Hepatocellular carcinoma in Central Europe: prognostic features and survival

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Abstract

Background and aims—We investigated the influence of baseline characteristics of patients with hepatocellular carcinoma (HCC) on prognosis and developed a multivariate Cox model predicting survival. All patients were from Central Europe.

Methods—All 245 patients seen at the Department of Gastroenterology and Hepatology at the University of Vienna, Austria, from July 1991 to March 1998 were included in this retrospective study. Nineteen different clinical characteristics and survival time from date of diagnosis were noted. Factors determining survival time were analysed by univariate and multivariate analysis using Cox proportional hazard regression models and a new classification model was constructed. The validity of this model was tested on an independent group of 89 patients, seen from April 1998 to September 1999.

Results—Median survival in patients with HCC was 8.0 months. In a multivariate analysis bilirubin (>2 mg/dl), portal vein thrombosis, prothrombin time (<70%), alpha fetoprotein (>180 µg/l), tumour mass >50%, and enlarged lymph nodes were independent predictors of survival. A newly constructed Cox proportional hazard model (Vienna survival model for HCC=VISUM-HCC) identified three disease stages with different durations of survival (median survival stage 1, 15.2 months; stage 2, 7.2 months; and stage 3, 2.6 months; p=0.00001). Applying the VISUM-HCC survival model to patients in Okuda stage 2 identified subgroups with an excellent and very poor prognosis for which different treatment modalities should be offered.

Conclusions—Our patients with HCC had a poor median survival of eight months. Six easily measurable clinical variables were significant predictors of survival in patients with HCC. The new VISUM-HCC survival model may be useful for stratifying patients with HCC for various clinical treatment modalities.

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Hepatocellular carcinoma (HCC) as a sequela of chronic liver disease is increasingly seen in industrialised nations.[1] A number of studies analysed the influence of demographic characteristics, tumour related factors such as size or number of nodules, and factors related to liver function on survival. Okuda and colleagues[2] proposed a widely used classification scheme of HCC which includes serum bilirubin, serum albumin, tumour mass, and ascites as parameters. The International Union against Cancer's (UICC) TNM classification considering only tumour related factors has poor prognostic value,[3] mostly because liver function is not taken into account. These prognostic models were developed many years ago and were not modified. However, the epidemiological and clinical basis of these models has changed over time. The aetiology of the underlying liver disease leading to cirrhosis and HCC varies both in time and with geographic area: in Western industrial countries and in Japan, hepatitis B virus related HCC is decreasing[4 5] whereas hepatitis C virus (HCV) associated HCC is increasing.[6 7] In China, aflatoxin B1 is an important cofactor of hepatic carcinogenesis, often associated with p53 mutations.[8 9] The geographic variation of HCC is also reflected by younger age of patients from South East Asia and higher prevalence of chronic viral hepatitis as opposed to a more dominant role of chronic alcoholic liver disease in Western countries. Furthermore, overall incidence rates are changing, showing a rise in the rate of HCC in the USA[1] and Europe.[10 11] Also, treatment options and outcomes vary considerably[12] and change over time. For example, surgery is a therapeutic option considered more often in South East Asian patients.[12–14] As data collected in one region may not be representative of other areas, survival estimates derived from baseline clinical data must be collected regionally to account for these variables. In addition, increased screening efforts in recent years to detect tumours of a smaller size[15] may explain differences in clinical presentation, epidemiological features, and survival in different parts of the world.

In this study a prognostic model was established for European patients based on baseline data obtained by 245 consecutive patients with HCC seen at a tertiary referral centre at a university clinic. Univariate and multivariate regression analysis was used to define independent prognostic factors present at the time of diagnosis. Those factors were incorporated into a new Cox regression model describing survival of our patient population.

Abbreviations used in this paper: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBsAg, hepatitis B virus surface antigen; PTV, portal vein thrombosis; PT, prothrombin time; AFP, α fetoprotein; RRD, relative risk of death; UICC, International Union against Cancer.

This model was confirmed by testing on an independent group of patients with HCC.

