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APPROVAL SHEET

Multivariate analysis of prognostic factors for survival following doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma.

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ABSTRACT COVER PAGE

Multivariate analysis of prognostic factors for survival following doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma.

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Abstract

Purpose. To identify prognostic factors for survival in hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization with doxorubicin-eluting beads (DEB-TACE).

Methods. This is a retrospective, single-center analysis of patients with HCC treated with DEB-TACE. Tumor- and patient-related factors were recorded for univariate and multivariate analyses via Kaplan-Meier and Cox regression. Infiltrative HCC phenotype and portal vein invasion (PVI) were correlated, and patients having either or both were classified as “radiographically advanced HCC” (RAdv-HCC). The primary endpoint was overall survival, which was calculated from the time of first DEB-TACE.

Results. 135 patients underwent 248 procedures. 215 (86.7%) were outpatient procedures, and mean length of stay was 0.33 days; 25 (10.1%) were readmitted within 30 days. 130 had cirrhosis; 62, 50 and 18 were Child's A, B and C, respectively. 41 had infiltrative HCC phenotype, 28 of whom also had PVI. Multivariate analysis of survival in all patients showed AFP, performance status (PS), RAdv-HCC, Child’s classification, albumin and ascites to predict survival. In patients without RAdv-HCC, AFP, PS, Child classification, albumin and INR were independent predictors. Elevated bilirubin was not an independent risk factor for death.

Conclusion. Independent prognostic factors in HCC patients undergoing DEB-TACE are identified. Elevated bilirubin was not an independent risk factor. These data can be used in HCC patient selection and counseling for DEB-TACE.

COVER PAGE

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INTRODUCTION

Conventional transarterial chemoembolization with lipiodol and doxorubicin (1) or cisplatin (2) (cTACE) is known to prolong survival in certain patients with unresectable HCC, including some with unilateral portal vein invasion (PVI) (2). According to established guidelines however, Child's B and C cirrhotics and patients with PVI are poor candidates for TACE (3, 4). TACE with doxorubicin-eluting beads (DEB-TACE) is a relatively new modality associated with favorable systemic doxorubicin exposure/toxicity and liver-specific toxicity compared to cTACE. Studies have documented its safety and efficacy (5, 6). DEB-TACE also significantly increased objective response compared to cTACE in HCC patients with more advanced disease in a randomized trial (6).

As DEB-TACE is becoming more widely practiced, it is important to know which variables independently predict survival and whether cTACE limitations are applicable. This information would provide a basis upon which evidence-based treatment decisions can be made in multidisciplinary settings. Since most HCC patients in the US have competing (cirrhosis vs. cancer) risks for death, both tumor- and patient-related variables are relevant. The aim of our effort was to identify prognostic factors for survival in a large, single-center cohort of HCC patients treated with DEB-TACE.

MATERIALS AND METHODS

PATIENTS AND VARIABLES

Data were collected and reported in accordance with published guidelines (7). This is a retrospective review of patients with HCC referred from Piedmont Hospital's

(Atlanta, Georgia, USA) Hepatobiliary and Liver Transplant Services who underwent DEB-TACE procedures (LC Bead™, Biocompatibles UK Limited, Farnham, Surrey, UK) from March 2006-February 2011; end of study was October 2011. Our liver transplant program began in 2005, and we had limited experience with cTACE prior to our DEB-TACE experience, preventing meaningful comparison of the two procedures at our center. Survival was calculated from the time of first DEB-TACE. Investigational Review Board approval was obtained. HCC was confirmed by AASLD criteria (4) and/or biopsy. Patient-related data collected included age, race, gender, Eastern Cooperative Oncology Group performance status (ECOG PS) (8), clinically apparent ascites, hepatic encephalopathy, complete blood count, INR and serum levels of creatinine, total bilirubin, and albumin. Child's classification and Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) scores were calculated. Tumor-related data collected included pretreatment alpha-fetoprotein (AFP), discrete/measurable lesion(s) vs. infiltrative HCC phenotype (i.e., no discrete border between the lesions[s] and hepatic parenchyma), PVI on cross-sectional contrast-enhanced imaging and maximum tumor diameter. PVI was defined as tumor-related invasion of either the left or right main PV or a primary branch; thrombosis of the main PV or any branch not contiguous with the tumor was not classified as PVI. In patients with multifocal HCC, the largest tumor diameter was used in analyses. Infiltrative HCC phenotype and/or PVI patients undergoing DEB-TACE were classified as "radiographically advanced HCC" (RAdv-HCC) which was included as a single variable in the analyses because of increased statistical significance of this composite variable (see below); moreover, since most with PVI had infiltrative HCC and vice versa, doing so reduced the risk of diluting one's effect

by the other (multicollinearity). In addition, those without RAdv-HCC were analyzed separately.

Before undergoing DEB-TACE all patients were presented at a multidisciplinary hepatobiliary tumor board and deemed unresectable by experienced hepatobiliary surgeons. Unilateral PVI alone in an otherwise appropriate surgical candidate (Child's A, no biochemical or radiographic evidence of portal hypertension, ECOG PS = 0, non-infiltrative HCC) was not a contraindication to resection.

For patients with multiple lesions, treatment planning was based on intrahepatic tumor burden, proximity of lesions and perceived hepatic reserve (based on CTP score) – e.g., a Child's B cirrhotic with bilateral disease would be counseled that lesions in each hemiliver would be treated sequentially and not in one setting. As per our standard practice, follow-up consisted of triple-phase cross-sectional imaging and appropriate laboratory assessment 30 days after DEB-TACE in all surviving patients; patients in whom imaging was felt to show residual viable tumor and who had tolerated the prior procedure(s) were retreated. Laboratory and radiographic assessment were repeated at 90-day intervals. Imaging studies prior to and following treatment were reviewed at a multidisciplinary hepatobiliary tumor board. New lesions and lesions deemed to have persistent viable tumor (based on nodular arterial hyperenhancement with venous washout) underwent subsequent DEB-TACE. Follow-up of re-treated patients was the same as outlined above.

Patients were not excluded from DEB-TACE based solely on segmental PVI, Child's B or C classification or ECOG PS > 1, all contraindications to TACE according to AASLD (4) and the BCLC staging/treatment algorithm (3).

