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Clinical Investigation

# Efficacy and Safety of Liver-Directed Concurrent Chemoradiotherapy and Sequential Sorafenib for Advanced Hepatocellular Carcinoma: A Prospective Phase 2 Trial

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**Summary**

Liver-directed concurrent chemoradiotherapy (LD-CCRT) and sequential sorafenib treatment for advanced HCC provided favorable clinical outcomes with good tolerability. In particular, tumor reduction using an initial LD-

**Purpose:** Although sorafenib as a standard of care for advanced hepatocellular carcinoma (HCC) prolongs overall survival (OS), its efficacy is limited owing to its unsatisfactory objective response and marginal survival benefit. To counter these limitations, we designed a single-arm, phase II trial with liver-directed concurrent chemoradiotherapy (LD-CCRT) and sequential sorafenib treatment in patients with advanced HCC.

**Methods and Materials:** We enrolled advanced HCC patients diagnosed between 2014 and 2017 who were ineligible for curative treatment. During the first and last 5 days of 5-week radiation therapy, concurrent hepatic arterial infusion with 5-fluorouracil (500 mg/d) and leucovorin (50 mg/d) through an implanted port was administered 4 weeks after initiation of LD-CCRT and sequential sorafenib treatment (400 mg, twice daily). The primary endpoint was OS. This trial has been registered at clinicaltrials.gov.

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Research data are stored in an institutional repository and researchers who would like to share these research data should submit the research proposals and gain the approval from the research committee.

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CCRT enabled down staging, subsequent curative treatment, and long-term survival in about 20% of the study population.

**Results:** Among the enrolled patients (n = 47), objective response rates 4 weeks after LD-CCRT and during/up to sorafenib maintenance were 44.7% and 53.2%, respectively. Overall, 9 patients (19.1%) underwent curative resection or transplantation after down staging. The median radiation dose was 60 Gy. The median OS was 24.6 months for the entire cohort and 13.0 months for the subgroup with tumor invasion into the main portal trunk or its first branch, whereas the median progression-free survival for the cohort and subgroup was 6.8 and 5.6 months, respectively. The most frequent treatment-related adverse events were diarrhea (36.2%) and hand-foot skin reaction (34%), which were manageable with conservative treatment.

**Conclusions:** LD-CCRT and sequential sorafenib treatment provided favorable OS and progression-free survival with good tolerability. Tumor reduction using an initial LD-CCRT enabled down staging, subsequent curative treatment, and long-term survival in about 20% of the patients with advanced HCC. However, further randomized trials are required to confirm these results. 

## Introduction

Sorafenib, the first proven molecular targeted agent with survival benefit for advanced-stage hepatocellular carcinoma (HCC), is currently recommended as a standard of care.[1,2] However, transarterial therapy is the most common treatment modality used in advanced-stage HCC patients worldwide.[3] Actually, compared with a placebo, sorafenib treatment alone prolonged the median OS by only <8 weeks at most, with an almost negligible tumor shrinkage of 2.65%.[4,5] Because further curative treatment could not be achieved in such practice settings, there have been various types of efforts to improve prognosis for such patients.[6-8] Under this condition, a growing body of evidence suggests that alternatives to sorafenib, including locoregional treatments, might improve survival in patients with advanced-stage HCC, but the evidence to support this remains inadequate.[7-9]

Several trials have reported that high-dose external beam radiation therapy (EBRT) is effective in advanced-stage HCC without causing significant damage to the adjacent noncancerous organs, leading to sustained local tumor control and higher survival rates compared with historical controls.[10,11] Recently, EBRT has been listed in the National Comprehensive Cancer Network guidelines as one of the feasible locoregional treatments for inoperable HCC, and the combination of other locoregional or systemic treatments with EBRT has also been widely evaluated with some promising results.[7,12,13] Consistent with these findings, liver-directed concurrent chemoradiotherapy (LD-CCRT) for advanced-stage HCC has shown promising radiologic response rates and improved median OS in several observational studies.[3-16] Moreover, according to a recent study,[17] radiation dose escalation by intensity modulated radiation therapy (IMRT) improved OS in these patients, along with a higher conversion rate of curative resection.

Therefore, based on evidence that an initial tumor reduction by LD-CCRT may effectively overcome the therapeutic limitations of sorafenib monotherapy as the standard of care in advanced-stage HCC, we designed a single-arm, phase II trial to assess the efficacy and safety of LD-CCRT and sequential sorafenib treatment.

