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Diffuse Infiltrative Hepatocellular Carcinoma: Assessment of Presentation, Treatment, and Outcomes

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Abstract

Background—Data on infiltrating hepatocellular carcinoma (HCC) are limited. We sought to define treatment and outcome of patients treated with infiltrating HCC compared with patients who had advanced multifocal HCC.

Methods—Between January 2000 and July 2011, a total of 147 patients with advanced HCC were identified from the Johns Hopkins Hospital database (infiltrative, $n = 75$; multifocal, $n = 72$). Clinicopathologic data were compared by HCC subtype.

Results—Patients with infiltrating HCC had higher alfafetoprotein levels (median infiltrative, 326.5 ng/mL vs. multifocal, 27.0 ng/mL) and larger tumors (median size, infiltrating, 9.2 cm vs. multifocal, 5.5 cm) ($P < 0.05$). Imaging failed to reveal a discrete lesion in 42.7 % of patients with infiltrating HCC. Most infiltrating HCC lesions presented as hypointense on T1-weighted images (55.7 %) and hyperintense on T2-weighted images (80.3 %). Among patients with infiltrating HCC, most (64.0 %) were treated with intra-arterial therapy (IAT), and periprocedural mortality was 2.7 %. Patients treated with IAT had longer survival versus patients receiving best support care (median survival, IAT, 12 months vs. best supportive care, 3 months; $P = 0.001$). Survival after IAT was similar among patients treated with infiltrating HCC versus multifocal HCC (hazard ratio 1.29, 95 % confidence interval 0.82–2.03; $P = 0.27$). Among infiltrating HCC patients, pretreatment bilirubin > 2 mg/dL and alfa-fetoprotein > 400 ng/mL were associated with worse survival after IAT ($P < 0.05$). Patients with progressive disease after IAT had higher risk of death

versus patients who had stable/responsive disease (hazard ratio 3.53, 95 % confidence interval 1.49–8.37; $P = 0.004$).

Conclusions—Patients with infiltrative HCC often present without a discrete lesion on imaging. IAT for infiltrative HCC was safe and was associated with survival comparable to IAT outcomes for patients with multifocal HCC. Infiltrative HCC morphology is not a contraindication to IAT therapy in select patients.

Hepatocellular carcinoma (HCC) is a common malignancy that is frequently associated with hepatitis and cirrhosis.^{1,2} HCC can present with different morphologic subtypes, including nodular, massive, and diffuse/infiltrative.^{3–5} Patients with nodular HCC can present with single or multiple encapsulated nodules.^{6–8} Patients with nodular HCC may be candidates for transplantation, resection, or ablation, while others are more appropriately treated with intra-arterial therapy (IAT).⁹ Patients with massive or large HCC tumors of >10 cm are not candidates for transplantation or ablation; rather, these patients are most commonly treated with IAT or, in a small subset, surgical resection.¹⁰ Treatment options for patients with diffuse, infiltrating HCC are more limited and remain poorly defined. Data on the presentation, treatment, and outcome of patients with infiltrating HCC are not well characterized.

Infiltrating HCC can be difficult to diagnose because it often lacks a well-demarcated boundary on cross-sectional imaging and can therefore blend into the background of the cirrhotic liver.^{3,11} Many patients present with advanced disease.^{4,11–13} Treatment can be challenging, partly as a result of the difficulty in assessing the tumor extent within the liver. In addition, because of its large, diffuse nature and propensity to involve the portal vein, diffuse infiltrating HCC may be difficult to treat and treatment can be associated with increased complications as well as marginal long-term benefit. Most data on infiltrating HCC have been reported as part of larger heterogeneous cohorts of HCC patients.^{14,15} As such, previous studies are limited both because infiltrating HCC has not been the investigative focus, as well as the small sample sizes (<20 patients) included. The objective of the current study was to examine the presentation, imaging characteristics, as well as treatment of patients with infiltrating HCC. We sought to define the short- and long-term survival of patients treated for infiltrating HCC compared with patients who had advanced multifocal HCC. In addition, we define those factors associated with outcome among patients with infiltrative HCC.

MATERIALS AND METHODS

Patients and Data Collection

Between January 1, 2000, and July 1, 2011, a total of 147 patients with advanced HCC were identified from the Johns Hopkins Hospital database (infiltrative, $n = 75$; multifocal, $n = 72$). The study was approved by the Johns Hopkins institutional review board. Data collected included patient demographics; Eastern Cooperative Oncology Group (ECOG) performance status; primary tumor size, number; Child-Turcotte-Pugh score; serum laboratory exams [e.g., alfa-fetoprotein (AFP), international normalized ratio (INR), bilirubin, creatinine]; Model for End-Stage Liver Disease (MELD) score; presence of vascular invasion; and hepatitis status. Detailed data on imaging characteristics of the HCC were also collected. Complete response, partial response, stable disease, and progressive disease were assessed using standard European Association for the Study of the Liver (EASL) criteria, as previously described.^{16,17} Data on the type of treatment, as well as periprocedural and long-term outcomes were also collected. IAT was classified as drug-eluting beads–transarterial chemoembolization (DEB-TACE), conventional TACE, and yttrium-90 (Y-90). Survival status was determined by both hospital records and the Social Security Death Index.

