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Original Article

Combined transarterial chemoembolization and radiotherapy as a first-line treatment for hepatocellular carcinoma with macroscopic vascular invasion: Necessity to subclassify Barcelona Clinic Liver Cancer stage C

Yeon Joo Kim [a,1], Jinhong Jung [a,*], Ji Hyeon Joo [a], So Yeon Kim [b], Jin Hyoung Kim [b], Young-Suk Lim [c], Han Chu Lee [c], Jong Hoon Kim [a], Sang Min Yoon [a,*]

[a] Department of Radiation Oncology; [b] Department of Radiology; and [c] Department of Gastroenterology, Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background and purpose: Systemic therapy such as sorafenib is the standard for Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC); however, the survival benefits are modest especially for HCC with macroscopic vascular invasion (MVI). Transarterial chemoembolization (TACE) plus external beam radiotherapy (RT) is an alternative treatment to sorafenib, with favorable clinical results. We evaluated the outcomes of respiratory-gated RT and TACE in treatment-naïve BCLC stage C HCC patients with MVI and proposed a subclassification model.

Methods: In this study, 639 patients received TACE plus RT for HCC with MVI as a first-line treatment between January 2010 and December 2015.

Results: Main/bilateral portal vein and/or inferior vena cava tumor thrombus was observed in 353 (55.2%) patients. The median radiation dose was 39 Gy (range 24–50) with a 2.5-Gy (2–5) median fraction size. The median overall survival was 10.7 months, with 1- and 2-year survival rates of 46.5% and 23.9%, respectively. In the multivariate analysis, Child–Pugh classification B, tumor size >10 cm, infiltrative/diffuse type, presence of extrahepatic metastasis, alpha-fetoprotein >150,000 ng/mL, and radiation dose ≤40 Gy were significant predictors for poor overall survival. Subclassification of patients into very low, low, intermediate, and high-risk groups showed median survivals of 84.8, 14.7, 10.3, and 5.7 months, respectively ($p < 0.001$).

Conclusion: TACE plus RT is an effective and safe treatment for HCC with MVI and could be considered a first-line treatment option. The subclassification scheme accurately predicted the prognosis of these patients and may be useful for tailored treatment.

 Radiotherapy and Oncology 141 (2019) 95–100

Liver cancer is the second most common cause of cancer death worldwide, with hepatocellular carcinoma (HCC) the most prevalent primary liver cancer [1–3]. More than half of HCC patients are diagnosed at an advanced stage, often with macroscopic vascular invasion (MVI) which has limited treatment options and poor prognosis [4–6]. According to the updated Barcelona Clinic Liver Cancer (BCLC) staging, systemic therapy including sorafenib and lenvatinib is the only recommended first-line treatment option for BCLC stage C patients [7]. However, the survival benefits of systemic agents are modest, with low tumor response rate in previous randomized trials, especially in patients with MVI [8–10].

The combination of transarterial chemoembolization (TACE) and external beam radiotherapy (RT) has emerged in several guidelines as a treatment option, alternative to sorafenib for HCC patients with MVI [11,12]. RT focused on MVI can reduce the extent of vascular invasion, lead to the restoration of blood flow to the normal liver, decrease intrahepatic or distant metastasis, and consequently potentiate the effect of additional TACE [13–15]. Previous retrospective studies reported response rates of

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; MVI, macroscopic vascular invasion; TACE, transarterial chemoembolization; RT, radiotherapy; GTV, gross tumor volume; AFP, alpha-fetoprotein; IVC, inferior vena cava.

* Corresponding authors.
E-mail addresses: jung.jinhong@amc.seoul.kr (J. Jung), drsmyoon@amc.seoul.kr (S.M. Yoon).
[1] Current address: Department of Radiation Oncology, Kangwon National University Hospital, Chuncheon, Republic of Korea.

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40–58% and median survivals of 7–10.6 months following TACE plus RT for HCC with MVI [13,16]. Recently, the results of a randomized trial also confirmed the benefit of TACE plus RT for HCC with MVI, demonstrating longer progression-free survival, time to progression, and overall survival (OS) compared to those of sorafenib [17]. However, the survival outcomes and prognoses after TACE plus RT for treatment-naïve HCC patients with MVI in a large patient cohort are still needed.