Patients and methods

PATIENTS

Two groups of patients were included in the study. The first group ("model group") consisted of all 245 (58 females (23.7%), 187 males (76.3%)) patients of Caucasian origin with HCC seen at the Department of Gastroenterology and Hepatology, University of Vienna from July 1991 to March 1998. The demographic and clinical characteristics of this group are shown in table 1; 1.6% of our patients were of non-European origin.

Liver cirrhosis was diagnosed either by histology or by the typical combination of clinical, laboratory, and gastroscopic findings together with the presence of ultrasound verified ascites strongly suggestive of liver cirrhosis. Liver biopsy was available in 191 (78%) patients. Patients were grouped according to the following diagnostic characteristics: hepatitis B virus surface antigen (HBsAg) positivity, anti-HCV positivity, and chronic alcoholism (>60 g ethanol/day); haemochromatosis was diagnosed either by histological assessment of liver biopsy or by determination of the C282Y mutation of the HFE gene. Death was assessed by examining the Austrian national death registry.

An independent second group of patients included all 89 patients (14 females (15.7%), 75 males (84.3%)) seen at our institution after the model group. In none of the 19 baseline parameters tested was a statistically significant difference found between the model and testing groups (see table 1).

DIAGNOSIS OF HCC AND STAGING CLASSIFICATION

As a tertiary referral centre we do not recruit our patients through a surveillance programme for HCC; diagnosis in most of our patients was a chance finding during ultrasound examination or triggered by symptoms. The diagnosis of HCC was confirmed by liver biopsy in 191 (78%) patients in the model group; in patients without histological confirmation of HCC (22%), diagnosis was made by high α fetoprotein (AFP) values (>700 μg/l) and demonstration of a tumour by ultrasonography or computed tomography scan. Grading information according to Edmondson and Steiner's[16] classification was available in 167 patients. When histological diversity was observed in a tumour, the higher grade according to the classification system was taken to be the overall grade. Tumours were classified according to the TNM classification of the UICC[17] and according to the staging system proposed by Okuda.[2] Tumour mass was estimated using computed tomography scans according to Okuda.[2] Enlarged lymph nodes were defined as lymph nodes greater than 1 cm in diameter at the portal, coeliac, retrocrural, or retroperitoneal lymph node station.[18] Portal vein thrombosis was diagnosed either by ultrasound or contrast enhanced computed tomography scans.

The treatment modalities in the model group were: liver resection (n=34; median survival 20.7 months), liver transplantation (n=38; median survival 21.0 months), chemotherapy (n=38; median survival 8.0 months), and 145 patients received palliative care (median survival 4.4 months). Although patients undergoing surgery or liver transplantation had significantly longer survival (log rank test, p<0.01) than patients receiving chemotherapy or palliative care, we do not report these differences as treatment induced because the patient's underlying clinical state was clearly a major determinant of the mode of therapy chosen and no randomised study has shown this to significantly prolong survival.[19–21] Excluding the small number of patients with liver transplantation from our study population did not change survival compared with the overall group (log rank test, NS).

STATISTICS

Descriptive statistics

Data are presented as median (95% confidence interval). χ^2 tests for nominal data and t tests for numerical data were used to compare baseline characteristics. Reported p values are two sided and p values <0.05 were considered significant. The Kaplan-Meier method[22] was used to determine patient survival and the log rank test to compare survival between subgroups.

Regression analysis

Univariate and multivariate regression analyses were performed using the Cox proportional hazard regression model[23 24] to determine the effect of various variables on survival. Nineteen different variables were chosen to be included in the univariate analysis: bilirubin, prothrombin time (PT), ascites, albumin, AFP, portal vein thrombosis (PVT), enlarged lymph nodes, distant metastases, unilobar/bilobar, tumour >50%, diameter >2 cm, number of tumour nodules, histological grading according to Edmondson and Steiner, HBsAg positivity,

Table 1   Patient characteristics and aetiology at time of diagnosis of hepatocellular carcinoma

