Chemoembolization for Hepatocellular Carcinoma:
Comprehensive Imaging and Survival Analysis in a 172-Patient Cohort[1]

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Purpose: To determine comprehensive imaging and long-term survival outcome following chemoembolization for hepatocellular carcinoma (HCC).

Materials and Methods: One hundred seventy-two patients with HCC treated with chemoembolization were studied retrospectively in an institutional review board approved protocol; this study was HIPAA compliant. Baseline laboratory and imaging characteristics were obtained. Clinical and laboratory toxicities following treatment were assessed. Imaging characteristics following chemoembolization were evaluated to determine response rates (size and necrosis) and time to progression (TTP). Survival from the time of first chemoembolization treatment was calculated. Subanalyses were performed by stratifying the population according to Child-Pugh, United Network for Organ Sharing, and Barcelona Clinic for Liver Cancer (BCLC) staging systems.

Results: Cirrhosis was present in 157 patients (91%); portal hypertension was present in 139 patients (81%). Eleven patients (6%) had metastases at baseline. Portal vein thrombosis was present in 11 patients (6%). Fifty-five percent of patients experienced some form of toxicity following treatment; 21% developed grade 3 or 4 bilirubin toxicity. Post-chemoembolization response was seen in 31% and 64% of patients according to size and necrosis criteria, respectively. Median TTP was 7.9 months (95% confidence interval: 7.1, 9.4) but varied widely by stage. Median survival was significantly different between patients with BCLC stages A, B, and C disease (stage A, 40.0 months; B, 17.4 months; C, 6.3 months; $P < .0001$).

Conclusion: The determination of TTP and survival in patients with HCC is confounded by tumor biology and background cirrhosis; chemoembolization was shown to be a safe and effective therapy in patients with HCC.

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Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. It is the sixth most common malignancy worldwide and is the third most common cause of cancer-related mortality (1,2). Curative options are scarce; transplantation remains the standard of care for patients with limited disease as defined by the Milan criteria (3). Given the advanced stage of disease at presentation, numerous noncurative treatment modalities are routinely used, including therapies such as transarterial chemoembolization (4–7).

Although locoregional therapies continue to establish a role in the management of HCC, there remain important gaps in knowledge regarding outcomes using strictly defined objective imaging criteria. Response Evaluation Criteria in Solid Tumors guidelines describe tumor response for systemic treatments and provide minimal guidance for locoregional therapies. This is because locoregional therapies are administered at staged intervals, with different tumors being treated a variable number of times and at different time points. Hence, for locoregional therapies, the concept of assessing size and lesion necrosis continues to have an evolving role in determining response (8,9); these issues are addressed by the European Association for the Study of the Liver (EASL) and other guidelines (8,10). Also, despite the fact that response rate following systemic and locoregional therapy in HCC has been shown to predict a survival benefit, time to progression (TTP) has emerged as an important imaging endpoint that may also be used to predict survival benefit (10–13). The heterogeneity of presentation, differences in tumor natural history, and advanced stage of HCC have resulted in substantial difficulties in the design of clinical trials. Finally, the variability and lack of standardization of locoregional therapies have also made data interpretation and analyses difficult.

The purpose of this study was to determine the response rate (size and necrosis), TTP, and survival in a cohort of patients with HCC following chemoembolization.

Materials and Methods

Patient Cohort

Between January 1, 2000, and December 31, 2008, 172 patients underwent treatment with chemoembolization for HCC at a single institution. Institutional review board authorization was obtained; this study was Health Insurance Portability and Accountability Act compliant.

Pretreatment Evaluation and Staging

All patients underwent pretreatment assessment including history, physical examination, and laboratory assessment. Clinical criteria for treatment with chemoembolization included (a) imaging or pathologic diagnosis of HCC, (b) Eastern Cooperative Oncology Group performance status of 0–2, (c) bilirubin level of 3.0 mg/dL or less (≤51.3 μmol/L), (d) limited portal vein thrombosis (with hepatopedal flow), and/or (e) extrahepatic metastases (patients with cirrhosis often exhibit reactive lymphadenopathy in the periportal,

cardiophrenic, or retroperitoneal lymph nodes; for this analysis, lymph nodes larger than 2.0 cm in these locations were also classified as extrahepatic metastases) (14). Cirrhosis was defined as the presence of any of the following: nodular liver surface at imaging, portal hypertension, or evidence of cirrhosis at pathologic evaluation of the biopsy specimen. Portal hypertension was defined as the presence of either (a) splenomegaly with thrombocytopenia (platelets < 100 000/μL) or (b) portosystemic shunts (patent umbilical veins, coronary/gastroesophageal varices, splenorenal shunts) (15). Biopsy was performed to confirm HCC if the lesion was larger than 2 cm but did not meet standard imaging criteria (7,8,16,17) or if the maximum dimension of the lesion was 1–2 cm (17). Tumor burden was defined by means of subjective assessment as the percentage of the total liver volume that was involved by the tumor. Baseline diagnostic imaging was performed by using contrast material–enhanced magnetic resonance (MR) imaging or triphasic computed tomography (CT). Patients were staged by using the Child-Pugh, United Network for Organ Sharing (UNOS), Okuda, Barcelona Clinic Liver Cancer (BCLC), and

Advances in Knowledge

- Median time to progression (TTP) was 7.9 months.
- Patients with Barcelona Clinic for Liver Cancer (BCLC) stage C disease had significantly lower TTP compared with patients with BCLC stages A and B (A, 8.8 months; B, 9.4 months; C, 3.5 months; $P = .0005$).
- Median survival of all patients with BCLC stages A, B, and C disease was significantly different: A, 40.0 months; B, 17.4 months; C, 6.3 months.