Statistical Analysis

Mean and median values were used to describe continuous data, with discrete variables displayed as totals and frequencies. Univariate comparisons were assessed by the chi-square test for dichotomous and categorical variables and the Mann–Whitney *U* test for continuous variables. Cumulative event rates were calculated by the method of Kaplan and Meier and survival curves were compared by the log rank test. Overall survival time was calculated from the date of diagnosis to the date of last follow-up or death; modeling of survival was performed by Cox proportional hazard models. Relative risks were expressed as hazard ratios (HR) with a 95 % confidence interval (CI). All reported *P* values are two-tailed, and for all tests, *P* < 0.05 was considered statistically significant. All statistical analyses were performed by SPSS software, version 19.0 for Microsoft Windows (SPSS, Chicago, IL).

RESULTS

Patient and Tumor Characteristics

Table 1 shows the clinicopathologic features of the 147 patients included in the study. Among the 75 patients with infiltrating HCC, the mean patient age was 60 years (range, 30–88 years) and the majority of patients were male (*n* = 63; 84.0 %) (Table 1). Nearly every patient presented with an ECOG performance status of 0–2 (*n* = 71; 94.7 %). Most patients had hepatitis (*n* = 46; 61.3 %) (hepatitis B, *n* = 12, 16.0 %; hepatitis C, *n* = 31, 41.3 %; hepatitis B + C, *n* = 3, 4.0 %); 13 (17.3 %) patients had cirrhosis secondary to alcohol abuse. The median MELD score was 10 (range, 2–29) with most patients being either Child-Pugh A (*n* = 31, 41.3 %) or B (*n* = 31, 41.3 %). Median AFP level was 326.5 ng/mL at presentation. Among patients with infiltrative HCC, median tumor size was 9.2 cm (1.3–18.5 cm) and most often the lesion involved either the right hemi-liver (*n* = 32, 45.1 %) or both sides of the liver (*n* = 28, 39.4 %).

Although certain clinicopathologic characteristics were similar among patients who presented with infiltrating versus multifocal HCC, other factors differed (Table 1). Specifically, patients with infiltrating HCC presented with higher AFP levels (median 326.5 ng/mL) compared with patients who had multifocal HCC (median 27.0 ng/mL) (*P* < 0.001). In addition, patients with infiltrating HCC had larger tumors on presentation (median size, infiltrating HCC, 9.2 cm vs. multifocal HCC, 5.5 cm; *P* = 0.005).

Most patients with infiltrating HCC (60.0 %) were evaluated with both a computed tomographic (CT) scan and magnetic resonance imaging (MRI) (Table 2). Characterization of the morphologic features failed to reveal a discrete lesion in 42.7 % of patients with an infiltrating HCC. On MRI, most infiltrating HCC lesions presented as hypointense on T1-weighted images (55.7 %) with T2 hyperintensity (80.3 %) (Fig. 1A). Miliary enhancement was noted on the initial postcontrast images in a subset of patients (16.4 %). Another prominent feature of infiltrating HCC lesions was the presence of portal vein thrombosis (68.0 %), which displayed neovascularity or T1 enhancement in the hepatic arterial phase in a small number of patients (9.8 %). Patients with infiltrating HCC were more likely to have certain findings on cross-sectional imaging. Specifically, patients with infiltrating HCC were less likely to demonstrate washout in the portal venous phase (infiltrative, 50.8 % vs. multifocal HCC, 77.4 %; *P* = 0.02). In addition, patients with infiltrating HCC more commonly had portal vein thrombosis (infiltrative, 68.0 % vs. multifocal, 25.0 %; *P* < 0.001) and direct tumor invasion of adjacent structures (infiltrative, 74.7 % vs. multifocal, 20.8 %; *P* < 0.001). When a thrombus was present, arterialization of the thrombus was noted in 8.1 and 3.8 % of patients with infiltrative versus multifocal HCC, respectively (*P* = 0.07).