	Model group		Testing group	
	Number	Percentage	Number	Percentage
n	245		89	
Median age (y)	63.3		61.1	
Female median age	66.3		61.1	
Male median age	61.3		64.1	
Sex distribution				
Male	187	76.3	75	84.3
Female	58	23.7	14	15.7
Sex ratio (M:F)	3.2:1		5.4:1	
Liver cirrhosis	212	86.5	79	88.8
Child-Pugh-stage				
A	84	34.3	38	42.7
B	93	38.0	28	31.5
C	35	14.3	13	14.6
No liver cirrhosis or undetermined	33	13.5	10	11.2
Chronic viral hepatitis	118	48.2	36	40.5
HBsAg+/anti-HCV−	24	9.8	7	7.9
Anti-HCV+/HBsAg−	90	36.7	28	3.5
HBsAg+/anti-HCV+	4	1.6	1	1.1
Non-viral aetiology (HBsAg−/ anti-HCV−)	127	51.8	53	59.5
Chronic alcoholism	86	35.1	38	42.7
Cryptogen	28	11.4	9	10.1
Haemochromatosis	10	4.1	4	4.5
Other causative factors	3	1.2	2	2.2

There were no statistically significant differences between the two groups.

age, smoking, sex, alcohol, and anti-HCV positivity. When used as continuous variables, bilirubin and AFP were introduced after logarithmic transformation because of the skewed distribution. When dichotomous variables were used instead of continuous variables, the cut off level chosen was its median value. When the median value was close to the normal limit, the latter was used as a cut off. Four clinical variables (bilirubin, albumin, AFP, PT) were assessed both as continuous and dichotomous variables. The assumption of proportional hazards was examined graphically by observing a constant vertical difference between plots of log integrated hazard against time for various levels of each variable.[25] Significant variables in univariate analysis were included in Cox's multivariate regression analysis and the backward elimination method was used.

Evaluation of the survival model

To evaluate our survival model, we calculated the relative risk of death (RRD) for each patient using the significant prognostic variables obtained in the multivariate analysis. The following equation was used:

$$\lambda_{i(t)}/\lambda_{0(t)}=\exp(\beta_1(x_{1i}-x_1)+ ... + \beta_p(x_{pi}-x_p))$$

where $\lambda_{i(t)}$ is the hazard rate for survival of a particular patient at time t, $\lambda_{0(t)}$ is the hazard calculated at the average values of the variables in the model, β_1 to β_p are the regression coefficients of the variables, x_{1i} to x_{pi} are the values of the variables of a particular patient, and x_1 to x_p are the mean values of these variables from all patients.[26 35] Variables were introduced as dichotomous variables. The higher the values for RRD, the worse is the prognosis; lower values indicate a better prognosis.

A complete set of variables is required for this analysis. Therefore, we replaced missing data by mean values obtained in the whole series so as not to reduce the number of patients.

The predictive power of the model was tested in an independent group ("testing group") of patients. After the RRD for each of the patients in the model group was calculated the model group was divided into three subgroups of similar size but identical risk. Survival curves for these subgroups were estimated using the Kaplan-Meier method. Regression coefficients of the significant variables obtained in the multivariate analysis of the model group were also used to compute the RRD in the testing group of patients. The testing group was also divided into three subgroups with identical risk, as defined by the same RRD boundaries as in the model group and survival curves were calculated as described above. Validation of the final model was assessed by comparing the corresponding survival curves of the model group and the testing group of patients. If there were no statistically significant differences between the corresponding survival curves, the validity of the model was confirmed. Survival of different prognostic stages was compared using the log rank test.

All statistical calculations were done using Statistica for Windows (version 5.1, StatSoft, Inc., USA 1997).

Results

PATIENT CHARACTERISTICS (TABLE 1)

Our study population consisted of typical Western European patients. Chronic HCV infection was the underlying aetiology in one third of our patients, another third presented with chronic alcoholism, and only 10% had chronic hepatitis B virus infection. Liver cirrhosis was present in 90% of patients with HCC; only a small percentage had no liver cirrhosis. Our patients presented in an advanced stage of disease with a poor median survival of only eight months (see table 1).

