

Appraisal of Long-Term Outcomes of Liver-Directed Concurrent Chemoradiotherapy for Hepatocellular Carcinoma with Major Portal Vein Invasion

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Backgrounds and Aims: Molecular-targeted agents are acceptable standards to treat advanced-stage hepatocellular carcinoma (HCC), however, their therapeutic benefit, ie, sorafenib, was significantly offset in case of major vessel invasion. Liver-directed concurrent chemo-radiotherapy (LD-CCRT) provided favorable outcomes in terms of survivals and tumor shrinkage, so, we appraised its long-term therapeutic efficacy.

Patients and Methods: Advanced HCC patients with portal vein invasion (main trunk or the 1st order branch) were enrolled. During a 5-week radiotherapy course, concurrent hepatic arterial infusion chemotherapy (HAIC) with 5-fluorouracil and leucovorin was administered through an implanted port on the first and last 5 days. Four weeks after LD-CCRT, a maintenance HAIC using 5-fluorouracil and cisplatin was administered every 4 weeks.

Results: Among 152 patients, the objective response rates as the best response by modified Response Evaluation Criteria In Solid Tumors were 48.0% after LD-CCRT and 55.3% during subsequent HAIC maintenance. After LD-CCRT, biological responses in alpha-fetoprotein and protein induced by the absence of vitamin K or antagonist-II levels were achieved in 46.2% and 52.6%, respectively. Sixteen patients (10.5%) underwent curative resection or liver transplantation after down-staging. Median overall survival and progression-free survival were 13.5 and 6.9 months, respectively.

Conclusion: LD-CCRT followed by maintenance HAIC yielded favorable survival outcomes in advanced HCC patients with major portal vein invasion. Through initial tumor reduction, LD-CCRT induced down-staging with subsequent curative treatment feasible in 10.5% of patients, resulting in long-term survival. Further prospective trials are warranted to confirm these results.

Keywords: hepatocellular carcinoma, portal vein invasion, concurrent chemoradiotherapy, prognosis, response

Plain Language Summary

-Treatment options other than molecular-targeted agents are still limited for advanced stage-hepatocellular carcinoma (HCC) with major portal vein invasion.

-We assessed their survival outcomes undergoing liver-directed concurrent chemoradiotherapy (LD-CCRT) followed by maintenance hepatic arterial infusion chemotherapy (HAIC).

-Among 152 patients, median overall survival and progression-free survival were 13.5 and 6.9 months, respectively. The objective response rates as the best response by modified Response Evaluation Criteria in Solid Tumors were 48.0% after LD-CCRT and 55.3% during the planned

treatment course. After LD-CCRT, biological responses in alpha-fetoprotein and protein induced by the absence of vitamin K or antagonist-II levels were achieved in 46.2% and 52.6%, respectively. Sixteen patients (10.5%) underwent curative resection or liver transplantation after down-staging.

- LD-CCRT followed by maintenance HAIC yielded favorable survival outcomes in advanced stage-HCC patients with major portal vein invasion. Through initial tumor reduction, LD-CCRT induced down-staging with subsequent curative treatment feasible in 10.5% of patients. Further prospective trials are warranted to confirm these results.

Introduction

Approximately 10–40% of hepatocellular carcinoma (HCC) patients are diagnosed at an advanced stage with major portal vein (PV) tumor invasion. The expected prognosis in such cases is typically poor, despite the administration of optimal systemic therapy according to the best practice guidelines.^{1–3} Sorafenib is the first approved oral multi-kinase inhibitor for prolonging the overall survival (OS) of patients with advanced-stage HCC. Along with lenvatinib, it is currently regarded as the standard of care.^{1,3,4} However, data supporting the survival benefits from molecular-targeted agents among patients with advanced-stage HCC with major PV invasion are still limited. For example, among patients treated with sorafenib,⁵ the OS markedly decreased from 14.3 to 5.7 months in case of extrahepatic spread and/or macrovascular invasion.^{6–8} Furthermore, although the median OS reached approximately 13 months in the Phase III trial comparing lenvatinib and sorafenib as the first-line treatment for advanced-stage HCC, patients with major PV invasion at baseline were primarily excluded in that phase III trial. Thus, there is a pressing need for more effective treatment strategies in these patients. Recently, we could observe many literatures indicating that alternative strategies including loco-regional treatment (LRT) could improve survival outcomes compared to molecular-targeted agents alone.^{1,9,10}