Treatment and Outcome

Among the 75 patients with infiltrating HCC, the majority (64.0 %) was treated with IAT, while only a small number were treated with resection (4.0 %). At the time of surgery, resection included a nonanatomic resection ($n = 2$) or formal hemi-hepatectomy ($n = 1$). Both patients who underwent a nonanatomic resection had positive surgical margins. One patient with an occult infiltrating HCC underwent transplantation. A third of patients with infiltrating HCC received periprocedural sorafenib (33.3 %); radiotherapy was provided in a minority of patients (8.0 %).

The median, 1- and 3-year overall survival of patients with infiltrating HCC was 10 months, 43 and 29 %, respectively (Fig. 2). In comparison, the median and 3-year survival of patients with nodular, multifocal disease was 15 months and 31.4 %, respectively ($P = 0.18$). When we analyzed patients with infiltrative HCC, several factors were noted to be associated with survival. Specifically, the median survival of patients with an AFP level of >400 ng/mL was 5 months compared with 17 months for patients with lower AFP levels ($P = 0.009$) (HR 2.24, 95 % CI 1.18–4.26; $P = 0.01$). Patients with higher MELD scores (HR 1.14, 95 % CI 1.06–1.22) and those patients who were Child-Pugh B (HR 2.2, 95 % CI 1.1–4.6) or C (HR 3.8, 95 % CI 1.6–8.8) also had a higher risk of death (all $P < 0.05$). Patients treated with IAT had a longer survival compared with patients who received best support care (median survival, IAT, 12 months vs. best supportive care, 3 months; $P = 0.001$). Among the 48 patients with infiltrating HCC who were managed with IAT, the 1- and 3-year overall survival was 49 and 34 %, respectively. Overall survival after IAT was similar among patients treated with infiltrating HCC versus multifocal HCC (median survival, infiltrating HCC, 14 months vs. multifocal HCC, 13 months; $P = 0.96$) (HR 1.29, 95 % CI 0.82–2.03; $P = 0.27$). Patient undergoing IAT had comparable tumor characteristics compared with patients treated with best supportive care, but IAT patients had better preserved liver function with more Child C patients in the best supportive care group (BSC) (Table 3).

Among the 48 patients with infiltrative HCC who received IAT, 115 total IAT procedures were performed with the median number of IAT treatments per patient being 2 (range 1–8). The majority of patients treated with IAT underwent DEB-TACE (91.7 %), while a minority underwent conventional TACE (6.3 %) or Y-90 (2.0 %). After IAT therapy of infiltrative HCC, response by EASL criteria was partial, stable, or progressive in 33.3, 45.8 and 20.8 % of patients, respectively (Fig. 1B, C). No patient had a complete response. The mean pre-IAT bilirubin was 1.5 mg/dL compared with a mean post-IAT bilirubin of 2.1 mg/dL ($P = 0.01$). A subset of patients underwent a second ($n = 28$) or third ($n = 18$) IAT session. The mean bilirubin after the second or third was 2.0 ng/mL and 2.4 ng/mL, respectively. After the initial IAT treatment, 2 patients (2.1 %) died within 30-days of IAT; 30-day mortality after subsequent IAT sessions was similar (second IAT, 3.5 %; third IAT, 0 %).

Although the presence of portal vein invasion was not associated with survival among patients with infiltrative HCC treated with IAT, the pretreatment bilirubin level was (Table 4). Specifically, a pretreatment total bilirubin >2 mg/dL was associated with a shorter median survival (3 months) compared with patients who had an initial total bilirubin of ≤ 2 mg/dL (24 months) ($P = 0.001$). Patients with an elevated AFP also tended to have a worse survival (median survival, AFP > 400 ng/mL, 4 months vs. AFP ≤ 400 ng/mL, 21 months) ($P = 0.03$). Patients who had progressive disease after IAT had a survival of only 2 months compared with 12 months for patients who had stable or responsive disease ($P = 0.001$) (Fig. 3). Patients who had stable or responsive disease after the first IAT were more likely to undergo subsequent IAT treatment (OR = 10.80, 95 % CI 1.95–59.76; $P = 0.006$). The number of patients with progressive disease decreased after subsequent IAT treatments (progressive disease: first IAT, 20.8 % vs. second IAT, 10.7 % vs. third IAT, 11.1 %). Multiple IAT sessions were associated with increased survival, with an incremental

reduction in death after each additional IAT session (HR 0.65, 95 % CI 0.46–0.94; $P=0.02$).