MEDIAN SURVIVAL (TABLE 2)

Overall median survival was 8.0 months (fig 1A) and did not differ between male and female patients. A total of 202 (82.45%) patients had died by the time of analysis. Survival of HCC patients without liver cirrhosis was longer than that of patients with liver cirrhosis (21.3 *v* 6.8 months; p=0.0024). Within the group of cirrhotic patients, median survival rates in Child-Pugh stages A, B, and C were 12.0, 6.8, and 1.9 months, respectively (A *v* B, p=0.04608; B *v* C, p=0.00003) (fig 1B). Patients with chronic hepatitis B had the worst

Table 2 Median survival time of patients with hepatocellular carcinoma

Parameter	n	Median survival (95% confidence interval)	Log rank test
Overall	245	8.0 (6.4–11.9)	
Female	58	8 (6.1–12.0)	p=0.6289
Male	187	8.6 (5.9–15.3)	
Underlying cirrhosis	212	6.8 (5.5–9.9)	p=0.0024
No liver cirrhosis	33	21.3 (13.9–62.5)	
Child-Pugh stage			
A	84	12.0 (9.4–17.3)	p=0.0001
B	93	6.8 (4.5–11.4)	
C	35	1.9 (1.5–3.0)	
Aetiology			
Chronic alcoholism	86	6.8 (5.1–11.4)	p=0.1309
Hepatitis B	24	3.4 (2.8–6.0)	
Hepatitis C	90	11.0 (6.7–15.3)	
Haemochromatosis	10	18.7 (16.0–*)	
Edmondson-Steiner			
G1	40	13.3 (6.1–17.3)	p=0.0666
G2	83	11.1 (7.5–20.9)	
G3	44	4.7 (2.8–11.0)	
Okuda			
Stage 1	40	15.8 (12.7–37.3)	p=0.0001
Stage 2	161	10.2 (7.5–13.9)	
Stage 3	44	2.7 (2.0–4.3)	
TNM classification			
Stage 3	64	12.8 (7.6–25.3)	p=0.0028
Stage 4	152	5.8 (4.3–7.2)	
VISUM classification			
Stage 1	131	15.2 (12.4–27.1)	p=0.0001
Stage 2	63	7.2 (4.4–12.7)	
Stage 3	51	2.6 (2.0–3.4)	
Age distribution			
<30	2	37.3	
30–40	4	5.6	
40–50	23	8.6	
50–60	72	11.0	
60–70	92	10.4	
70–80	48	5.3	
>80	4	29.2	
AFP distribution			
0–7	45	13.9 (10.7–27.1)	p=0.0179
7–20	34	10.2 (6.1–22.3)	
20–100	36	11.9 (4.6–17.0)	
100–500	40	8.4 (4.2–15.3)	
>500	81	5.4 (3.7–8.0)	
PVT			
Yes	56	4.0 (2.8–6.0)	p=0.0007
No	162	9.6 (7.9–15.3)	

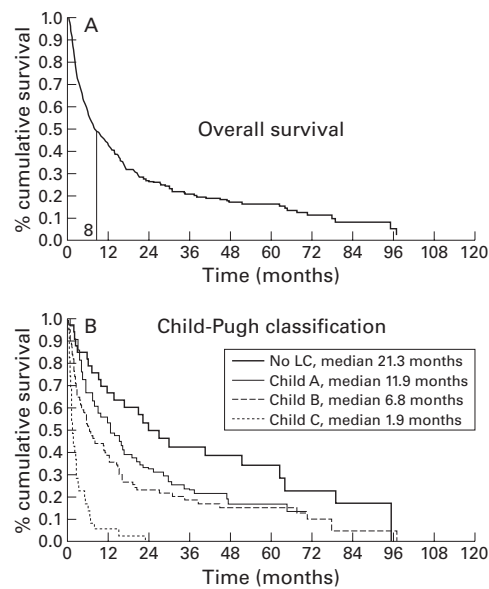PTV, portal vein thrombosis; AFP, α fetoprotein.

