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Prognostic features and survival of hepatocellular carcinoma in Italy: impact of stage of disease

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Abstract

The aim of this study was to evaluate the prognostic factors at presentation and survival in Italian patients with hepatocellular carcinoma (HCC). Clinical and demographic data of 176 patients consecutively observed from 1993 to 1997 were evaluated by univariate and multivariate analyses. Overall median survival was 18 months. At univariate analysis, low albumin, high bilirubin, high alkaline phosphatase, high alpha-fetoprotein (AFP); high platelet count, hepatitis B surface antigen (HBsAg)-positivity, the presence of ascites, of encephalopathy, of portal vein thrombosis (PVT), male sex, no treatment, poor differentiation, untreatable tumours and incidental diagnosis were each associated with shorter survival. HBsAg-positive subjects more often presented with untreatable lesions or diffuse tumours ($P=0.001$ and $P=0.007$, respectively) and had significantly worse survival ($P=0.0057$). By multiple regression analysis, low albumin, high bilirubin, abnormal AFP, presence of PVT and of untreatable lesions were independent risk factors for worse survival. Thus, the most important factors influencing survival are the degree of functional impairment of the liver, the presence of hepatitis B viral (HBV) infection, the type of diagnosis and the aggressiveness of the tumour.

Keywords: Child–Pugh score; Cirrhosis; Portal vein thrombosis; Sex; HBV infection

1. Introduction

Hepatocellular carcinoma (HCC) accounts for more than one million new cases per year and represents the seventh most frequent cancer among males and the ninth among females [1,2]. The incidence is increasing all over the world; this could be partly due to the improved diagnostic capabilities which allow better identification of HCC. However, autopsy studies seem to support the view of a true increase in incidence [3–5]. History could account for different clinical manifestation and survival in the different areas of the world. Despite implementation of screening programmes and earlier diagnosis, the prognosis is generally poor, regardless of race and origin, as not more than 20–40% of HCC are detected at a curable stage [6,7]. It is also not completely clear whether screening strategies have really improved patients' survival or whether this apparent increase in survival is simply due to anticipated diagnosis [8]. In recent years, different types of treatment have been used: however, the heterogeneity of patients' selection and the lack of randomised studies have made it difficult to assess their impact on survival [9–13].

Natural history and features that influence survival in HCC patients have been well described in the Asian population [7] and, more recently, also in Northern European and in US series [14,15]. However, survival can be influenced by factors like viral aetiology, which are more common in Mediterranean countries. Only a few studies have been devoted to investigating the survival and prognostic features of HCC in such populations [8,16,17]; furthermore they mostly dealt with specific characteristics (i.e. HCC in Child–Pugh A patients [8] or small HCC [17]). Our goal was therefore to investigate clinical and prognostic factors at presentation in a series of Italian patients with HCC in the attempt to evaluate possible differences between a Mediterranean population compared with the Asian or American series.

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2. Patients and methods

Records of all patients with HCC, consecutively admitted between 1993 through to 1997, were reviewed. Follow-up ended on 31 December 1999. During this period patients were usually seen as outpatients every 6 months or at closer intervals in cases where clinical conditions required it. All patients included in the analysis had a diagnosis based on at least one imaging procedure such as ultrasonography and/or computed tomography (CT) confirmed by an histological evaluation of the liver lesion or by serum alpha-fetoprotein (AFP) more than 400 ng/dl or by lipiodol CT. A proportion of patients were diagnosed during regular ultrasonographic follow-up performed in known cirrhotic patients every 6 months; in the others, diagnosis was incidental. Patients with renal or cardiac insufficiency, chronic obstructive pulmonary disease or preexisting tumours, other than hepatocellular carcinoma, were excluded.

Collected parameters included: age, sex, underlying hepatic disease (cirrhosis, chronic hepatitis); incidental diagnosis or detection through programmed screening; aetiological factors (hepatitis B or C virus (HBV/HCV), alcohol abuse or the co-existence of more than one risk factor; pathological characteristic of the neoplastic lesions (number, size, location, vascular invasion, histological grading); biochemical data (albumin, bilirubin, alanine (ALT) and aspartate aminotransferases (AST), prothrombin time (PT), alkaline phosphatase, γ-glutamyltranspeptidase (GGT), platelet count), Child–Pugh score [18], the presence of ascites, encephalopathy, portal vein thrombosis (PVT) at presentation and a history of gastrointestinal bleeding.

