A Multicenter Phase 2 Trial Evaluating the Efficacy and Safety of Preoperative Lenvatinib Therapy for Patients with Advanced Hepatocellular Carcinoma (LENS-HCC Trial)

Akihiko Ichida[a]   Junichi Arita[a]   Etsuro Hatano[b, c]   Susumu Eguchi[d]
Akio Saiura[e]   Hiroaki Nagano[f]   Junichi Shindoh[g]   Masaji Hashimoto[g]
Nobuyuki Takemura[h]   Kojiro Taura[c]   Yoshihiro Sakamoto[i]   Yu Takahashi[j]
Yasuji Seyama[k]   Yasuharu Sasaki[l]   Kohei Uemura[m]   Norihiro Kokudo[h]
Kiyoshi Hasegawa[a]

[a]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; [b]Department of Gastroenterological Surgery, Hyogo Medical University, Kobe, Japan; [c]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [d]Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [e]Department of Hepatobiliary-Pancreatic Surgery, Juntendo University School of Medicine, Tokyo, Japan; [f]Department of Gastroenterological, Breast and Endocrine Surgery, Graduate School of Medicine, Yamaguchi University, Yamaguchi, Japan; [g]Hepatobiliary-Pancreatic Surgery Division, Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan; [h]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan; [i]Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, Tokyo, Japan; [j]Division of Hepatobiliary and Pancreatic Surgery, Cancer Institute Hospital for Japanese Foundation for Cancer Research, Tokyo, Japan; [k]Department of Hepato-Biliary-Pancreatic Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan; [l]JCRAC Data Center, Department of Data Science, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan; [m]Biostatistics and Bioinformatics Course, The University of Tokyo, Tokyo, Japan

Abstract

Introduction: The phase III REFLECT trial demonstrated that lenvatinib was superior to sorafenib in terms of progression-free survival (PFS), time to progression, and objective response rate (ORR) for patients with unresectable hepatocellular carcinoma (HCC). This study assessed the efficacy and safety of preoperative lenvatinib therapy for patients with oncologically or technically unresectable HCC. ***Methods:*** In this multicenter single-arm phase II trial, patients with advanced HCC and factors suggestive of a poor prognosis (macroscopic vascular invasion, extrahepatic metastasis, or multinodular tumors) were enrolled. Patients with these factors, even with technically resectable HCC, were defined as oncologically unresectable because of the expected poor prognosis after surgery. After 8 weeks of lenvatinib therapy, the patients were assessed for

Correspondence to:
Kiyoshi Hasegawa, hasegawa-2su@h.u-tokyo.ac.jp

resectability, and tumor resection was performed if the tumor was considered technically resectable. The primary endpoint was the surgical resection rate. The secondary endpoints were the macroscopic curative resection rate, overall survival (OS), ORR, PFS, and the change in the indocyanine green retention rate at 15 min as measured before and after lenvatinib therapy. The trial was registered with the Japan Registry of Clinical Trials (s031190057). ***Results:*** Between July 2019 and January 2021, 49 patients (42 oncologically unresectable patients and 7 technically unresectable patients) from 11 centers were enrolled. The ORR was 37.5% based on mRECIST and 12.5% based on RECIST version 1.1. Thirty-three patients underwent surgery (surgical resection rate: 67.3%) without perioperative mortality. The surgical resection rate was 76.2% for oncologically unresectable patients and 14.3% for technically unresectable patients. The 1-year OS rate and median PFS were 75.9% and 7.2 months, respectively, with a median follow-up period of 9.3 months. ***Conclusions:*** The relatively high surgical resection rate seen in this study suggests the safety and feasibility of lenvatinib therapy followed by surgical resection for patients with oncologically or technically unresectable HCC.

Introduction

For patients with hepatocellular carcinoma (HCC) and factors suggestive of a poor prognosis such as macroscopic vascular invasion, extrahepatic metastasis, and multinodular tumors, surgical treatment is not recommended in the American Association for the Study of the Liver Disease/Barcelona Clinic for Liver Cancer (AASLD/BCLC) Staging System and treatment guidelines; instead, systemic therapy is mainly recommended [1, 2]. At some centers, however, surgery has been actively performed even for these patients, given the absence of other effective treatments. The median survival time (MST) after resection is reported to range from 27.6 to 34.4 months for those with portal vein tumor thrombus (PVTT) [3, 4], 45.8 months for those with bile duct tumor thrombus (BDTT) [5], 47.4–53.6 months for those with hepatic vein tumor thrombus (HVTT) [6, 7], and 16.7–17.8 months for those with inferior vena cava tumor thrombus (IVCTT) [6, 7]. The outcomes of surgical treatment for extrahepatic metastasis have been mainly reported for a small number of well-selected patients, with the MST ranging from 8 to 14 months for patients with lymph node metastases, from 12 to 21 months for patients with adrenal metastases, from 16 to 52 months for patients

with lung metastases, and from 3 to 69 months for patients with peritoneal dissemination [8, 9]. For patients with multinodular tumors, the MST of patients who underwent non-curative resection with residual tumors in the liver was reported to be 29 months [10]. As the postoperative outcomes of these patients were unsatisfactory, these tumors were considered to be oncologically unresectable despite being technically resectable [11]. Multidisciplinary treatment combining surgical and nonsurgical treatments, such as surgery after preoperative therapy, has been attempted to improve the prognosis of these patients.

The objective of preoperative treatment in cases judged as being technically unresectable is to make the tumor technically resectable. Meanwhile, there are two objectives in cases that are judged as being oncologically unresectable: (1) to control micrometastasis and (2) to select surgical candidates after confirming that the tumor is unlikely to progress within a short period of time. In particular, the second objective is unique to preoperative treatment and cannot be achieved with postoperative treatment. As a preoperative treatment for HCC, the efficacies of transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiotherapy, and sorafenib have been evaluated and reported. Although several retrospective studies have reported on the use of preoperative TACE and HAIC, a benefit for prognosis has not been clearly demonstrated [12–15]. The efficacy of neoadjuvant radiotherapy for hepatitis B virus-related HCC with PVTT was recently demonstrated in a randomized controlled trial [16]; however, its efficacy for HCC arising from other etiologies needs to be evaluated. The utility of sorafenib has only been reported in case reports and small-sized case series [11]. The scarcity of these reports may be attributable to sorafenib's small partial or complete response rate. Thus, the efficacy of multidisciplinary treatment using conventional nonsurgical treatments has been limited.