DISCUSSION

Infiltrative HCC is a morphologic subtype of liver cancer characterized by a diffuse phenotype that is often ill defined. Although other morphologic subtypes such as focal nodular or large / massive constitute the majority of HCC lesions, infiltrative HCC accounts for 7 to 13 % of HCC cases.^{5,11} Although infiltrative HCC is not uncommon, it remains poorly characterized in the literature. Because infiltrative HCC almost always presents as an advanced diffuse tumor, surgery is rarely indicated. Rather, locoregional therapy in the form of chemoembolization is generally the only available therapeutic option. Data on treatment of patients with infiltrative HCC are, however, uncommon in the literature. In fact, even large series that have compared TACE among patients with unresectable infiltrative versus focal HCC have included only a small number of patients with infiltrative disease ($n=19$).¹⁵ The current study is important because it is one of the largest reported series to examine the presentation, treatment and outcome of patients with infiltrative HCC. We characterize both the clinical presentation, as well as the radiographic characteristics of patients with infiltrating HCC. Perhaps more importantly, we examine a relatively large cohort of patients with infiltrative HCC ($n=48$) who underwent IAT. Several previous investigators have suggested that infiltrative HCC is a strong relative contra-indication to IAT given its diffuse nature and frequent association with portal thrombus. Our data are important because they suggest that IAT is both safe and feasible in patients with infiltrative HCC. We report that IAT was well tolerated when utilized for patients with infiltrative HCC but also seemed to be associated with a therapeutic benefit comparable to that seen among HCC patients with other morphologic subtypes. Specifically, overall survival after IAT was similar among patients treated with infiltrating HCC versus multifocal HCC (median survival, infiltrating HCC, 14 months vs. multifocal HCC, 13 months; $P=0.96$) (HR 1.29, 95 % CI 0.82–2.03; $P=0.27$). In addition, our study is also one of the first to report EASL response data for patients with infiltrative HCC treated with IAT. Of note, roughly 80 % of patients had responsive or stable disease after IAT.

The clinicopathologic features and imaging characteristics of infiltrating HCC remain poorly defined. An elevated AFP can be indicative of a large tumor burden and more extensive disease. Indeed, we found that patients with infiltrative HCC not only had larger tumors, but also had a much higher median AFP level compared with patients with advanced multifocal HCC. Although many patients with advanced HCC can present with a markedly elevated AFP level, high AFP levels tend to be specific but not as sensitive as a marker for HCC.¹⁸ Interestingly, among those patients with infiltrative HCC 49.3 % presented with an AFP of <400 ng/mL. On cross-sectional imaging, nodular HCC lesions often present with a discrete mass. In contrast infiltrative HCC can be subtle with a more diffuse permeative appearance.¹¹ In the current series, over 40 % of patients with infiltrative HCC failed to have a discrete lesion identified on imaging. We did, however, note several distinct features of infiltrative HCC, with the majority of lesions being hypointense on T1-weighted images and hyperintense on T2 images (Fig. 1). On MRI, infiltrating HCC lesions were also less likely to demonstrate washout in the portal venous phase versus multifocal HCC lesions. Another prominent feature of infiltrating HCC was the presence of portal vein thrombosis, which was noted in the majority of patients. Neovascularity or T1 enhancement of the portal vein thrombus in the hepatic arterial phase with distension of the vessel was also noted, and has been described by others as a particularly classic feature of infiltrating HCC.^{3,4,11,13}

Because resection and transplantation are not options for the majority of patients with infiltrating HCC, IAT has been advocated as a potential therapeutic option.^{15,19} Lopez et al.

reported a small series ($n = 19$) of patients with infiltrative HCC who underwent IAT.¹⁵ In that study, the authors compared patients who had focal HCC versus infiltrating HCC who underwent conventional TACE. Interestingly, the authors noted that patients with infiltrating HCC had more procedure-related mortalities with 16 % of patients dying within 30-days of IAT. Because of this high periprocedural mortality rate, the authors recommended caution in utilizing IAT for patients with infiltrating HCC. In contrast, in the current study, we noted that IAT was relatively safe and well tolerated. After initial IAT treatment, only 2.1 % of patients died within 30 days of IAT, and the 30-day mortality after subsequent IAT sessions was similar (second IAT, 3.5 %; third IAT, 0 %). The reason for the difference in periprocedural mortality in our study versus the report by Lopez et al.¹⁵ may be related to patient selection. In the current series, the overwhelming majority of patients were Child-Pugh A or B, had an ECOG performance status of 0–2, and presented with a mean pre-IAT bilirubin of 1.5 mg/dL. Our data strongly suggest that in well-selected patients with infiltrating HCC, IAT can be utilized safely with low periprocedural mortality.