Among various LRTs, external beam radiation therapy (EBRT) has become widely popular primarily due to technological advances, including the introduction of 3-dimensional conformal radiation therapy (3D-CRT) and more recently, intensity-modulated radiotherapy (IMRT).^{11,12} These technologies allow the delivery of high tumoricidal radiation doses with minimal risk of damage to adjacent non-tumorous tissues. As a result, a high-dose EBRT for advanced HCC can lead to a long-lasting local tumor control as well as a higher

probability of down-staging which allows curative resection or OLT with improved survival, in comparison with historical controls.^{12–14} According to several observational studies, liver-directed concurrent chemoradiotherapy (LD-CCRT) for advanced-stage HCC was associated with the favorable clinical outcomes.^{15–17} In particular, Kim et al¹⁶ reported that the objective response rates (ORR) during the LD-CCRT-based treatment course was up to 53.2% and that 19.1% underwent curative resection or transplantation after down-staging, in contrast to only a minimal tumor shrinkage effect by sorafenib, ie at least about 2 ~5%.^{18,19} Another studies also supported anti-tumor effect by an intra-arterial infusion of 5-fluorouracil with or without EBRT.^{20–25}

Based on the available evidence that effective initial tumor shrinkage by LD-CCRT may facilitate subsequent treatments with curative intent among advanced-stage HCC patients with major PV invasion, we aimed to assess clinical outcomes of LD-CCRT, in terms of not only survival outcomes but ORR and the proportion of conversion to curative treatment, of LD-CCRT.

Patients and Methods

Participants and Treatments

Patients who underwent LD-CCRT for advanced-stage HCC between 2011 and 2016 at Severance Hospital, Seoul, Republic of Korea, were retrospectively analyzed. HCC was diagnosed by histological or radiological evaluation with reference to the international guidelines.^{1,3,26,27} The eligibility criteria for LD-CCRT are described in [Table 1](#). For example, LD-CCRT was not performed for patients with diffuse or multifocal bi-lobal tumors which cannot be included in a technically feasible RT field from the viewpoint of safety based upon liver function and radiation dosage to organs. In addition, the exclusion criteria were also described in [Table 1](#).

LD-CCRT and subsequent maintenance HAIC were performed according to the previous studies by Kim et al¹⁶ and Park et al²⁸ respectively. Provided that patients have intrahepatic lesions eligible for transarterial chemo-embolization (TACE),^{29–31} they could be included in the study at physicians' discretion. The overall process of the treatment delivery was described in the [Supplementary Table 1](#).

This study protocol was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board (IRB) of Severance Hospital. The informed consent was waived because of the retrospective nature of the study. All patient

Table I Patients' Enrollment

Eligibility Criteria for LD-CCRT
Age 20–75 years
At least one unidimensional lesion measurable according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)
Preserved liver function with a Child-Pugh score ≤ 7
Eastern Cooperative Oncology Group (ECOG) performance status score: 0 or I
White blood cell count $\geq 3000/\mu\text{L}$
Absolute neutrophil count $\geq 750/\mu\text{L}$
Platelet count $\geq 60 \times 10^3/\mu\text{L}$
Serum alanine aminotransferase level < 10 times the upper limit of the normal range
Serum creatinine level ≤ 2.0 mg/dL
Primary tumor confined to a technically feasible RT field, without diffuse intra-hepatic spread
Exclusion criteria enrollment
History of other anti-cancer treatment for HCC after the diagnosis of advanced-stage HCC
Presence of extrahepatic metastasis
Other uncontrolled comorbidities or malignant neoplasm
Prior organ transplant
Active peptic ulcer

identifiers were removed once the data from the patient medical record is collected.