Figure 1   (A) Cumulative survival rate for all 245 patients included in the study. Median survival was 8.0 months. (B) Cumulative survival of patients with hepatocellular carcinoma with cirrhosis Child stage A (n=84), Child stage B (n=93), and Child stage C (n=35), and without liver cirrhosis (No LC) (n=33). Survival was significantly different between patients with and without cirrhosis (log rank test, p=0.00041).

median survival (3.4 months), less than that of patients with chronic alcoholism (6.8 months) or hepatitis C (11.0 months). G3 grading in the Edmondson-Steiner classification (table 2), higher staging according to the classifications of Okuda (fig 2A, table 2) or TNM (table 2),
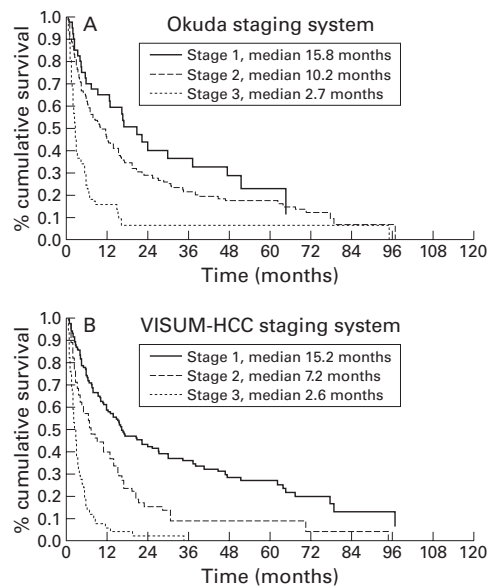

Figure 2   (A) Cumulative survival of patients with hepatocellular carcinoma (HCC) (n=245) grouped according to Okuda stages: stage 1 (n=40), stage 2 (n=161), and stage 3 (n=44). Survival was statistically different between stages 2 and 3 (log rank test, p=0.0001) but not between stages 1 and 2 (log rank test, p=0.06331). (B) Cumulative survival rate of patients grouped according to the newly developed staging system VISUM-HCC, incorporating the six significant predictive variables (bilirubin >2 mg/dl, prothrombin time <70%, portal vein thrombosis, tumour mass >50%, enlarged lymph nodes, α fetoprotein >125 kU/l), as determined by multivariate analysis.

Table 3   Prognostic significance of variables in the univariate analysis

	Variable included	Regression coefficient (β)	p Coefficient
1	Bilirubin (<2 mg/dl)	0.644192	0.000016
2	PT (<70%)	0.621770	0.000077
3	Ascites (yes-no)	0.591207	0.000126
4	Albumin (<3.5g/dl)	0.507730	0.000635
5	PVT	0.545117	0.000901
6	AFP (<125 kU/l)	0.475678	0.001034
7	Enlarged lymph nodes	0.495509	0.001757
8	Distant metastases	0.492607	0.002174
9	Unilobar/bilobar	−0.005126	0.025371
10	Tumour >50% (yes-no)	0.318607	0.026102
11	Diameter (>2 cm)	−0.005125	0.029782
12	No of tumour nodules	−0.004821	0.039713
13	Edmondson-Steiner	0.223954	0.079851
14	HBV (HBsAg+)	0.363311	0.109207
15	Age	0.010530	0.127132
16	Smoking	0.227728	0.149910
17	Sex	−0.081306	0.631941
18	Alcohol	0.000294	0.835254
19	HCV (anti-HCV+)	0.006705	0.963396

HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B virus surface antigen; PTV, portal vein thrombosis; PT, prothrombin time; AFP, α fetoprotein.

and the presence of PVT (table 2) were associated with a lower median survival. The overall median survival rate was 41.2% at one year, 26.6% at two years, 22.9% at three years, 18.2% at four years, and 15.9% at five years.

FACTORS AFFECTING SURVIVAL
Univariate analysis (table 3)
Using univariate analyses the following 12 clinical variables had significant influence on survival (table 3): bilirubin <2 mg/dl, PT <70%, ascites, albumin <3.5 g/dl, PVT, AFP <180 μg/l, enlarged lymph nodes, distant metastases, unilobar/bilobar, tumour >50% of liver mass, tumour diameter >2 cm, and number of tumour nodules. In contrast, in univariate analysis, sex, age, smoking, HBsAg positivity, anti-HCV positivity, alcoholism, and histological grading did not significantly influence survival.

