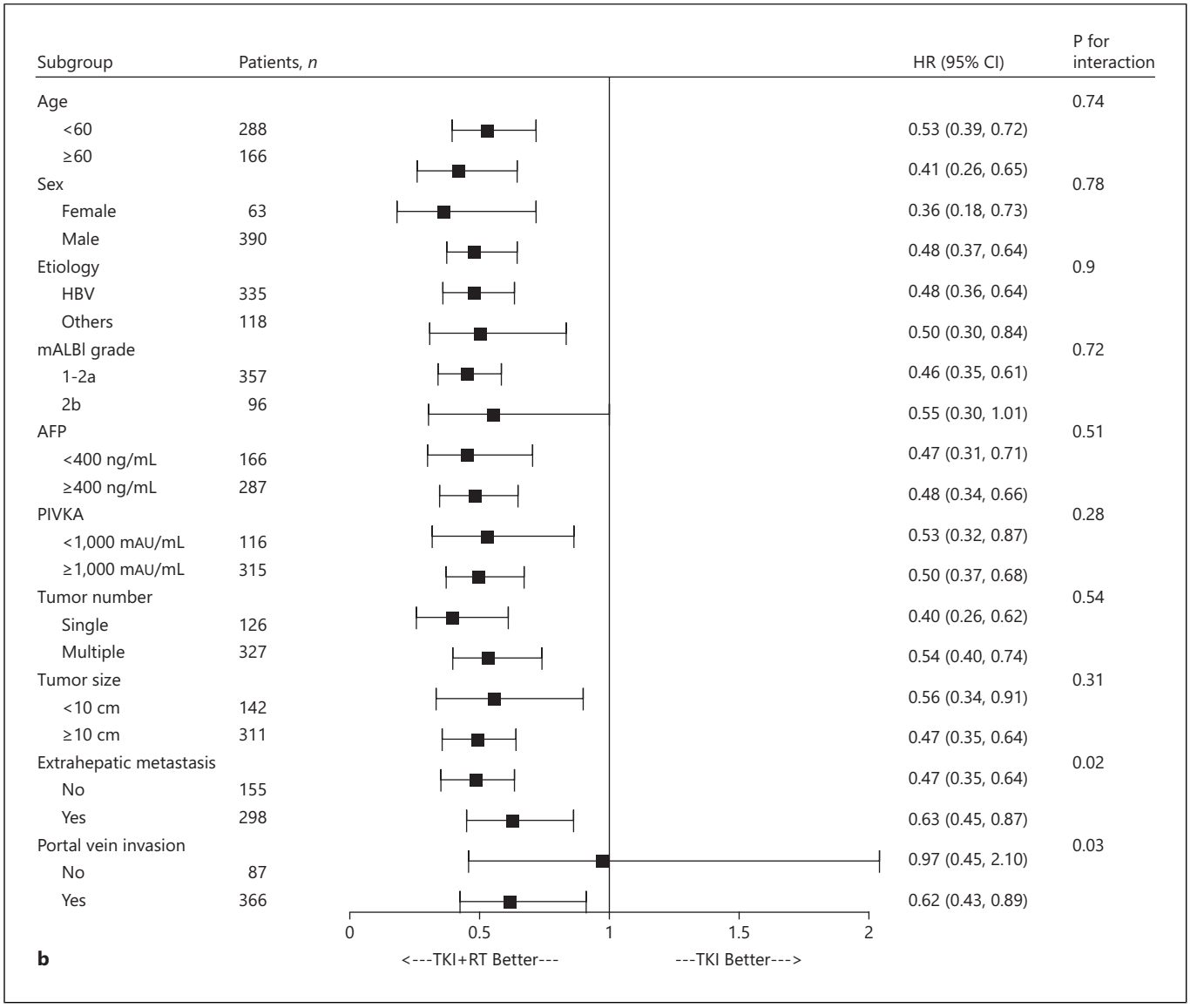

Fig. 4. Subgroup analysis of OS (**a**) and PFS (**b**) in the overall cohort (n = 453).

indications or optimal strategy for intrahepatic EBRT combination with systemic therapy, and a further randomized trial exploring this is warranted. However, the strength of this study is the inclusion of treatment-naïve BCLC stage C patients and analysis of relatively large number of patients. Subgroup analysis and several sensitivity analyses are another strength of the study, which sought to reduce bias and assess the robustness and reproducibility of the data. In conclusion, intrahepatic EBRT should be considered for BCLC-C patients planned for TKI, in order to improve OS and PFS with an aim to control intrahepatic progression and preserving liver function.

Statement of Ethics

The study protocol was reviewed and approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2022-02-099-001). As the study used only de-identified data routinely collected during hospital visits, the requirement to obtain informed patient consent was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This paper was supported by the Research & Business Foundation of Sungkyunkwan University (Grant No. S-2019-2739-000).

Author Contributions

All authors contributed substantially and in accordance with the guidelines of the International Committee of Medical Journal Editors. M.J.G. and H.C.P. participated in study design, statistical analysis and interpretation, and writing the article. J.I.Y., D.H.S., and M.S.C. participated in study conception and design, editing, and proofreading. W.K. and G.G. participated in data collection and data analysis. Y.P. and J.H.L. participated in study supervision and resources. K.C.K. and S.W.P. participated in supervision and administrative support. All authors were responsible for final approval and were accountable for all aspects of the work.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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