BCLC stage C includes heterogenous patient populations according to the tumor burden, including a single, small HCC with vascular invasion into small branches of the portal vein, multiple, large HCCs with main portal vein invasion or multiple vascular invasions including the hepatic vein and inferior vena cava (IVC), an oligometastasis in the visceral organs, and extensive extrahepatic metastases. Accordingly, the prognosis of BCLC stage C patients widely varies, which hinders clinicians from choosing proper treatment options. Therefore, there is a strong need for subclassification model for BCLC stage C, which would also be helpful for interpreting clinical trials comparing treatment modalities. For this reason, a large, homogenous patient population is essential for building a clinically valid subclassification model. In the present study, we retrospectively evaluated the outcomes of combined TACE plus RT in treatment-naïve BCLC stage C HCC patients with MVI. We also proposed a subclassification model for appropriate assessment of prognosis and tailored treatment.

Patients and methods

Patients

Patients who were treated with TACE and respiratory-gated three-dimensional conformal RT for HCC between January 2010 and December 2015 were retrospectively reviewed. The eligibility criteria for this study were as follows: (1) the presence of MVI; (2) no history of previous treatments for HCC such as surgery, radiofrequency ablation, TACE, sorafenib, or RT; (3) Child–Pugh classification A or B hepatic function; and (4) a European Cooperative Oncology Group performance status (ECOG PS) of 0–2. Patients with extrahepatic nodal or visceral metastases who received combined TACE and RT for MVI as a first-line treatment were included in this study. However, patients who received incomplete irradiation of less than 80% of the planned dose or had double primary cancer were excluded.

HCC was diagnosed on the basis of pathologic findings and/or according to the American Association for the Study of Liver Diseases criteria [18]. The presence of MVI was assessed by four-phase dynamic computed tomography (CT) with the following criteria: (1) an intraluminal filling defect adjacent to the HCC in portal and/or hepatic vein, and/or IVC, and (2) an enhancement of this filling defect on arterial phase and a washout on the portal/delayed phases [17]. The Institutional Review Board of Asan Medical Center approved this study and waived the requirement for informed consent because of the retrospective nature of the analysis.

Treatment

For TACE, 2 mg/kg cisplatin (Dong-A Pharmaceutical, Seosan, Korea) was infused using a catheter placed directly into the feeding artery. Embolization was performed using an emulsion of 5–10 mL of iodized oil (Lipiodol; Laboratoire Guerbet, Aulnay-sous-Bois, France) and cisplatin mixture and gelatin sponge cubes (Gelfoam; Upjohn, Kalamazoo, MI). Transarterial chemoinfusion without gelatin sponge particles was performed according to the severity of portal vein blood flow impairment. TACE or transarterial chemoinfusion was performed before or after RT within an interval of 4 weeks and was repeated every 6–8 weeks in considering the residual HCCs, response to treatment, and background hepatic function.

For RT, four-dimensional CT (GE LightSpeed RT 16; GE Healthcare, Waukesha, WI) images were acquired during free breathing. The four-dimensional CT images synchronized with respiratory data were sorted into 10 CT series based on the respiratory phase (0–90%). The target volumes were delineated at the end-exhale phase CT images. The gross tumor volume (GTV) included the MVI and a 2-cm margin into the contiguous HCC in most patients with huge, infiltrative HCC. In patients with small HCC, the GTV included entire HCC as well as the MVI. In selected cases of extensive portal vein invasion with Child–Pugh B liver function, the GTV consisted of the MVI itself without including the HCC. The internal target volume was delineated as the sum of the individual GTVs, as defined within the gated phases of respiration. The planning target volume was a 0.7-cm expansion of the internal target volume. Compact iodized oil and/or a diaphragm were used as surrogates for tumor localization.