Readmission within 30 days of the procedure and the reason for admission were recorded. Post-embolization syndrome (PES) was defined as nausea/vomiting, fever, leukocytosis and/or otherwise unexplained abdominal pain (7).

TREATMENT

All patients were treated with LC Bead containing doxorubicin, using 100-300 μ diameter beads, 300-500 μ diameter beads or both. This varied in the same patient on separate procedures, preventing meaningful analysis of the effect of bead size on outcome.

Patients received sedation with intravenous midazolam, fentanyl, and hydromorphone. All procedures were performed using common femoral artery access; pre-treatment celiac and superior mesenteric arteriography was obtained through 4-5 French diagnostic catheters. Infusions were performed through a 0.027-inch microcatheter advanced coaxially into the tumor feeding vessel(s) under fluoroscopic guidance. One hundred fifty mg doxorubicin was prepared. Each vial's contents were resuspended in contrast-containing diluent to create a final administration volume of 20 mL. Subsequent infusion was performed at approximately 1-3 ml solutions/minute under fluoroscopic observation until treatment endpoint (stasis or near-stasis in first- or second-order tumor feeding vessels or complete administration of the beads) was reached, followed by completion angiography. Two patients participating in a clinical trial received "lobar" infusions as directed by the trial protocol; otherwise, all infusions were into segmental or higher-order arteries.

In the recovery area, patients were given as-needed analgesics, anti-emetics, and intravenous hydration for 2-6 hours, and then assessed to determine if discharge or admission were appropriate, based on need for pain and/or nausea control. A 6-12 day course of oral predinsone (5 mg) and as-needed oral acetaminophen/hydrocodone 325 mg/5 mg) and promethazine (25mg) suppositories were prescribed.

STATISTICAL ANALYSES

Statistical analyses were performed with Stata 11.2 (Statacorp, College Station, Texas, USA). All lab values and other patient characteristics used in the analyses were those that existed at first treatment. Univariate survival analyses were done using the Kaplan-Meier method for categorical variables and Cox regression for continuous variables; multivariate analyses were done using Cox regression. Variables with a p-value ≤0.10 on univariate analysis were included in multivariate analyses. Statistical significance was defined as a p value ≤ 0.05.Total bilirubin, hereafter referred to as "bilirubin," was analyzed as a continuous variable and also categorized as > 1.0, > 1.5, > 2.0, > 3.0, > 3.5 and > 4.0 $mg \cdot dl^{-1}$ to identify any significant threshold(s). AFP was analyzed as a categorical value with cutoff levels of >9.0 (upper limit of normal in our laboratory), > 50, > 100, > 200, > 300, > 400, > 500 and > 1000 $ng \cdot ml^{-1}$. All other numerical lab values (e.g., albumin, INR) were analyzed as continuous variables. Child's classification was analyzed as a composite variable in Cox regression modelling, and the individual laboratory and clinical components of Child's classification were analyzed in separate models to minimize the impact of multicollinearity. Where

appropriate, means are given ± standard deviation; each hazard ratio (HR) is accompanied by the corresponding 95% confidence interval.

RESULTS

A total of 168 patients underwent DEB-TACE treatment for HCC. Thirty-three underwent liver transplantation and were excluded from survival analyses, as their procedure was as a bridge to transplantation and not as definitive HCC therapy. Liver transplantion in these patients was performed a mean of 159.4 ± 193.7 days after DEB-TACE; one patient who was being treated as a bridge to transplantation died of spontaneous bacterial peritonitis (SPB) on post-procedure day 17 and was included in survival analyses. This patient and the other 134 patients underwent 248 DEB-TACE procedures (mean 1.91 procedures per patient). Patient characteristics are listed in Table 1 (overall population) and Table 2 (cirrhotics). Of the 4 patients with bilirubin > 4.0 $mg \cdot dl^{-1}$ (Table 1), the values were 5.8, 6.1, 10.8 and 18.1 $mg \cdot dl^{-1}$; the respective intervals to death were 1091, 415, 15 and 40 days.

Mean length of stay (LOS) was 0.33 ± 1.31 days (range 0-14). Two hundred fifteen (86.7% of 248 procedures) were discharged home the day of the procedure, 20 (8.1%) were discharged on post-procedure day 1, three on day 2, five on day 3, two each on days 5 and 8, and one on day 14. There were 25 (10.1%) hospital admissions within 30 days related to the procedure: PES, n = 11; encephalopathy, n = 5; gastrointestinal bleeding, n = 4; SBP, n = 3; gastric ulceration in a patient with a replaced left hepatic artery, n = 1; pancreatitis, n = 1. Death within 30 days occurred in 10 of 248 procedures (4.0%) and was due to complications of cirrhosis/portal hypertension (n = 7), pneumonia

(n = 1) and unknown (n = 2). Unadjusted survival is shown in Figure 1; 86 patients (63.7%) were dead at end of study.

Most patients with PVI had infiltrative HCC, and vice versa. Forty-one patients had infiltrative HCC, including 28 with PVI; 11 patients had PVI without infiltrative HCC. Therefore, 39 patients had PVI, and a total of 52 patients were classified as RAdv-HCC. One of our earliest patients (fifth overall) with Child's B cirrhosis (CTP score = 7), PVI and infiltrative HCC tolerated three DEB-TACE procedures without complication and survived 1190 days; another, who was also receiving sorafenib, with Child's A cirrhosis, PVI and infiltrative HCC tolerated seven procedures without complication and survived 579 days.

Survival Analyses – Overall

On univariate analysis the following characteristics were significantly associated with survival: all AFP categories, including abnormal AFP > 9 $ng \cdot ml^{-1}$ (upper limit of normal; p = 0.0009, Figure 2) and > 1000 $ng \cdot ml^{-1}$ (p < 0.0001); infiltrative HCC (p < 0.0001); PVI (p = 0.0003); RAdv-HCC (p < 0.0001, Figure 3); albumin (p < 0.0001); ascites (p = 0.0002); encephalopathy (p = 0.001); INR (p < 0.0001); ECOG PS (p < 0.0001); multifocal HCC (p = 0.0005); MELD >10 (p = 0.008), and Child's classification (p < 0.0001, Figure 4a). Bilirubin as a continuous variable and categorized as > 1.5 (p = 0.017) and > 2.0 $mg \cdot dl^{-1}$ (p = 0.037, Figure 5a) was also significant on univariate analysis; no other bilirubin category was significant; this did not change after eliminating those with bilirubin > 4.0 $mg \cdot dl^{-1}$. Additionally, for those with measurable lesion(s) (i.e.,

not infiltrative), largest tumor size > 5.0 cm was not significantly associated with survival (p = 0.32), nor was it significant as a continuous variable (p = 0.06).