Multivariate analysis (table 4)
The 12 significant baseline parameters determined by univariate analysis were included in a multivariate Cox regression analysis. Variables were selected using backward elimination. Six parameters remained significant independent predictors of survival: bilirubin <2 mg/dl, PVT, PT <70%, AFP <180 μg/l, tumour mass >50% of liver mass, and enlarged lymph nodes (table 4) These variables were used as parameters in our model.

VISUM–HCC MODEL (TABLE 5)
The six significant variables were applied to construct a new survival model. We scored the variables either 0 (absent) or 1 (present) to simplify the practical use of the new model (table 5). In our new model, designated Vienna survival model for HCC (VISUM-HCC), stage 1 was defined as 0–2 points, stage 2 as 3 points, and stage 3 as 4–6 points. Survival was different between the three stages (fig 2B) with a median survival of 15.2 months in stage 1, 7.2 months in stage 2, and 2.6 months in stage 3 (log rank test, p=0.00021 stage 1 *v* stage 2 and p=0.00002 stage 2 *v* stage 3).

Table 4 Significant prognostic variables on survival: multivariate analysis with dichotomous variables

X model	df	p Model	Variables included	Regression coefficient (β)	p Coefficient
60.7090	6	0.00000	Bilirubin (<2mg/dl)	0.557808	0.000351
			PVT	0.550046	0.001098
			PT (<70%)	0.520451	0.001441
			AFP (<125 kU/l)	0.411822	0.005211
			Tumour >50% (yes-no)	0.332785	0.023364
			Enlarged lymph nodes	0.354986	0.029949

PTV, portal vein thrombosis; PT, prothrombin time; AFP, α fetoprotein.

Table 5 VISUM-HCC: Vienna survival model for hepatocellular carcinoma

Parameter	Points	
	0	1
Bilirubin (mg/dl)	≤2	>2
PT (%)	>70	≤70
AFP (kU/l)	≤125	>125
Tumour >50%	≤50%	>50%
Enlarged lymph nodes	No	Yes
PVT	No	Yes
Stage 1: 0–2 points	Σ points*:	
Stage 2: 3 points		
Stage 3: 4–6 points	Stage*:	

PTV, portal vein thrombosis; PT, prothrombin time; AFP, α fetoprotein.
*The sum of the points (Σ points) gives the VISUM-HCC stage of the patient.

EVALUATION OF THE SURVIVAL MODEL

We evaluated our model by comparing survival, as predicted by the model group, with survival of patients in the testing group. The RRD, predicted by the six independent parameters found in the multivariate analysis, was calculated for each patient according to the following equation detailed in the methods section:

$$\lambda_{i(t)}/\lambda_{0(t)}=\exp[0.557808\times(\text{bilirubin}-0.41)$$
$$+0.520451\times(\text{PT}-0.61)+0.550046\times$$
$$(\text{PVT}-0.23)+0.411822\times(\text{AFP}-0.5)$$
$$+0.332785\times(\text{tumour}>50\%-0.4)+0.354986$$
$$\times(\text{enlarged lymph nodes}-0.24)]$$

In this equation, all variables were introduced as dichotomous variables: bilirubin (<2 mg/dl=0, ≥2 mg/dl=1), prothrombin time (<70%=1, ≥70%=0), enlarged lymph nodes (absent=0, present=1), PVT (absent=0, present=1), tumour mass >50% (no=0, yes=1), and AFP (<180=0, ≥180=1). The model group was divided into three subgroups of similar size and consisted of 82, 81, and 82 patients, respectively; this resulted in RRD of <0.7781, 0.7781–1.2597, and >1.2597. Regression coefficients obtained in the model group were used to calculate the RRD for each
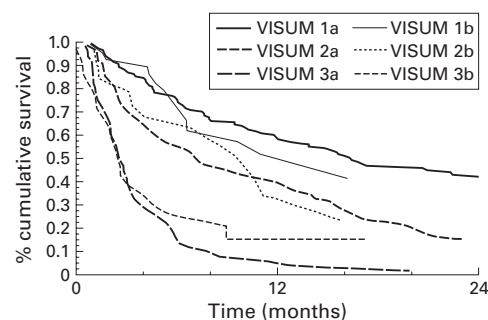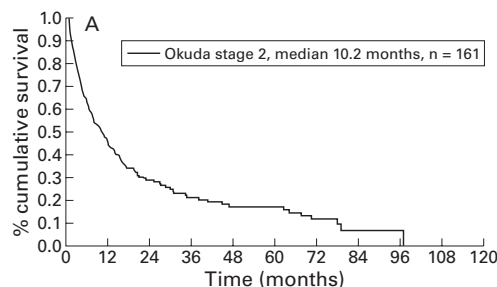