## Methods and Materials

### Participants

From December 2014 to November 2017, patients with advanced-stage HCC were screened for eligibility. HCC was diagnosed by histologic or radiologic evaluation.[1,2,18] Eligibility criteria for LD-CCRT were as follows: age 20 to 75 years; advanced HCC (ie, Barcelona Clinic Liver Cancer stage C) not amenable to curative treatments; at least 1 unidimensional lesion measurable according to modified Response Evaluation Criteria in Solid Tumors[19]; Eastern Cooperative Oncology Group performance status score of 0 or 1; preserved liver function with Child-Pugh score ≤7; adequate hematologic, hepatic, and renal function (white blood cell count of ≥3000/μL, absolute neutrophil count ≥750/μL, platelet count ≥60 × $10^3$/μL, serum alanine aminotransferase level <10 times the upper limit of normal levels, and serum creatinine level ≤2.0 mg/dL); and the main tumor lesion confined to a technically feasible radiation field. Patients with diffuse or multifocal bilobal tumors were not considered eligible for LD-CCRT, as whole-liver irradiation can cause serious hepatic toxicity. However, when the patient had intrahepatic lesions beyond the main tumor area covered by LD-CCRT and such tumors could be controlled using transarterial chemo-embolization (TACE), the case was considered eligible for this study.[20] Patients with regional lymph node involvement were included. In addition, patients with equivocal or minute extrahepatic spread at baseline were also included because this trial was designed to administer sequential sorafenib

treatment after the completion of LD-CCRT. Other exclusion criteria were as follows: other anticancer treatment for HCC after the diagnosis of advanced-stage HCC; presence of other uncontrolled comorbidities or malignant neoplasms; any prior organ transplant; and prior treatment of active gastric or duodenal ulcer.

This study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, and written informed consent was obtained from each participant. Our institute's review board approved this study.

## Treatment protocols

During hepatic arterial angiography, if appropriate, TACE was performed for intrahepatic metastatic lesions, principally depending on the anatomic distribution of intrahepatic tumors; a mixture of 5 mL iodized oil contrast medium (Lipiodol; Guerbet, Aulnay-sous-Bois, France) and 30 to 50 mg adriamycin was infused followed by embolization using absorbable gelatin sponge particles.[20] This TACE procedure was primarily aimed at treating HCC nodules beyond the main tumor area, which would be covered by LD-CCRT,[20] and thus the irradiated lesion was not treated with TACE. To avoid any risk of hepatic decompensation after TACE, gelatin sponge embolization was not performed when portal blood flow was severely impaired or superselection of feeding artery was not technically feasible according to the discretion of intervention radiologists. Thereafter, an implanted port was inserted into the proper or common hepatic artery, which feeds the main tumor area.[14] Response evaluation of lesions treated with TACE was performed about 3∼5 weeks after TACE.

All patients underwent 3-dimensional conformal radiation therapy (3D-CRT) or image guided IMRT, which can cover the gross main tumor area. Before July 2015, the method for radiation therapy (3D-CRT vs IMRT) was determined primarily based on anatomic considerations. Since July 2015, however, most patients undergo IMRT, if eligible, because the National Health Insurance Service in the Republic of Korea will reimburse patients for this procedure. The gross tumor volume (GTV) was defined as radiographically abnormal areas detected using computed tomography (CT) or magnetic resonance imaging. A minimum of 5 mm around the GTV or internal target volume (ITV) was added to determine the clinical target volume. In defining the planning target volume (PTV), an additional 5 mm for setup error and internal organ motion was added to the clinical target volume. All patients were educated about respiratory control, and an abdominal compressor was applied to restrict diaphragmatic movement. Furthermore, 4-dimensional CT was used to consider the tumor movement for every respiratory phase.

For 3D-CRT, 45 Gy in 25 fractions was typically prescribed to PTV. For IMRT, we used simultaneous integrated boost to deliver a high dose to the center of PTV and a low dose to the rim of PTV. This technique allows the delivery of ablative doses of radiation therapy (RT) to the center of the tumors while protecting the abutting luminal sensitive organs at risk. The center of target volume, GTV or ITV, received a radiation dose of 50 to 75 Gy in 20 to 25 fractions using a simultaneous integrated boost technique, whereas the rim of target volume, the surrounding PTV, received a lower radiation dose of 45 to 60 Gy in 20 to 25 fractions.[17] A planning risk volume was created considering the critical normal organ movement, and target volumes were subtracted from the adjacent luminal organ if there was overlap. The organ at risk is the priority constraint over the PTV for treatment planning. The main constraints were as follows: stomach $D_{2cc} \leq 45$ Gy, duodenum $D_{2cc} \leq 45$ Gy, mean dose of liver minus PTV $\leq 28$ Gy, and $V_{30\ Gy}$ of liver minus PTV $\leq 30\%$. An alpha-to-beta ratio of 10 was used to calculate the biologically effective dose (BED) to the tumor.

During the first and last 5 days of RT, concurrent hepatic arterial infusion of 5-fluorouracil (500 mg/d) and leucovorin (50 mg/d) was administered via the implanted port system.[14] Four weeks after completing LD-CCRT, sequential sorafenib treatment was commenced at a dosage of 400 mg twice daily until progression or unacceptable toxicity. To monitor safety, patient visits were scheduled every 2 weeks for the first 4 weeks and every 4 weeks thereafter. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Dose modification and treatment interruptions were allowed according to drug-related toxicity grade as recommended.