Follow-Up

Treatment responses were assessed approximately 1 month after the completion of LD-CCRT and then every 8 ~ 12 weeks, using modified Response Evaluation Criteria in Solid Tumors (mRECIST).³² During follow up, patients who successfully achieved down-staging underwent curative surgical resection or orthotopic liver transplantation (OLT) under a multi-disciplinary approach.³³ Such approaches were considered, when complete response (CR) or partial response (PR) by mRECIST³² was achieved and serum alpha-fetoprotein (AFP) and protein induced by the absence of vitamin K or antagonist-II (PIVKA-II) decreased to <20 ng/mL and <40 mAU/mL, respectively, through the

treatment.^{15,34} Tumor resectability was determined in a multi-disciplinary approach through reviewing CT scans before and during the treatment.³⁵ All gross lesions should be resected with a clear margin based on radiological image. The resection type was determined based on functional reserve of the liver (FRL) and patient's performance status. For major liver resection defined as the resection of ≥ 3 anatomical segments, at least 40% of the total liver volume should be required as a future FRL. OLT was considered for patient with deteriorating liver function; those with pre-operative total bilirubin ≥ 2 mg/dL or platelet counts $<100,000/\mu\text{L}$, or with future remnant liver volume/total liver volume $<30\%$ were considered for OLT.

The primary endpoint was the OS, and the secondary endpoints were progression-free survival (PFS), ORR (defined as the rate of CR or PR), and the proportion of patients undergoing curative surgical resection or OLT after down-staging. Patients were evaluated for any treatment-related adverse event throughout the planned treatment period. Adverse events were noted as per the standards and terminology set by the Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events version 4.03.

Statistical Analysis

Data are expressed as mean \pm standard deviation, median (interquartile range [IQR]) or number (%). Differences among categorical variables were analyzed for statistical significance with chi-square test (or Fisher's exact test, if appropriate), respectively. Survival outcome was estimated using Kaplan–Meier analysis with a comparison by Log rank test. Hazard ratios (HR) were calculated using Cox regression analysis. OS was calculated as the time interval from the date of treatment initiation to the date of death, whereas PFS was calculated as the time interval from the date of treatment initiation to the date of progression, or any kind of death in the absence of confirmed progression. The Statistical analyses were performed using IBM® SPSS® Statistics Version 25.0 (IBM Corporation in Armonk, NY, US). All statistical tests with p-value of <0.05 were considered as significant.

Results

Patient Characteristics

In total, 152 patients with major PV invasion who underwent LD-CCRT were analyzed ([Supplementary Figure 1](#)).

Table 2 Characteristics of the Study Patients (n=152)

Variables	
Age (years)	56 (50–63)
Male	137 (90.1%)
Etiology of HCC	
HBV/HCV/Alcoholic/Others	129(84.9%)/4(2.6%)/3(2.0%)/16(10.5%)
Cirrhosis	127 (83.6%)
Child-Pugh class A/B	128(84.2%)/24(15.8%)
ALBI grade 1/2/3	34 (22.4%)/110 (72.3%)/8(5.3%)
ALBI score	-2.21 (-2.54 ~ -1.89)
Performance status, ECOG 0/1	82(53.9%)/70(46.1%)
Tumor size (cm)*	8.8 (6–8.8)
Number of tumors	
1/2/3/4/≥5	66(43.4%)/29(19.1%)/9(5.9%)/2(1.3%)/46(30.3%)
Depth of portal vein invasion	
Vp3/Vp4	95(62.5%)/57(37.5%)
Infiltrative tumor morphology	82 (53.9%)
Tumor invasion to the right atrium or IVC	7 (4.6%)
Location of tumor	
One lobe/Bi-lobes	109(71.7%)/43(28.3%)
AFP (ng/ml)	1656 (38–21591)
PIVKA-II (mAU/ml)	2000 (266–2167)
White blood cells ($\times 10^3/\mu\text{l}$)	5.63 (4.53–7.16)
Hemoglobin (g/dL)	12.9 (11.6–13.9)
Platelet count ($\times 10^3/\mu\text{l}$)	153.5 (111–209)
ALT (IU/L)	37 (23–56)
Albumin (g/dL)	3.5(3.2–3.9)
Total bilirubin (mg/dL)	0.8 (0.6–1.1)
Prothrombin time-INR	1.07 (1.0–1.15)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; IVC, inferior vena cava; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; ALT, alanine aminotransferase; INR, international normalized ratio.