Lenvatinib (Eisai Inc., Woodcliff Lake, NJ, USA), an oral multikinase inhibitor that targets VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT, was approved in Japan in March 2018 for the treatment of unresectable HCC. In the phase III REFLECT trial, lenvatinib demonstrated non-inferiority in the overall survival (OS) and improvements in progression-free survival (PFS), time to progression, and objective response rate (ORR), compared with sorafenib – which was the only first-line systemic therapy available for about a decade [17]. With its high response rate of 40.6%, based on a masked independent imaging review performed
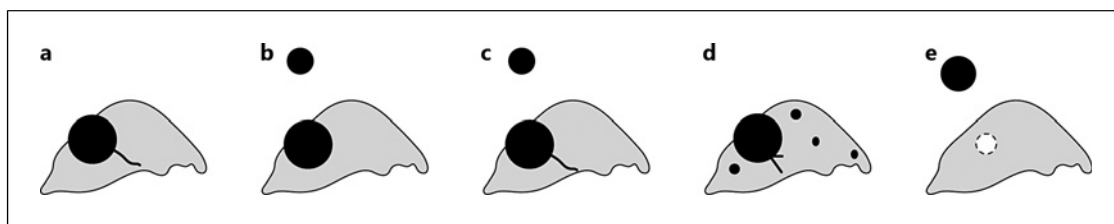
Fig. 1. Types of tumor conditions. **a** Intrahepatic macroscopic vascular invasion. **b** Synchronous extrahepatic metastases. **c** Both (**a**, **b**). **d** Macroscopic residual tumor. **e** Metachronous extrahepatic metastases.

using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [18], lenvatinib is expected to play an important role as a preoperative therapy; however, only retrospective studies have been reported to date. This prospective phase 2 study aimed to evaluate the efficacy and safety of preoperative lenvatinib therapy for patients with oncologically or technically unresectable HCC, i.e., those with factors suggestive of a poor prognosis, such as macroscopic vascular invasion, extrahepatic metastasis, and multinodular tumors.

Methods

The primary endpoint of this multicenter prospective single-arm trial was the surgical resection rate. The secondary endpoints were the macroscopic curative resection rate, OS, ORR, PFS, and change in indocyanine green retention rate at 15 min (ICG R15) before and after lenvatinib therapy. Patients were enrolled between July 2019 and January 2021.

Patients
Patients with advanced HCC without a history of systemic therapy for HCC and with at least one factor suggestive of a poor prognosis (macroscopic vascular invasion, extrahepatic metastasis, or multinodular tumors) were eligible for inclusion. Specifically, patients with one of five types of tumor conditions, as presented in Figure 1, were included in this trial. The relationship between factors suggestive of a poor prognosis and each tumor type is as follows: type A, macroscopic vascular invasion; type B, extrahepatic metastasis; type C, both macroscopic vascular invasion and extrahepatic metastasis; type D, multinodular tumors; and type E, extrahepatic metastasis. In types A and C, patients with BDTT, or with PVTT invading the main portal vein, excluded from the REFLECT trial [17], were also enrolled in the present trial and treated with lenvatinib with caution. In types B, C, and E, distant metastases were defined as those limited to a single organ, adrenal metastases were included if they were unilateral, and lymph node metastases were included if they were confined to the abdominal cavity. The maximum number of tumors was defined as up to 5 for lung metastases, 2 for lymph node metastases, 5 for peritoneal dissemination, 1 for bone metastases, and 1 for puncture route recurrence after local ab-

lative therapy. Type D was defined as cases in which the resection of all intrahepatic tumors was not feasible, but the resection of the main tumors was expected to provide a survival benefit or to improve quality of life. The exclusion criteria included patients younger than 20 years, an Eastern Cooperative Oncology Group Performance Status of 2 or more, a white blood cell count lower than 3,000/mm^3, a neutrophil count lower than 1,500/mm^3, a hemoglobin level lower than 8.5 g/dL, a platelet count lower than 75,000/mm^3, a creatinine clearance of less than 40 mL/min, a urinary protein level of greater than 1 g/day, a Child-Pugh score of 7 or higher, active malignancies, uncontrolled comorbidities (uncontrolled hypertension, heart failure, angina pectoris, arrhythmia, significant psychiatric disorders, etc.), and bleeding or thrombotic disease. Technically, unresectable HCC was defined based on assessment of the tumor resectability by a multidisciplinary team at each participating institution. Patients with technically resectable HCC and the aforementioned factors suggestive of a poor prognosis (macroscopic vascular invasion, extrahepatic metastasis, or multinodular tumors) were defined as being oncologically unresectable.

Procedures
The pretreatment workup consisted of a hepatic dynamic CT with chest-to-pelvis imaging using delayed phase, EOB-dynamic MRI, as well as standard clinical laboratory tests, including tumor markers and the assessment of hepatic functional reserve by measuring ICG R 15. After enrollment, patients received oral lenvatinib (12 mg/day for body weight ≥60 kg or 8 mg/day for body weight <60 kg). The tumor response was assessed every 4 weeks using contrast-enhanced CT or MRI in accordance with mRECIST and RECIST version 1.1 [18, 19]. After 8 weeks of lenvatinib therapy, resectability was assessed by a multidisciplinary team at each participating institution, as at the time of study enrollment. Tumor resection was performed 1 week or more after the end of lenvatinib therapy if the tumor was considered technically resectable, in the absence of rapid tumor growth. The timing of resection was accelerated only in cases with special reasons, such as difficulty in continuing lenvatinib therapy because of adverse events. In patients who were deemed to have unresectable tumors, who had residual tumors after resection, or who developed recurrence after resection, subsequent treatment was performed at the discretion of each institution. Six months after the enrollment of each patient and 6 months after the enrollment of the last patient, the type and efficacy of additional treatments, whether the tumor had progressed, and the patient outcomes were investigated. Adverse

events associated with lenvatinib therapy were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 [20]. Safety assessments included a physical examination, hematological and biochemical laboratory testing, and urinalysis. Postoperative complications were assessed according to the Clavien-Dindo classification [21].