## Assessment of treatment outcomes

The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), objective response, disease control rate, and proportion of patients undergoing curative surgical resection or transplantation after down staging. Radiologic response was assessed using liver dynamic CT or magnetic resonance imaging (if appropriate) 4 weeks after the completion of LD-CCRT and then every 8 weeks during sorafenib maintenance phase according to modified Response Evaluation Criteria in Solid Tumors.[19] During follow-up, using a multidisciplinary team approach, curative surgical resection or transplantation, if eligible, was allowed for patients who achieved successful down-staging showing a favorable treatment response.

## Statistical analysis

Sample size was calculated based on previous literature that focused on patients with advanced-stage HCC. We calculated that a total of 47 patients were required to detect a 4-month difference (10 months in patients treated with LD-CCRT[20,21] vs 6 months in patients treated with sorafenib[5,22,23]) in the median OS with 80% power, 5%

**Table 1** Baseline clinical characteristics of entire study population (N = 47) and a subgroup undergoing sequential sorafenib (n = 34)

| Variables | Values | |
|---|---|---|
| | Entire study population (n = 47) | Subgroup undergoing sequential sorafenib (n = 34) |
| Age, years | 57 (51-63) | 56 (51-63.5) |
| Male sex | 42 (89.4%) | 29 (85.3%) |
| Etiology | | |
| HBV/HCV/nonB, nonC | 36 (76.6%)/1 (2.1%)/10 (21.3%) | 30 (88.2%)/0 (0%)/4 (11.8%) |
| Degree of portal vein invasion | | |
| Vp4 (main trunk) | 10 (21.3%) | 8 (23.5%) |
| Vp3 (the 1st branch) | 13 (27.7%) | 9 (26.5%) |
| Vp2 (the 2nd branch) or less | 24 (51.0%) | 17 (50.0%) |
| Morphologic type | | |
| Infiltrative/nodular | 22 (46.8%)/25 (53.2%) | 16 (47.1%)/18 (52.9%) |
| Size of main tumor, cm | 8.4 (6.5-12.0) | 8.3 (6.5-12.1) |
| Volume of main tumor, cc | 268.4 (75.5～617.1) | 190.5 (49.7-605.8) |
| Tumor number | | |
| 1 | 17 (36.2%) | 15 (44.1%) |
| 2 | 6 (12.8%) | 5 (14.7%) |
| 3 | 4 (8.5%) | 2 (5.9%) |
| 4 | 1 (2.1%) | 0 (0.0%) |
| ≥5 | 19 (40.4%) | 12 (35.3%) |
| AFP, ng/mL | 187.1 (15.6-5911.5) | 187.1 (10.9-5911.6) |
| PIVKA-II, mAU/mL | 3528.5 (236.5-12406.3) | 2037.0 (236.5-7106.5) |
| Liver cirrhosis | 27 (57.4%) | 18 (52.9%) |

*Abbreviations:* AFP = alpha-fetoprotein; HBV = hepatitis B virus; HCV = hepatitis C virus; PIVKA-II = protein induced by vitamin K absence-II. Values were expressed as median (interquartile range) or no. (%).

type I error, an accrual time of 12 months, a total study time (follow-up period included) of 18 months, and 10% drop-out rate.

The primary data set comprised all enrolled patients (intention-to-treat analysis). OS and PFS were calculated, using Kaplan-Meier analysis, as time intervals between the date of treatment initiation and the date of death or progression, and survival differences were compared using log-rank test.

Statistical analysis was performed using IBM SPSS version 23.0 (IBM Corporation, Armonk, NY), and a 2-sided $P$ value of $<.05$ was considered statistically significant. The trial is registered at clinicaltrials.gov.

## Results

### Patient characteristics

A total of 47 patients were analyzed, and Table 1 shows their baseline clinical characteristics before an initiation of the treatment schedule planned in this study (n = 47). The median age was 57 years, with a male predominance (89.4%). Chronic hepatitis B virus infection was the most common etiology (76.6%), and 57.4% of the patients had liver cirrhosis at enrollment. The median tumor size was 8.4 cm, with the median tumor volume of 268.4 cc, and 19 patients (40.4%) had ≥5 tumors. The percentage of patients with portal vein tumor invasion in the main portal trunk (Vp4) or its first branch (Vp3) and that with an infiltrative tumor morphology[24,25] were 49% and 46.8%, respectively. Four patients had direct tumor invasion into the inferior vena cava or the right atrium. The median levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence (PIKVA)-II were 187.1 ng/mL and 3528.5 mAU/mL, respectively.