Baseline characteristics are summarized in [Table 2](#). The median age was 56 years (IQR 50–63 years), and the patients were predominantly male (90.1%). Chronic hepatitis B virus (HBV) infection was the most common etiology (84.9%), and 127 (83.6%) patients had cirrhosis at enrollment. The majority of patients (128 [84.2%]) belonged to Child-Pugh A, but 15.8% had Child-Pugh B.

The median size of the largest HCC was 8.8 cm (IQR 6–8.8 cm), and 46 patients (30.3%) had ≥ 5 tumors. There were 57 (37.5%) patients with tumor invasion into Vp4 and 95 (62.5%) with tumor invasion into Vp3. Eighty-two (53.9%) patients had infiltrative tumor morphology.^{36–38} Only 7 (4.6%) patients had direct tumor invasion into the

inferior vena cava (IVC) and/or right atrium. The median AFP and PIVKA-II levels were 1655.5 (IQR 38–21,591) ng/mL and 2000 (IQR 266–2167) mAU/mL, respectively.

Treatment Delivery and Responses

Four weeks after LD-CCRT, the ORR was 48.0%. Subsequently, patients underwent a median of 4 (IQR 2–6) cycles of HAIC. During the planned treatment courses, the ORR as their best responses increased to 55.3% ([Table 3](#)). Among a subgroup (n=56) undergoing TACE before the start of LD-CCRT, the ORRs 4 weeks after LD-CCRT and during the planned treatment courses were 55.4% and 62.5%, respectively. Radiological responses of malignant portal vein thrombosis as a non-measurable lesion by mRECIST³² 4 weeks after LD-CCRT were as follows; CR (n=2, 1.3%), PR (n=52, 34.2%), stable disease (n=85, 55.9%), and progressive disease (n=13, 8.6%). During the planned treatment courses, they were 2.0% (n=3), 37.5% (n=57), 52.0% (n=79), and 8.6% (n=13), respectively.

Four weeks after LD-CCRT, 46.1% and 52.6% had favorable biological response (defined as a $\geq 50\%$ decrease in tumor marker from the baseline) by AFP and PIVKA-II, respectively. During the planned treatment courses, they were 65.1% and 65.8%, respectively. In detail, from the baseline (median 1656 ng/mL, IQR [38–21,591]). The AFP level significantly decreased to 553 ng/mL (IQR 22 ~ 5282) 4 weeks after LD-CCRT and 50 (8 ~ 1793) during the planned treatment courses (both $p < 0.001$ by Wilcoxon signed ranks test). Likewise, from the baseline (median 2000 mAU/mL, [IQR 266–2167]), the PIVKA-II level significantly decreased to 257 mAU/mL (IQR 41 ~ 2000) 4 weeks after LD-CCRT and 76 mAU/mL (29 ~ 1019) during the planned treatment courses (both $p < 0.001$ by Wilcoxon signed ranks test). Detailed changes in tumor size and their correlations with tumor markers were described in waterfall plots ([Supplementary Figure 2A](#), [2B](#), and [2C](#)) and the association between radiological and biological responses were summarized in [Supplementary Table 2](#) and [Supplementary Figure 3](#)).