Of all individual variables analyzed, infiltrative HCC phenotype had the highest predictive value (chi-square test statistic = 24.15) on univariate analysis, almost twice the test statistic for the next highest, PVI (12.92); combining infiltrative HCC and PVI into RAdv-HCC yielded a test statistic of 30.29. The median survivals for those with and without RAdv-HCC were 176 and 640 days, respectively (Figure 3).

Multivariate analysis of all patients showed AFP > 9 $ng \cdot ml^{-1}$ (HR 2.3 [1.2-4.3]), ECOG PS > 0 (HR 2.1 [1.3-3.4]), RAdv-HCC, (HR 1.7 [1.0-2.7]) and Child's classification were independent predictors of death; the hazard ratios for Child's B and Child's C were 2.3 (1.4-3.9) and 5.7 (3.0-11.1), respectively. These data are summarized in Table 3. MELD > 10 was not independently significant. We replaced Child's classification with its 5 individual components in an otherwise identical Cox regression model, and albumin (HR 0.5 [0.3-0.7]) and ascites (HR 1.9 [1.2-3.0]) were the only significant Child's variables on multivariate analysis (Table 3). Bilirubin as a continuous variable (HR 1.0 [0.9-1.1]), and all categorical levels, was not; as above, eliminating those with bilirubin > 4.0 $mg \cdot dl^{-1}$ had no meaningful impact on this. Encephalopathy (HR 1.0 [0.6-2.0]) and INR (HR 1.0 [0.4-2.8]) were also not statistically significant.

Survival Analyses – those without Radiographically Advanced HCC

It was felt relevant to separately investigate prognostic factors in those without PVI and/or infiltrative HCC (n = 83), as DEB-TACE perhaps should be restricted to this

group. In these patients, ECOG PS ($p = 0.0002$), ascites ($p = 0.004$) , all AFP categorical levels, albumin ($p < 0.0001$), INR ($p = 0.0001$), multifocal HCC ($p = 0.046$), MELD > 10 ($p = 0.045$) and Child's classification ($p < 0.0001$) were significantly associated with survival on univariate analyses. Bilirubin was not; Figure 5b shows the survival curves in those with bilirubin > 2.0 $mg \cdot dl^{-1}$ vs. ≤ 2.0 $mg \cdot dl^{-1}$.

On multivariate analysis in those without RAdv-HCC, ECOG PS > 0 (HR 2.6;1.3-5.3), AFP (for AFP > 9 $ng \cdot ml^{-1}$ the HR was 2.3 [1.3-6.7]) and Child's classification were independently associated with outcome; using AFP > 9 $ng \cdot ml^{-1}$ in the Cox model, HRs for Child's B and Child's C were 2.3 (1.1-4.8) and 6.9 (1.3-20.3), respectively. These data are summarized in Table 4, and Kaplan-Meier survival curves by Child's classification are shown in Figure 4b. MELD > 10 was again not independently significant. Additionally, all other AFP cutoff levels in this subgroup were independently significant when included separately in the model with the other independent predictors. The impact of extremely elevated AFP on the finding that even an AFP > 9 $ng \cdot ml^{-1}$ was significant was assessed by eliminating those with AFP > 400 $ng \cdot ml^{-1}$ (n = 16); despite doing so, AFP > 200 $ng \cdot ml^{-1}$ remained significant ($p = 0.008$) in univariate and multivariate analyses: the HR of AFP > 200 $ng \cdot ml^{-1}$ in the multivariate model with other significant variables was 5.0 (1.0-25.3) in this group.

Analyzing the individual components of Child's classification in the Cox model with AFP > 200 $ng \cdot ml^{-1}$ showed albumin (HR 0.4 [0.3-0.7]) and INR (HR 21.5 [3.2-146.2]) as the only significant Child's variables. Ascites (HR 0.8 [0.3-2.0]) and encephalopathy (HR 0.8 [0.3-2.2]) were not independently significant. Interestingly, the HR in this multivariate analysis for bilirubin was 0.64 (0.4-0.9), indicating a lower chance of death with

increasing bilirubin. However, in univariate analysis as a continuous variable, bilirubin was not significant (HR 0.98 [0.7-1.4]); moreover, none of the categorical levels of bilirubin were significant by Kaplan-Meier analysis.

DISCUSSION

The increasing incidence of cirrhosis and HCC mandate ongoing efforts to refine and expand the array of treatment options for HCC. Liver transplantation and surgical resection are potentially curative but limited to a minority of patients. DEB-TACE is becoming more widely practiced, as the HCC incidence is increasing (9-11) and initial clinical trial results were promising (5, 6).

Since most HCC patients in the USA have cirrhosis and are at significant risk of non-tumor-related death, non-tumor-related variables are important to include in survival analyses. Such variables associated with outcomes after cTACE have been reported (12-17). As the role of DEB-TACE is expanding, it is important we understand the pre-treatment factors associated with survival following DEB-TACE, and whether the same prognostic factors associated with cTACE apply – especially given the potentially superior side effect profile of DEB-TACE and better objective response rate in patients with more advanced disease states, defined as Child's B cirrhosis, ECOG PS = 1, disease in both hemilivers or recurrent disease (6). Overall differences in response rate in that study, however, were not statistically significant ($p = 0.11$); a difference in survival between cTACE and DEB-TACE was not assessed (6). Others have also not found significant differences in tumor response rates and survival upon prospectively comparing cTACE and DEB-TACE (18).