Definition of Endpoints

The primary endpoint, which was the surgical resection rate, was defined as the percentage of patients who underwent surgical resection after lenvatinib therapy regardless of curability. The secondary endpoint, which was the macroscopic curative resection rate, was defined as the percentage of patients who underwent R0 or R1 resection. OS and PFS were defined as the time from the date of lenvatinib initiation until the end of follow-up or death and until the date of progressive disease (PD), respectively. ORR was defined as the percentage of patients with a complete response (CR) or a partial response (PR) as evaluated using mRECIST or RECIST version 1.1.

Statistical Analysis

In the REFLECT trial, the ORR of lenvatinib and sorafenib was reported to be 24.1% and 9.2%, respectively, by an investigator review performed according to mRECIST and 40.6% and 12.4%, respectively, by a masked independent imaging review according to mRECIST [17]. We set the sample size of the present trial based on the results of the investigator review so that the efficacy of lenvatinib could be adequately verified even if the actual response rate was as low as that evaluated by the investigator review. The expected surgical resection rate was set at 24%, assuming that patients who responded would be able to undergo resection. The threshold of the surgical resection rate was set at 9%, based on the ORR of sorafenib. The sample size was calculated to be 44 patients by setting the significance level at a one-sided value of 0.05 and the power at 0.8. Finally, the target number of patients was set at 50, allowing for an approximately 10% drop-out rate.

The point estimate and Clopper-Pearson's exact 90% confidence interval for the surgical resection rate were calculated. Survival curves for OS and PFS were generated using the Kaplan-Meier method and were compared using the log-rank test. Regarding the change in ICG R 15, the absolute values of ICG R 15 measurements before and after lenvatinib therapy were compared using the Wilcoxon rank sum test. Missing values were supplemented for the primary endpoint, but not for the secondary endpoints, using the non-responder imputation method. Two-sided p values were calculated, and p values of <0.05 were considered statistically significant. The SAS ver.9.4 (SAS Institute Inc. Cary, NC, USA) software package was used for all the statistical analyses.

Results

Baseline Patient Characteristics

Between July 2019 and January 2021, a total of 49 patients from 11 centers were enrolled. Table 1 summarizes the patient characteristics and baseline statuses.

Hypertension and diabetes mellitus were the most common comorbidities, with no other serious comorbidities present. Among patients with a history of previous treatment for HCC, 9 had undergone radiofrequency ablation (RFA), 8 had undergone surgical resection, 8 had undergone TACE, 2 had undergone HAIC, and 1 had undergone percutaneous ethanol injection therapy, with 9 patients receiving multiple treatments. The most common type of tumor condition was type A. The types and degrees of vascular invasion in type A and C patients are summarized in Supplemental Table 1 (for all online suppl. material, see https://doi.org/10.1159/000535514). In type B patients, 5 had lymph node metastasis and 1 had lung metastasis. One type C patient had lymph node metastasis. In type E patients, 4 had peritoneal dissemination, 2 had lung metastasis, and 1 had lymph node metastasis. Overall, 85.7% of the patients had oncologically unresectable HCC. Online supplementary Table 2 shows the relationships between the resectability and type of tumor condition. Of the 7 cases that were judged as being technically unresectable, the reason was insufficient remnant liver volume in 5 cases, extensive PVTT in one case, and extensive BDTT in one case.

Treatment Characteristics

Figure 2 shows the course of treatment for the 49 patients. Among the 42 patients with oncologically unresectable HCC, 1 patient died immediately after study enrollment because of accidental trauma. In accordance with the statistical analysis protocol, this patient was included in the analysis of the primary endpoint (non-responder imputation method) but was excluded from the analysis for the other outcomes with missing data. A total of 34 patients completed 8 weeks of lenvatinib therapy. For the remaining patients, lenvatinib therapy was interrupted because of adverse events ($n = 8$), tumor progression ($n = 3$), worsening of comorbidities ($n = 2$), or impending rupture of the tumor ($n = 1$). Adverse events causing the interruption of lenvatinib therapy included fatigue in 4 patients, decreased appetite in 1, cholecystitis in 1, thrombocytopenia in 1, and hypertension in 1. Although the duration of lenvatinib therapy was shortened, surgical resection was performed in 6 patients with lenvatinib interruptions arising from adverse events and in 1 patient with a lenvatinib interruption arising from an impending tumor rupture. As a result, resection was performed in 33 patients, with a surgical resection rate of 67.3% (90% confidence interval, 54.7–78.3%). The surgical resection rate was 76.2% (32/42) for oncologically unresectable

Table 1. Baseline characteristics and efficacy of lenvatinib

	$n = 49$
Age in years, median (range)	71 (49–85)
Male sex, n (%)	41 (83.7)
Performance status, n (%)	
0	39 (79.6)
1	10 (20.4)
Comorbidity, n (%)	
Hypertension	28 (57.1)
Diabetes mellitus	21 (42.9)
Indocyanine green retention rate at 15 min, % (range)	14.5 (3–48)
Child-Pugh score, n (%)	
5	31 (63.3)
6	18 (36.7)
Previous treatment(s) for hepatocellular carcinoma, n (%)	16 (32.7)
Tumor size in mm, median (range)	68 (10–260)
Tumor number, median (range)	1 (1–14)
AFP in ng/mL, median (range)	76 (2–105,450)
DCP in mAU/mL, median (range)	2,320 (13–473,047)
Stage II[a], n (%)	13 (26.5)
Stage IIIA[a], n (%)	5 (10.2)
Stage IIIB[a], n (%)	18 (36.7)
Stage IVA[a], n (%)	5 (10.2)
Stage IVB[a], n (%)	8 (16.3)
Type of tumor condition, n (%)	
A: Intrahepatic macroscopic vascular invasion	33 (67.3)
B: Synchronous extrahepatic metastases	6 (12.2)
C: Both A and B	1 (2.0)
D: Macroscopic residual tumor	2 (4.1)
E: Metachronous extrahepatic metastases	7 (14.3)
Resectability, n (%)	
Oncologically unresectable	42 (85.7)
Technically unresectable	7 (14.3)
Efficacy of lenvatinib based on mRECIST[b], n (%)	
Complete response	1 (2.1)
Partial response	17 (35.4)
Stable disease	26 (52.4)
Progressive disease	4 (8.3)
Efficacy of lenvatinib based on RECIST 1.1[b], n (%)	
Complete response	0
Partial response	6 (12.5)
Stable disease	39 (81.3)
Progressive disease	3 (6.3)

AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; mRECIST, modified Response Evaluation Criteria in Solid Tumors. [a]Stage is based on the American Joint Commission on Cancer 8th edition staging system. [b]The efficacy of lenvatinib therapy is described for the 48 cases in which imaging studies were performed for the evaluation.

patients and 14.3% (1/7) for technically unresectable patients. Among the 9 patients initially deemed as having oncologically unresectable HCC in whom resection was not performed, the reasons for not performing surgery were an inadequate response to lenvatinib therapy in 6 patients, refusal to undergo surgery in 1 patient, worsening of comorbidities in 1 patient, and a reduced performance status in 1 patient. Among the 6 patients initially deemed as having technically unresectable HCC in whom resection was not performed, the reasons for not performing surgery were an inadequate response to lenvatinib therapy in 4 patients, refusal to undergo surgery in 1 patient, and worsening of comorbidities in 1 patient. The median duration of lenvatinib therapy was 57 days (range, 1–118 days). In all, 11 cases needed dose reduction of lenvatinib during the treatment period. The median relative dose intensity during the 8-week lenvatinib therapy was 98.2% (range, 14.3–100.0%). The ORR was 37.5% (18/48) based on mRECIST and 12.5% (6/48) based on RECIST version 1.1 (Table 1).

Surgical Outcomes

Table 2 summarizes the surgical outcomes for the 33 patients who underwent surgery. Major hepatectomy was performed for 14 patients. Of the 15 patients who underwent minor hepatectomy, 4 underwent a sectionectomy, 4 underwent a segmentectomy, and 7 underwent a limited resection. The macroscopic curative resection rate (R0 + R1) was 60.4% (29/48). No deaths occurred within 90 days. Among the 12 patients with postoperative complications, 7 patients had complications ≥ grade 3 (bile leakage in 4 patients and intra-abdominal abscess in 3 patients).

Long-Term Outcomes

The median follow-up period was 9.3 months. Figure 3 shows the OS and PFS data for the 49 patients. The 1-year survival rate was 75.9%, and the median PFS was 7.2 months. There was no difference in the OS rates between the patients with oncologically unresectable HCC and those with technically unresectable HCC ($p = 0.330$, Fig. 4). Patients who underwent surgery had a better OS than those who did not undergo surgery ($p < 0.001$, online suppl. Fig. 1). The baseline characteristics and efficacy of lenvatinib in patients who underwent surgery and in those who did not are presented in online suppl. Table 3.

Safety Analysis

The adverse events that were observed during lenvatinib therapy are summarized in Table 3. Grade 3 adverse events were observed in 23 patients (46.9%), and grade 4
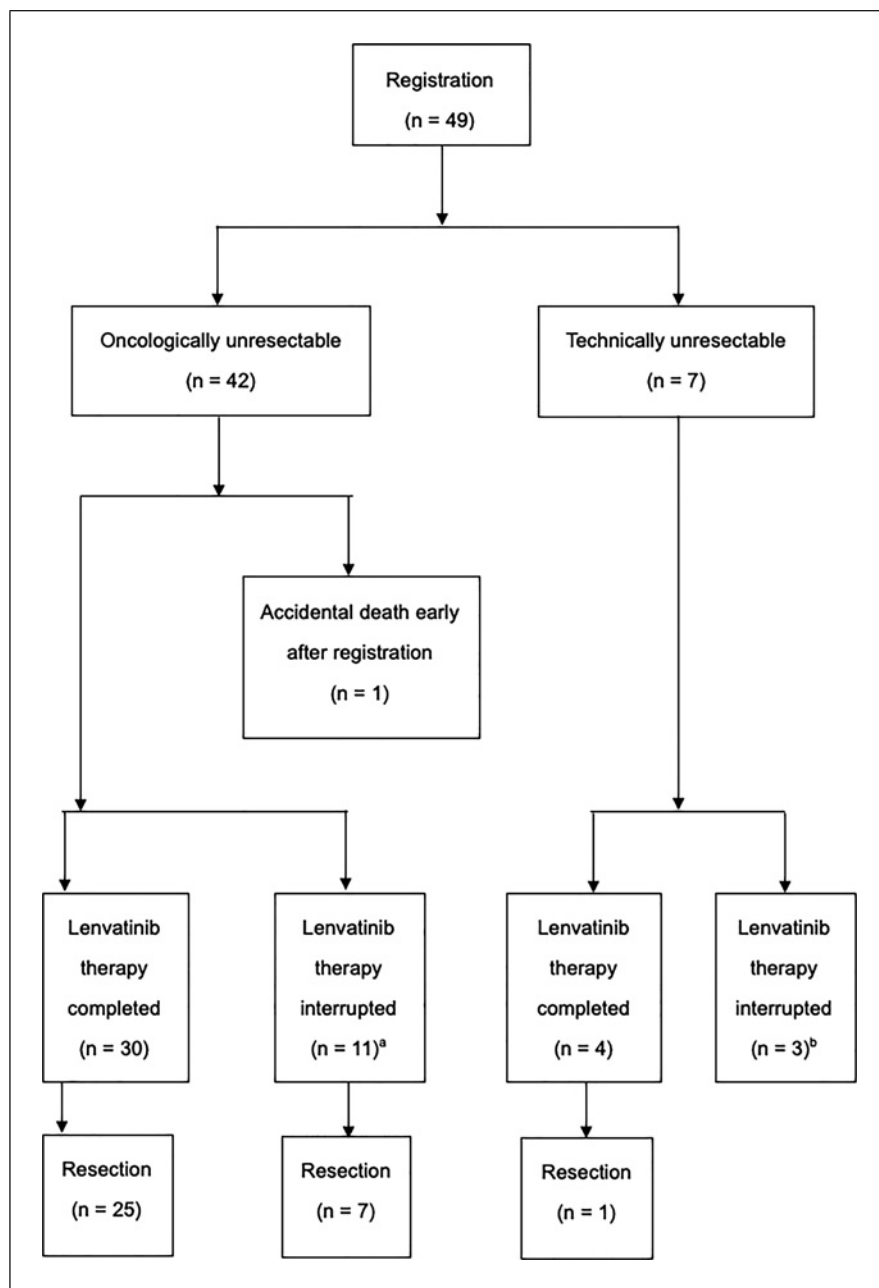
Fig. 2. Flowchart of the 49 patients registered in the LENS-HCC trial. [a]The causes of the interruptions were adverse events ($n = 7$), tumor progression ($n = 2$), worsening of comorbidities ($n = 1$), and impending tumor rupture ($n = 1$). [b]The causes of the interruptions were adverse events ($n = 1$), tumor progression ($n = 1$), and worsening of comorbidities ($n = 1$).

