



Intermediate-stage (BCLC stage B) infiltrative hepatocellular carcinoma: safety and efficacy of chemoembolization

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Abstract

Objectives To evaluate the safety and efficacy of chemoembolization in patients with intermediate-stage infiltrative Hepatocellular carcinoma (HCC).

Materials and methods This retrospective study evaluated outcomes in treatment-naïve patients who received chemoembolization as first-line treatment for intermediate-stage infiltrative HCC between 2002 and 2022. Of the 2029 treatment-naïve patients who received chemoembolization as first-line treatment for intermediate-stage HCC, 244 (12%) were identified as having the infiltrative type. After excluding two patients lost to follow-up, 242 patients were evaluated.

Results Median post-chemoembolization overall survival (OS) was 16 months. Multivariable Cox analysis identified four factors predictive of OS: Child–Pugh class B (hazard ratio [HR], 1.84; $p=0.001$), maximal tumor size ≥ 10 cm (HR, 1.67; $p<0.001$), tumor number ≥ 4 (HR, 1.42; $p=0.037$), and bilobar tumor involvement (HR, 1.64; $p=0.003$). These four factors were used to create pretreatment prediction models, with risk scores of 0–1, 2–4, and 5–7 defined as low, intermediate, and high risk, respectively. Median OS times in these three groups were 34, 18, and 8 months, respectively ($p<0.001$). The objective tumor response rate following chemoembolization was 53%. The major complication rate was 9% overall and was significantly higher in the high-risk group (22%) than in the low (2%) and intermediate (3%) risk groups ($p<0.001$).

Conclusion Chemoembolization is safe and effective in selected patients with intermediate-stage infiltrative HCC. Chemoembolization is not recommended in high-risk patients with intermediate-stage infiltrative HCC because of poor OS and high rates of major complications.

Clinical relevance statement A pretreatment prediction model was developed using four risk factors associated with overall survival following chemoembolization for intermediate-stage infiltrative hepatocellular carcinoma. This model may provide valuable information for clinical decision-making.

Key Points

- Four risk factors (Child–Pugh score B, maximal tumor size ≥ 10 cm, tumor number ≥ 4 , and bilobar tumor involvement) were used to create pretreatment prediction models, with risk scores of 0–1, 2–4, and 5–7 defined as low, intermediate, and high risk, respectively.
- Median overall survival (OS) times and major complication rate in these three groups were 34, 18, and 8 months, and 2%, 3%, and 22%, respectively ($p<0.001$). Chemoembolization is not recommended in high-risk patients with intermediate-stage infiltrative Hepatocellular carcinoma (HCC) because of poor OS and high rates of major complications.

Keywords Carcinoma, hepatocellular · Chemoembolization, therapeutic · Neoplasm staging · Survival analysis

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Abbreviations

AFP	Alpha-fetoprotein
AUC	Areas under the curve
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence interval
CR	Complete response
CT	Computed tomography
EASL	European Association for the Study of the Liver
HCC	Hepatocellular carcinoma

HR	Hazard ratio
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
ROC	Receiver operating characteristic
SD	Stable disease
SIR	Society of Interventional Radiology

Introduction

The Barcelona Clinic Liver Cancer (BCLC) staging system has classified patients with intermediate-stage hepatocellular carcinoma (HCC; BCLC stage B) as having Child–Pugh class A/B liver function; four or more tumors, irrespective of size, or two or three tumors of maximal diameter > 3 cm; and the absence of cancer-related symptoms, macrovascular invasion, or extrahepatic metastasis [1–3]. Chemoembolization is regarded as a first-line treatment option for patients with intermediate-stage HCC [4–8].

Infiltrative type of HCC is associated with poor overall survival (OS) [9–11] and is frequently diagnosed in an advanced stage, with macrovascular invasion and/or extrahepatic metastases (BCLC stage C) [12, 13]. However, the type of HCC has not been considered for the BCLC staging system [4–7]. Awareness of the poor prognosis of patients with infiltrative HCC resulted in the reclassification of BCLC stage B into three subcategories, one of which was the infiltrative type, in the 2022 update of the BCLC treatment recommendations [14]. This update recommended systemic treatment for patients with infiltrative HCC, even those with BCLC stage B tumors [14].