Generally, risk factors for death in our patients were similar to those reported for cTACE: worse survival is associated with more advanced tumor characteristics and liver dysfunction. Specifically, our data show the independent significance of several variables, including AFP, ECOG PS, and Child's classification; infiltrative HCC phenotype and PVI were the two most predictive of death. Combining these 2 variables into a single category, RAdv-HCC, resulted in stronger and independent statistical association with outcome. Bilirubin, a frequently-used value in determining advisability of DEB-TACE, had no practical prognostic value on multivariate analyses, had little univariate association with survival in the overall cohort and had no univariate association with survival in the group without RAdv-HCC. This is in contrast to a retrospective univariate analysis (19). A more recent multivariate analysis of prognostic factors for survival after cTACE in 362 patients did not specifically evaluate bilirubin but showed similar independent risk factors to ours: Child's classification, PVI, and AFP; tumor size and multiple tumors were independent predictors of death in their cohort (15). Multifocal disease was significant in our population on univariate analysis, and tumor size as a continuous variable trended toward significance, but both lost significance after controlling for other factors.

Since other variables did have independent significance, our data suggest it is reasonable to not use bilirubin as a sole factor in determining DEB-TACE candidacy. Rather, albumin and ascites had better and more practical predictive value overall, whereas albumin and INR were more predictive in those without RAdv-HCC. Our patients with bilirubin > 4.0 $mg \cdot dl^{-1}$ and short survival times had other significant prognostic factors, possibly explaining the lack of independent significance of bilirubin

when controlling for those factors. Child's classification, which incorporates multiple variables and better signifies overall functional hepatic reserve, was independently significant in both cohorts and, thus, appears more useful than its individual variables. Additionally, Child's classification was more predictive in our population than MELD, and it has also been shown to be superior to MELD in predicting survival after cTACE (20); similar to our data, these authors showed albumin to be the Child's variable most predictive of survival after cTACE. An experience of 172 patients included World Health Organization (WHO) radiographic criteria in a Cox model and found observation of a WHO response, PVI, extrahepatic metastases and AFP to independently predict survival; Child's classification did not have independent prognostic significance (16).

In our patients without RAdv-HCC, we found that AFP, ECOG PS and Child's classification remained independent predictors of survival. It is interesting that all AFP cutoff levels were independently significant, including AFP > 9 $ng \cdot ml^{-1}$, the upper limit of normal. This is at least somewhat attributable to the high impact of those with > 400 $ng \cdot ml^{-1}$, as eliminating this subgroup rendered AFP > 9 $ng \cdot ml^{-1}$ statistically insignificant in both univariate and multivariate analyses. AFP > 200 $ng \cdot ml^{-1}$, however, remained an important threshold, as this level did independently predict outcome in those who had AFP < 400 $ng \cdot ml^{-1}$.

It is important to note that our RAdv-HCC cohort is not identical to the "advanced stage" subgroup in the BCLC classification (BCLC-C) (3), as our composite variable is tumor-related only and, thus, does not incorporate ECOG PS or Child's classification. Additionally, the BCLC staging system does not directly account for infiltrative HCC phenotype. As such, our data with respect to "radiographically advanced HCC" do not

pertain to advanced disease in staging systems that incorporate patient-related variables, including BCLC, and we are not proposing an additional variable to consider in the field of HCC research. Given the statistical magnitude of its association with outcome in our population (Table 3, Figure 3), however, we felt it worthy of being included in our report, and it seems reasonable to use this variable in treatment decision-making. These patients did significantly worse (Figure 3), and our data suggest they might be better served with other therapeutic options – or perhaps even observation on a case-by-case basis.

Patients with Child's B and C cirrhosis undergoing DEB-TACE should be counseled as to their increased risk of death. Our data suggest that Child's B/C cirrhosis may not be an absolute contraindication to TACE but should be balanced against their perceived tumor-related risk of death, and we incorporate it in treatment planning – e.g., multiple and/or bilateral tumors are treated sequentially, and as superselectively as feasible, rather than simultaneously. It is also sensible to incorporate liver transplant candidacy in treatment planning. Our data indicate that a person with Child's C cirrhosis who is not a transplant candidate derive little benefit by undergoing DEB-TACE (Figure 4); again, other treatment options may be considered. Alternatively, if a Child's B or C cirrhotic who is a transplant candidate needs effective tumor control while waiting, the risk-benefit analysis may favor DEB-TACE.

Our study is retrospective and has limitations. Selection bias undoubtedly exists, as we do not present data on patients referred for DEB-TACE that were denied. It is also possible that our patient selection changed over time, given the lack of rigid inclusion criteria from the beginning. Our early successes in patients with poor

prognostic factors (Child's B, PVI, infiltrative HCC) perhaps created a willingness to continue treating patients with these traits. We did not question this until the herein objective analysis of our data and, thus, do not think our selection criteria became significantly more restrictive during the study period; as a result of our data, however, we are now more restrictive, especially with Child's B and C and those with PVI and/or infiltrative HCC. Additionally, the data presented are from a single center and are observational only, and we are thus not able to firmly state which factors are most important in terms of patient selection for other centers.

In summary, our data show prognostic factors for survival following DEB-TACE are similar to those reported for cTACE. Our experience confirms that, while DEB-TACE can be performed safely in the outpatient setting in patients with HCC, patient survival is often limited by non-tumor-related (Child's classification, ECOG PS) and tumor-related (AFP, PVI, infiltrative phenotype) factors; and DEB-TACE may not provide the benefit we anticipated in our early experience. With the increasing incidence of HCC, however, continued growth in the number of patients appropriately undergoing DEB-TACE is expected. Child's classification is seemingly superior to its individual variables in predicting survival in these patients.

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Table 1. Patient characteristics – overall.