### Treatment delivery and responses

The patient flow diagram is shown in Figure E1 (available online at https://doi.org/10.1016/j.ijrobp.2020.01.027). During hepatic arterial angiography for insertion of the implanted port system, 16 (34.0%) patients underwent TACE for treatment of synchronous intrahepatic lesions according to the discretion of intervention radiologists. The representative images of patients undergoing TACE to treat synchronous intrahepatic lesions are shown in Figure E3 (available online at https://doi.org/10.1016/j.ijrobp.2020.01.027). Twelve and 35 patients were treated with 3D-CRT and IMRT, respectively. The median prescribed radiation dose was 60 Gy (interquartile range [IQR], 50−75 Gy), and the median BED was 78 $Gy_{10}$ (IQR, 55.2-97.5 $Gy_{10}$). Five patients could not undergo sequential sorafenib treatment owing to migration to Child-Pugh class B, all of whom had Child-Pugh score 6 at baseline. Finally, a total of

**Table 2** Radiologic responses

| Radiologic response | Four weeks after LD-CCRT | During planned treatment schedule |
|---|---|---|
| CR | 1 (2.1) | 2 (4.3) |
| PR | 20 (42.6) | 23 (48.9) |
| SD | 12 (25.5) | 8 (17.0) |
| PD | 13 (27.7) | 13 (27.7) |
| Not evaluable | 1 (2.1) | 1 (2.1) |

*Abbreviations:* CR = complete response; LD-CCRT = liver-directed concurrent chemoradiotherapy; PD = progressive disease; PR = partial response; SD = stable disease. Values were expressed as no. (%).

34 patients underwent sequential sorafenib treatment, and their baseline clinical characteristics before initiation of the treatment schedule planned in this study are shown in Table 1. The median daily average dose of sorafenib was 800 mg/d (IQR, 633.2−800 mg/d).

The objective response (defined as complete response or partial response) rates 4 weeks after the completion of LD-CCRT and during the planned treatment schedule (ie, up-to sorafenib maintenance period) were 44.7% and 53.2%, respectively (Table 2). Locoregional (ie, at intra-RT field) disease control was achieved in 89.4% after the completion of LD-CCRT. When the first event of disease progression was confirmed, patterns of treatment failure were as follows (in case of multiple progressive disease lesions, each category was counted): in-RT field (defined as treatment failure within the irradiated field, n = 3) and intrahepatic out-of-RT field failure (n = 15), regional lymph node involvement (n = 1), and distant metastasis (n = 16).

Four weeks after the completion of LD-CCRT, 57.4% and 85.1% of the patients had favorable biological responses, which were defined as ≥50% reduction in AFP and PIVKA-II serum levels from the baseline, respectively. Overall, 9 patients (19.1%) underwent curative resection or transplantation after successful down staging. The only significant predictor for potential candidates undergoing curative resection/transplantation was the objective response during the planned treatment schedule (88.9% vs 44.7%, $P = .025$). Furthermore, those undergoing curative resection or transplantation showed a trend toward higher proportion of a single lesion (44.4% vs 34.2%), radiologic objective response rate after LD-CCRT (66.7% vs 39.5%) and female gender (22.2% vs 7.9%), and a lower rate of Vp3 or Vp4 (33.3% vs 52.6%), compared with the remainder ($P > .05$). In a subgroup of patients with tumor invasion into the main portal trunk or its first branch, 3 patients (13.0%) underwent curative resection or transplantation.

## Survival outcomes

Among the entire population, the median OS (Fig. 1A) and PFS (Fig. 1B) were 24.6 (95% confidence interval [CI], 10.9-38.4) and 6.8 (95% CI, 2.1-11.6) months, respectively. OS rates at 6 and 12 months were 88.9% and 66.8%, respectively, and PFS rates at 6 and 12 months were 53.5% and 31.5%, respectively.

Detailed characteristics of a subgroup with Vp3 or Vp4 are described in Table 3. Among them, the median OS (Fig. 2A) and PFS (Fig. 2B) were 13.0 (95% CI, 5.3-20.6) and 5.6 (95% CI, 2.3-8.8) months, respectively. OS rates at 6 and 12 months were 76.6% and 55.0%, respectively, and PFS