Blood supply to HCCs is predominantly provided by the hepatic artery, enabling chemoembolization to efficiently and directly deliver chemotherapeutic agents and embolic materials to these tumors through the hepatic artery. Furthermore, improvements in chemoembolization devices and techniques have increased patient survival while decreasing chemoembolization-associated mortality [15, 16]. Chemoembolization may therefore be an attractive option for the treatment of intermediate-stage infiltrative HCCs.

To date, however, the safety and efficacy of chemoembolization for patients with intermediate-stage infiltrative HCC are unclear, probably due to the low incidence of these tumors. The present study evaluated the safety and efficacy of chemoembolization for the treatment of intermediate-stage infiltrative HCC. In addition, factors associated with survival outcomes were evaluated.

Materials and methods

Patient inclusion and data acquisition

This retrospective study was approved by the Institutional Review Board in our institution, which waived the requirement for written informed consent due to the retrospective design of this study. Prospectively collected data of patients who underwent chemoembolization for HCC were retrospectively searched to identify treatment-naïve patients who underwent chemoembolization as first-line treatment for BCLC stage B HCC with infiltrative nature showing permeative ill-defined arterial enhancement with delayed washout without a distinct margination on any portion of the tumor on pre-procedural images (hereafter, intermediate-stage infiltrative HCC) [17]. Pre-procedural images were reviewed by two experienced radiologists and HCCs were diagnosed with images only on

Table 1 Baseline characteristics of the study patients with intermediate-stage infiltrative HCC

Variable	All patients
Patients	242
Age, mean \pm SD, year (range)	56 \pm 10 (24–83)
Sex	
Male	210 (87)
Female	32 (13)
Etiology	
HBV	194 (80)
HCV	12 (5)
Alcoholics	21 (9)
Others	15 (6)
Child–Pugh class	
A	204 (84)
B	38 (16)
Maximal tumor size	
< 10 cm	149 (62)
\geq 10 cm	93 (38)
Tumor number	
2–3	74 (31)
\geq 4	168 (69)
Tumor involvement	
Unilobar	69 (29)
Bilobar	173 (71)
AFP (ng/mL)	
\geq 400	121 (50)
< 400	121 (50)
Portal hypertension	
Yes	66 (27%)
No	176 (73%)

Abbreviations: *SD*, standard deviation; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *AFP*, alpha-fetoprotein

the basis of the European Association for the Study of Liver (EASL) guidelines [6]. 2029 treatment-naïve patients received chemoembolization as first-line treatment for intermediate-stage HCC between March 2002 and April 2022. Of the 2029 patients, 244 patients (12%) were identified as having the infiltrative type of HCC (intermediate-stage infiltrative HCC). Among the 244 patients, two patients lost to follow-up were excluded. Finally, 242 patients were analyzed for this study.

Chemoembolization method

The details of the chemoembolization procedure have been described previously [18]. Chemoembolization was performed by eight experienced interventional radiologists, each with at least 10 years of experience with TACE. Cisplatin-based chemoembolization (dose: 2 mg/kg of body weight) was performed using a 1.7–2.4-F microcatheter (Progreat Lambda, Terumo; Renegade, Boston Scientific; Carnelian, Tokai Medical Products). A 1:1 emulsion of cisplatin and iodized oil (Lipiodol®, Guerbet) was infused into the feeding artery, followed by embolization with gelatin particles (Upjohn) until arterial flow stasis was observed.

Follow-up

Patients were initially followed-up 1 month after chemoembolization by contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and laboratory tests. Patients were subsequently followed up every 2–3 months