	N=135 (100%)
Gender	
Male	105 (77.8)
Cirrhotic	130 (96.3)
Number of DEB-TACE procedures	
1	67 (49.6)
2	38 (28.1)
3	20 (14.8)
4	7 (5.2)
5	2 (1.5)
7	1 (0.7)
Total bilirubin ($mg \cdot dl^{-1}$)	
< 1.0	45 (33.3)
1.0-1.9	60 (44.4)
2.0-3.0	21 (15.6)
3.1-4.0	5 (3.7)
> 4.0	4 (3.0)
Albumin ($mg \cdot dl^{-1}$)	
> 3.5	24 (17.8)
2.8-3.5	67 (49.6)
< 2.8	44 (32.6)
INR	

< 1.7	127 (94.1)
1.7-2.3	8 (5.9)
> 2.3	0 (0)
AFP ($ng \cdot ml^{-1}$)	
< 9 (upper limit of normal)	37 (27.4)
9.1-200	43 (31.9)
201-400	8 (5.9)
401-1000	9 (6.7)
>1000	38 (28.2)
ECOG performance status	
0	86 (63.7)
1	38 (28.1)
2	11 (8.1)
Infiltrative HCC	41 (30.3)
Segmental portal vein invasion	39 (28.9)
“Advanced HCC”	52 (38.5)
Largest tumor size > 5.0 cm (excluding those with infiltrative HCC; n=94)	29 (30.9% of 94)

Table 2. Patient characteristics – cirrhotics.

	N=130 (100%)
Etiology of liver disease	
Hepatitis C	76* (58.5)
Hepatitis B	17 (13.10)
Alcohol	16 (12.3)
Non-alcoholic fatty liver disease	10 (7.7)
Other	4 (3.0)
	* 9 also abused alcohol
Child's classification	
A	62 (47.7)
B	50 (38.5)
C	18 (13.9)
Total bilirubin ($mg \cdot dl^{-1}$)	
< 1.0	41 (31.5)
1.0-1.9	60 (46.2)
2.0-3.0	20 (15.4)
3.1-4.0	5 (3.9)
> 4.0	4 (3.1)
Albumin ($mg \cdot dl^{-1}$)	
> 3.5	21 (16.1)
2.8-3.5	65 (50.0)
2.8	44 (33.9)

INR	
< 1.7	122 (93.9)
1.7-2.3	8 (6.2)
> 2.3	0 (0)
AFP ($ng \cdot ml^{-1}$)	
< 9 (upper limit of normal)	34 (26.2)
9.1-200	43 (33.1)
201-400	8 (6.2)
401-1000	9 (6.9)
>1000	36 (27.7)
ECOG performance status	
0	84 (64.6)
1	35 (26.9)
2	11 (8.5)

Table 3. Hazard ratios of independently significant variables in all patients.

	Hazard ratio (95% confidence interval)	p value
"Advanced HCC"	1.7 (1.0-2.7)	0.045
ECOG PS > 0	2.1 (1.3-3.4)	0.001
AFP > 9 $ng \cdot ml^{-1}$	2.3 (1.2-4.3)	0.008
Child's A	Reference	
Child's B	2.3 (1.4-3.9)	0.001
Child's C	5.7 (3.0-11.1)	<0.0001
Albumin*	0.5 (0.3-0.7)	0.0001
Ascites*	1.9 (1.2-3.0)	0.01

* analyzed separately from Child's classification

Table 4. Hazard ratios of independently significant in patients without radiographically advanced (RAdv) hepatocellular carcinoma (HCC).

	Hazard ratio (95% confidence interval)	p value
ECOG PS > 0	2.8 (1.4-5.6)	0.003
AFP >9 $ng \cdot ml^{-1}$	2.3 (1.3-6.7)	0.0096
Child's A	Reference	
Child's B	2.3 (1.1-4.8)	0.031
Child's C	6.9 (1.3-20.3)	0.0005
Albumin*	0.4 (0.3-0.7)	0.02
INR*	21.5 (3.2-146.2)	0.002

* analyzed separately from Child's classification

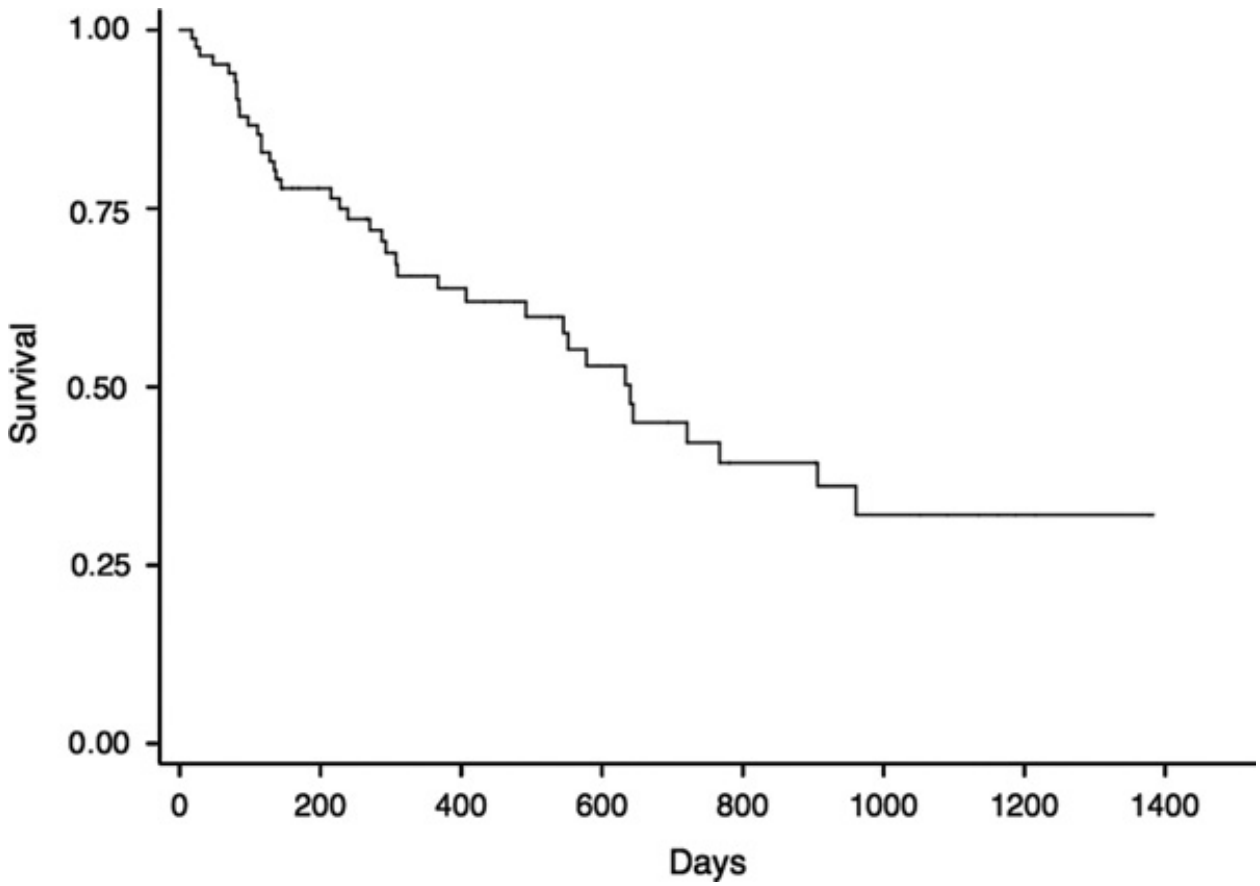


Figure 1. Overall survival.