Implication for Patient Care

- TTP in patients treated with chemoembolization for hepatocellular carcinoma appears to be comparable to that in patients treated with biologic agents (eg, sorafenib), without the associated systemic toxicities.

Cancer of the Liver Italian Program classifications (16,18,19).

Treatment

Treatment with chemoembolization was consensus-based by a multidisciplinary team in HCC conference at our institution. On the day of treatment, patients underwent angiography to determine vascular anatomy and variants and to assess portal flow (20). Chemotherapeutic agents (30 mg doxorubicin, 100 mg cisplatin, and 30 mg mitomycin) mixed with 10 mL lipiodol were injected at the branch or segmental arterial level, followed by injection of 300–500 μm permanent embolic particles (Embospheres; BioSphere Medical, Rockland, Mass) (21–23). Patients were subsequently admitted for the management of potential postembolization syndrome. Additional chemoembolization sessions were performed if *(a)* the first treatment was thought to incompletely treat the lesion (or lesions) on cross-sectional images (represented by viable tumor), *(b)* the multifocality of disease did not allow complete targeting of tumor in one treatment session, or *(c)* alternate blood supply from parasitized hepatic arteries were identified at initial diagnostic angiography.

Response Evaluation

Patients underwent imaging (triphasic CT or contrast-enhanced MR imaging) 1 month after treatment to assess response in the treated lesions and subsequently underwent imaging every 2–3 months (8). Five radiologists who were well-versed in the radiographic changes that follow locoregional therapies performed baseline and response assessments (R.J.L., R.K.R., F.H.M., K.T.S., and R.S.). Given the scope of this analysis and time constraints, only one reader per patient was assigned. During imaging assessment, response was assessed according to World Health Organization (WHO) and EASL criteria, and a search was performed for the appearance of new lesions or extrahepatic metastases. All scans obtained from baseline to last follow-up, transplantation, or death were evaluated. Target lesions were identified and measured;

untreated lesions were not included in the response analysis. Target lesions were defined as follows: In patients with solitary HCC lesions, the one lesion was used for assessment of response; in patients with multifocal disease, since chemoembolization treatments are performed as staged procedures at our institution, we used the largest tumor treated during the first session to follow for response assessment (40).

WHO criteria.—WHO criteria recommend using the product of the tumor's maximum dimension with its perpendicular dimension for measurement. Response of the target lesions were assessed with WHO criteria by using the following definitions: complete response was defined as 100% decrease in sum of products; partial response, 50% or more decrease in sum of products of the target lesions; and progressive disease, greater than 25% increase in the sum of the products from maximum response or new intra- or extrahepatic lesions. All others findings were defined as stable disease (8,24). Of importance, when assessing response according to WHO criteria, the entire lesion was always measured, rather than only the enhancing portion, as has been reported by other investigators (25).

EASL criteria.—Enhancement characteristics and degree of necrosis in the treated lesions were studied (26). EASL response in treated lesions are based on the following: complete response was defined as absence of any enhancing tissue; partial response, greater than 50% decrease in enhancing tissue; and stable disease, less than 50% decrease in enhancing tissue (8,13). Progressive disease was defined as any increase in the amount of enhancing tissue that clinically would translate into additional locoregional therapy (ie, repeat chemoembolization).

α-Fetoprotein.—Among patients with available α-fetoprotein (AFP) findings, an exploratory analysis was performed in patients with baseline AFP level greater than 200 ng/mL and greater than 400 ng/mL to facilitate comparison of our data with data from those centers using these values as their cut-off levels for HCC diagnosis (27). The post-

treatment AFP levels were compared with the baseline (greater than 50% reduction, greater than 90% reduction, complete normalization) (28).

Progression Analysis

For purposes of calculating TTP, an endpoint was defined as progression according to any of the following modes: WHO, EASL, or UNOS stage, portal vein thrombus extension, or appearance of new lesion. Despite the fact that patients underwent pretreatment scanning, the starting point for all variables was the date of first chemoembolization session. Patients without imaging follow-up available were censored as "nonprogressors" on the day of first treatment. A patient undergoing multiple treatments to the same lesion to completely devascularize the lesion, or one needing two separate embolization sessions to completely cover the tumor bed because of alternate blood supply, was considered to have undergone one cycle. All patients were permitted to undergo one treatment cycle to the target lesion(s), after which any imaging findings that fulfilled any of the above criteria for progressive disease (and potentially necessitated additional chemoembolization treatment) was counted as progression. Per guidelines, the development of a new lesion was confirmed in retrospect as progression at the time it was first detected, even if definitive imaging criteria for new HCC were met at subsequent imaging (10).

Toxicity

All patients were followed up clinically for toxicities and adverse events according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0 (29). Toxicities were recorded at any time during follow-up and were only censored to curative treatment (ie, transplantation or resection). Toxicity was recorded only if the grade increased from baseline.

Statistical Analyses and Survival

Prior to final statistical analysis, preliminary data were analyzed by using univariate and graphical methods, wherever applicable, to facilitate inspection

and interpretation of the data. Outliers and influential observations were identified and checked for accuracy. Data error due to data entry oversight was appropriately corrected. All data were summarized by using appropriate descriptive statistics (eg, mean and standard deviation for continuous variables, count and frequency for categorical variables). Kaplan-Meier analysis was used to evaluate patient survival. Median time to response, TTP, and survival were calculated and compared by using the log-rank test (30). For the purposes of survival calculations, death was defined as an endpoint; patients were censored at the date of last follow-up or date of resection or transplantation (if applicable). Median follow-up time was determined by using the reverse Kaplan-Meier method (31).