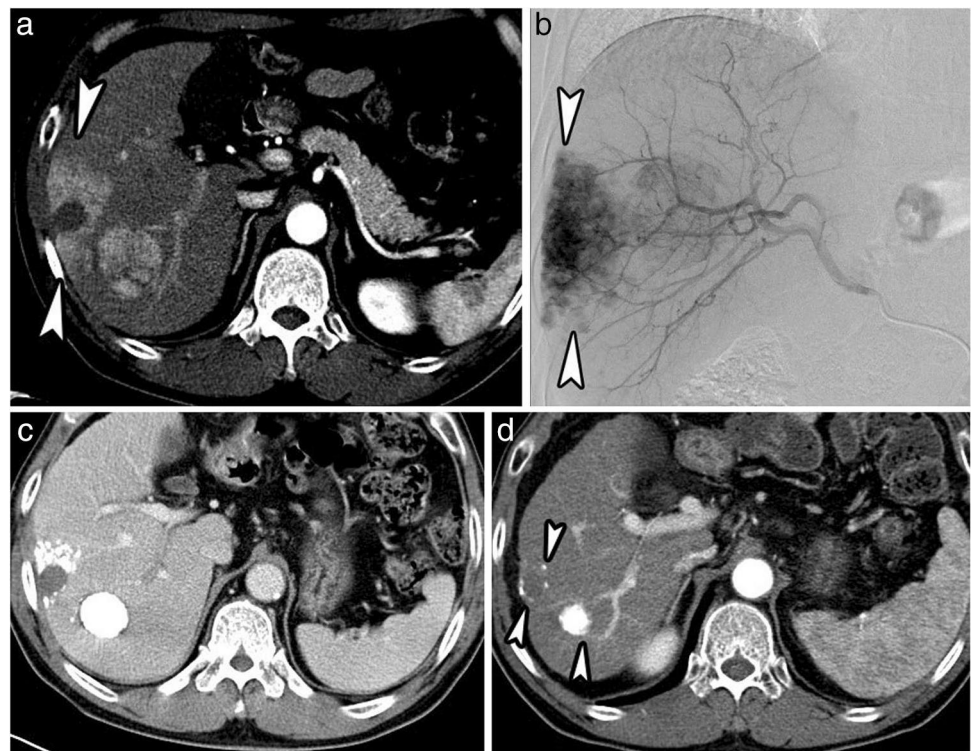
during the first 2 years, and then every 3–6 months until HCC recurrence. Chemoembolization was repeated in patients who showed insufficient responses after a single session and in those with recurrent tumors.

Data analysis

The primary study endpoints were OS and the identification of pretreatment risk factors associated with OS. The following pretreatment factors were analyzed: age, sex, HCC etiology, Child–Pugh class, maximal tumor size (≥ 10 cm vs. < 10 cm), tumor number (2–3 vs. ≥ 4), extent of tumor involvement (unilobar vs. bilobar), serum alpha-fetoprotein (AFP) concentration (< 400 ng/mL vs. ≥ 400 ng/mL), and portal hypertension (presence vs. absence). Portal hypertension was diagnosed in patients who met at least one of the following criteria: esophageal varices, noticeable portosystemic collaterals, ascites, and splenomegaly with thrombocytopenia (platelet count $< 100,000/\text{mm}^3$) [19].

Secondary study endpoints were radiologic tumor response, progression-free survival (PFS), and complications following chemoembolization. Tumor response was evaluated 1 month following chemoembolization using the European Association for the Study of the Liver (EASL) criteria, with responses divided into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [20]. Patients who achieved CR or PR were classified as showing an objective tumor response. PFS was defined as the time from the first

Fig. 1 A 58-year-old man with intermediate-stage infiltrative HCC. Contrast-enhanced CT in the arterial phase (**a**) and arteriography via a common hepatic artery (**b**) showing hypervascular tumors in the right hemiliver. The largest tumor (arrowheads) had infiltrative tumor morphology (maximal diameter, 6 cm). **c** Follow-up CT 1 month later showing compact lipiodol uptake by the tumors without a residual viable mass, and a decrease in maximal diameter. The patient remains alive at the end of this study, 120 months after chemoembolization. **d** Follow-up CT 5 years after chemoembolization, showing a further decrease in tumor sizes (arrowheads) without any viable tumor. The patient remains alive at the end of this study, 120 months after chemoembolization



chemoembolization session until tumor progression, based on EASL guidelines, or death from any cause.