The organs at risk included whole and normal livers, both kidneys, spinal cord, duodenum, stomach, esophagus, and large intestine. The dose per fraction to the planning target volume was 2–5 Gy using 6- or 15-MV X-rays at five fractions per week using a linear accelerator (Varian Medical Systems, Palo Alto, CA). The total dose was determined by the volume of the normal liver, liver function, and the maximum dose to the organs at risk according to the previous guidelines [13]. Three-dimensional conformal RT technique was used by using a RT planning system (Eclipse version 10.0; Varian Medical Systems) and the actual beam delivery was performed with a respiratory-gated beam delivery technique.

Evaluation and statistical analysis

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.03. Worsening of the Child–Pugh score was also calculated.

The OS was estimated from the date of diagnosis to the date of death or last follow-up. Survival was calculated using the Kaplan–Meier method. The univariate and multivariate analyses were performed using Cox proportional hazards models. Backward elimination Cox regression was utilized for multivariate analysis. Categorical variables were transformed into dummy variables. Variables with p-values <0.2 in the univariate analysis were included in the multivariate analysis. The level of statistical significance was set at $p < 0.05$. The discriminative performance of the proposed subclassification model for overall survival was qualified by analyzing the C-index with 95% confidence intervals. All statistical analyses were performed using R version 3.4.1 (web-r.org).

Results

A total of 1332 patients received combined TACE plus RT between January 2010 and December 2015 for HCC with MVI. Among them, 646 patients diagnosed with progressive HCC showing MVI during treatment for HCC were excluded due to previous treatments including surgical resection, radiofrequency ablation, percutaneous ethanol injection, TACE over four-week-interval before RT, and any RT and/or sorafenib. Among the remaining 686 patients, 47 were additionally excluded due to incomplete RT ($n = 30$), Child–Pugh class C liver function ($n = 8$), double primary malignancies ($n = 6$), MVI alone without definite primary HCC ($n = 2$), or a different fractionation regimen such as stereotactic body RT ($n = 1$) (Fig. 1). A total of 639 patients satisfied the eligibility criteria and were included in the analysis (Table 1). The median age was 58 years (range 34–87 years) and most were male

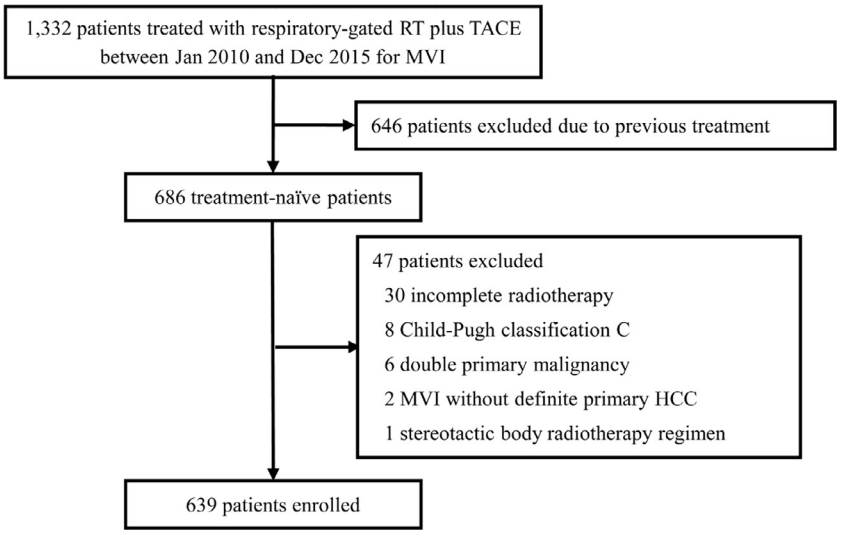

Fig. 1. Study profile. *Abbreviations:* RT, radiotherapy; TACE, transarterial chemoembolization; MVI, macroscopic vascular invasion; HCC; hepatocellular carcinoma.

Table 1
Baseline patient characteristics.