Hazard ratios were calculated by using univariate and multivariate Cox proportional hazards regression models. Independent variables entered into the multivariate model predicting patient survival included age, sex, ethnicity, cirrhosis, portal hypertension, Eastern Cooperative Oncology Group performance status, UNOS stage, WHO response, EASL response, and baseline AFP levels. Portal vein thrombosis, metastases, tumor distribution, and maximum baseline tumor dimension were not included into the multivariate model because they were captured by means of UNOS stage. Bilirubin and ascites were not included in the multivariate model because they were captured by Child-Pugh class. These variables were excluded to eliminate multi-colinearity in the multivariate regression model. Throughout the report, confidence interval estimation was performed by using the Wald method and statistical significance was established at an α level of .05. All statistical analyses were performed by using statistical software (SAS version 9.2; SAS Institute, Cary, NC).

Results

Patient Sample

Tables 1 and 2 display baseline data for the 172-patient cohort. Median age was

60 years (range, 33–89 years); 140 patients (81%) were male. Hepatitis C (85 patients [49%]) and alcohol (29 patients [17%]) were the most common contributing factors for cirrhosis. The majority of patients had a performance status of 0 (90 patients [52%]) and had not undergone prior treatment (155 patients [90%]). In 71 patients (41%), HCC was confirmed at biopsy. Most patients had

Table 1

Baseline Demographics in Patients with HCC

Parameter	No. of Patients ($n = 172$)
Age (y)	
<65	108 (63)
≥65	64 (37)
Sex	
Male	140 (81)
Female	32 (19)
Ethnicity	
Caucasian	115 (67)
Hispanic	23 (13)
African American	17 (10)
Asian	17 (10)
Cause	
Hepatitis C virus	85 (49)
Alcohol	29 (17)
Hepatitis B virus	19 (11)
Cryptogenic	18 (10)
Primary biliary cirrhosis	4 (2)
Hemochromatosis	3 (2)
Autoimmune	2 (1)
Hepatitis C and alcohol	2 (1)
Hepatitis C and B viruses	1 (0.5)
NASH	1 (0.5)
Unknown	8 (5)
ECOG performance status	
0	90 (52)
1	77 (45)
2	5 (3)
Prior treatment	
None	155 (90)
Resection	8 (5)
Radiofrequency ablation	8 (5)
Percutaneous ethanol injection	1 (0.5)
Method of diagnosis	
Biopsy	71 (41)
Imaging	101 (59)

Note.—Data in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group, NASH = nonalcoholic steatohepatitis.

Table 2

Baseline Characteristics and Disease Stages in Patients with HCC

Parameter	No of Patients ($n = 172$)
Imaging finding	
Cirrhosis	
Present	157 (91)
Absent	15 (9)
Ascites	
Present	30 (17)
Absent	142 (83)
Portal hypertension	
Present	139 (81)
Absent	33 (19)
Tumor characteristics	
Distribution	
Solitary	74 (43)
Multifocal	98 (57)
Tumor location	
Bilobar	105 (61)
Unilobar	67 (39)
Tumor burden*	
0%–25%	159 (92)
26%–50%	7 (4)
51%–75%	6 (3)
76%–100%	0 (0)
Portal vein thrombosis	
Absent	161 (94)
Present	11 (6)
Metastases	
Absent	161 (94)
Present	11 (6)
Largest tumor size†	
Overall	172 [5.4, 1–20.2]
<5 cm	106 (62) [3.2, 1–4.9]
5–10 cm	45 (26) [6.9, 5–9.7]
>10 cm	21 (12) [13.7, 10.5–20.2]
Laboratory data	
AFP (ng/mL)	
≤200	112 (65)
>200	60 (35)
Total bilirubin (mg/dL)	
<2	131 (76)
2–3	32 (19)
>3	9 (5)
Albumin (mg/dL)	
>3.5	26 (15)
2.8–3.5	95 (55)
<2.8	51 (30)
Staging	
Child-Pugh class	
A	96 (56)
B	73 (42)
C	3 (2)

Table 2 (continues)

Table 2 (continued)

Baseline Characteristics and Disease Stages in Patients with HCC

Parameter	No of Patients (n = 172)
BCLC stage	
A	62 (36)
B	73 (42)
C	34 (20)
D	3 (2)
UNOS stage	
T1	4 (2)
T2	61 (35)
T3	43 (25)
T4a (≥4 tumors)	42 (24)
T4b (portal vein thrombosis)	11 (6)
N (lymph nodes >2 cm)	9 (5)
M (extrahepatic metastases)	2 (1)

Note.—Data in parentheses are percentages.

* Indicates percent of liver involved by tumor.

† Data in brackets are the mean tumor size and range, respectively, in centimeters.

Table 3

Clinical and Laboratory Toxicities

Parameter	No. of Patients (n = 172)
Clinical toxicity (grade 1–2), adverse event	
Fatigue	62 (36)
Abdominal pain	57 (33)
Nausea/vomiting	43 (25)
Anorexia	21 (12)
Diarrhea	14 (8)
Fever/chills	5 (3)
Weight loss	5 (3)
Groin injury	3 (2)
Biochemical toxicity (grade 3–4)	
Bilirubin	36 (21)
Albumin	32 (19)
ALT	25 (15)
AST	44 (26)
Alkaline phosphatase	7 (4)

Note.—Data in parentheses are percentages. ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Figure 1

Figure 1: Waterfall plot demonstrates post-chemoembolization change in tumor size.