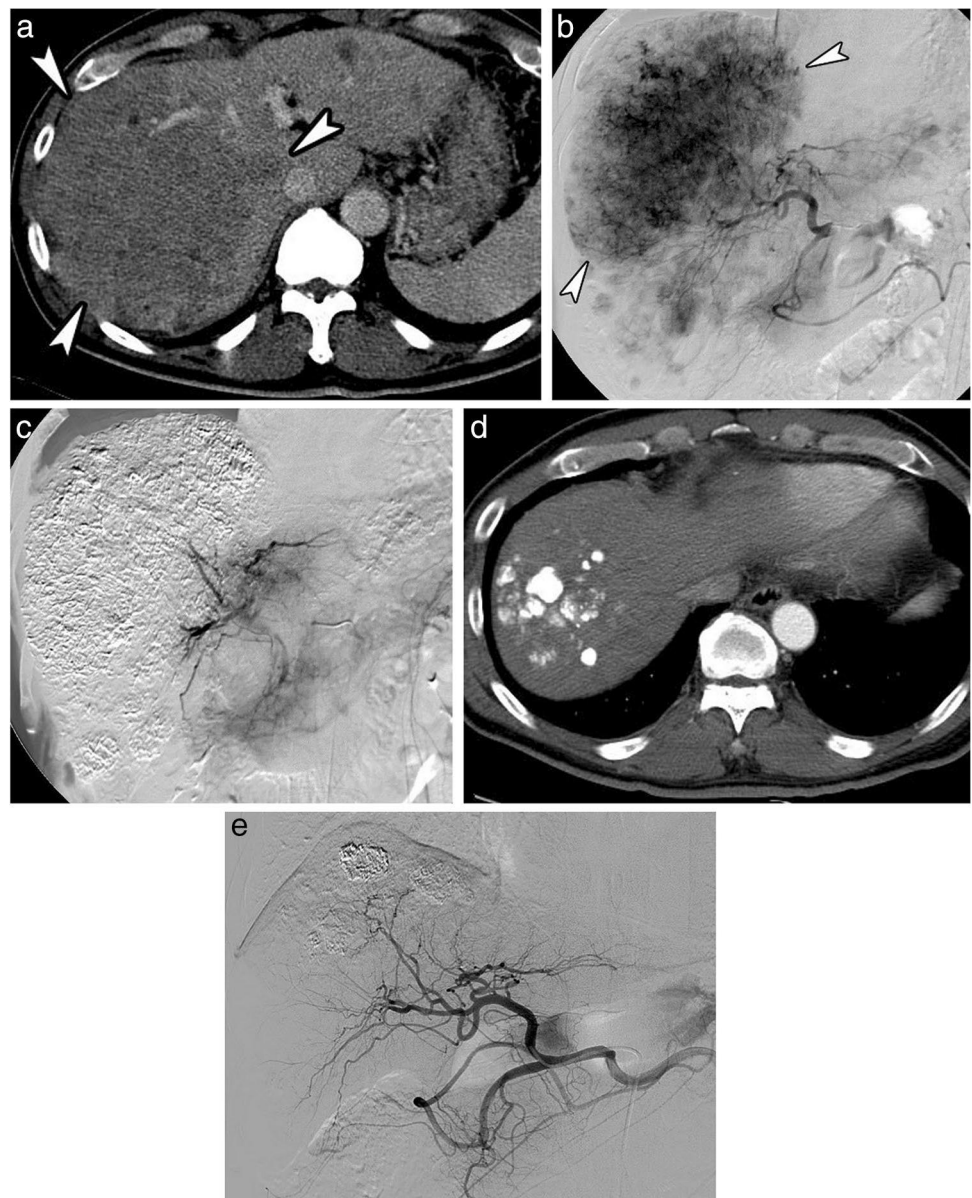
Based on the Society of Interventional Radiology (SIR) reporting standards [21], major complications were defined as those necessitating additional treatment, including a hospital stay beyond the normal postoperative course, increased level of care, substantial morbidity, or death (SIR classifications C–E). Mortality was defined as death within 30 days from the time of chemoembolization.

Statistical analysis

Pretreatment factors associated with OS following chemoembolization were evaluated by univariate analysis, with

variables showing $p < 0.05$ on univariate analyses included in a multivariable Cox regression analysis using the backward elimination method to identify pretreatment factors independently associated with OS. Risk points were assigned to these variables according to their β regression coefficients, and a pretreatment risk-prediction model was developed [22]. Three prognostic categories (low, intermediate, and high-risk groups) were identified based on changes in risk estimates for each one-point increase in scores. The discrimination capability of the risk score was assessed by using the time-dependent receiver operating characteristic (ROC) curve at 1 year and 3 years. Cumulative survival outcomes were evaluated by the Kaplan–Meier method and compared by log-rank tests and Cox proportional hazards model. The rates of major complication were compared in the three low,