Figure 3 Survival curves of patients stratified according to VISUM-HCC criteria between the model group (group A) and the testing group (group B); no significant difference was found.

patient in the testing group; the testing group was also divided into three subgroups with identical boundaries as in the model group. These three subgroups consisted of 34, 15, and 40 patients, respectively. Survival curves were estimated according to Kaplan-Meier and corresponding curves were compared using the log rank test. Differences in survival of the corresponding groups with identical RRD in the model group and the testing group were not statistically significant, confirming the validity of the model (the overall median survival rate was 41.2% at one year in the model group and 36% at one year in the testing group; NS). Figure 3 compares survival curves of patients stratified according to VISUM-HCC criteria between the model group and the testing group; no significant difference was found.

COMPARISON OF VISUM–HCC AND OKUDA STAGING SYSTEM

Figure 2 shows cumulative survival according to Okuda stages and VISUM-HCC staging system. Survival differed significantly between VISUM-HCC stages 1, 2, and 3, respectively, whereas in Okuda stages only survival in stages 2 and 3 was statistically different but not between stages 1 and 2. In fig 4 the survival curve of patients with Okuda stage 2 (fig 4A) is shown. To further subdivide patients into groups with different survivals, we applied VISUM-HCC criteria to patients in Okuda stage 2 (fig 4B); this divided Okuda stage 2 into three subgroups with significantly different survivals (log rank test, p=0.0000). Thus patients in Okuda stage 2 with a median survival of 10.2 months could be further classified according to VISUM-HCC criteria into
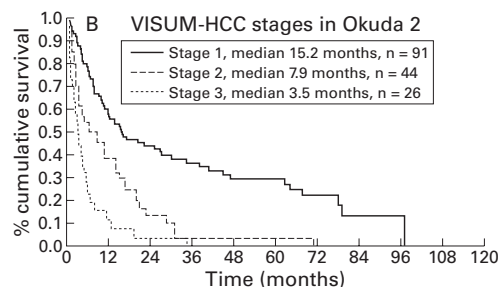

Figure 4 (A) Okuda stage 2, (B) Okuda stage 2 grouped according to VISUM-HCC; significantly different survival rates were noted between stages 1, 2, and 3.

groups with median survival of 15.2 months, 7.9 months, and 3.5 months, respectively. Okuda stages 1 and 3 could not be further subdivided by applying VISUM criteria.

Discussion

This study reports the results of a large single institution series on prognostic features and survival of patients with HCC in Central Europe. Based on univariate and multivariate analysis of clinical variables, a new survival model (Vienna survival model for HCC, VISUM-HCC) was characterised and tested on an independent group of patients. The new VISUM-HCC survival model may be useful for stratifying patients with HCC for clinical treatment modalities.

In our series, as in others,[27] the diagnosis of HCC was made at an advanced stage of the disease. Only 16% were in Okuda stage 1 and almost all patients were either TNM stage 3 or 4. This is more advanced than in reports from other Western countries showing 52%[28] and 57%[29] in Okuda stage 1 or 18% in stage 1 or 2 according to TNM classification.[30 31] The indolent nature of the disease in the early stages, lack of an institutionalised screening programme for HCC in liver cirrhosis, and a low index of suspicion in a region of low prevalence of HCC in the general population may explain these differences. In addition, our referral centre evaluates many HCC patients for liver transplantation and performs staging aggressively. This may have produced a shift towards higher stages of HCC. Due to the referral bias, our HCC population may therefore be skewed towards more advanced tumour stages and lower median survival.