Characteristics		*N* = 639 (%)
Age (median, range) (years)		58 (34–87)
Sex	Male	563 (88.1)
	Female	76 (11.9)
ECOG performance status	0	163 (25.5)
	1–2	476 (74.5)
Child–Pugh classification	A	393 (61.5)
	B	246 (38.5)
Etiology	Hepatitis B	553 (86.5)
	Non-hepatitis B	86 (13.5)
Maximum tumor diameter	≤10 cm	336 (52.5)
	>10 cm	303 (47.5)
Number of tumor	Single	234 (36.6)
	Multiple	405 (63.4)
Extent of tumor	Unilobar	302 (47.3)
	Bilobar	337 (52.7)
Type of tumor	Nodular	177 (27.7)
	Infiltrative/diffuse	462 (72.3)
Extent of vascular invasion	Unilateral PV	286 (44.8)
	Main/bilateral PV and/or IVC	353 (55.2)
Bile duct invasion	No	579 (90.6)
	Yes	60 (9.4)
Extrahepatic metastasis	No	470 (73.6)
	Yes	169 (26.4)
Alpha-fetoprotein	≤150,000 ng/mL	396 (62)
	>150,000 ng/mL	51 (8)
	Unknown	192 (30)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PV, Portal vein; IVC, inferior vena cava.

(88.1%). Chronic hepatitis B virus infection was the major cause of liver disease (86.5%) and 61.5% of patients had Child–Pugh class A hepatic function. The median maximal diameter of the HCC was 9.9 cm (range 1.1–23.2 cm). Most patients had multiple lesions (63.4%) and infiltrative/diffuse type of HCC (72.3%). Unilateral portal vein invasion was observed in 44.8% of the patients and main/-bilateral portal vein and/or IVC invasion in 55.2% patients. Extrahepatic metastasis was diagnosed in 169 (26.4%) patients, most commonly in the regional lymph nodes (67 patients, 39.6%) followed by the lung (64 patients, 37.9%). Most patients (97.7%) were treated with TACE followed by RT, except for 15 patients who received TACE after RT within 4 weeks. The median radiation dose was 39 Gy (range 24–50 Gy) and the median fraction size was 2.5 Gy (range 2–5 Gy).

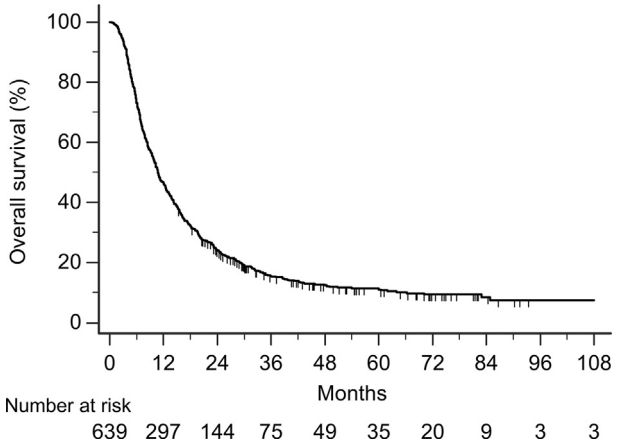

Fig. 2. Overall survival of all patients.

The median follow-up period for all patients was 10.7 months (range 0.5–131.7 months). The one- and two-year OS rates were 46.5% and 23.9%, respectively, with a median OS of 10.7 months (Fig. 2). In univariate analysis, ECOG PS 1–2, Child–Pugh class B, tumor size >10 cm, multiple tumors, bilobar involvement, infiltrative/diffuse type, main/bilateral portal vein and/or IVC invasion, presence of extrahepatic metastasis, alpha-fetoprotein (AFP) >150,000 ng/mL, and radiation dose ≤40 Gy were unfavorable prognostic factors for OS (Table 2). In multivariate analysis, Child–Pugh class B, tumor size >10 cm, infiltrative/diffuse type, presence of extrahepatic metastasis, AFP >150,000 ng/mL, and radiation dose ≤40 Gy were significant predictors for poor OS.

Based on these prognostic factors and the investigators' clinical experiences, we suggested a subclassification model for HCC with MVI (Table 3). We excluded treatment-related factors in order to evaluate the prognosis using baseline patient- and tumor-related factors. AFP was also excluded since 30% of the patients in this study had no available AFP record and a single cut-off value from a wide range of values would not be applicable to all patients. The patient cohorts were stratified according to baseline liver function (Child–Pugh classification), extrahepatic disease, and intrahepatic tumor burdens (extent of vascular invasion, tumor size, tumor type). Although main/bilateral portal vein or IVC invasion

Table 2
Univariate and multivariate analyses for overall survival.