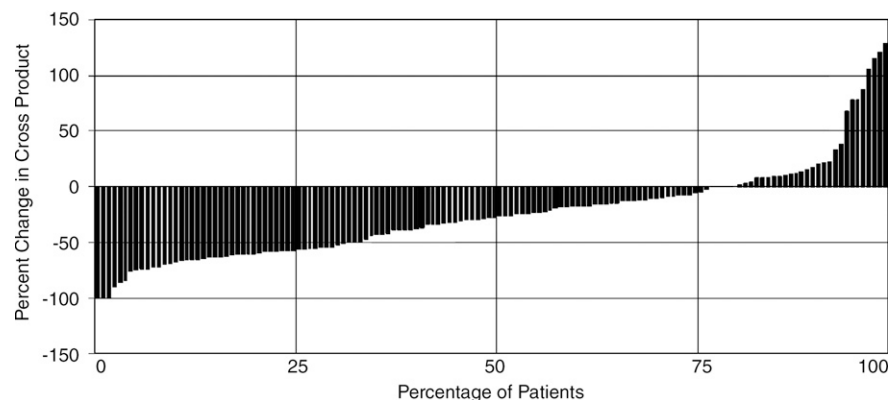cirrhosis (157 patients [91%]) and portal hypertension (139 patients [81%]). Seventy-four patients (43%) had solitary HCC with a tumor burden of less than 25% [159 patients (92%)] and no vascular invasion (161 patients [94%]). Eleven (6%) had extrahepatic metastases (nine patients had enlarged lymph nodes, one had lung nodules, and one had peritoneal metastases). The mean size of the largest tumor was 5.4 cm. In most patients, bilirubin level was less than 2.0 mg/dL. There were 96 patients (56%) with Child-Pugh class A, 135 (78%) with BCLC A or B, 61 (35%) with UNOS T2, and 43 (25%) with UNOS T3 disease.

Treatment and Follow-up

The median number of treatments was one per patient (interquartile range, 1–2; range, 1–5) for the entire cohort; the median number of treatments in patients who did not undergo transplantation was two per patient (interquartile range, 1–2; range, 1–5). The median length of hospitalization was 2 days (interquartile range, 1–2 days; range, 1–11 days). No patient received sorafenib (Nexavar; Bayer, Berlin, Germany) or other transarterial locoregional therapy. Nine patients underwent radiofrequency ablation in small, de novo HCCs at progression.

Clinical and Laboratory Toxicities

Table 3 lists the clinical and laboratory toxicities. The most common findings after treatment included fatigue (62 patients [36%]), pain (57 patients [33%]), and nausea/vomiting (43 patients [25%]). Grade 3–4 bilirubin toxicities were also noted (36 patients [21%]).

Imaging Outcomes

Response rate.—Of 172 patients, 143 (83%) underwent imaging follow-up; 29 patients (17%) had no imaging follow-up (early transplantation, n = 18; death within 3 months, n = 2; no posttreatment imaging follow-up available, n = 9). Overall, 568 scans were reviewed, for a mean of 2.8 follow-up scans per patient. Table 4 lists response and TTP analyses stratified by stage. Figure 1 is a waterfall plot demonstrating percent change in tumor size following treatment (from baseline). Although a WHO partial response rate of 31% (44 of 143) was seen in this analysis, 77% (110 of 143) of lesions showed decrease in size following treatment. According to EASL, the response rate was 64% (91 of 143) (complete response, 23%; partial response, 41%). The median time to partial response in responders was 4 months (95% confidence interval: 2.8, 5.8 months) by WHO criteria and 1.3 months (95% confidence interval: 1.2, 1.8 months) by EASL criteria. Response rates were similar between patients with Child-Pugh class A (WHO: 26 of 80 [33%]; EASL: 47 of 80 [59%]) and class B (WHO: 19 of 61 [31%]; EASL: 43 of 61 [70%]) disease. WHO partial response rate by tumor size was as follows: smaller than 5 cm, 32 of 90 (36%); 5–10 cm, nine of 33 (27%); and larger than 10 cm, four of