Fig. 2 A 51-year-old man with intermediate-stage infiltrative HCC. Contrast-enhanced CT in the portal venous phase (a) and hepatic angiographic image (b) showing diffuse infiltrative masses involving both hemilivers. The maximal diameter of the largest tumor was 14 cm (arrowheads). c Performance of chemoembolization through both hepatic arteries. Follow-up CT (d) and hepatic angiography (e) after four sessions of chemoembolization, 1 year after initial TACE, showing a marked reduction in tumor volume without residual viable tumor. This patient survived 71 months after initial chemoembolization



intermediate, and high-risk groups, as determined by the pretreatment risk-prediction model, using χ^2 tests. All statistical analyses were performed using SPSS software (version 21.0, SPSS), with two-sided p values < 0.05 considered statistically significant.

Results

Patient characteristics

The majority of study participants were positive for hepatitis B virus (80%) and had Child–Pugh class A liver function (84%), bilobar tumor involvement (71%), and tumor number ≥ 4 (69%). One-half (50%) had serum AFP concentrations ≥ 400 ng/mL, 38% had huge (≥ 10 cm) tumors, and 27% had portal hypertension (Table 1).

Overall survival after TACE

A total of 1289 chemoembolizations were performed in the 242 patients with intermediate-stage infiltrative HCC. The median number of chemoembolization sessions was four per patient (range, 1–23 sessions; interquartile range, 2–7 sessions). During the follow-up period after chemoembolization, 215 (89%) of the 242 patients died and 27 (11%) remained alive (Figs. 1 and 2). The 1-, 3-, and 5-year OS rates were 60%, 23%, and 14%, respectively, and the median OS after chemoembolization was 16 months (95% confidence interval [CI], 14–18 months).

Multivariable Cox regression analyses revealed that Child–Pugh score B (hazard ratio [HR], 1.84; $p = 0.001$), maximal tumor size ≥ 10 cm (HR, 1.67; $p < 0.001$), tumor number ≥ 4 (HR, 1.42; $p = 0.037$), and bilobar tumor

involvement (HR, 1.64; $p = 0.003$) were risk factors significantly associated with OS (Table 2). These four risk factors were incorporated into a pretreatment risk-prediction model. Risk points were assigned based on the β regression coefficients of the four risk factors, with one point assigned for tumor number ≥ 4 , two points for Child–Pugh class B, two points for maximal tumor size ≥ 10 cm, and two points for bilateral tumor involvement (Table 2). The risk scores for all patients were calculated as the sum of these corresponding risk points, and patients with scores of 0–1 ($n = 48$), 2–4 ($n = 109$), and 5–7 ($n = 85$) were categorized into the low-, intermediate-, and high-risk groups, respectively, with median OS of 34 months (95% CI, 25–44 months), 18 months (95% CI, 14–21 months), and 8 months (95% CI, 6–11 months), respectively (Fig. 3). OS rates differed significantly between the low- and intermediate-risk groups (HR = 1.59, 95% CI = 1.09–2.33, $p = 0.02$) and between the intermediate- and high-risk groups (HR = 2.27, 95% CI = 1.68–3.06, $p < 0.001$) (Table 3). The discrimination capability of the risk score was assessed by using the time-dependent ROC curve at 1 year and 3 years and areas under the curve (AUC) were 0.74 and 0.70, respectively (Fig. 4).