Characteristics		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	≤60 years (vs. >60 years)	1.03 (0.86–1.22)	0.774		
ECOG performance status	1–2 (vs. 0)	1.48 (1.22–1.80)	<0.001		
Child–Pugh classification	B (vs. A)	2.05 (1.72–2.44)	<0.001	1.60 (1.30–1.98)	<0.001
Etiology	Non-hepatitis B (vs. hepatitis B)	0.96 (0.75–1.23)	0.727		
Maximum tumor diameter	>10 cm (vs. ≤10 cm)	1.88 (1.59–2.23)	<0.001	1.43 (1.15–1.77)	0.001
Number of tumor	Multiple (vs. single)	1.55 (1.30–1.85)	<0.001		
Extent of tumor	Bilobar (vs. unilobar)	1.43 (1.21–1.69)	<0.001		
Type of tumor	Infiltrative/diffuse (vs. nodular)	1.32 (1.09–1.60)	0.004	1.31 (1.05–1.65)	0.018
Extent of vascular invasion	Main/bilateral PV ± IVC (vs. unilateral)	1.44 (1.21–1.70)	<0.001		
Bile duct invasion	Yes (vs. no)	0.93 (0.70–1.24)	0.632		
Extrahepatic metastasis	Yes (vs. no)	1.70 (1.41–2.05)	<0.001	1.42 (1.13–1.77)	0.002
Alpha-fetoprotein[†]	>150,000 ng/mL (vs. ≤150,000 ng/mL)	2.02 (1.49–2.73)	<0.001	1.77 (1.29–2.42)	<0.001
Radiation dose	≤40 Gy (vs. >40 Gy)	1.16 (0.96–1.72)	0.001	1.32 (1.04–1.68)	0.022

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PV, portal vein; IVC, inferior vena cava; HR, hazard ratio; CI, confidence interval.
[†] Missing data in 192 patients.

Table 3
Subclassification model of patients with hepatocellular carcinoma showing macroscopic vascular invasion.

Child-Pugh classification	A						B					
Extrahepatic metastasis	No			Yes			No			Yes		
Number of the following risk factors: - Main/bilateral PV or IVC invasion - Size > 10 cm - Infiltrative/diffuse type	0	1-2	3	0	1-2	3	0	1-2	3	0	1-2	3
Number of patients	36	206	55	6	76	14	10	109	54	3	47	23
Median survival (months)	84.8	14.8	11	15.1	9.5	6.7	9.5	10.7	5.3	7.1	5.9	4.4
Risk classification	Very low	Low	Intermediate	Low	Intermediate	High	Intermediate		High			

Abbreviations: PV, portal vein; IVC, inferior vena cava.

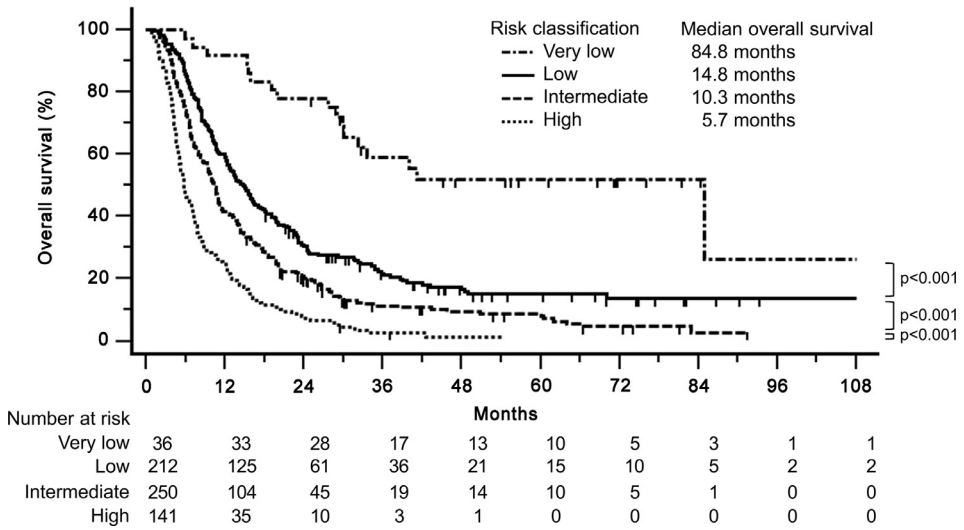

Fig. 3. Overall survival stratified according to the proposed subclassification model.