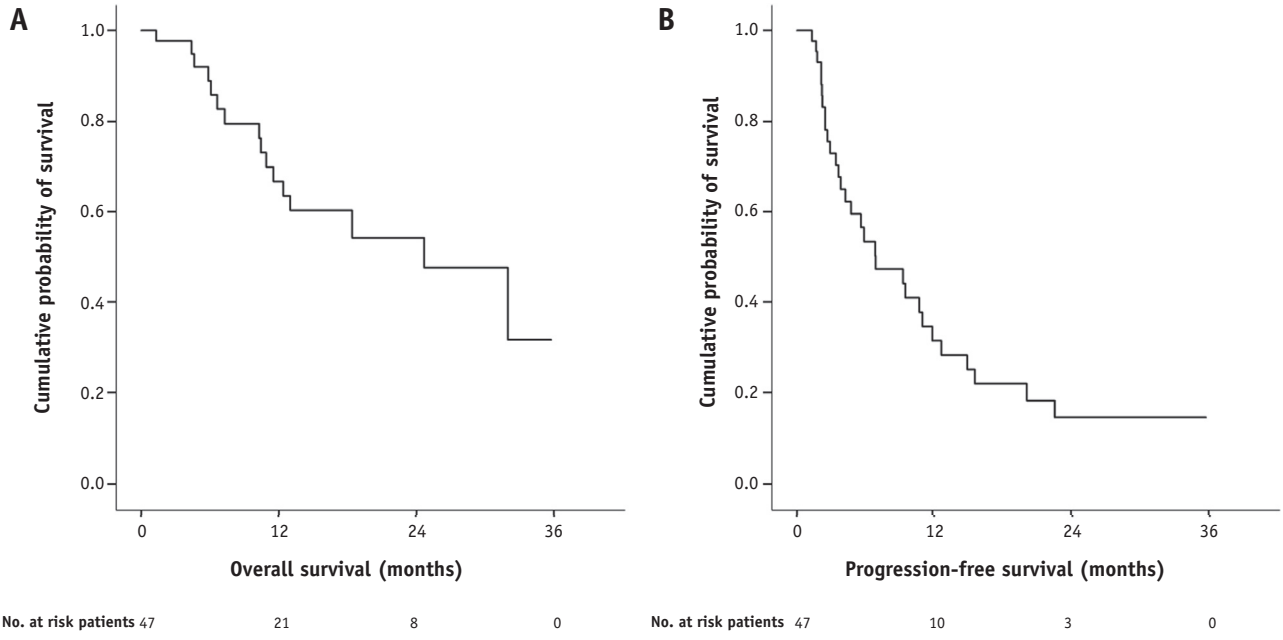


**Fig. 1.** Kaplan-Meier curve for overall survival (OS) (A) and progression-free survival (PFS) (B) among the entire population.

**Table 3** Baseline clinical characteristics of a subgroup with tumor invasion into main portal trunk or its first branch (n = 23)

| Variables | Values |
|---|---|
| Age, years | 56 (51-62) |
| Male sex | 21 (91.3%) |
| Etiology | |
| HBV | 17 (73.9%) |
| HCV | 1 (4.3%) |
| nonB, nonC | 5 (21.8%) |
| Child-Pugh score | |
| 5 | 11 (47.8%) |
| 6 | 12 (52.2%) |
| ALBI grade | |
| 1 | 6 (26.1%) |
| 2 | 16 (69.6%) |
| 3 | 1 (4.3%) |
| Morphologic type | |
| Infiltrative | 17 (73.9%) |
| Nodular | 6 (26.1%) |
| Tumor size, cm | 10.0 (6.5-12.2) |
| Tumor number | |
| 1 | 9 (39.2%) |
| 2 | 3 (13.0%) |
| 3 | 1 (4.3%) |
| 4 | 1 (4.3%) |
| ≥5 | 9 (39.2%) |
| AFP, ng/mL | 237.5 (81.3-12981.0) |
| PIVKA-II, mAU/mL | 3745.0 (288.0-21832.0) |
| Liver cirrhosis | 13 (56.5%) |

*Abbreviations:* AFP = alpha-fetoprotein; ALBI = Albumin-Bilirubin; HBV = hepatitis B virus; HCV = hepatitis C virus; PIVKA-II = protein induced by vitamin K absence-II.
Values were expressed as median (interquartile range) or no. (%).

rates at 6 and 12 months were 44.6% and 24.8%, respectively. Notably, among the 9 patients undergoing curative resection or transplantation, the median duration of time to the last follow-up was 26.4 months (IQR, 16.1−30.2). Only 1 case of death was observed at 32.0 months from the date of treatment initiation, owing to HCC recurrence and the subsequent disease progression. Representative images for the patient undergoing liver transplantation after successful down staging during treatment course at baseline (Fig. E3A, available online at https://doi.org/10.1016/j.ijrobp.2020.01.027) and just before liver transplantation (Fig. E3B, available online at https://doi.org/10.1016/j.ijrobp.2020.01.027) are shown.

## Treatment-related adverse events

Treatment-related adverse events during the planned treatment schedule are presented in Table 4. The most frequent treatment-related adverse events were diarrhea (36.2%) and hand-foot skin reaction (34%), all of which were manageable with conservative care. Overall, 5 patients experienced deteriorated liver function, defined as Child-Pugh score increment by 2 or more from baseline, during (n = 1) and after LD-CCRT (n = 4). In addition, among 3 patients undergoing sequential sorafenib treatment, sorafenib was discontinued owing to duodenal hemorrhage (n = 2) and hepatic encephalopathy (n = 1). An alternative treatment with hepatic arterial infusion chemotherapy based on a 5-fluorouracil and cisplatin regimen through the implanted port system[26] was allowed.