Radiologic tumor response, progression-free survival, and major complications

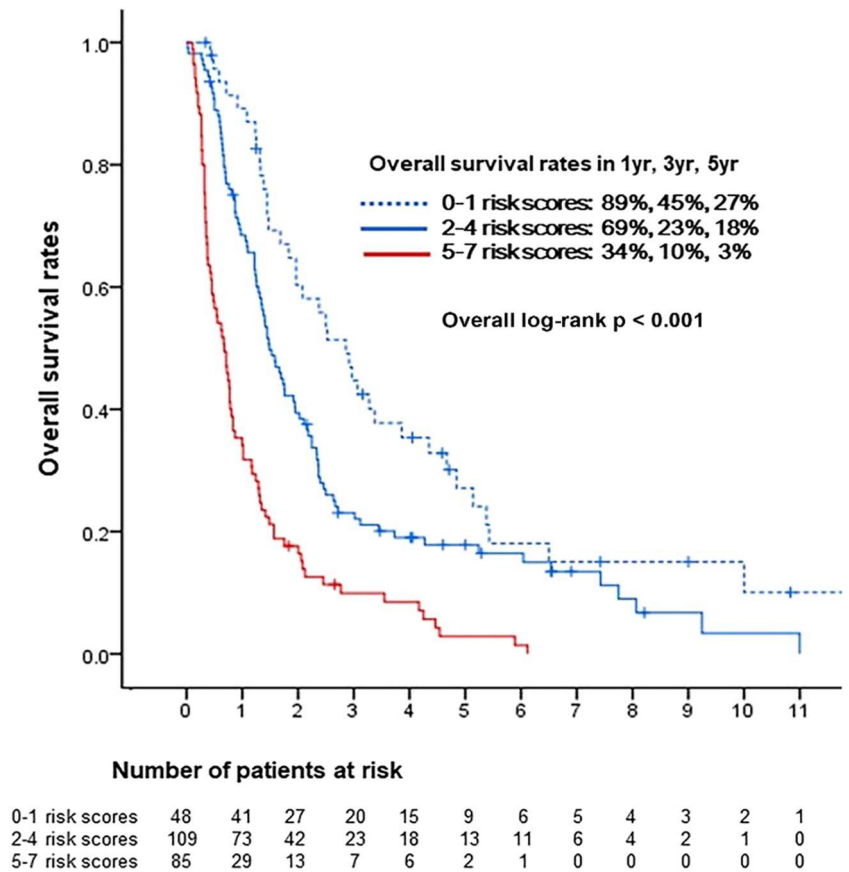
Two patients died prior to the evaluation of radiologic tumor response at 1 month; these two patients were considered to have PD. Of the 242 patients, 32 (13%) achieved CR, 97 (40%) achieved PR, 82 (34%) had SD, and 31 (13%) showed PD 1 month after chemoembolization. The objective tumor response rate in these patients (CR + PR) was therefore 53% (129/242). The objective tumor response rate was 83% (40/48)

Table 2 Univariable and multivariable analyses of factors associated with Overall survival after TACE

Variables	Univariable analysis			Multivariable analysis			Beta coefficients	Risk point
	HR	95% CI	p value	HR	95% CI	p value		
Age	0.99	0.98–1.01	0.294	-	-	-		
Male sex	1.18	0.79–1.76	0.418	-	-	-		
Etiology								
HBV	1		0.857	-	-	-		
HCV	1.18	0.62–2.24	0.609	-	-	-		
Alcoholic	1.06	0.45–2.52	0.887	-	-	-		
Others	0.99	0.46–2.15	0.995	-	-	-		
Child–Pugh score B	1.91	1.33–2.74	< 0.001	1.84	1.28–2.65	0.001	0.61	2
Serum AFP level ≥ 400 ng/mL	1.26	0.96–1.64	0.097	-	-	-		
Maximal tumor size ≥ 10 cm	1.97	1.49–2.60	< 0.001	1.67	1.26–2.22	< 0.001	0.51	2
Tumor number ≥ 4	1.93	1.42–2.63	< 0.001	1.42	1.02–1.97	0.037	0.35	1
Presence of portal hypertension	1.20	0.89–1.62	0.241	-	-	-		
Bilobar tumor involvement	1.90	1.40–2.59	< 0.001	1.64	1.19–2.27	0.003	0.49	2

Abbreviations: HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein

Fig. 3 Kaplan–Meier curves for overall survival according to stratified risk groups



in the low-risk group, 67% (73/109) in the intermediate-risk group, and 19% (16/85) in the high-risk group ($p < 0.001$).

During follow-up, 232 (96%) patients showed tumor progression or died. The median PFS after TACE was 6 months (95% CI, 5–7 months). The median PFS after TACE was 11 months in the low-risk group, 7 months in the intermediate-risk group, and 4 months in the high-risk group ($p < 0.001$).

Of the 242 patients, 23 (9%) experienced major complications, including hepatic failure in ten patients, allergic reaction related to cisplatin in four, tumor lysis syndrome in three, spontaneous bacterial peritonitis in two, acute renal failure in two, and chemoembolization-related cholecystitis in two. Two patients died of hepatic failure within 30 days after chemoembolization, making the mortality rate 0.8%. The rates of major complications in the low, intermediate, and high-risk groups were 2% (1/48), 3% (3/109), and 22% (19/85), respectively ($p < 0.001$).