Notably, during the planned treatment courses, 16 patients (10.5%) underwent curative resection or OLT after successful down-staging. The median time from the initiation of LD-CCRT to the last follow-up among these 16 patients was 34.8 (IQR 21.1–60.9) months. Seven cases of death were observed between 7.2 and 61.6 months (median 22.0 months, IQR 15.0–59.0 months). Overall, there was no post-operative complication of $>$ grade III by the Clavien-Dindo classification,³⁹ except one post-OLT mortality. There was one intra-operative complication

Table 3 Treatment Response

Radiological Response 4 Weeks After LD-CCRT	
CR	2 (1.3%)
PR	71 (46.7%)
SD	52 (34.2%)
PD	27 (17.8%)
Radiological Response During the Planned Treatment Courses	
CR	3 (2.0%)
PR	81 (53.3%)
SD	41 (27%)
PD	27 (17.8%)
Biological Response 4 Weeks After LD-CCRT	
AFP response	70 (46.1%)
PIVKA-II response	80 (52.6%)
Biological Response During the Planned Treatment Courses	
AFP response	99 (65.1%)
PIVKA-II response	100 (65.8%)
Changes in AFP Level	
4 weeks after LD-CCRT	553 (22 ~ 5282)*
During the planned treatment courses	50 (8 ~ 1793)*
Changes in PIVKA-II Level	
4 weeks after LD-CCRT	257 (41 ~ 2000)*
During the planned treatment courses	76 (29 ~ 1019)*

Note: *All $p < 0.001$ from each baseline level by Wilcoxon signed ranks test.

Abbreviations: LD-CCRT, liver-directed concurrent chemoradiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

of weak pulsation after hepatic artery anastomosis during living donor OLT, for which the anastomosis of right hepatic artery of the graft to the common hepatic artery of the recipient was switched to transposition anastomosis with the left gastric artery of the recipient; this patient had no significant post-OLT complication. Two patients developed biliary strictures most likely 6 months after OLT, both of which were successfully treated with the endoscopic and/or percutaneous approaches. Among patients undergoing surgical resection, there was no significant post-operative complication; 5 patients developed the small amount of pleural effusion, all of which resolved spontaneously without any intervention.

Survival Outcomes and Prognosis Factors

Overall, a total of 107 patients died and the median OS was 13.5 months (95% confidence interval [CI] 11.003–16.077) (Figure 1). The median PFS was 6.9 months

(95% CI 6.326–7.474) (Figure 2). Treatment modalities after progression of disease included continuing intra-arterial chemotherapy (6.1%), LRTs such as TACE or Transarterial chemoinfusion (TACI) (16.0%), and systemic chemotherapy including systemic 5-fluorouracil plus cisplatin chemotherapy (9.9%) and sorafenib (23.7%). Palliative radiotherapy was delivered to patients with bone metastases (1.5%). The majority of patients with disease progression (32.2%) received supportive care.

Table 4 shows that only significant prognostic factor for OS was ALBI score (HR 1.523, 95% CI 1.032–2.246; $p = 0.034$).

Subgroup Analysis for Patients with Elevated AFP or PIVKA-II Levels at Baseline

Among 126 (82.9%) patients with baseline AFP > 20 ng/mL, 54.0% showed the favorable biological response 4 weeks after LD-CCRT. Such AFP responders were more likely to have the higher ORR 4 weeks after LD-

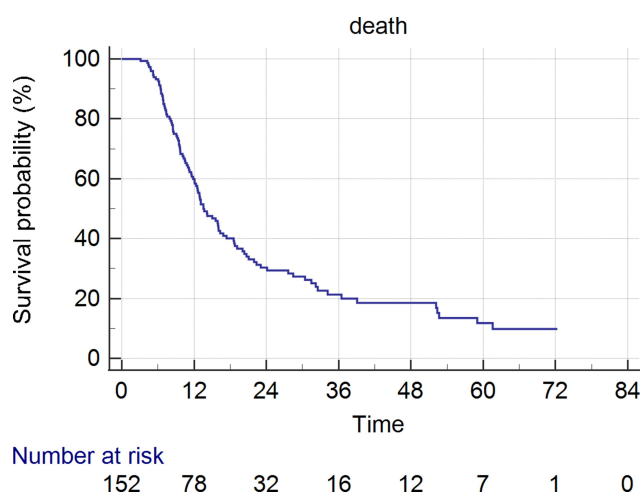


Figure 1 Kaplan-Meier analysis of OS.