## Potential predictors of clinical outcomes

The potential predictors of OS included the degree of portal vein invasion ($P = .088$), objective response during the planned treatment schedule ($P = .006$), biological response by PIVKA-II level after LD-CCRT ($P < .001$), and BED ($P = .008$) (Fig. 3). Those of PFS included the biological response by PIVKA-II level after LD-CCRT ($P = .011$), Child-Pugh score ($P = .023$), and BED ($P = .039$) (Fig. E4, available online at https://doi.org/10.1016/j.ijrobp.2020.01.027). Furthermore, those of objective response during the planned treatment schedule included tumor number ($P = .072$), biological responses by AFP ($P = .006$) or PIVKA-II ($P = .040$) level after LD-CCRT, Child-Pugh score ($P = .005$), and BED ($P = .014$) (Table E1, available online at https://doi.org/10.1016/j.ijrobp.2020.01.027).

## Discussion

In this prospective clinical trial, LD-CCRT and sequential sorafenib treatment showed encouraging results, with an objective response in 53.2% of the subjects and a median OS of 24.6 months among patients with advanced-stage HCC, given that >90% of the enrolled patients had poor oncological prognostic factors such as massive tumor (≥10 cm), infiltrative tumor morphology, major portal vein invasion (Vp3 or Vp4), tumor invasion into the inferior vena cava or the right atrium, AFP ≥ 400 ng/mL, or PIVKA-II ≥ 1000 mAU/mL. Even for patients with Vp3 or Vp4, a relatively better median OS of approximately 13 months was observed, considering that from historical controls. Many previous reports showed that such patients had poor prognosis despite appropriate systemic therapy according to the guidelines.[1,2,22,23,27] From a recent phase III trial comparing survivals between lenvatinib and sorafenib arms as a first-line modality in advanced-stage HCC,[28] enrolled patients had the median OS of approximately 13 months. However, given that those with major portal vein invasion at baseline were primarily excluded in that phase III trial, the median OS of 13.0 months in our patient subgroup with Vp3 or Vp4 was a noteworthy finding.

In this study protocol, EBRT and hepatic arterial infusion of 5-fluorouracil were administered concurrently. First of all, the therapeutic benefit of 5-fluorouracil as an anticancer agent has been widely reported.[29,30] Furthermore, the main characteristics of hepatic arterial infusion include lack of embolization, which can lead to a lesser degree of ischemic insult compared with conventional TACE against

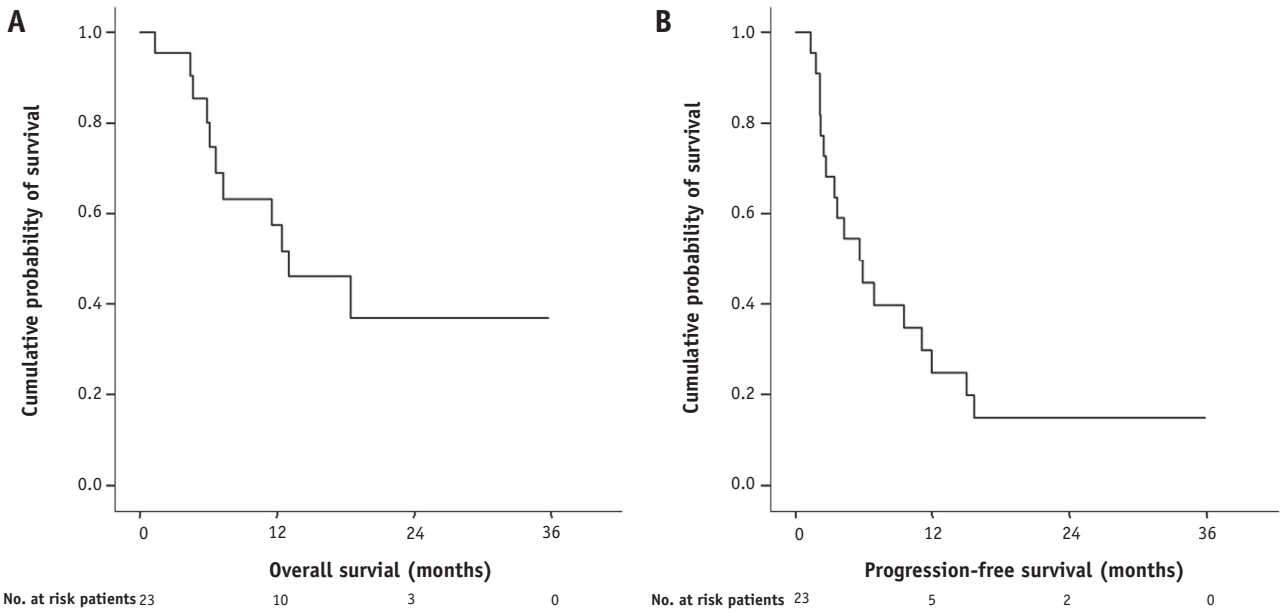


**Fig. 2.** Kaplan-Meier curve for overall survival (OS) (A) and progression-free survival (PFS) (B) among a subgroup with Vp3 or Vp4.

the large primary tumor in the presence of severely reduced portal blood flow.[27,31-34] In addition to its anticancer effect, 5-fluorouracil would be, in part, helpful as a radiosensitizer to treat HCC.[35-40] Therefore, some kind of synergistic effect against HCC would be expected.