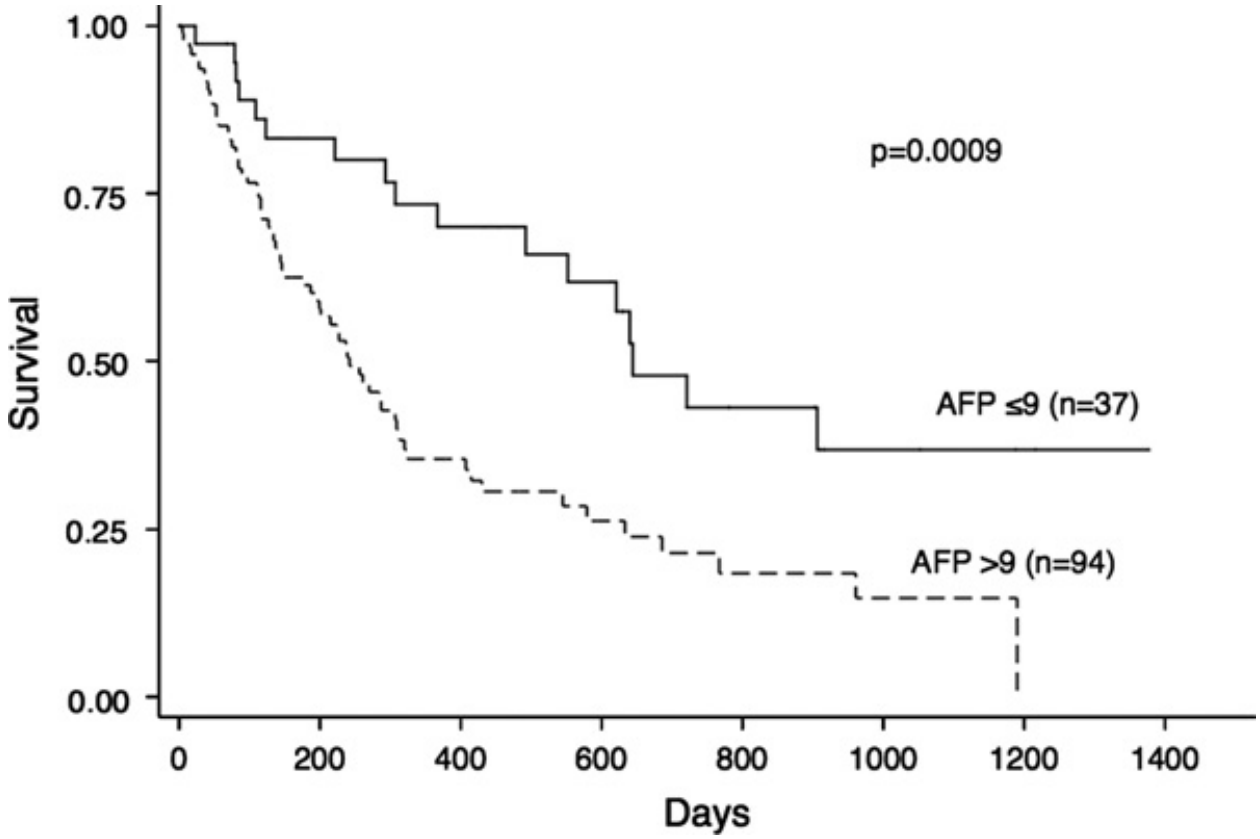


Figure 2. Survival in all patients by alpha-fetoprotein (AFP) > 9 $ng \cdot ml^{-1}$, the upper limit of normal.