Type of treatment (surgery, transcatheter arterial chemoembolisation (TACE), percutaneous alcohol injection (PEI), antihormonal therapy) was also recorded.

2.1. Statistical analysis

Data were reported as means±standard deviation (S.D.) or medians and ranges. The Student *t*-test and the Chi-square test were used where necessary and appropriate. Baseline data of the patients were reported as means ±S.D. or medians and ranges. The univariate analysis to identify predictors of survival was performed by the Kaplan–Meier method and compared by the Mantel log-rank test. Results in the univariate analysis were considered significant if the probability of occurrence by chance was 5% or less ($P < 0.05$). Twenty-one variables were assessed: AFP levels, age, albumin, alkaline phosphatase, ALTs, ascites, ASTs, bilirubin, encephalopathy, aetiology, GGT, platelet count, the presence of PVT, previous variceal haemorrhage, PT, sex, size of the tumour, treatment, tumour histology, tumour location and type of diagnosis. For continuous variables, the cut-off was set at the median value. These variables were subsequently analysed by Cox's regression analysis; forward variable selection was used for model building and maximum partial likelihood estimates used for variable removal. For univariate and multivariate analysis, the Child–Pugh variable was also divided into its components.

Statistical analysis was performed by Statistical Package for the Social Sciences (SPSS 10.0, Chicago, IL, USA).

3. Results

3.1. Patient characteristics

176 patients with a diagnosis of HCC were identified. In 90 patients (51%) diagnosis was incidental, in 38 (22%) diagnoses were made during screening and in 48 (27%) the method of diagnosis was unknown. 137 (78%) patients were males and 39 (22%) were females with a M/F ratio of 3.5:1. The mean age at diagnosis was 64.3±7.5 years (range: 43–82 years), men being significantly younger than females (males versus females: 63.7±7.5 versus 66.4±7.4; $P = 0.049$). Most patients had liver cirrhosis (96%; $n = 169$), while only few had chronic active hepatitis (4%; $n = 7$).

HCV infection was present in 116 (66%) patients; it was the only aetiological factor in 81 (46%) patients. HBV infection was present in 32 (18%) of the patients and represented the only aetiological risk factor in 19 (11%) of the patients. Mixed aetiology (dual HCV and HBV infections; HCV or HBV infection plus alcohol) was present in 41 patients (23%). Aetiological features were different among males and females with a prevalence of HCV infection in women (74 versus 47%) and a prevalence of alcohol abuse among males (9.5 versus 0%).

The whole series was characterised by a prevalence of Child–Pugh A score (42%; $n = 74$) versus B (31%; $n = 54$) and C (27%; $n = 48$) score ($P < 0.042$). Males and females were equally distributed among the three levels.

Only a few patients underwent surgery (3%; $n = 6$); a large percentage of patients (56%; $n = 99$) were not suitable for any form of treatment, with 40% of the patients having multinodular tumours at presentation.

3.2. Tumour characteristics

At presentation, 4 patients (23%) had one lesion less than or equal to 3 cm in diameter; in 63 (36%) one lesion >3–5 cm was already present, while in 72 (41%) one or more lesions larger than 5 cm in size were present. There was no statistically significant difference in the size of lesions at presentation between subjects in whom diagnosis was made by ultrasonographic

screening (incidental diagnosis versus screening: lesions >5 cm: 46.7% versus 34.2%; lesions $\leqslant 5$ cm: 53.3% versus 65.2%) ($P=0.112$).

Most lesions were located in the right lobe ($n=143$: 81%), while only a few were found in the left lobe ($n=5$: 3%). In 28 patients (16%), a diffuse tumour was already present at presentation. Hepatitis B surface antigen (HBsAg)-positive subjects more often presented with untreatable lesions or with diffuse tumours in comparison with anti-HCV-positive patients ($P=0.001$ and $P=0.007$, respectively).

A definite histological diagnosis was available in only 94 (53%) patients. In most patients, a well-differentiated or moderately differentiated form of the tumour was present. Only a few patients had a poorly differentiated tumour (10 patients (6%)).