Table 4

Imaging and Survival Analyses

Staging	No. of Patients*	EASL Partial Response	WHO Partial Response	Median TTP (mo)[†]	Median Survival (mo)[†]	No. of Transplant Patients
Child-Pugh class A						
Overall	90 (74)	45 (61)	25 (34)	9.4 (7.5, 11.5)	15.1 (12.8, 18.2)	28 (31)
PVT absent						
Overall no PVT	82 (67)	43 (64)	25 (37)	9.6 (7.6, 11.7)	15.6 (14.7, 19)	28 (34)
UNOS T1/T2	32 (24)	20 (83)	7 (29)	11.3 (7.2, 32.9)	… (15.1, …)	14 (44)
UNOS T3	23 (18)	12 (67)	9 (50)	12.8 (6.1,…)	19.1 (12.9, 23.8)	8 (35)
UNOS T4a	27 (25)	11 (44)	9 (36)	9.4 (7.3, 11.5)	15.1 (12.6, 18.6)	6 (22)
PVT present (overall UNOS T4b)	8 (7)	2 (29)	0 (0)	2.4 (…, 8.9)	5.9 (4.1, 12)	0 (0)
Child-Pugh class B						
Overall	68 (56)	41 (73)	19 (34)	7 (5.3, 9.2)	12.8 (9.9, 24.5)	29 (43)
PVT absent						
Overall no PVT	65 (53)	40 (75)	19 (36)	7.7 (5.8, 10.6)	17.4 (10.8, 24.4)	29 (45)
UNOS T1/T2	32 (25)	19 (76)	9 (36)	6.8 (4.2, 9.2)	25.9 (12.8, 45.5)	21 (66)
UNOS T3	18 (16)	12 (75)	4 (25)	7.0 (3.1, 19.6)	18.7 (10.7, 26.4)	3 (17)
UNOS T4a	15 (12)	9 (75)	6 (50)	7.7 (5.8, …)	9.3 (4.7, 17.9)	5 (33)
PVT present (overall UNOS T4b)	3 (3)	1 (33)	0 (0)	2.0 (…, 2.8)	3.5 (…, …)	0 (0)
Child-Pugh class C	3 (2)	1 (50)	0 (0)	4.4 (…, …)	11.3 (…, …)	1 (33)
BCLC A						
Overall	62 (47)	38 (81)	15 (32)	8.8 (6.8, 20.2)	40 (15, 46)	35 (56)
Child-Pugh A	30 (22)	19 (86)	6 (27)	11.3 (7.2, 32.8)	…(15, …)	14 (47)
Child-Pugh B	32 (25)	19 (76)	9 (36)	6.8 (4.2, 9.1)	26 (12.9, 45)	21 (66)
BCLC B						
Overall	73 (61)	40 (67)	27 (44)	9.4 (7.3, 11.5)	17.4 (13.9, 18.8)	22 (30)
Child-Pugh A	43 (36)	22 (61)	17 (47)	9.6 (7.3, 11.9)	17.5 (14.8, 20.7)	14 (33)
Child-Pugh B	30 (25)	18 (72)	10 (40)	7.7 (5.8, 19.6)	12.7 (10, 20.7)	8 (27)
BCLC C						
Overall	23 (22)	8 (36)	2 (9)	6.3 (2.4, 8.9)	6.6 (4, 9.3)[‡]	0
Child-Pugh A						
PVT absent	9 (9)	2 (22)	2 (22)	7.9 (6.3, …)	10.3 (6, 15.7)	0
PVT present	8 (7)	2 (29)	0	2.4 (…, 8.9)	5.9 (4.1, 12)	0
Child-Pugh B						
PVT absent	3 (3)	3 (100)	0	… (…, …)	9.3 (…, …)	0
PVT present	3 (3)	1 (33)	0	2.0 (…, 2.8)	3.5 (…, …)	0
BCLC D (Child-Pugh C)	3 (2)	1 (50)	0	4.4 (…,…)	11.3 (…, …)	1 (33)

Note.—Except where indicated, data are numbers of patients, and data in parentheses are percentages. Table includes 132 patients without extrahepatic metastases for imaging (WHO partial response, EASL partial response) and 161 patients for survival and TTP analyses (patients without imaging follow-up were censored as nonprogressors at the time of first treatment). PVT = portal vein thrombosis.

* Data in parentheses are numbers of patients with imaging follow-up.

[†] Data in parentheses are 95% confidence intervals.

[‡] One patient underwent resection.

20 (20%). EASL partial response rate by tumor size was as follows: smaller than 5 cm, 66 of 90 (73%); 5–10 cm, 14 of 33 (42%); and larger than 10 cm, 11 of 20 (55%).

Median TTP.—TTP for the entire cohort (n = 143) was 7.9 months (95% confidence interval: 7.1, 9.4 months); 75% of patients were progression-free at 16 weeks. Figure 2 displays TTP in Kaplan-Meier format.

AFP level.—Baseline AFP level greater than 200 ng/mL was observed in 60 patients (35%). Follow-up AFP levels were available in 52 of these patients and showed the following responses: a greater than 50% reduction in AFP in 26 patients (50%), a greater than 90% reduction in 16 patients (31%), and complete normalization in three patients (6%). Baseline AFP level greater than 400 ng/mL was observed in 50 (29%) of

172 patients. In 42 of these 50 patients, follow-up AFP findings were available and showed the following responses: greater than 50% reduction in AFP in 21 patients (50%), greater than 90% reduction in 15 patients (36%), and complete normalization in three patients (7%).