Discussion

Although grossly infiltrative HCC is related to poor OS [9–11], the relationships between these tumors classified by BCLC stage and OS had not been determined [4–7]. The safety and efficacy of chemoembolization for intermediate-stage infiltrative HCC are unclear, perhaps due to the

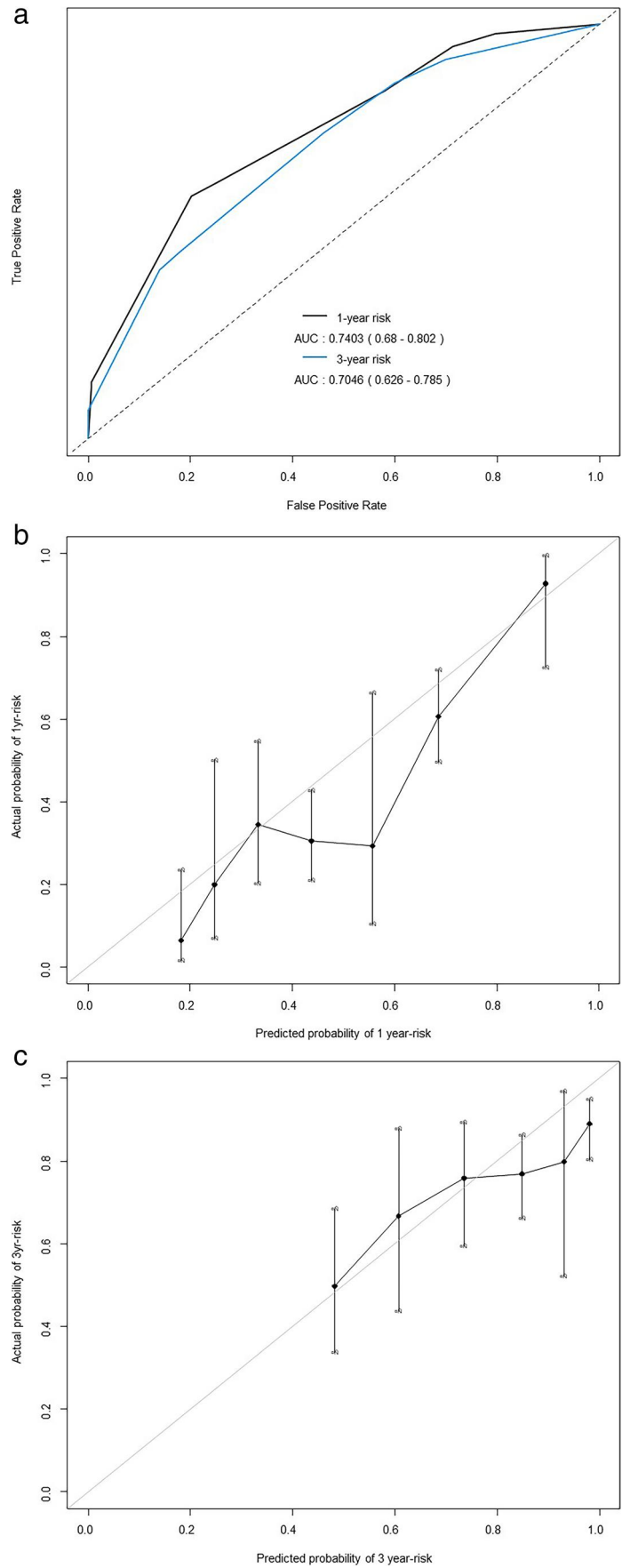
relatively rare incidence of these tumors. The results of the present study suggest that Child–Pugh class B, maximal tumor size ≥ 10 cm, tumor number ≥ 4 , and bilobar tumor involvement were risk factors significantly associated with poorer OS in patients with intermediate-stage infiltrative HCC undergoing chemoembolization. Categorization of these patients into low, intermediate, and high-risk groups based on their risk scores showed that higher risk scores were significantly associated with reduced OS. These findings suggest that chemoembolization may be considered as first-line treatment in low-risk patients, but chemoembolization may have little survival benefit in high-risk patients when considering its reduced OS.