3.3. Survival analysis

At the end of follow-up, in December 1999, 35 patients (20%) had dropped out, 121 (69%) had died. The most relevant causes of death were: tumour progression in 72 (41%), hepatic failure without relevant tumour progression in 23 (13%), gastrointestinal haemorrhage in 15 (9%), complication of hepatic resection in 2 (1%), spontaneous bacterial peritonitis in 1 (0.6%), pulmonary embolism in 1 (0.6%), and of unknown causes in 7 (4%). Overall median survival was 18 months from the date of diagnosis. The overall actuarial probability of survival was 73% at 6 months, 65% at 1 year, 36% at 2 years, 22% at 3 years, 17% at 4 years and 11% at 5 years.

Analysis of 1-year and 3-year survival rates showed that while 1-year survival in patients with favourable characteristics (e.g. high albumin or absence of ascites) was quite often over 70%, 3-year survival was, with a few exceptions (e.g. female sex or patients discovered during screening) well below 30%.

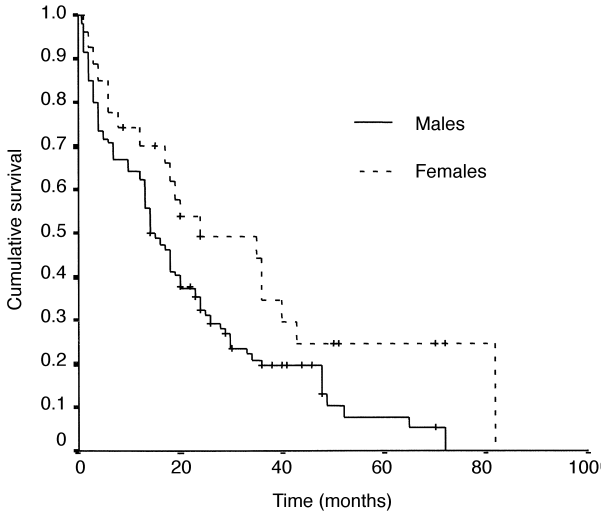

Fig. 2. Survival according to the sex of the patients ($P=0.033$).

Survival curves were statistically different when compared for: Child–Pugh classification (the worse the score, the worse was the survival: A versus C $P=0.0001$; A versus B $P=0.056$; B versus C $P=0.020$) (Fig. 1); sex (there was better survival in females than in males — $P=0.033$, Fig. 2 — this difference still being present after adjustment for the Child–Pugh score, $P=0.045$); treatment received, the difference being in favour of the treated patients (surgery was excluded from the analysis because of the very few cases treated) ($P=0.0128$); presence of HBV infection (survival was significantly worse than in anti-HCV-positive subjects) ($P=0.0057$) (Fig. 3). The population sample was large enough to disclose differences among the treated and untreated patients, but did not permit a subdivision based upon the type of

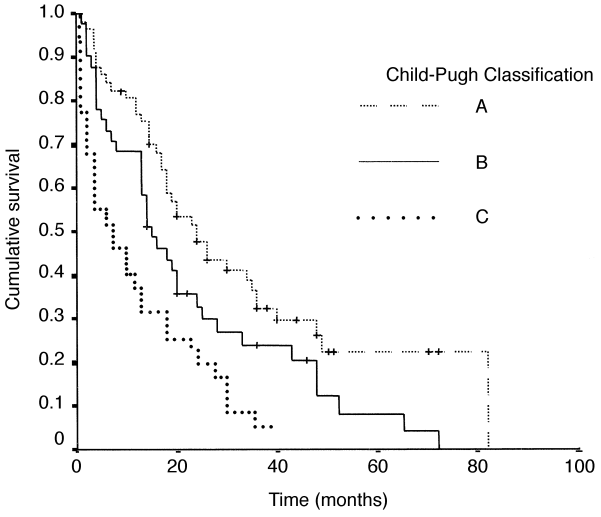

Fig. 1. Survival dividing the patients according to Child–Pugh score (Child–Pugh score A versus C $P=0.0001$; A versus B $P=0.056$; B versus C $P=0.020$).