Survival Analyses

No patient was lost to follow-up for the survival analyses. At the time of study

Figure 2
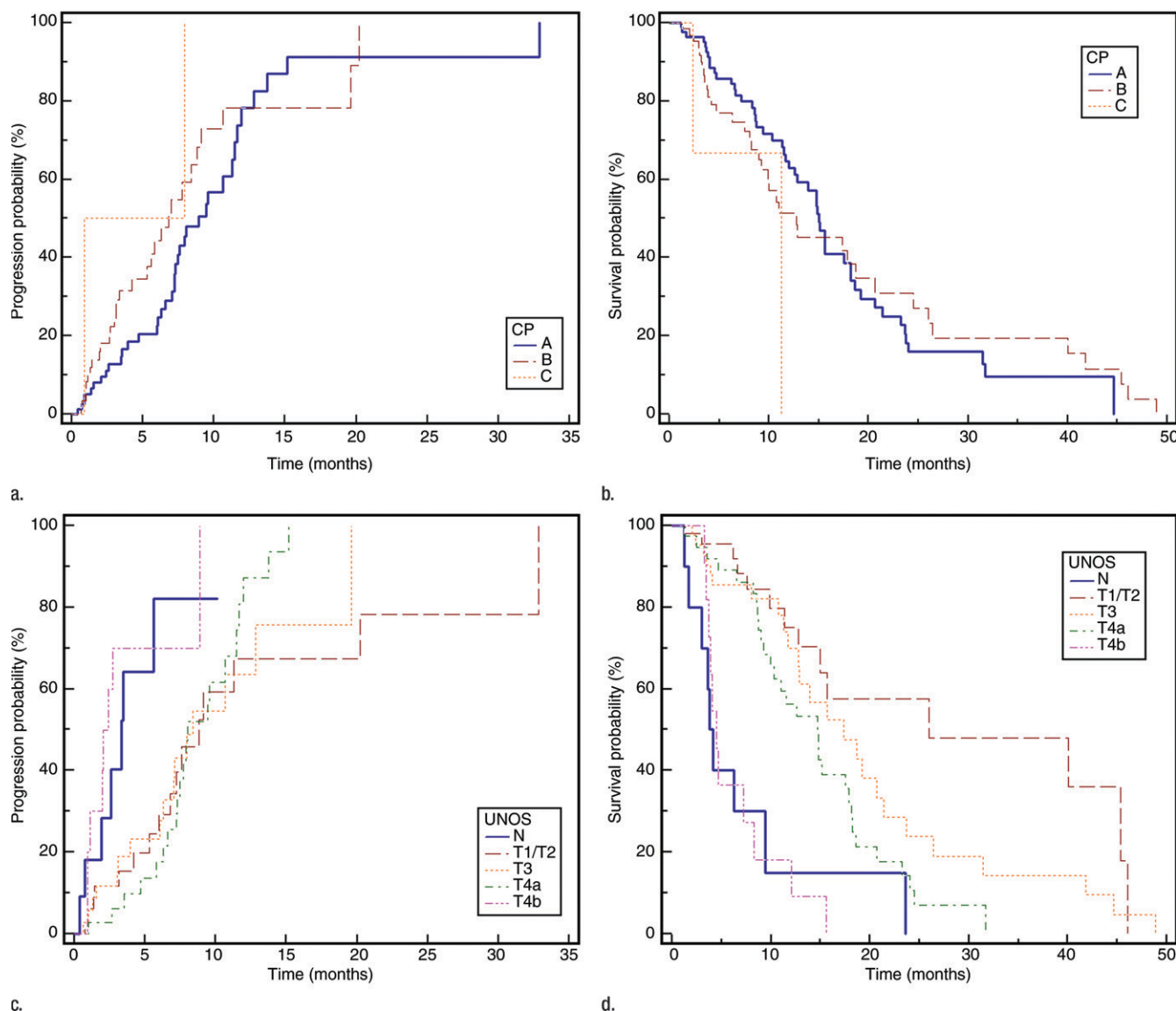
Figure 2: Kaplan-Meier curves demonstrate **(a)** TTP substratified by Child-Pugh class *(CP)* (*P* = .1351), **(b)** survival substratified by Child-Pugh class (*P* = .2927), **(c)** TTP substratified by UNOS stage (*P* = .0001), **(d)** survival substratified by UNOS stage (*P* < .0001). *(Fig 2 continues.)*

closure, 112 patients had died (55 [49%] with disease progression, 48 [43%] with stable disease and grade ≥1 bilirubin toxicity, and nine [8%] with stable disease and no bilirubin toxicities). To mitigate the effect of extrahepatic metastases, Table 4 reports survival for the 161 patients who were free of metastases at baseline. The median follow-up period was 38.9 months (95% confidence interval: 31.9, 51.9 months). Sixty-one patients underwent curative transplanta-

tion (*n* = 59) or resection (*n* = 2); survival is reported censored to the date of transplantation. Survival of patients with Child-Pugh class A and Child-Pugh class B BCLC B disease was 17.5 and 12.7 months, respectively (*P* = .62). Median survival was significantly different between patients with BCLC A, B, and C disease (stage A, 40.0 months; B, 17.4 months; C, 6.6 months; *P* = .001). The median survival of patients with (*n* = 11) and those without (*n* = 161)

metastases was 4.2 months (95% confidence interval: 15.6, 24.2 months) and 18.6 months (95% confidence interval: 2.9, 9.4 months) (*P* < .0001), respectively. Figure 2 displays survival as Kaplan-Meier curves.

Univariate and Multivariate Analyses

Table 5 presents the hazard ratios by category of various predictors of survival in HCC. Significant prognosticators of survival on univariate and multivariate

Figure 2 (Continued)

e.

f.
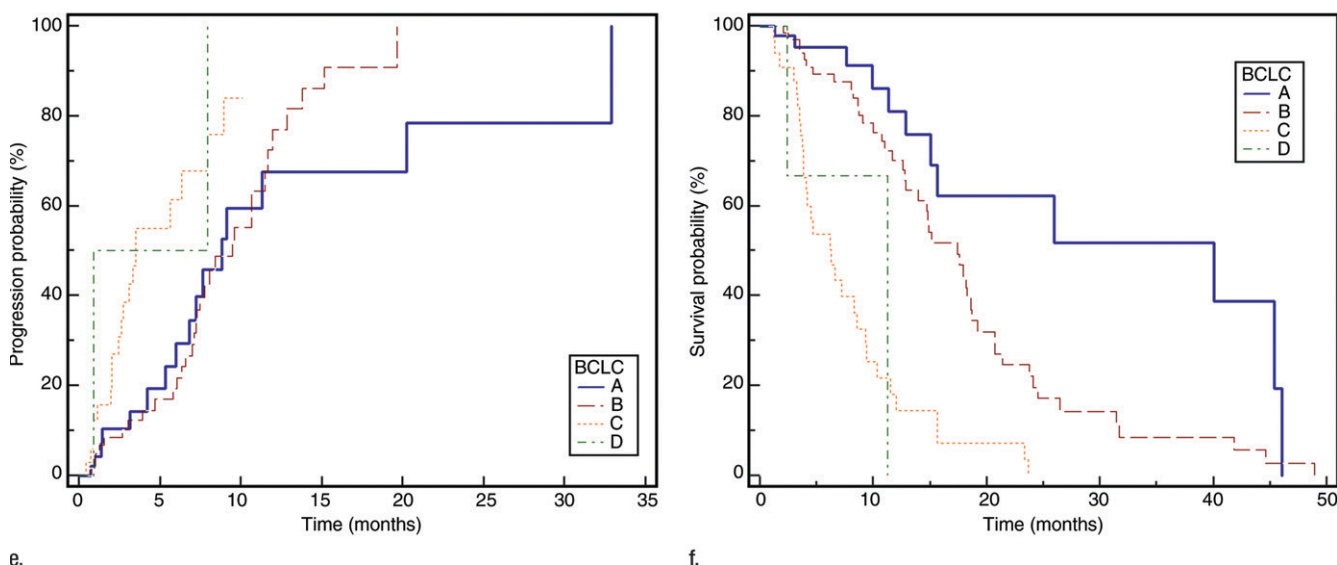
Figure 2 *(continued):* Kaplan-Meier curves show **(e)** TTP substratified by BCLC stage (*P* = .0009), and **(f)** survival substratified by BCLC stage (*P* < .0001).