The tumor shrinkage effect of sorafenib alone is actually negligible; it is reported to be approximately 3% at most.[22,23] In this situation, the probability of conversion to curative treatments after successful down-staging would be extremely low. With the assumption that tumor size reduction by LD-CCRT and subsequent sorafenib treatment having tumoristatic effects can effectively provide a synergistic therapeutic effect against HCC, we conducted this study to evaluate the efficacy of LD-CCRT and sequential sorafenib treatment. In our study, about half of the patients experienced radiologic objective response, and overall, 19.1% of them underwent subsequent curative resection or transplantation through successful down staging induced by LD-CCRT. Excellent survival outcomes were observed in these patients, and only 1 patient died at 32.0 months after the date of treatment initiation. Consistent with this finding, Lee et al[16] also showed a 5-year OS rate of 49.6% among patients undergoing curative treatment after successful down staging. EBRT-based locoregional treatment may be a useful modality for down staging of advanced-stage HCC.[7,16] First, it can facilitate liver mobilization in the operation field through tumor size reduction. Second, because the biological behaviors of advanced tumors are better evaluated during the period of "neo-adjuvant" treatment, more appropriate selection of candidates for curative treatments might be possible. Furthermore, from a previous report regarding LD-CCRT,[16] functional reserve liver volume increases substantially after LD-CCRT, which is characterized by marked atrophy of the irradiated region and compensatory hypertrophy of the nonirradiated region. Such compensatory hypertrophy of the nonirradiated region might be comparable to what is observed after surgical resection of the liver and is more

**Table 4** Treatment-related adverse events

| | All grades | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Hand-foot skin reaction | 16 | 34.0% | 2 | 4.3% | - | - |
| Fatigue | 6 | 12.8% | - | - | - | - |
| Stomatitis | 6 | 12.8% | - | - | - | - |
| Nausea | 8 | 17.0% | - | - | - | - |
| Anorexia | 1 | 2.1% | - | - | - | - |
| Hypertension | 1 | 2.1% | - | - | - | - |
| Fever | 1 | 2.1% | - | - | - | - |
| Myalgia | 1 | 2.1% | - | - | - | - |
| Diarrhea | 17 | 36.2% | - | - | - | - |
| Chest pain | 1 | 2.1% | - | - | - | - |
| Headache | 1 | 2.1% | - | - | - | - |
| Dizziness | 1 | 2.1% | - | - | - | - |
| Duodenal hemorrhage | 2 | 4.2% | 1 | 2.1% | - | - |
| Pruritis | 1 | 2.1% | - | - | - | - |
| Alopecia | 5 | 10.6% | - | - | - | - |
| Abdominal pain | 6 | 12.8% | 2 | 4.3% | - | - |
| Alanine aminotransferase elevation | 17 | 36.2% | - | - | - | - |
| Hyperbilirubinemia | 16 | 34.0% | 5 | 10.6% | - | - |
| Hypoalbuminemia | 16 | 34.0% | - | - | - | - |