CCRT (57.4% vs 34.5%, respectively; $p=0.010$ by chi-square test), and the longer OS (22.4 vs 10.8 months; $p<0.001$ by Log rank test) and PFS (9.0 vs 5.1 months; $p=0.003$ by Log rank test) than non-responders.

Likewise, among 137 (90.1%) patients with baseline PIVKA-II >40 mAU/mL, 58.4% showed the favorable biological response 4 weeks after LD-CCRT. Such PIVKA-II responders were more likely to have the higher ORR 4 weeks after LD-CCRT (65.0 vs 21.1%, respectively; $p<0.001$ by chi-square test) and the longer OS (20.3 vs 11.5 months, respectively; $p=0.001$ by Log rank test) and PFS (7.7 vs 5.7 months, respectively; $p=0.016$ by Log rank test) than non-responders.

Table 4 Prognostic Factors for Overall Survival

Variables	HR (95% CI)	p-value
Age	0.999 (0.980 - 1.018)	0.935
Male	1.073 (0.574 - 2.006)	0.826
Cirrhosis	1.461 (0.863 - 2.475)	0.158
Child-Pugh class B	1.528 (0.947 - 2.466)	0.082
ALBI score	1.523 (1.032 - 2.246)	0.034
Tumor size ≥ 10 cm	1.272 (0.864 - 1.874)	0.223
Number of tumors ≥ 4	1.194 (0.799 - 1.784)	0.386
Depth of portal vein invasion (Vp4)	1.242 (0.842 - 1.833)	0.275
Infiltrative tumor morphology	1.161 (0.789 - 1.707)	0.448
AFP ≥ 400 ng/ml	1.132 (0.770 - 1.666)	0.528
PIVKA-II ≥ 1000 mAU/ml	1.058 (0.724 - 1.548)	0.770
Platelet count, $\times 10^3/\mu\text{l}$	1.000 (0.998 - 1.002)	0.938

Abbreviations: HR, hazard ratio; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II; INR, international normalized ratio.

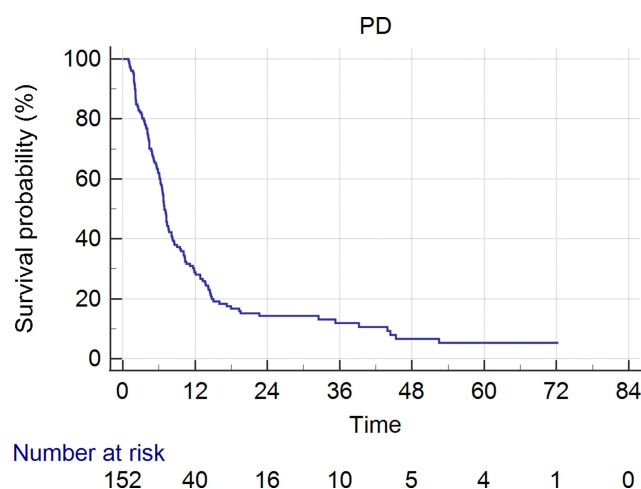


Figure 2 Kaplan-Meier analysis of PFS.

Subgroup Analysis for Patients with HBV-Related HCC

Among 129 patients with HBV-related HCC, the ORRs 4 weeks after LD-CCRT and during the planned treatment courses were 49.6% and 55.8%, respectively. Likewise, 43.4% and 53.5% had favorable biological response by AFP and PIVKA-II, respectively, 4 weeks after LD-CCRT. They were 63.6% and 65.9%, respectively, during the planned treatment courses. The median OS and PFS were 14.1 (95% CI 11.358–16.902) and 7.2 (95% CI 6.553–7.847) months, respectively.