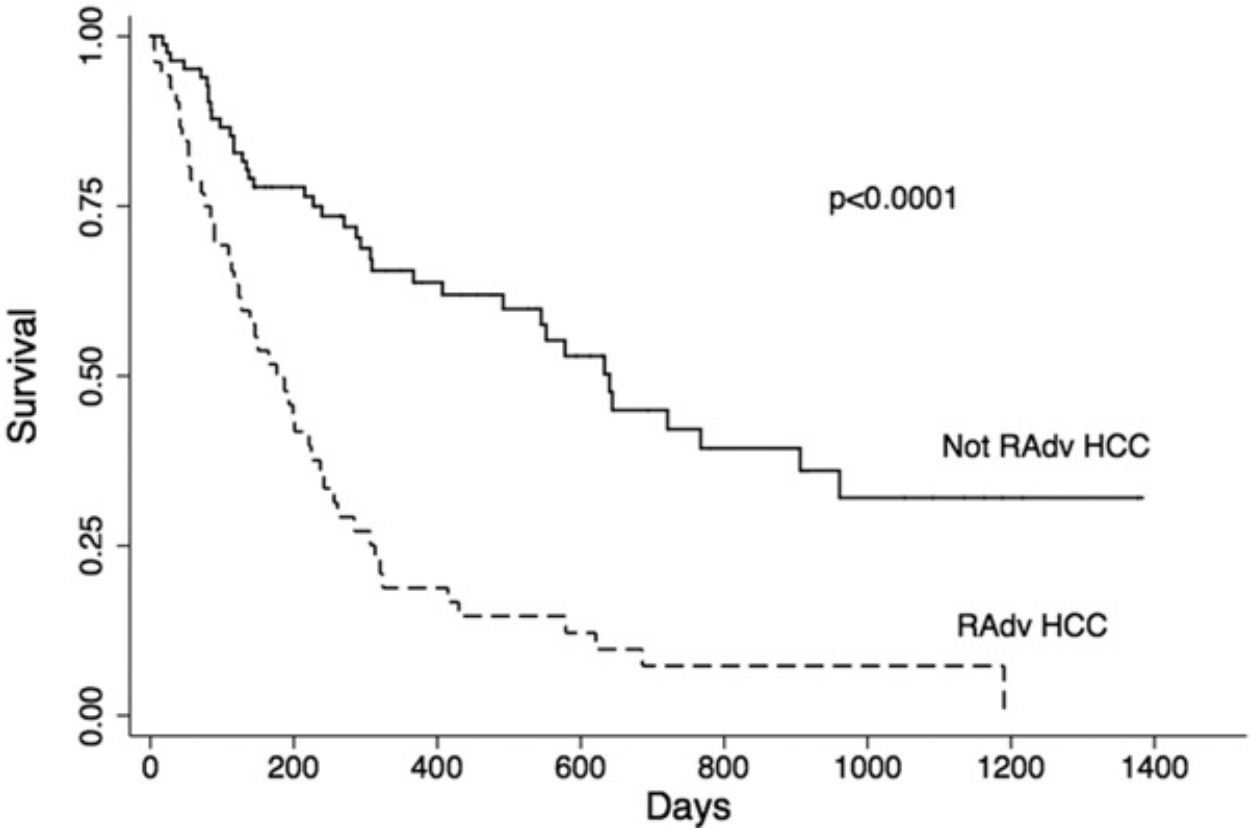
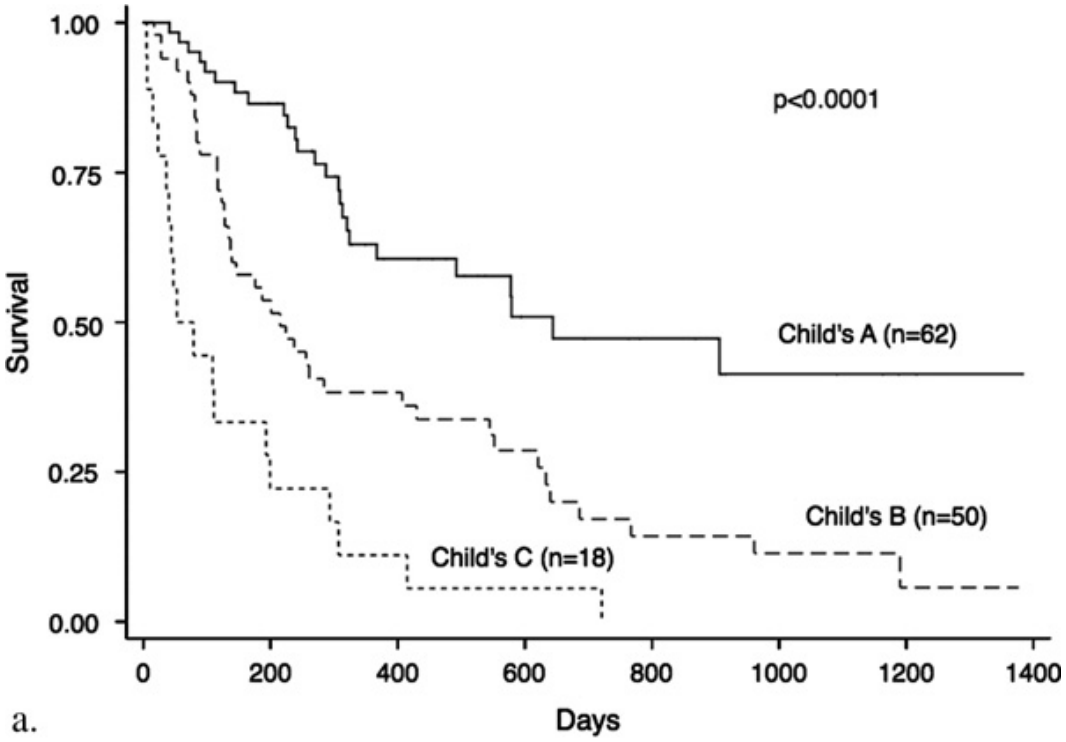
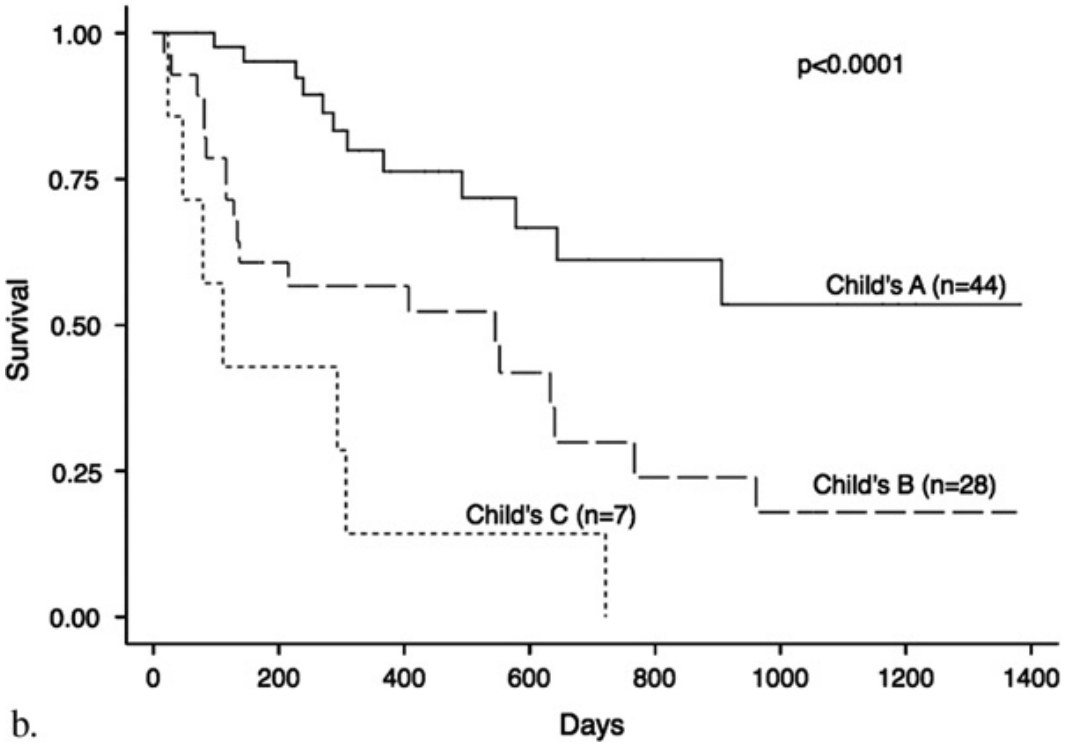


Figure 3. Survival in all patients by radiographically advanced (RAdv) hepatocellular carcinoma (HCC).