analysis included UNOS stage, baseline AFP levels, and WHO response. Presence of extrahepatic metastases (*P* = .0005) and/or vascular invasion (*P* = .0002) was seen to be associated with significantly worse survival. Baseline AFP levels of 200 ng/mL or less (*P* = .0015) and observation of WHO response after treatment (*P* = .0015) were associated with improved survival.

Discussion

Chemoembolization as a treatment option for HCC has been used for decades. Since then, outcomes have been improved by advances in interventional techniques and refinement in patient selection. In fact, chemoembolization was established as the standard of care for intermediate-stage HCC in 2002 when randomized studies in selected patients with Child-Pugh class A disease demonstrated a survival benefit (32,33). Chemoembolization is now recognized as the standard of care for intermediate-stage HCC (7,8).

The incidence of HCC is increasing worldwide (34). Progress has been made in the past decade in the management of HCC with surgical, systemic, and locoregional treatments. Effective locoregional

treatment modalities for HCC necessitate the ability to accurately assess response by using imaging and to compare with systemic agents. Our study included a large cohort of HCC patients treated at a single institution with chemoembolization, where comprehensive imaging follow-up and investigator-assessed response permitted the exploratory analysis of TTP analyses using strict objective imaging criteria. Such imaging outcomes following chemoembolization obtained in a systematic manner that includes EASL guidelines have not been thoroughly reported.

In our study, the safety of chemoembolization was found to be similar to that in recent reports. Georgiades et al (35) described a 22% incidence of grade 3 bilirubin toxicities at 1-year follow-up, which is in line with our findings of 21% grade 3–4 hyperbilirubinemia. The incidence of postembolization syndrome was also in keeping with that in previous reports; 55% of our patients experienced symptoms attributable to chemoembolization (36).

Although response rate has traditionally been used as an endpoint in phase 2 studies prior to advancing to phase 3, this concept is being challenged with the advent of molecular tar-

geted therapies (37,38). Clinically relevant survival advantages have been seen with therapies that produce marginal response (10,11,13). The most powerful evidence supporting TTP as a surrogate for survival was published in a phase 3 trial in advanced HCC in which patients were to receive either sorafenib or placebo; median TTP was 5.5 months in the sorafenib group and 2.8 months in the placebo group (*P* < .001). Response rate was 2% for sorafenib and 1% for placebo. Despite the lack of response, a survival benefit was identified, suggesting that improvements in survival may be obtained with cytostatic agents (10). Although this finding challenges the role of using imaging to assess response for targeted agents, there are no conclusive data to extend this concept to locoregional therapies such as transarterial chemoembolization. A consensus panel did agree on avascularity and necrosis as components of response in capturing antitumor effects of therapies such as chemoembolization (8). This suggests that in single-arm studies (without comparators), tumor response will continue to be integral to the identification of antitumor effect.

We analyzed various outcomes (such as TTP) as a function of *(a)* Child-Pugh

class substratified by tumor stage (UNOS stage/portal vein thrombosis) and *(b)* BCLC stage. As outcomes are based on different staging schemes, the creation of such tables for other forms of systemic and locoregional therapies would allow direct comparisons of these treatment options. These data may also assist in designing clinical trials for chemoembolization. Our median TTP with chemoembolization was 7.9 months, and the progression-free rate at 16 weeks was 75%. Recent single-arm studies have reported a median TTP of 4.2 months and median survival of 9.2 months in patients with treatment-naïve inoperable HCC treated with sorafenib (38) and a progression-free survival at 16 weeks of 62.5% for patients treated with bevacizumab and erlotinib (39).

The data from this cohort showed minimal differences in survival between patients with Child-Pugh classes A and B disease without UNOS substratification. This may be due to the fact that patients with Child-Pugh A disease had a higher rate of advanced HCC (T4a+T4b) in our population when compared with patients with Child-Pugh B disease (39% vs 26%). This finding stresses the importance of using staging systems that combine liver function, vascular invasion, and tumor burden when comparing outcomes (10). The differences in outcomes become more evident when using the BCLC staging system.

In the multivariate analyses, presence of extrahepatic metastases and/or vascular invasion was seen to be associated with significantly worse survival; baseline AFP levels of 200 ng/mL or lower and observation of WHO response after treatment were associated with improved survival. EASL response was not found to be a significant prognostic factor. This may be due to the arterial occlusive effect of transarterial chemoembolization; decreased contrast agent delivery to the tumors (which leads to falsely classifying a tumor as showing response) and embolization of tumor vascularity may result in the development of new parasitized collateral vessels that would result in locally recurrent disease.