adverse events were observed in 1 patient (2.0%). The only grade 5 adverse event was a case of accidental trauma that occurred immediately after study enrollment. The most frequent adverse events were hypoalbuminemia, thrombocytopenia, and proteinuria. The hepatic functional reserve worsened slightly after lenvatinib therapy, with a median ICG R 15 of 14.5% (range, 3–48%) before treatment and 17.3% (range, 5–52%) after treatment ($p < 0.001$). The ICG R 15 trends for 48 patients are presented in online supplementary Figure 2.

Discussion

This trial, which is the first prospective trial to assess the efficacy and safety of preoperative lenvatinib therapy for patients with oncologically or technically unresectable HCC, demonstrated the feasibility and safety of lenvatinib therapy followed by surgical resection. The present study showed that the surgical resection rate of patients with oncologically or technically unresectable HCC with macroscopic vascular invasion, extrahepatic

Table 2. Surgical outcomes

	n = 33
Surgical procedure, n (%)	
Liver resection alone	23 (69.7)
Major hepatectomy[a]	13 (39.4)
Minor hepatectomy	10 (30.3)
Liver resection and metastasectomy	6 (18.2)
Major hepatectomy[a]	1 (3.0)
Minor hepatectomy	5 (15.2)
Metastasectomy alone	4 (12.1)
Operation time in min, median (range)	389 (91–794)
Blood loss in mL, median (range)	445 (0–22471)
Surgical margin, n (%)	
R0	27 (81.8)
R1	2 (6.1)
R2	4 (12.1)
Morbidity, n (%)	
Bile leakage	5 (15.2)
Intra-abdominal abscess	3 (9.1)
Ascites	2 (6.5)
Portal vein thrombosis	1 (3.0)
Pleural effusion	1 (3.0)
Major complication[b], n (%)	7 (21.2)
Postoperative hospital stay in days, median (range)	11 (6–53)
90-day mortality, n (%)	0

[a]Major hepatectomy was defined as a hemihepatectomy or larger major liver resection. [b]Clavien-Dindo grade 3 or higher.

metastasis, and/or multinodular tumors after 8 weeks of lenvatinib therapy was as high as 67.3% (90% confidence interval, 54.7–78.3%). There were no surgery-related deaths and no serious postoperative complications associated with the administration of lenvatinib, suggesting the safety of preoperative lenvatinib therapy. In addition, the degree of worsening of the hepatic functional reserve was small and not clinically problematic. Despite the rapid and dramatic advances in molecular targeted therapies for advanced HCC, little evidence has been reported regarding the feasibility of such therapies prior to surgical resection. The largest advantage of the present study may be that it is the first prospective study to demonstrate the safety of preoperative lenvatinib therapy.

Previous retrospective studies have reported resection rates of 15.0% [22], 2.8% [23], 88.9% [24], and 21.8% [25] for advanced HCC after lenvatinib therapy, respectively. The reason for the variability in these resection rates may be due to the different background characteristics of the patients and the varying durations of lenvatinib therapy, which ranged from 8 weeks to 6 months. The relatively high resection rate of 67.3% in the

present study can be attributed to two reasons: the high disease control rate (DCR), and the large number of patients with oncologically unresectable HCC. Of note, the REFLECT trial reported a high ORR of 40.6% based on a masked independent imaging review that was performed using mRECIST [17]. Similar to the REFLECT trial, the proportion of patients who responded in the present study was as high as 37.5% (Table 1). In addition, there were more patients with stable disease (SD) and fewer patients with PD in the present study. This outcome was presumably due to the shorter treatment period in the present study and the fact that surgery was performed earlier than scheduled in some patients who could not continue lenvatinib therapy because of adverse events or impending tumor rupture. As a result, the DCR (CR + PR + SD) in the present study was more than 90%. For oncologically unresectable cases, surgery was aggressively performed when there was no tumor progression during the 8-week treatment period, which could explain the high resection rate.

The most common adverse events in the present study were hypoalbuminemia and thrombocytopenia, while thrombocytopenia and fatigue were the most common adverse events ≥ grade 3 (Table 3). On the other hand, hypertension, which was the most common adverse event in the REFLECT trial [17], was less frequent. This difference may be due to differences in patient background and the duration of lenvatinib therapy. In the present study, 34 patients (69.4%) already had hypoalbuminemia and 23 patients (46.9%) had thrombocytopenia prior to lenvatinib administration. The majority of patients whose lenvatinib treatments were interrupted because of adverse events also underwent resection, and no postoperative complications related to the adverse events of lenvatinib therapy occurred in this series. The reported half-life of lenvatinib is as short as 34.5 h [26], and adverse events associated with lenvatinib are considered to be transient and did not compromise the safety of subsequent surgery. The median interval from the end of lenvatinib therapy to surgery was 13 days (range, 7 days–43 days), and this interval was not influenced by the grade of adverse events or by the need for interruption of lenvatinib therapy.