Survival for patients with infiltrating HCC was poor with a median overall survival of only 10 months. Factors associated with survival included factors associated both with underlying liver function (e.g. MELD score, Child-Pugh score), as well as tumor biology (e.g., AFP level). IAT treatment also had a survival benefit for patients with infiltrative HCC. Specifically, patients treated with IAT had a significantly longer survival compared with patients who received best support care. Myung et al. had previously reported that bland TAE was associated with a survival benefit over supportive care among patients with infiltrating HCC and good liver function.²⁰ Unlike this previous study, we compared the outcome of IAT for infiltrating HCC versus multifocal HCC and found that survival was similar between both groups of patients. Among patients with infiltrating HCC, we also noted several factors that were associated with a worse outcome. Specifically, patients who presented with a pretreatment total bilirubin >2 mg/dL and those with an AFP of >400 ng/mL did not have as much of a survival benefit with IAT. In fact, the benefit of IAT could be determined by the response measured by EASL criteria on postprocedural imaging. After IAT therapy of infiltrative HCC, most patients had either a partial response or stable disease, while roughly one-fifth of patients had progression. We found that patients with stable or progressive disease had a survival almost four times that of patients with progressive disease. Taken together, these data suggest that IAT can provide a survival benefit to a subset of patients with infiltrating HCC and the potential benefit is associated with adequacy of the IAT therapy as assessed by EASL criteria on post-IAT cross-sectional imaging.

The current study had several limitations. We were only able to identify 75 patients with infiltrative HCC. Because of the relatively small number of patients with infiltrative HCC identified for this study, there were limitations with regard to statistical modeling and power. In addition, like all retrospective studies, comparison of patients with infiltrative HCC treated with IAT versus best supportive care may be subject to selection bias. Patients with infiltrative HCC treated with IAT had comparable tumor characteristics versus patients treated with best supportive care; however, the former group did have better preserved liver function. As such, interpretation of our data must be considered with this in mind. Although it is important to note that this comparison was not the focus of the current study, the benefit of IAT is suggested by two findings: first, the median survival of 12 months for infiltrative HCC patients treated with IAT compared favorably with previously reported data of a median survival of only 3–6 months for patients with untreated HCC—especially those with advanced disease; and second, IAT resulted in nearly 80 % partial or stable disease as assessed by EASL criteria.

In conclusion, patients with infiltrative HCC often presented with large tumors, markedly elevated AFP levels, and certain radiologic characteristics. Most infiltrating HCC lesions

were hypointense on T1-weighted and hyperintense on T2-weighted images on MRI. Another prominent feature of infiltrating HCC lesions was the presence of portal vein thrombosis and the finding that infiltrating HCC was less likely to demonstrate washout on MRI. Although previous investigators have suggested that infiltrative HCC is a strong relative contraindication to IAT, we demonstrated that IAT had a low periprocedural mortality and therefore appears to be safe and feasible in this cohort of patients. In addition, IAT for infiltrative HCC may be associated with a survival benefit comparable with patients who have multifocal disease. As such, IAT in well-selected patients should be strongly considered. IAT had the most benefit among those patients with infiltrating HCC who presented with a bilirubin level of <2 mg/dL and those with lower AFP levels. Data presented herein should help inform the management of patients with infiltrating HCC.

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FIG. 1.

A Extensive infiltrative T1-weighted hypointense (*a*), T2-weighted with fat saturation hyperintense (*b*) mass (M). Heterogeneously enhancing in arterial phase (*c*) with washout on portal phase (*d*) involving right more than left hepatic lobe, on delayed images (*e*) shows extensive tumor thrombus in the portal vein (*) compatible with infiltrating HCC. **B** A 75-year-old woman with infiltrative HCC. Before treatment (*a–e*), there is a mass (M) of 12.6 × 8.5 cm hypointense in T1-weighted (*a*) heterogeneously hyperintense in T2-weighted (*b*) images. The mass shows diffusion restriction with apparent diffusion coefficient (ADC) value of $1.03 \times 10^{-3} \text{ mm}^2/\text{s}$ (*d*). After contrast administration, there is enhancement in arterial phase (*d*) with washout on delayed images (*e*). The patient underwent IAT (*f–j*); the lesion persisted as hypointense in T1-weighted (*f*) and heterogeneously hyperintense in T2-

weighted (*g*) images. The mass decreased in size to 10×6.8 cm, showing increase in ADC (*h*) value 1.77×10^{-3} mm²/s, decreased enhancement (*arrows*) in arterial phase (*i*), and increased necrotic areas in delayed images (*j*) consistent with partial response. **C** Sixty-seven-year-old man with a history of infiltrative cryptogenic HCC. Axial images show a large lesion (*arrows*) measuring 16×11 cm with innumerable smaller lesions hypointense on T1-weighted (*a*) heterogeneously hyperintense on T2-weighted (*b*) images. After contrast administration, arterial phase (*c*) demonstrated uptake of contrast within the mass with washout on portal phase (*d*). After IAT treatment, the mass increased in size (16×14 cm) with persistent hypointense in T1-weighted (*e*) heterogeneously hyperintense on T2-weighted (*f*) images. Postcontrast images showed avid enhancement in hepatic arterial phase (*g*) with washout on portal venous phase (*h*). All other lesions (*arrowheads*) are overall increased in size, compatible with progressive disease