Treatment-Related Adverse Events

Treatment-related adverse events during the planned treatment schedules are summarized in Table 5. Three key events associated with RT for liver, ie ascites, hepatic encephalopathy, and melena were evaluated using the SOMA-LENT grading classification.⁴⁰ Overall, deterioration in liver function (defined as a shift in Child-Pugh score by 2 or more points from the baseline) after LD-CCRT was observed in 46 patients (30.3%), while 38 patients (25.0%) demonstrated newly developed ascites. Among 129 patients with chronic HBV infection, three patients (2.3%) developed virologic breakthrough, all of whom were treated with appropriate antiviral therapy.⁴¹ After LD-CCRT, 32 patients (21.1%) developed radiation gastritis, while 16 patients (10.5%) experienced upper gastrointestinal bleeding, which was successfully managed with endoscopic hemostasis and medical management. Among patients receiving maintenance HAIC after LD-CCRT, HAIC was discontinued in one patient due to HCC

Table 5 Treatment-Related Adverse Events

	Total	Early Period of < 6 Months					Late Period of ≥ 6 Months			
		Grade 1	Grade 2	Grade 3	Grade 4		Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase elevation	77 (50.7%)	33 (21.7%)	11 (7.2%)	4 (2.6%)	-		29 (19.1%)	7 (4.6%)	1 (0.7%)	-
Hyperbilirubinemia	57 (37.5%)	25 (16.4%)	8 (5.3%)	2 (1.3%)	-		23 (15.1%)	7 (4.6%)	1 (0.7%)	-
Hypoalbuminemia	120 (78.9%)	27 (17.8%)	61 (40.1%)	-	-		21 (13.8%)	37 (24.3%)	2 (1.3%)	-
Anemia	125 (82.2%)	28 (18.4%)	43 (28.3%)	11 (7.2%)	-		34 (22.4%)	31 (20.4%)	8 (5.3%)	-
Neutropenia	119 (78.3%)	28 (18.4%)	43 (28.3%)	34 (22.4%)	-		13 (8.6%)	30 (19.7%)	10 (6.6%)	-
Thrombocytopenia	141 (92.8%)	34 (22.4%)	61 (40.1%)	28 (18.4%)	-		25 (16.4%)	40 (26.3%)	19 (12.5%)	-
AKI	17 (11.2%)	6 (3.9%)	1 (0.7%)	-	-		8 (5.3%)	1 (0.7%)	1 (0.7%)	-
Gastritis	31 (20.4%)	11 (7.2%)	8 (5.3%)	11 (7.2%)	-		-	5 (3.3%)	1 (0.7%)	-
Melena*	16 (10.5%)	-	2 (1.3%)	6 (3.9%)	5 (3.3%)		1 (0.7%)	1 (0.7%)	4 (2.6%)	1 (0.7%)
Hepatic encephalopathy*	10 (6.6%)	-	-	-	1 (0.7%)		-	2 (1.3%)	3 (2.0%)	4 (2.6%)
Ascites*	38 (25.0%)	-	21 (13.8%)	11 (7.2%)	-		-	11 (7.2%)	12 (7.9%)	1 (0.7%)

Note: *By LENT-SOMA grading.

rupture, in one patient due to hepatic encephalopathy, and in two patients due to sepsis.

Discussion

HCC with major portal vein invasion has poor prognosis and the median OS among such patients is expected to range from 7 to 8.5 months according to the real-life experience in the Republic of Korea.^{2,8} An effective systemic therapy is an important option for the treatment of HCC in the subset of patients with extrahepatic metastasis. However, considering that HCC is a rapidly growing locally aggressive disease frequently leading to the patients' death before extrahepatic metastasis have developed, there has been various attempts to locally control the disease with LRTs, so far. For instance, the previous study showed that locally advanced HCC patients treated with LD-CCRT showed the higher ORRs at post-treatment 1 (46.8% VS 16.1%, respectively, $P<0.001$) and 3 (39.3% vs 21.4%, $P=0.04$) months than those treated with selective internal radiation therapy (SIRT), however, long-term response rates and survival rates were comparable.⁴² Two recent comparative trials comparing SIRT vs sorafenib in locally advanced HCC patients, ie SARAH and SIRveNIB, showed comparable median OS between the two treatment groups, but the response rate was higher in the SIRT as compared to sorafenib group, suggesting the potential of SIRT as more likelihood to control the tumor within the liver.^{18,43}