Of note in the present study was the low rate of major complications (21.2%) and the zero mortality among patients who underwent surgical resection (Table 2). One reason for the lack of serious complications was the relatively mild worsening of the hepatic functional reserve. Although some reports have described a worsening of the Child-Pugh and modified albumin-bilirubin scores early after the initiation of lenvatinib therapy [27], the
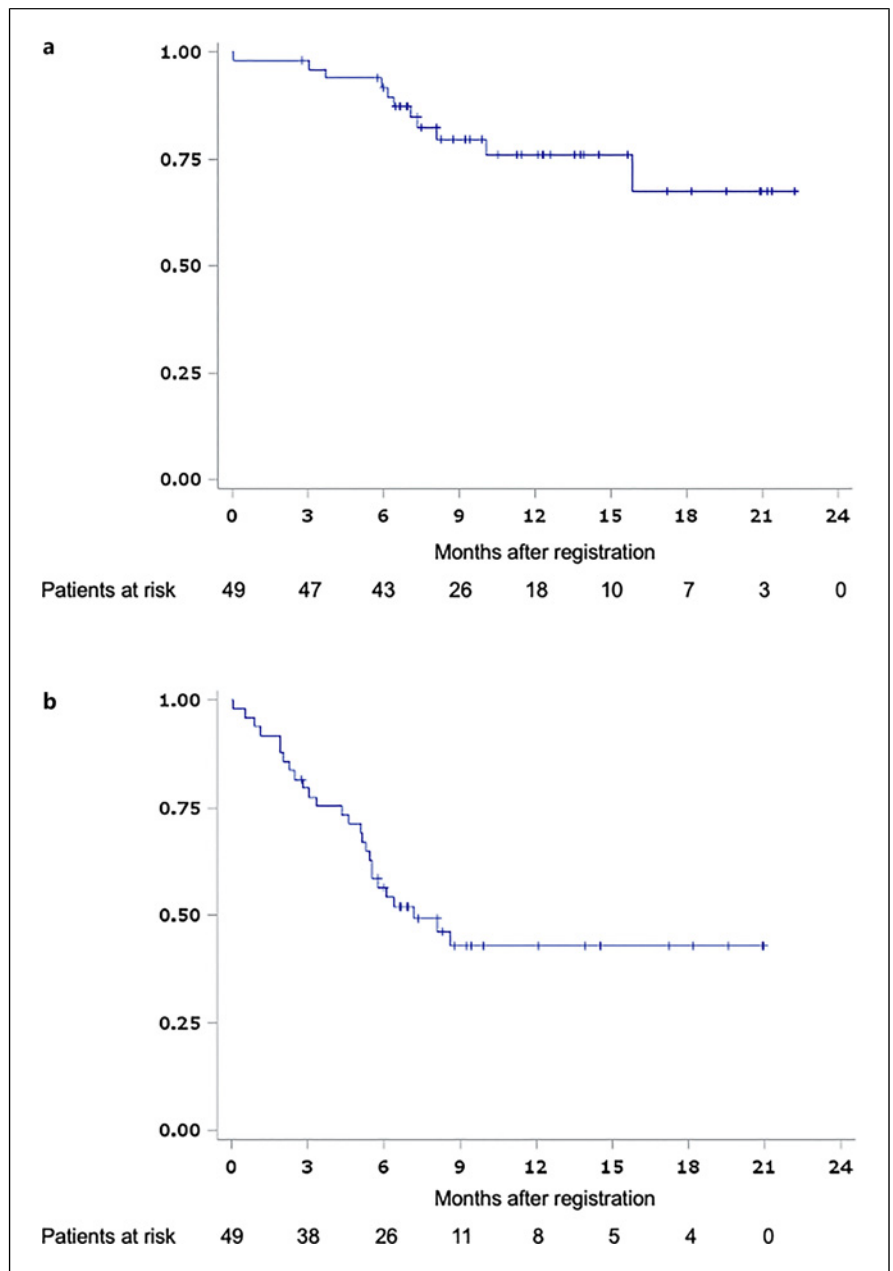
Fig. 3. a Overall survival. **b** Progression-free survival.

worsening of the ICG R 15 values, which is considered a measure of hepatic functional reserve for liver resection, was mild in the present study, with a median worsening of approximately 3%. Previously, three cases with a worsening in the ICG R 15 after 6 months or more of lenvatinib therapy were reported; however, the ICG R 15 recovered soon after the interruption of lenvatinib therapy, and in two cases, liver resection could be performed without any complications [28]. The results of the present study indicate that surgical treatment, including

liver resection, can be safely performed if lenvatinib is discontinued for at least 1 week after 8 weeks of lenvatinib therapy.

The results of the present study suggest favorable long-term outcomes of surgery after lenvatinib therapy with a 1-year survival rate of 75.9% (Fig. 3a), although the median follow-up period was not sufficient at 9.3 months. In addition, the prognosis of patients who underwent surgical resection was significantly better than that of patients who did not,
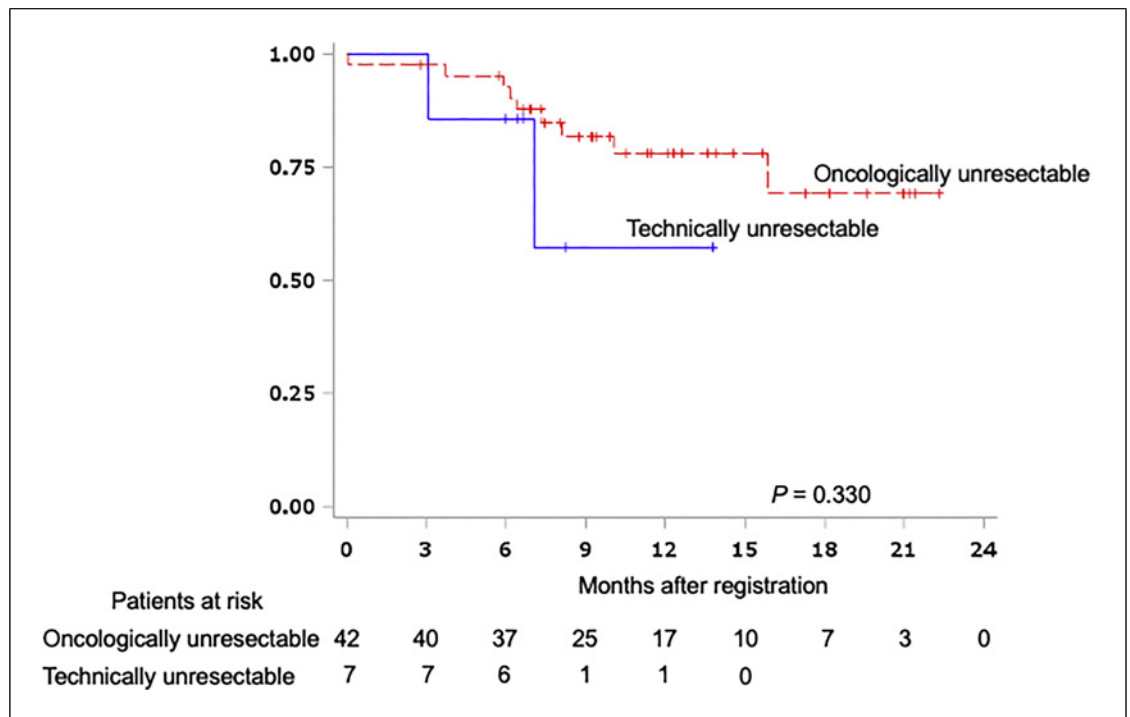
Fig. 4. Overall survival stratified according to initial resectability.