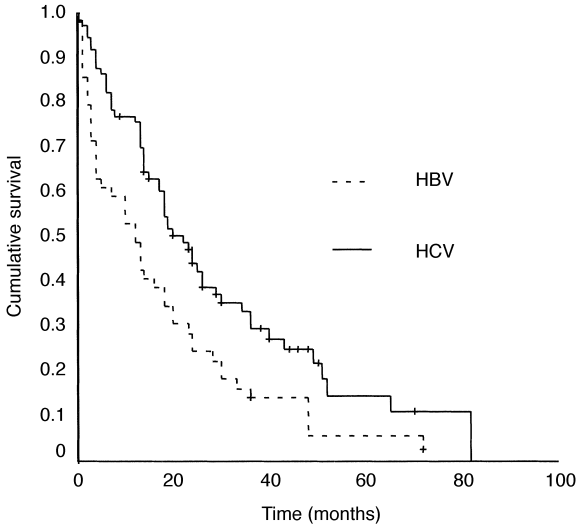

Fig. 3. Survival according to the presence of hepatitis B viral (HBV) or hepatitis C viral (HCV) infection ($P=0.0057$).

Table 1
List of variables examined at univariate analysis. 95% confidence interval and significance are referred to median survival ($n = 141$; $n = 35$ are missing to follow-up)

Variable	Patients	Number of events	1-Year survival (%)	3-Year survival (%)	Median survival (months)	95% Confidence interval	Significance (log-rank test)
Variables with prognostic significance at univariate analysis							
AFP[a,b]							
⩽32.5 IU/l	70	58	72.8	31.7	23	18.19–27.81	0.0026
>32.5 IU/l	61	54	63.6	14.3	14	11.01–16.99	
Albumin[a]							
⩽33 g/l	78	70	52.5	16.8	12	7.19–16.81	0.0047
>33 g/l	63	51	84.0	29.7	23	17.70–28.30	
Alkaline phosphatase[a]							
⩽327 UI/l	73	61	80.8	30.7	22	15.90–28.10	0.0005
>327 UI/l	68	60	51.1	13.4	12	7.26–16.74	
Ascites[b]							
Absent	91	76	77.9	29.2	20	16.48–23.52	
Moderate	20	17	60.0	18.2	13	5.73–20.27	0.0002
Severe	29	27	34.4	0	4	1.36–6.64	
Bilirubin[a]							
⩽20.5 μmol/l	70	58	74.2	32.6	22	15.78–28.22	0.0009
>20.5 μmol/l	71	63	58.8	11.9	14	10.98–17.02	
Encephalopathy[b]							
Absent	123	104	70.6	25.1	18	14.76–21.24	0.0001
Moderate	16	15	43.7	6.2	7	5.06–8.94	
Severe	1	1	–	–	1	–	
Aetiology							
Anti-HCV-positive	88	71	74.8	29.1	22	16.51–27.49	0.0057
HBsAg-positive	24	22	51.6	10.7	12	7.71–16.29	
Platelet count[a] (10^9/l)[b]							
⩽109	73	61	78.0	27.3	20	15.28–24.72	0.0271
>109	67	59	54.8	17.7	14	9.54–-8.46	
Portal vein thrombosis (PVT)[b]							
No	120	100	72.3	24.9	19	15.32–22.68	0.0001
Yes	19	19	24.9	10.5	4	1.19–6.81	
Sex							
Males	113	99	64.6	18.8	16	12.56–19.44	0.033
Females	28	22	74.5	38.2	24	16.34–31.66	
Treatment[b]							
Yes	73	60	80.6	29.9	20	15.36–24.64	0.0128
No	66	59	50.0	15.4	10	3.03–16.97	
Tumour histology[b]							
Well differentiated	52	41	80.7	30.0	22	16.90–27.10	
Moderately differentiated	20	17	74.3	22.7	18	10.21–25.79	0.0333
Poorly differentiated	9	8	44.4	0	10	1.23–18.77	
Unknown	56	52	53.5	18.6	13	6.73–19.27	
Tumour location							
Left lobe	4	3	50.0	50.0	7	0.00–38.36	
Right lobe treatable	86	69	76.6	30.9	24	20.11–27.89	0.00001
Right lobe untreatable	32	30	53.3	7.2	13	5.30–20.70	
Diffuse	19	19	47.3	5.2	10	0.00–21.38	
Type of diagnosis[b]							
Incidental	79	76	56.9	13.1	13	10.11–15.89	
Screening	33	22	88.7	45.3	33	18.88–47.12	0.0005
Unknown	26	23	65.3	23.0	18	5.51–30.49	