In this study, we present locally advanced-stage HCC patients with major PV invasion receiving LD-CCRT with HAIC maintenance. Out of the total study population, 143 patients (94.0%) had poor oncological prognostic factors, including massive tumor (≥ 10 cm), infiltrative tumor morphology, tumor invasion into the main portal trunk (Vp4), tumor invasion into the IVC and/or right atrium, AFP level ≥ 400 ng/mL, or PIVKA-II level ≥ 1000 mAU/mL. In this population, LD-CCRT followed by maintenance HAIC demonstrated encouraging results, not only producing an objective response in 55.3% of subjects but also improving the median OS to 13.5 months. The median OS of 13.5 months in our study population with Vp3 or Vp4 invasion is notable given that patients with major PV invasion at baseline were excluded in that phase III trial. Even though our study is only a one-arm study with a retrospective design, our findings could at least reappraise the necessity of future prospective randomized clinical trials comparing the efficacy between active LRT and systemic chemotherapy in patients with advanced HCC with major PV invasion. Despite major

portal vein invasion, LD-CCRT showed potential to convert unresectable HCC to resectable HCC. During the planned treatment courses, 10.5% of patients achieved successful down-staging from LD-CCRT and underwent curative resection or transplantation. The optimal treatment strategy for successful down-staging remains to be determined. Despite several positive results, repeated TACE alone is considered to be contraindicated in this population due to the potential of hepatic insufficiency resulting from ischemic insult.^{44–47}

HAIC may be an eligible LRT option; however, the evidence for its efficacy remains weak.²⁵ EBRT is also complicated by issues of systemic or local failure outside the RT field, notwithstanding the excellent intra-RT field disease control rate. Our findings indicate that EBRT-based LRT may be a useful strategy for down-staging of advanced-stage HCC.⁴⁸

Our treatment protocol for LD-CCRT has several advantages for the curative treatment for advanced-stage HCC. Most importantly, the FRL increased substantially after LD-CCRT,¹⁵ which is induced by a marked atrophy of the irradiated region and a compensatory enlargement of the non-irradiated region.⁴⁹ Another advantage is that, optimal candidates for curative treatments could be selected through better assessment of the biological behaviors of advanced tumors during the period of so-called “neo-adjuvant” treatment. Finally, 5-fluorouracil could be useful as a radio-sensitizer for treating HCC as well as its anti-cancer effect;^{50–55} therefore, a synergistic effect against HCC might be expected. Although not all patients with advanced-stage HCC with major PV invasion would be eligible for EBRT-based active LRTs in real-world practice, the feasibility of EBRT-based active LRTs should be carefully assessed through a multi-disciplinary approach.

This study has several limitations. In the first place, it was a single-arm study with a retrospective design from the single institution and the higher proportion of male patients might be another problem, both of which can lead to selection bias. Therefore, additional multi-center, randomized controlled trials are required to prove the utility of LD-CCRT. However, our findings provided a rationale for further prospective clinical trials to assess the efficacy of alternative LRTs other than molecular-targeted agents alone as a recommended first-line modality in treating advanced-stage HCC with major PV invasion. Similarly, given that novel systemic agents such as atezolizumab plus bevacizumab will presently become available in the clinical setting,⁵⁶ the potential benefits of induction LD-CCRT as a neo-adjuvant treatment should be studied further. Another

limitation is that our results might not be generalizable to all HCC patients, since chronic HBV infection was the most predominant etiology among our study population.^{41,57,58}

Furthermore, there was limited availability of second-line systemic agents in South Korea during the study period. Additional long-term follow-up to evaluate the entire clinical course of advanced-stage HCC is advisable.

Conclusion

In conclusion, LD-CCRT followed by maintenance HAIC demonstrated not only favorable outcomes through initial tumor size reduction but also acceptable tolerability in patients with advanced-stage HCC with major PV invasion. To confirm these results, further prospective clinical trials are required.

Disclosure

The authors declare no conflicts of interest.

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