FIG. 2. Overall survival among patients with infiltrating HCC. Survival is stratified by receipt of IAT versus best supportive care ($P < 0.001$)

FIG. 3. Overall survival after IAT stratified by EASL response. Patients who had progressive disease after IAT had a survival of only 2 months compared with 12 months for patients who had stable or responsive disease ($P = 0.001$)

TABLE 1

Clinicopathologic factors and treatment characteristics of patients with infiltrative and multifocal hepatocellular carcinoma

Variable	All patients (n = 147)	Infiltrative HCC (n = 75)	Multifocal HCC (n = 72)	P
Age (year)	60 (30–88)	60 (30–88)	60 (30–83)	0.78
Male gender	120 (81.6 %)	63 (84.0 %)	57 (79.2 %)	0.53
Ethnicity				0.17
White	90 (61.2 %)	41 (54.7 %)	49 (68.1 %)	
Black	38 (25.9 %)	23 (30.7 %)	15 (20.8 %)	
Other	19 (12.9 %)	11 (14.7 %)	8 (11.1 %)	
Performance status				0.95
ECOG 0–2	138 (93.9 %)	71 (94.7 %)	67 (93.1 %)	
ECOG 3–4	9 (6.1 %)	4 (5.3 %)	5 (6.9 %)	
Hepatitis				0.12
B	18 (12.2 %)	12 (16.0 %)	6 (8.3 %)	
C	55 (37.4 %)	31 (41.3 %)	24 (33.3 %)	
B and C	4 (2.7 %)	3 (4.0 %)	1 (1.4 %)	
Alcohol abuse	25 (17.0 %)	13 (17.3 %)	12 (16.7 %)	0.83
Creatinine (mg/dL)	0.8 (0.4–4.3)	0.8 (0.4–2.0)	0.8 (0.5–4.3)	0.49
INR	1.1 (0.9–3.0)	1.2 (0.9–2.4)	1.1 (0.9–3.0)	0.11
Total bilirubin (mg/dL)	1.1 (0.2–19.7)	1.2 (0.3–19.7)	1.0 (0.2–16.0)	0.08
AFP (ng/mL)	117.0 (1.0–>500000)	326.5 (4.0–>500000)	27.0 (1.0–133161)	<0.001
Encephalopathy	16 (10.9 %)	6 (8.1 %)	10 (14.1 %)	0.30
Ascites	44 (29.9 %)	22 (29.3 %)	22 (30.6 %)	0.86
MELD score	9 (2–27)	10 (2–29)	9 (2–27)	0.34
Child-Pugh				0.38
Class A	68 (43.3 %)	31 (41.3 %)	37 (51.4 %)	
Class B	57 (38.8 %)	31 (41.3 %)	26 (36.1 %)	
Class C	21 (14.3 %)	13 (17.3 %)	9 (12.5 %)	
Liver-directed therapy				0.04
Best supportive care	32 (21.8 %)	21 (28.0 %)	11 (15.3 %)	
Intra-arterial therapy	95 (64.6 %)	48 (64.0 %)	47 (65.3 %)	
Surgery	20 (13.6 %)	6 (8.0 %)	14 (19.4 %)	
Type of IAT therapy				0.13
DEB-TACE	91 (95.7 %)	44 (91.7 %)	47 (100 %)	
Conventional TACE	3 (3.2 %)	3 (6.3 %)	–	
Y90	1 (1.1 %)	1 (2.1 %)	–	
No. of IAT treatments	2 (1–8)	2 (1–8)	2 (1–6)	0.50
Time between IAT treatments (mo)	1 (0–40)	1 (0–40)	1 (0–18)	1.0
RFA alone	7 (4.8 %)	2 (2.7 %)	5 (6.9 %)	0.92
Surgical resection				0.08
Minor hepatectomy	6 (60.0 %)	2 (66.7 %)	4 (57.1 %)	

Variable	All patients (n = 147)	Infiltrative HCC (n = 75)	Multifocal HCC (n = 72)	P
Major hepatectomy	4 (40.0 %)	1 (33.3 %)	3 (42.9 %)	0.89
Transplantation	3 (1.4 %)	1 (1.3 %)	2 (2.8 %)	
Systemic therapy				0.34
Sorafenib	47 (32.0 %)	25 (33.3 %)	22 (30.6 %)	0.04
Cytotoxic chemotherapy	2 (1.4 %)	2 (2.7 %)	–	
Radiotherapy	4 (2.7 %)	4 (5.3 %)	–	