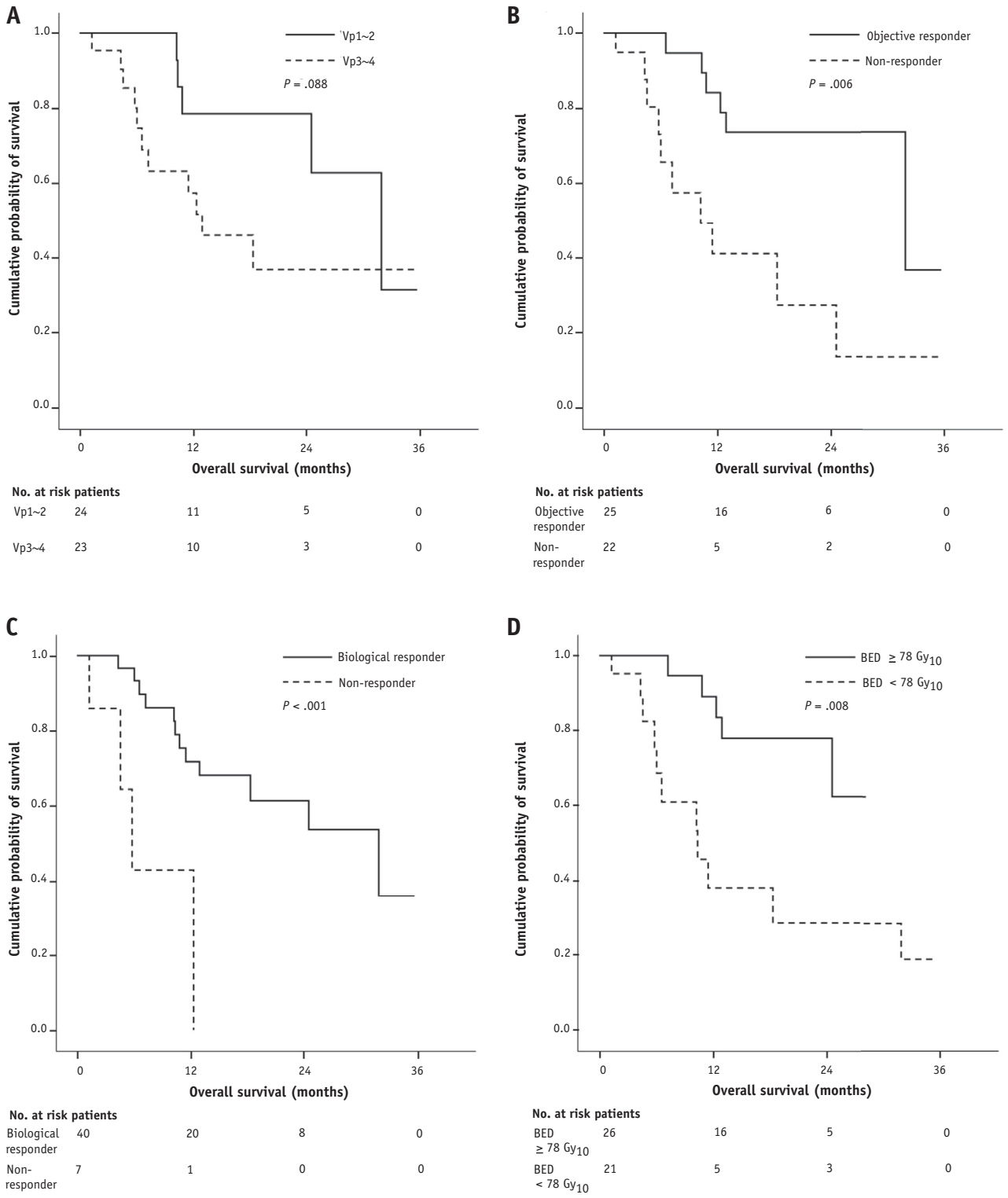


**Fig. 3.** Kaplan-Meier curve for overall survival (OS) according to the degree of portal vein invasion (A), objective response during the planned treatment schedule (B), biological response by protein induced by vitamin K absence-II (PIVKA-II) level after liver-directed concurrent chemoradiotherapy (LD-CCRT) (C), and biologically effective dose (BED) (D).

outstanding than what is observed after portal vein embolization.[41,42] Therefore, a careful assessment of the feasibility of active locoregional treatments in advanced-stage HCC through a multidisciplinary approach is required.[43]

Furthermore, along with its promising efficacy, LD-CCRT with subsequent sorafenib treatment is also acceptable in terms of safety and tolerability. All treatment-related adverse events were manageable with conservative

care, even though 2 patients experienced duodenal hemorrhage after LD-CCRT. We reviewed the cone beam CT scans to evaluate the accumulated dose of these patients; the maximum dose ($D_{max}$) to the duodenum and the dose received by 2 cc of the duodenum ($D_{2\ cc}$) were 61.3 and 59.1 Gy in 1 patient and 48.5 and 42.4 Gy in the other patient, respectively, which were higher doses than initially designed. This is most likely due to respiratory and bowel movements during radiation. Furthermore, we cautiously speculated that sequential sorafenib treatment and underlying portal hypertension could in part hinder a normal recovery from radiation-induced mucosal damage in duodenum.

This study had some limitations. First, it was a 1-arm phase II clinical trial with a small sample size, and therefore, we also recognize that our results might make the conclusions more hypothesis generating than conclusive and that further prospective randomized controlled trials are required to substantiate our results. Furthermore, given that HCC populations are very heterogeneous, there is a possibility that statistical assumptions could be subject to change according to the enrolled HCC populations. In similar context, a thorough evaluation of various potential prognostic factors might not be feasible. Second, during the study period, the use of second-line systemic agents was limited in South Korea. A further long-term follow-up would better evaluate the entire clinical course of advanced-stage HCC. Third, because concurrent hepatic arterial infusion of 5-fluorouracil (500 mg/d) and leucovorin (50 mg/d) via the implanted port system has not yet become a popular treatment modality so far, there exist many barriers among clinicians in adopting this practice. Therefore, further protocols to deliver other chemotherapeutic agents (eg, cisplatin) with or without drug-eluting bead during hepatic arterial angiography should be required.[7,8] And last, although 3D-CRT or IMRT with conventional fractionation using advanced techniques was preferred in the present study primarily owing to close proximity of the large tumor to the gastrointestinal tract, we also recognize that SBRT or particle beam treatment may lead to better efficacy in terms of dosimetric advantage.[44,45] Therefore, further studies adopting SBRT or particle beam treatment for advanced stage HCC will be valuable.

In conclusion, LD-CCRT and sequential sorafenib treatment demonstrated favorable survival outcomes with acceptable tolerability in patients with advanced-stage HCC. Furthermore, remarkable tumor reduction by initial LD-CCRT enabled down staging and subsequent curative treatment and long-term survival in a considerable proportion of patients. Further phase III trials are needed to confirm our results.

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