was not a significant factor in multivariate analysis, we included this factor in the criteria because the extent of MVI is an important prognostic factors influencing patient survival. According to the proposed stratification system, patients were classified into four risk groups: very low ($n = 36$), low ($n = 212$), intermediate ($n = 250$) and high ($n = 141$). The median survival times were 84.8, 14.7, 10.3 and 5.7 months, respectively ($p < 0.001$) (Fig. 3). The one-year OS rates were 91.7%, 59.0%, 41.2%, and 24.1%, respectively. The C-index for the discriminative performance of the subclassification model was 0.63 (95% confidence interval, 0.61–0.66).

Acute grade ≥3 constitutional symptoms including anorexia, nausea, and dyspepsia, occurred in one (0.2%) patient, respectively. Grade ≥3 liver enzyme and bilirubin increases were observed in 44 (8.1%) and 9 (1.5%) patients, respectively, within three months after RT. Ninety-seven (17.9%) patients experienced 2 or more Child–Pugh score worsening and hepatic failure without progression of intrahepatic HCC was observed in five (0.8%) patients. Grade ≥3 gastroduodenal bleeding occurred in 10 (1.6%) patients.

Discussion

In this analysis of patients with HCC showing MVI, combined TACE plus RT showed a median survival of 10.7 months with a low incidence of significant toxicities. Considering all patients were diagnosed with MVI, which showed a poorer OS among BCLC stage C patients, this survival outcome is acceptable for patients with advanced HCC. Moreover, there were also a variety of patient- and tumor-related prognosticators even in patients with MVI. Four risk groups were suggested according to the subclassification model described in the present study. This subclassification categorized the patients' prognosis after a first-line treatment of the combined TACE plus RT (median survival times for the very low-risk group: 84.8 months, low-risk group: 14.7 months, intermediate-risk group: 10.3 months, and high-risk group: 5.7 months; $p < 0.001$).

BCLC stage C HCC includes heterogenous patients with different extents of intrahepatic tumors or vascular invasion, extrahepatic spread, and baseline hepatic function or performance status. These factors are associated with differences in treatment responses and OS outcomes. Because the majority of the HCC patients present with BCLC stage C at the time of diagnosis, it is necessary to subclassify them to more accurately determine their prognosis after treatment and to determine the most suitable therapeutic strategies. Subclassification not only predicts the precise prognosis and offers a more effective treatment modality but may also be essential for the comparison of the clinical outcomes of therapeutic options. Therefore, several studies have suggested the subclassification of BCLC stage C HCC. Lee et al. reported the prognosis of patients with BCLC stage B or C HCC in a Korean multi-center registry database and subdivided the patients by identifying prognostic predictors. They subclassified BCLC C patients into groups with a combination of significant portal vein invasion and extrahepatic spread [19]. However, information regarding the treatment modalities and the prognostic value of MVI or extrahepatic spread within each treatment modality could not be suggested because this study was based on the registry cohorts. Jun et al. also conducted a subclassification of BCLC stage C HCC patients based on the number of prognosticators among tumor size, distant metastasis, type of HCC (infiltrative/diffuse type), and bile duct invasion [20]. Unfortunately the patients received various first-line treatment modalities, including surgical resection, TACE, hepatic arterial infusion chemotherapy, sorafenib, RT, and best supportive care. A recent retrospective study suggested a prognostic scoring system from the clinical data of patients who received sorafenib for BCLC stage C HCC [21]. In ECOG PS 0 group, the median OS of the low, intermediate and high-risk groups were 16.7, 9.6 and 4.5 months, respectively. In the ECOG PS 1 cohort, the median OS were 11.3, 6.3 and 3.2 months, respectively. The survival outcomes of each risk groups were comparable to those of the present study.