Data are presented as median (range) or n (%)

HCC hepatocellular carcinoma, *ECOG* Eastern Cooperative Oncology Group, *INR* international normalized ratio, *AFP* alfa-fetoprotein, *MELD* Model for End-Stage Liver Disease, *TACE* transarterial chemotherapy, *DEB* drug-eluting beads, *Y90* yttrium-90, *RFA* radiofrequency ablation

TABLE 2

Comparison of imaging characteristics of infiltrative and multifocal hepatocellular carcinoma

Variable	All patients (n = 147)	Infiltrative HCC (n = 75)	Multifocal HCC (n = 72)	P
Imaging modality				0.16
CT	33 (22.4 %)	14 (18.7 %)	19 (26.4 %)	
MRI	28 (19.0 %)	16 (21.3 %)	12 (16.7 %)	
CT and MRI	86 (58.5 %)	45 (60.0 %)	41 (56.9 %)	
Tumor size (cm)	6.5 (0.9–18.5)	9.2 (1.3–18.5)	5.5 (0.9–15.9)	0.005
Discrete mass	81 (55.1 %)	43 (57.3 %)	38 (52.8 %)	0.48
Location				0.16
Left	17 (11.6 %)	11 (14.7 %)	6 (8.3 %)	
Right	59 (40.1 %)	32 (21.8 %)	27 (37.5 %)	
Both	67 (45.6 %)	28 (37.3 %)	39 (54.2 %)	
Dominant location				0.14
Left	39 (26.5 %)	20 (26.7 %)	19 (27.1 %)	
Right	92 (62.6 %)	41 (54.7 %)	51 (72.9 %)	
Caudate	3 (2.0 %)	3 (4.0 %)	–	
Satellite lesions	44 (29.9 %)	18 (24.0 %)	26 (36.9 %)	0.28
Miliary enhancement ^a	15 (14.4 %)	10 (16.4 %)	5 (9.4 %)	0.56
T1 hypointensity ^a	66 (63.5 %)	34 (55.7 %)	32 (60.4 %)	0.99
T2 hyperintensity ^a	87 (83.7 %)	49 (80.3 %)	38 (71.7 %)	0.12
Washout ^a	72 (69.2 %)	31 (50.8 %)	41 (77.4 %)	0.02
Portal vein thrombus	68 (46.3 %)	51 (68.0 %)	18 (25.0 %)	<0.001
Thrombus arterialization ^a	7 (6.7 %)	5 (8.1 %)	2 (3.8 %)	0.07
T2 thrombus hyperintensity ^a	10 (9.6 %)	6 (9.8 %)	4 (7.5 %)	0.86
Lymphadenopathy	43 (29.3 %)	16 (21.3 %)	27 (37.5 %)	0.04
Cirrhosis	115 (78.2 %)	58 (77.3 %)	57 (79.2 %)	0.86
Portal hypertension	106 (72.1 %)	57 (76.0 %)	49 (68.1 %)	0.12
Largest spleen size (cm)	12.6 (7.0–22.5)	12.6 (7.0–20.6)	12.5 (8.0–22.5)	0.94
Varices				0.04
Esophageal/gastric	48 (32.7 %)	26 (34.7 %)	22 (30.6 %)	
Splenorenal	15 (10.2 %)	6 (8.0 %)	9 (12.5 %)	
Retroperitoneal	16 (10.9 %)	8 (10.7 %)	8 (11.1 %)	
Other abdominal	8 (5.4 %)	–	8 (11.1 %)	
Ascites grade				0.07
Grade 1	47 (32.0 %)	33 (44.0 %)	14 (19.4 %)	
Grade 2	34 (23.1 %)	18 (24.0 %)	16 (22.2 %)	
Grade 3	10 (6.8 %)	4 (5.3 %)	6 (8.3 %)	
Direct invasion	71 (48.3 %)	56 (74.7 %)	15 (20.8 %)	<0.001
Metastatic disease	26 (17.7 %)	17 (22.7 %)	9 (12.5 %)	0.13
Lung	9 (6.1 %)	6 (8.0 %)	3 (4.2 %)	

Variable	All patients (<i>n</i> = 147)	Infiltrative HCC (<i>n</i> = 75)	Multifocal HCC (<i>n</i> = 72)	<i>P</i>
Bone	5 (3.4 %)	5 (6.9 %)	–	
Adrenal	3 (2.0 %)	2 (2.7 %)	1 (1.4 %)	
Peritoneum	5 (3.4 %)	2 (2.7 %)	3 (4.2 %)	
Other	4 (2.7 %)	2 (2.7 %)	2 (2.8 %)	