Table 3 Hazard ratios of overall survival in the groups according to the Cox proportional hazards model

Groups	HR	95% CI		<i>p</i> value
Low		Reference		
Intermediate	1.59	1.09	2.33	0.017
High	3.61	2.42	5.38	<0.001
Intermediate		Reference		
High	2.27	1.68	3.06	<0.001

Abbreviations: *HR*, hazard ratio; *CI*, confidence interval

Fig. 4 Time-dependent receiver operating characteristic (ROC) (a) and calibration curves (b, c) for overall survival. The pre-treatment risk-prediction model showed areas under the curve of 0.74 and 0.70 at 1 and 3 years, respectively. AUC= areas under the curve



In general, chemoembolization is considered a first-line therapeutic approach in patients with intermediate-stage HCC [8, 23]. In clinical practice, however, responses to chemoembolization vary widely in patients with intermediate-stage infiltrative HCCs. Although many staging systems and prognostic scores lack validity in intermediate-stage infiltrative HCC, benefits and risks should be considered to provide better survival outcomes [24, 25]. Treatment response in intermediate-stage infiltrative HCC empirically depends on liver function, tumor numbers, and tumor sizes. The present study found that these risk factors were significantly associated with OS in patients with intermediate-stage infiltrative HCC, with higher risk scores associated with significant reductions in OS. Generally, patients are considered ideal candidates for chemoembolization if their expected median OS is > 30 months, although OS in these patients can vary widely [26–28]. The low-risk group in the present study had a median OS of 34 months and a rate of major complications of 2%, findings in the range of generally accepted ideal candidates for chemoembolization. Therefore, patients with low-risk intermediate-stage infiltrative HCC may be good candidates for first-line chemoembolization.

Evaluation of the high-risk group in the present study showed that the median OS was poor (8 months) and the rate of major complications was relatively high (22%). Poor prognosis in these patients is associated with high tumor burden and deterioration of liver function. Findings in the present study indicate that chemoembolization is not a suitable option in high-risk patients with intermediate-stage infiltrative HCC owing to their poor OS and high complication rates. Assessments of risks and benefits in these patients suggest that systemic drugs, such as lenvatinib, could be a good alternative option. These systemic treatments are effective in clinical practice, even in some patients with poor liver function and large tumor burden [29, 30].

Chemoembolization may be a good first-line treatment option in the intermediate-risk group of patients with intermediate-stage infiltrative HCC, due to its low complication rate (3%) and acceptable median OS (18 months). Other treatment options, such as hepatic arterial infusion chemotherapy (HAIC) and transarterial radioembolization (TARE) could be considered for infiltrative HCC. According to the previous study, HAIC showed better survival compared to chemoembolization in patients with infiltrative HCC [31]. TARE has an OS comparable to chemoembolization but is associated with a longer time to tumor progression, thereby improving patient quality of life [32, 33]. Studies are needed, however, to assess the efficacy and safety of TARE in patients with intermediate-stage infiltrative HCC. Systemic drugs, such as nivolumab or sorafenib, can be considered as an alternative option in patients with infiltrative HCC, who showed disease progression during HAIC treatment [34, 35].

This study had several limitations. First, despite being the largest cohort of its type, due to the rare incidence of

intermediate-stage infiltrative HCC, the sample size may be insufficient to validate the prediction model proposed in this study. External validation of this proposed prediction model is thus required. Second, the level of selective embolization may have differed among the operators, which may have introduced a selection bias. However, based on the infiltrative features of HCC in this study, the differences in levels of selective embolization may have been negligible. Finally, all patients in this study underwent cisplatin-based chemoembolization; thus, the results may differ in patients undergoing doxorubicin-based chemoembolization.

In conclusion, chemoembolization is safe and effective in selected patients with intermediate-stage infiltrative HCC. Chemoembolization is not recommended in high-risk patients with intermediate-stage infiltrative HCC because of poor OS and high rates of major complications.

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Declarations

Guarantor The scientific guarantor of this publication is Jin Hyoung Kim.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Three of the authors (Jin Hyoung Kim, Gun Ha Kim, Nayoung Kim) have significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval This study protocol was reviewed and approved by the Institutional Review Boards of Asan Medical Center (IRB No.2022–1451).

Study subjects or cohorts overlap There is no patient overlap in this study.

Methodology

- Retrospective
- Observational
- Performed at one institution

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