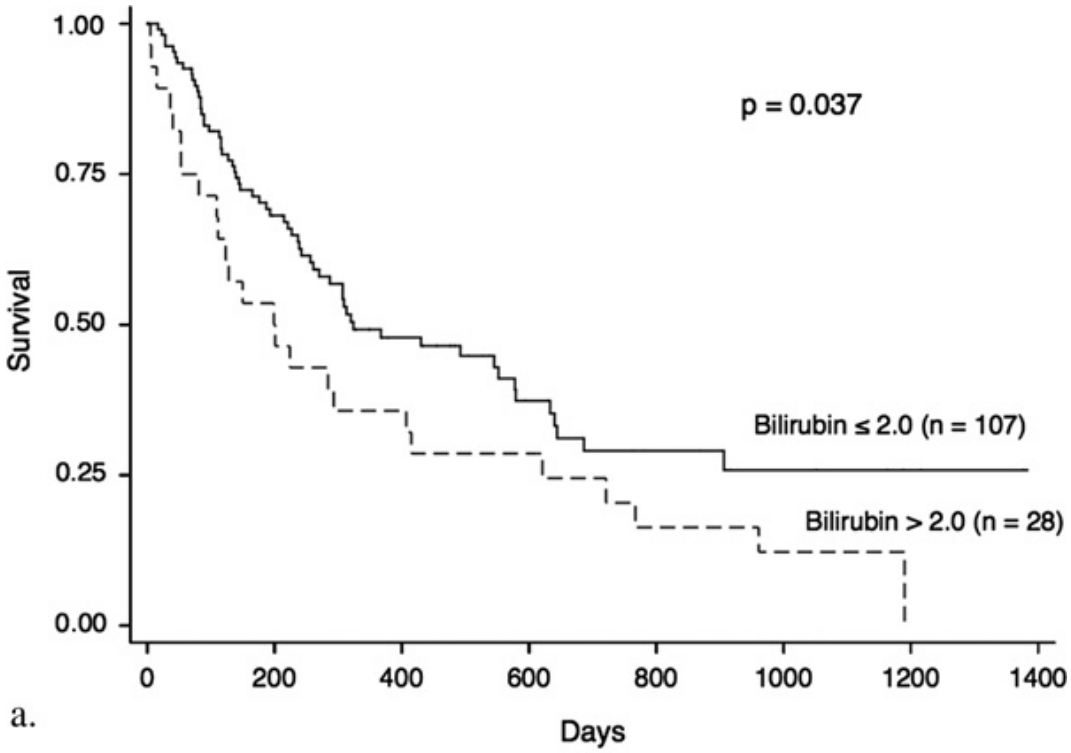


a.



b.

Figure 4. Survival by Child class in all patients (a) and in only those without radiographically advanced (RAdv) hepatocellular carcinoma (HCC) (b).



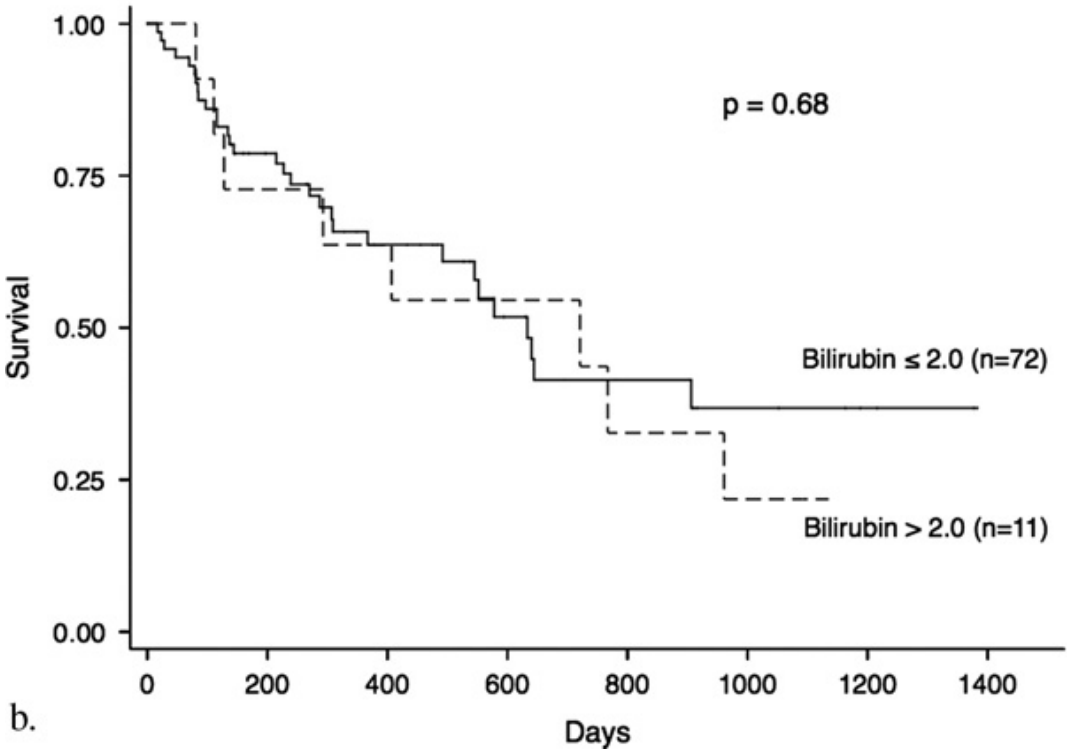


Figure 5. Survival by total bilirubin in all patients (a) and in only those without radiographically advanced (RAdv) hepatocellular carcinoma (HCC) (b).