Data are presented as median (range) or *n* (%)

CT computed tomography, *MRI* magnetic resonance imaging, *HCC* hepatocellular carcinoma

^aMRI subgroup

TABLE 3

Comparison of characteristics of patients with infiltrative hepatocellular carcinoma stratified by treatment (intra-arterial therapy vs. best supportive care)

Variable	IAT (n = 48)	BSC (n = 21)	P
Age (year)	48 (30–88)	57 (38–81)	0.49
Male gender	40 (83.3 %)	18 (85.7 %)	0.80
Ethnicity			0.20
White	31 (64.6 %)	9 (42.9 %)	
Black	11 (22.9 %)	9 (42.9 %)	
Other	6 (12.5 %)	3 (14.3 %)	
Performance status			0.16
ECOG 0–2	47 (97.9 %)	19 (90.5 %)	
ECOG 3–4	1 (2.1 %)	2 (9.5 %)	
Hepatitis			0.30
B	9 (18.8 %)	2 (9.5 %)	
C	17 (35.4 %)	12 (57.1 %)	
B and C	1 (2.9 %)	1 (4.8 %)	
Alcohol abuse	8 (16.7 %)	4 (19.0 %)	0.81
Creatinine (mg/dL)	0.8 (0.4–1.8)	0.9 (0.5–2.0)	0.27
INR	1.1 (0.9–2.4)	1.3 (1.0–1.8)	0.05
Total bilirubin (mg/dL)	1.0 (0.3–5.8)	3.3 (0.3–19.7)	0.001
AFP (ng/mL)	244.5 (6.0–>500000)	1563 (14–>500000)	0.09
Encephalopathy	3 (6.3 %)	2 (10.0 %)	0.59
Ascites	11 (22.9 %)	8 (38.1 %)	0.19
MELD score	8.0 (2.0–18.0)	13.0 (6.0–29.0)	0.001
Child-Pugh			0.001
Class A	24 (50.0 %)	4 (19.0 %)	
Class B	21 (43.8 %)	8 (38.1 %)	
Class C	3 (6.3 %)	9 (42.9 %)	
Tumor size (cm)	9.5 (1.3–17.5)	8.5 (2.0–18.5)	0.65
Satellite lesions	14 (31.1 %)	4 (23.5 %)	0.56
Portal vein thrombus	36 (76.6 %)	12 (75.0 %)	0.90
Direct invasion	37 (77.1 %)	15 (71.4 %)	0.62
Metastatic disease	14 (29.2 %)	3 (14.3 %)	0.19

Data are presented as median (range) or *n* (%)

INR international normalized ratio, *AFP* alpha-fetoprotein, *MELD* Model for End-Stage Liver Disease, *ECOG* Eastern Cooperative Oncology Group

TABLE 4

Factors associated with survival among 48 patients with infiltrative hepatocellular carcinoma treated with intra-arterial therapy

Variable	Univariate analysis	
	HR (95 % CI)	P
Age >60 year	1.29 (0.57–2.92)	0.53
Male gender	1.37 (0.41–4.61)	0.61
Performance status		0.22
ECOG 0–2	Ref.	
ECOG 3–4	2.48 (0.58–10.49)	
MELD score	1.18 (1.06–1.31)	0.003
Child-Pugh class		0.06
Class A	Ref.	
Class B/C	2.34 (0.98–5.59)	
Tumor size (cm)	1.11 (0.99–1.25)	0.08
Multiple lesions	0.70 (0.31–1.62)	0.41
Pretreatment total bilirubin >2 mg/dL	4.76 (1.83–12.37)	0.001
Pretreatment AFP > 400 ng/mL	2.31 (1.01–5.29)	0.04
Major vascular invasion	2.73 (0.81–9.18)	0.10
Lymphadenopathy	1.37 (0.54–3.46)	0.50
Metastatic disease	0.82 (0.34–1.98)	0.66
No. of IAT sessions (each incremental session)	0.65 (0.46–0.94)	0.020
AFP response ^a	0.44 (0.169–1.12)	0.09
EASL response		0.004
Stable/partial Response	Ref.	
Progressive disease	3.54 (1.49–8.37)	
Systemic therapy		
Cytotoxic chemotherapy	3.03 (0.38–24.16)	0.30
Molecular targeted therapy	1.15 (0.50–2.65)	0.74
Radiation	0.33 (0.04–2.44)	0.28

^aAFP response defined by >20 % decline from baseline

HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, MELD Model for End-Stage Liver Disease, AFP alpha-fetoprotein, IAT intra-arterial therapy, EASL European Association for the Study of the Liver