The overall median survival of 8.0 months in our patients was similar to other studies with median survival times of 2.1–10.0 months.[30 32–37] In patients with liver cirrhosis, Child-Pugh stage has a predominant influence on survival time.[28] The importance of liver function is also underscored by our multivariate analysis in which two (bilirubin and PT) of the three most powerful independent prognostic factors were parameters of liver function. The best predictive parameter relating to tumour was the presence or absence of PVT whereas tumour mass >50%, enlarged lymph nodes, or AFP >180 µg/l were of less significance. The independent prognostic factors in our patient population were similar but not completely identical to the findings of others.[30 38 39] In all studies bilirubin was an important parameter. In contrast with other reports,[30 38] low albumin was not predictive of survival. Similarly, the role of alkaline phosphatase,[39] tumour size,[2 35] PVT,[39] ascites,[2 35] AFP,[40] and metastases[35] were conflicting and may reflect the heterogeneity of the patient population.

A simplified survival model (VISUM-HCC) was then constructed by assigning 0 (absent) or 1 (present) to the six significant variables (bilirubin (<2 mg/dl), PT (<70%), PVT, AFP (≤180 µg /l), tumour size >50% of liver mass, and enlarged lymph nodes) identified in the multivariate analysis. The score separates three prognostic stages with different median survival times of 15.2, 7.2, and 2.6 months, respectively. Assignment of patients to one of the three prognostic stages provides clinically valuable information for the management of patients. Patients in VISUM-HCC stage 3 (with a median survival of 2.6 months) may not be considered for active treatment but rather be offered supportive care. In contrast, patients in VISUM-HCC stage 1 (with a median survival of 15.2 months) may benefit from surgical or non-surgical procedures.

Validation of a prognostic model is usually done by applying the model's coefficients to an independent group of patients. In many reports[35 39] the split sample technique is used by randomly assigning patients of the whole group to subgroups used to construct the model and to another subgroup on which the model is validated. Thus both groups belong to the same patient population and have similar risk factors. However, a truly independent group is preferable for validation. Our testing group consisted of 89 patients with HCC who were referred to our department in the years after the patients in the model group.

Various prognostic models have been developed for HCC.[2 35 39 41–44] We applied the staging models proposed by Okuda and UICC to our patients. In both models significant differences in survival between disease stages were found; however, both models had clear limitations when applied to our patients. In Okuda's model there was no significant survival difference between stages 1 and 2. The 95% confidence interval between stage 1 and stage 2 showed considerable overlap. In the VISUM-HCC model, prognostic stages 1, 2, and 3 were clearly separated with almost no overlap. UICC's TNM classification is of limited clinical usefulness because only a few patients were in stage 1 or 2 and the difference in survival between stages 3 and 4 was small.[3 30 38 39 45 46] TNM classification was less effective than Child's classification in patients with HCC and liver cirrhosis, which again underscores the important impact of liver function on survival.

The clinical management of patients in Okuda stage 1 is surgery such as liver resection or liver transplantation. In contrast, patients in Okuda stage 3 should receive only supportive care. The best treatment for patients in Okuda stage 2 is unclear and needs to be studied in randomised clinical trials. The large variation in the prognosis of patients in Okuda stage 2 makes clinical studies difficult to perform. The VISUM-HCC model can be used to design treatment trials in a more homogeneous patient population. This strategy identifies on the one hand patients in Okuda stage 2 with survival similar to Okuda stage 1 patients and on the other Okuda stage 2 patients with survival as poor as Okuda stage 3 patients. The recently developed CLIP score[43] includes similar parameters as our model and can better characterise patients in the intermediate Okuda stage. The BCLC staging classification[44] uses different parameters than our VISUM-HCC staging classification.

In conclusion, Austrian patients with HCC had a poor median survival of eight months. Six

easily measurable clinical variables were identified as significant predictors of survival in these patients. The VISUM-HCC model, including both liver function parameters and tumour characteristics, may be useful for stratifying patients with HCC for various clinical treatment modalities.

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