Patients at risk								
Oncologically unresectable	42	40	37	25	17	10	7	3	0
Technically unresectable	7	7	6	1	1	0			

although differences in patient background characteristics, such as tumor size and tumor markers, should be considered (online suppl. Fig. 1; online suppl. Table 2). The prognosis of patients with HCC and factors suggestive of a poor prognosis, such as macroscopic vascular invasion, extrahepatic metastasis, and multinodular tumors, has been poor, with limited treatment options available; however, surgery after lenvatinib therapy may become a promising treatment option. Nevertheless, the median PFS was as short as 7.2 months (Fig. 3b). To elucidate the reasons for the discrepancy between OS and PFS and to assess the long-term outcomes accurately, we plan to conduct additional surveys, including types of recurrence, in January 2024. At that time, we will also examine whether the prognosis of oncologically unresectable cases can be improved as compared with that of those treated with surgery alone.

One limitation of this study was that there was no clear consensus on candidates for preoperative therapy for advanced HCC, making it difficult to compare the patient background characteristics and treatment outcomes with other studies. In addition, no clear definition of oncologically and technically unresectable HCC was available at the time of enrollment. To develop criteria for the resectability of HCC, several factors should be considered including tumor size, number, location, vascular invasion, extrahepatic metastasis, and hepatic functional reserve. Furthermore, the level of surgical skill varies among institutions. Therefore, reaching a clear consensus is difficult. In the present study, advanced HCC was classified into 5 types, from A to E (Fig. 1), and the resectability of each patient was discussed by a multidisciplinary team at each participating institution to evaluate the tumor status of each patient with advanced HCC as objectively as possible. We expect that a clear definition of HCC resectability referencing the 5 types of tumor statuses used in the present study will be developed upon further discussion.

Another limitation is that both oncologically unresectable and technically unresectable cases were analyzed together. Ideally, the primary endpoint should be a parameter indicative of the long-term prognosis, such as the OS, in oncologically unresectable cases, and the surgical resection rate in technically unresectable cases. However, when the present trial was designed, we did not even know whether surgical resection could be performed safely after lenvatinib therapy. In light of this, we decided to conduct a phase II trial to evaluate the safety and feasibility of surgical resection following preoperative

Ichida et al.

Table 3. Adverse events during lenvatinib therapy (*n* = 49)

	Total, *n* (%)	Grade 1/2, *n* (%)	Grade 3/4/5, *n* (%)
Hypoalbuminemia	46 (93.9)	46 (93.9)	0
Thrombocytopenia	40 (81.6)	29 (59.2)	11 (22.4)
Proteinuria	36 (73.5)	31 (63.3)	5 (10.2)
Anemia	34 (69.4)	34 (69.4)	0
Fatigue	23 (46.9)	15 (30.6)	8 (16.3)
Decreased appetite	17 (34.7)	14 (28.6)	3 (6.1)
Hypertension	11 (22.4)	4 (8.2)	7 (14.3)
Hypothyroidism	11 (22.4)	10 (20.4)	1 (2.0)
Decreased white blood cell count	9 (18.4)	8 (16.3)	1 (2.0)
Neutropenia	9 (18.4)	8 (16.3)	1 (2.0)
Renal dysfunction	8 (16.3%)	8 (16.3)	0
Ascites	6 (12.2)	4 (8.2%)	2 (4.1)
Abdominal pain	6 (12.2)	6 (12.2)	0
Fever	5 (10.2)	4 (8.2)	1 (2.0)
Palmar-plantar erythrodysesthesia	4 (8.2)	4 (8.2)	0
Increased blood bilirubin	4 (8.2)	4 (8.2)	0
Hepatic encephalopathy	3 (6.1)	2 (4.1)	1 (2.0)
Cholecystitis	2 (4.1)	1 (2.0)	1 (2.0)
Nausea	2 (4.1)	2 (4.1)	0
Gingivitis	2 (4.1)	2 (4.1)	0
Pneumonia	2 (4.1)	2 (4.1)	0
Upper gastrointestinal hemorrhage	1 (2.0)	0	1 (2.0)
Fracture	1 (2.0)	0	1 (2.0)
Hyponatremia	1 (2.0)	0	1 (2.0)
Intra-abdominal hemorrhage	1 (2.0)	0	1 (2.0)
Elevated aspartate aminotransferase	1 (2.0)	1 (2.0)	0
GGT increased	1 (2.0)	1 (2.0)	0
Urinary tract infection	1 (2.0)	1 (2.0)	0
Tumor hemorrhage	1 (2.0)	1 (2.0)	0

GGT, gamma-glutamyl transferase. The adverse events grade was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

lenvatinib therapy in both oncologically unresectable and technically unresectable cases, prioritizing ease of patient enrollment.

The other limitation is that the adequacy of the 8-week treatment period has not been fully evaluated. In addition, the duration of treatment in this study was not constant, as the treatment durations of some patients were shorter than 8 weeks. Given the objective of preoperative systemic therapy, the optimal duration of preoperative lenvatinib therapy may differ between oncologically unresectable and technically unresectable cases. In a previous report, the median time until the best response with lenvatinib was reported to be 2.7 months [29]; although an 8-week treatment period is considered reasonable, further evaluation is necessary to determine the appropriate duration of treatment.

In conclusion, lenvatinib therapy for patients with advanced HCC resulted in a high DCR, enabling a high surgical resection rate. The safety and feasibility of lenvatinib therapy followed by surgical resection have been shown; however, further investigations are necessary to evaluate the long-term outcomes.

Statement of Ethics

The trial and its protocol were approved by the Clinical Research Review Board of the University of Tokyo (approval no. 2018046SP) and were registered with the Japan Registry of Clinical Trials (jRCT; no. jRCTs031190057). This study was

conducted in compliance with the Declaration of Helsinki and the Clinical Trials Act in Japan. All the patients provided written informed consent.