Our data showed that the prognostic factors for poor OS as follows were Child–Pugh class B, tumor size >10 cm, infiltrative/diffuse type, presence of extrahepatic metastasis, AFP >150,000 ng/mL, and radiation dose ≤40 Gy. These results are consistent with those of previous studies [13,22,23]. We suggested a subclassification model with three main points: tumor burden, liver function, and presence of extrahepatic disease. These factors were also used as main factors for subclassification of BCLC stage B patients by Bolondi et al. and BCLC stage C patients by Lee et al. [19,24]. Our subclassification system had excellent discriminatory power to subclassify patients with MVI within BCLC stage C and also has the advantage of a table form which could be simply its administration in the clinic, unlike complicated scoring systems which require calculation. Moreover, the present study included exclusively 639 homogenous patients who had HCC with MVI and received TACE plus RT as a first-line treatment. Therefore, we were able to exclude a bias regard to treatment modality.

MVI is a well-known poor prognostic factor for OS among patients with BCLC stage C HCC. According to the BCLC staging system, systemic treatment is the only recommended treatment option for this stage [7]. However, the median survival prolongation of patients with MVI who received sorafenib treatment was only 47 days compared to those who received placebo in recent pooled exploratory analysis from two randomized trials (184 days vs. 137 days) [6]. Although the combined TACE plus RT had not been considered as a first-line treatment of HCC patients with MVI in BCLC guidelines, a recent prospective randomized trial confirmed benefit of TACE plus RT compared to sorafenib as a first-line treatment for HCC with MVI [17]. The progression-free survival rate was significantly higher in the TACE plus RT group than that in the sorafenib group (at 12 weeks: 86.7% vs. 34.3%; $p < 0.001$) and the TACE plus RT group showed a significantly longer median time to progression (7.2 months vs. 2.7 months; $p < 0.001$) as well as median OS (12.8 months vs. 10.0 months; $p = 0.04$). Moreover, TACE plus RT for the very low-risk group showed a median survival of more than five years in the present study. Based on these results, excellent clinical outcomes could be expected in selected patients with MVI after a first-line TACE plus RT though the proportion was relatively small. Also, the combined TACE plus respiratory-gated RT showed minimal toxicities in the present study. In particular, the rates of hepatic failure without progression of intrahepatic HCC and grade ≥3 gastroduodenal bleeding were 0.8% and 1.6%, respectively. This was attributed to the advent of RT techniques, including four-dimensional CT-based RT planning, conformal liver irradiation, and the more accurate delivery of radiation beam in the treatment room.

The study has several limitations. First, due to its retrospective study design, it was inevitably subject to other biases. Only the patients who received more than 80% of the planned RT dose were included in this study, and the prognostic value of RT dose was therefore inconclusive. Finally, we excluded the RT dose from the subclassification model in order to evaluate the prognosis by only using the baseline patient and tumor-related factors. Second, other clinical outcomes, such as the response and progression-free survival rates of combined TACE plus RT were not evaluated in the present study because the main purpose of this analysis focused on the OS and the subclassification of patients with HCC with MVI. Third, our subclassification model contained the subjective factor of tumor type, which may be difficult to discriminate in

some clinical situations. Lastly, although the present subclassification model accurately predicted the prognosis of HCC patients with MVI, it requires external validation. Nevertheless, the present study provided valuable information about risk groups in advanced HCC with MVI with a relatively large number of cases that were homogenously treated according to a consistent treatment protocol.

In conclusion, combined TACE and respiratory-gated RT was an effective and safe first-line treatment modality for HCC patients with MVI. Further studies are needed to verify the solid benefit of this loco-regional treatment approach compared to the current standard systemic therapies and subclassification to define the population heterogeneity is the preceding step for it. The proposed subclassification model in the present study accurately predicted the prognosis of HCC with MVI and it is useful method for treatment decision-making and future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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