Table 5

Univariate and Multivariate Analyses

Predictor	Univariate Analysis (Kaplan Meier and Log-rank Test)		Multivariate Analysis (Cox Proportional Hazards Model)	
	Hazard Ratio	P Value	Hazard Ratio	P Value
Age (y)				
<65	1.26 (0.82, 1.94)	.2885	0.97 (0.55, 1.70)	.9060
≥65	1.00		1.00	
Sex				
Female	1.1 (0.65, 1.86)	.719	0.93 (0.48, 1.82)	.8368
Male	1.00		1.00	
Ethnicity				
African American	0.66 (0.34, 1.32)	.2402	0.98 (0.43, 2.21)	.9621
Hispanic	0.74 (0.39, 1.39)	.3485	0.42 (0.19, 0.91)	.0287
Asian	0.69 (0.34, 1.40)	.3041	0.98 (0.36, 2.61)	.9592
Caucasian	1.00		1.00	
Baseline bilirubin level				
<2 mg/dL	1.2 (0.69, 2.1)	.5182		
≥2 mg/dL	1.00			
Cirrhosis				
Absent	1.63 (0.89, 2.94)	.1085	2.39 (0.91, 6.29)	.0778
Present	1.00		1.00	
Portal hypertension				
Absent	1.25 (0.79, 1.98)	.3447	0.71 (0.33, 1.53)	.3797
Present	1.00		1.00	
Portal vein thrombosis				
Absent	0.22 (0.11, 0.43)	<.0001		
Present	1.00			
Metastases				
Absent	0.28 (0.14, 0.56)	.0004		
Present	1.00			
Distribution				
Solitary	0.61 (0.39, 0.96)	.0323		
Multifocal	1.00			
ECOG performance status				
0	0.47 (0.16, 1.33)	.1522	0.57 (0.17, 1.99)	.3797
1	0.89 (0.32, 2.49)	.8239	0.90 (0.26, 3.11)	.9704
2	1.00		1.00	
UNOS stage				
N/M	7.54 (3.18, 17.91)	<.0001	6.56 (2.28, 18.87)	.0005
T4b (portal vein thrombosis)	9.29 (4.03, 21.38)	<.0001	7.76 (2.60, 23.16)	.0002
T4a	2.71 (1.40, 5.23)	.003	1.98 (0.84, 4.66)	.1163
T3	1.67 (0.86, 3.23)	.1303	1.12 (0.49, 2.55)	.7941
T1/T2	1.00		1.00	
Child-Pugh class				
A	0.34 (0.08, 1.41)	.1360	0.34 (0.04, 2.92)	.3257
B	0.34 (0.08, 1.44)	.1421	0.55 (0.07, 4.59)	.5765
C	1.00		1.00	
Ascites				
Absent	0.64 (0.38, 1.07)	.0899		
Present	1.00			
WHO response				
No	2.11 (1.28, 3.48)	.0035	2.66 (1.29, 5.47)	.0080
Yes	1.00		1.00	

Table 5 (continues)

Table 5 (continued)

Predictor	Univariate Analysis (Kaplan Meier and Log-rank Test)		Multivariate Analysis (Cox Proportional Hazards Model)	
	Hazard Ratio	P Value	Hazard Ratio	P Value
EASL response				
No	1.58 (1.01, 2.49)	.0486	1.06 (0.59, 1.89)	.8448
Yes	1.00		1.00	
AFP level (ng/mL)				
≤200	0.51 (0.33, 0.78)	.0020	0.39 (0.23, 0.70)	.0015
>200	1.00		1.00	
Maximum baseline dimension				
<5 cm	0.59 (0.35, 1.02)	.0575		
5–10 cm	0.99 (0.56, 1.78)	.9487		
>10 cm	1.00			

Note.—Data in parentheses are 95% confidence intervals. Portal vein thrombosis, metastases, distribution, and dimension were not included in the multivariate model because they are captured by UNOS stage. Bilirubin level and ascites were not included in the multivariate model because they are captured by Child-Pugh score. ECOG = Eastern Cooperative Oncology Group.

There are limitations to this analysis. Nontarget lesions that were not treated during the first treatment session were not included in the response analysis at the lesion level; however, appearance of new lesions was incorporated in TTP analyses. Because of time and funding limitations, only one reader was assigned per patient. Although there are variations in chemoembolization technique, this bias is minimized by the single-center experience, providing an internal standard. Progression according to EASL enhancement was recorded when any enhancement that led to retreatment was noted rather than waiting for 30% increase as recommended (10). The confidence intervals of time-to-endpoint analyses using Kaplan-Meier techniques (TTP and survival) are dependent on the number of endpoints reached. Due to the low number of endpoints reached in the substratification analyses, the confidence intervals are correspondingly wide.

There is a need for prospective studies that assess the long-term effects of chemoembolization as well as a need to initiate combination or head-to-head studies that include targeted molecules. Guidance on the design and appropriate endpoints of such studies has been recently described (10). Novel imaging tools such as diffusion-weighted MR imaging and other functional instruments may become integral to such research and appear to be addressed by intergroup studies. The imaging outcomes reported herein are meant to be hypothesis-generating as future clinical trials are explored. A cooperative group study of chemoembolization with and without sorafenib is underway.

Chemoembolization is a safe and effective therapy for patients with HCC. We recommend using staging systems that combine liver function, vascular invasion, and tumor burden when comparing outcomes for HCC.

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