Conflict of Interest Statement

Funding Sources

Author Contributions

Study conception and design: A.I., J.A., E.H., S.E., K.U., N.K., and K.H. Acquisition of data: A.I., E.H., S.E., A.S., H.N., J.S., M.H., N.T., K.T., Y.S. (Yoshihiro Sakamoto), Y.T., Y.S. (Yasuji Seyama), and Y.S. (Yasuharu Sasaki). Analysis and interpretation of the data: A.I. and K.U. Drafting of the manuscript: A.I. All the authors participated in revising the article critically and provided their final approval for the publication of this manuscript.

Data Availability Statement

The data of this trial are available from the corresponding author upon reasonable request. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

References

1 Llovet JM, Pinyol R, Kelley RK, El-Khoueiry A, Reeves HL, Wang XW, et al. Molecular pathogenesis and systemic therapies for hepatocellular carcinoma. Nat Cancer. 2022; 3(4):386–401.

2 Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol. 2022;76(3):681–93.

3 Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016;65(5):938–43.

4 Kojima H, Hatano E, Taura K, Seo S, Yasuchika K, Uemoto S. Hepatic resection for hepatocellular carcinoma with tumor thrombus in the major portal vein. Dig Surg. 2015;32(6):413–20.

5 Kim DS, Kim BW, Hatano E, Hwang S, Hasegawa K, Kudo A, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a korea-Japan multicenter study. Ann Surg. 2020;271(5):913–21.

6 Kokudo T, Hasegawa K, Yamamoto S, Shindoh J, Takemura N, Aoki T, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol. 2014;61(3):583–8.

7 Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. Hepatology. 2017;66(2): 510–7.

8 Chua TC, Morris DL. Exploring the role of resection of extrahepatic metastases from hepatocellular carcinoma. Surg Oncol. 2012; 21(2):95–101.

9 Yoh T, Seo S, Taura K, Iguchi K, Ogiso S, Fukumitsu K, et al. Surgery for recurrent hepatocellular carcinoma: achieving long-term survival. Ann Surg. 2021;273(4):792–9.

10 Aoki T, Kubota K, Kubo S, Eguchi S, Izumi N, Kokudo N, et al. Analysis of patient outcome after non-curative resection for hepatocellular carcinoma using nationwide survey data in Japan. World J Surg. 2021;45(2):607–14.

11 Arita J, Ichida A, Nagata R, Mihara Y, Kawaguchi Y, Ishizawa T, et al. Conversion surgery after preoperative therapy for advanced hepatocellular carcinoma in the era of molecular targeted therapy and immune checkpoint inhibitors. J Hepatobiliary Pancreat Sci. 2022;29(7):732–40.

12 Choi SB, Kim KS, Park YN, Choi JS, Lee WJ, Seong J, et al. The efficacy of hepatic resection after neoadjuvant transarterial chemoembolization (TACE) and radiation therapy in hepatocellular carcinoma greater than 5 cm in size. J Korean Med Sci. 2009;24(2):242–7.

13 Cheng X, Sun P, Hu QG, Song ZF, Xiong J, Zheng QC. Transarterial (chemo)embolization for curative resection of hepatocellular carcinoma: a systematic review and meta-analyses. J Cancer Res Clin Oncol. 2014; 140(7):1159–70.

14 Mathurin P, Raynard B, Dharancy S, Kirzin S, Fallik D, Pruvot FR, et al. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. Aliment Pharmacol Ther. 2003;17(10):1247–61.

15 Wang J, Zheng Z, Wu T, Li W, Wang J, Pan Y, et al. Hepatic arterial infusion chemotherapy as a timing strategy for conversion surgery to treat hepatocellular carcinoma: a single-center real-world study. J Hepatocell Carcinoma. 2022;9:999–1010.

16 Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multi-center controlled study. J Clin Oncol. 2019; 37(24):2141–51.

17 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–73.

18 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52–60.

19 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.

20 National Cancer Institute [Internet]. Protocol development [cited 2023 Mar10]. Available from: https://ctep.cancer.gov/protocoldevelopment/ electronic_applications/docs/ctcae_v5_quick_ reference_5x7.pdf.

21 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6,336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.

22 Shindoh J, Kawamura Y, Kobayashi Y, Kobayashi M, Akuta N, Okubo S, et al. Prognostic impact of surgical intervention after lenvatinib treatment for advanced hepatocellular carcinoma. Ann Surg Oncol. 2021; 28(12):7663–72.

23 Kaneko S, Tsuchiya K, Yasui Y, Tanaka Y, Inada K, Ishido S, et al. Conversion surgery for hepatocellular carcinoma after tyrosine kinase inhibitor treatment. JGH Open. 2022;6(5):301–8.

24 Hidaka M, Hara T, Soyama A, Sasaki R, Matsushima H, Tanaka T, et al. The outcome of conversion liver resection surgery by lenvatinib treatment: a single center experience. Anticancer Res. 2022;42(6): 3049–54.

25 Itoh S, Toshida K, Morita K, Kurihara T, Nagao Y, Tomino T, et al. Clinical effectiveness of surgical treatment after lenvatinib administration for hepatocellular carcinoma. Int J Clin Oncol. 2022;27(11):1725–32.

26 Dubbelman AC, Rosing H, Nijenhuis C, Huitema AD, Mergui-Roelvink M, Gupta A, et al. Pharmacokinetics and excretion of (14) C-lenvatinib in patients with advanced solid tumors or lymphomas. Invest New Drugs. 2015;33(1):233–40.

27 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Early relative change in hepatic function with lenvatinib for unresectable hepatocellular carcinoma. Oncology. 2019;97(6):334–40.

28 Sugimoto R, Inada H, Tanaka Y, Senju T, Aratake Y, Nakanishi A, et al. Improved indocyanine green retention after short-term lenvatinib withdrawal in three patients with hepatocellular carcinoma. Clin J Gastroenterol. 2021;14(5):1484–90.

29 Saeki I, Yamasaki T, Yamashita S, Hanazono T, Urata Y, Furutani T, et al. Early predictors of objective response in patients with hepatocellular carcinoma undergoing lenvatinib treatment. Cancers. 2020;12(4):779.