(continued)

Table 1 (*continued*)

Variable	Patients	Number of events	1-Year survival (%)	3-Year survival (%)	Median survival (months)	95% Confidence interval	Significance (log-rank test)
Variables without prognostic significance in the univariate analysis							
Age[a]							
⩽65 years	68	58	66.1	25.7	19	16.36–21.64	0.3186
>65 years	73	63	66.9	19.5	15	11.73–18.27	
ALTs[a,b]							
⩽73 IU/l	69	57	64.9	23.8	18	13.22–22.78	0.8704
⩽73 IU/l	69	61	69.5	22.3	18	12.82–23.18	
ASTs[a,b]							
⩽92 IU/l	75	64	69.1	23.8	18	13.99–22.01	0.6482
>92 IU/l	65	56	64.2	21.4	18	11.86–24.14	
GGT[a,b]							
⩽83 IU/l	73	63	75.3	25.3	22	17.60–26.40	0.0598
>83 IU/l	67	57	56.3	18.3	13	10.15–15.85	
Prothrombin time (PT)[a]							
⩽74%	72	66	66.6	18.3	18	13.23–22.77	0.5719
>74%	69	55	66.4	27.1	18	13.12–22.88	
Size of tumours							
Single lesion ⩽3 cm	31	27	74.1	23.7	20	13.46–26.54	
Single lesion >3⩽5 cm	50	42	70.0	22.1	18	15.82–20.18	0.5512
Single or more lesions >5 cm	60	52	59.6	22.2	14	7.42–20.58	
Variceal bleeding[a]							
Absent	120	102	68.2	23.3	18	13.56–22.44	0.9076
Present	18	16	61.1	20.9	13	0.00–29.63	

AFP, alpha-fetoprotein; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; AST, asparate aminotransferase; GGT, γ-glutamyltranspeptidase.

[a] For continuous variables the cut-off was set at the median value.

[b] These categories do not total $n = 141$ due to missing data.

treatment received. Survival was also significantly better in patients in whom diagnosis was made during screening in comparison with incidental diagnosis ($P = 0.0005$).

There were no statistically significant differences between patients of different geographical origin (Northern or Southern Italy). No correlation was found with the number of lesions and with the size of the tumour. However, the subdivision of patients with right lobe tumours (representing 81% of the whole series) in patients who could be suitable for radical treatment or not (depending especially on the presence of ultrasonographic signs of vascular invasion, i.e. PVT) evidenced a marked difference in survival ($P = 0.005$).

Variables examined at univariate analysis, which were related to a shorter survival, are reported in Table 1. Cox's regression analysis showed that only decreased albumin level, increased AFP, increased bilirubin, the presence of PVT and of untreatable lesions were the most powerful independent negative prognostic factors for survival (Table 2).

4. Discussion

HCC still represents a diagnostic and therapeutic challenge: efforts have been directed towards improving

Table 2
Independent prognostic factors for survival in the multivariate analysis of 141 patients with hepatocellular carcinoma (HCC)

Variable	β	Standard error of the mean	Relative risk	95% Confidence interval	*P* value
Albumin	−0.69	0.24	0.5610	0.3767–0.8354	0.004
Alpha-fetoprotein (AFP)	1.04	4.9	1.5600	1.0311–2.3746	0.03
Bilirubin	0.21	0.06	1.5021	1.1635–1.9391	0.001
Portal vein thrombosis (PVT)	0.4	0.22	1.6062	1.0615–2.4303	0.02
Untreatable lesions	0.7	0.26	2.6569	1.3609–5.1871	0.004

early diagnosis and finding new therapies. However, results have not fulfilled expectations [6,7]. From this point of view, our results are paradigmatic: approximately 40% of patients, irrespective of having been diagnosed incidentally or during prospective ultrasonographic screening, were already unsuitable for treatment at presentation. A likely explanation is that the molecular characteristics of HCC may deeply influence HCC behaviour so that the usual screening strategies, with 6-month interval between sample testing, are ineffective. Our data suggest that special attention should be paid to HBsAg-positive subjects as it is evident that these patients carry a much higher risk of developing an aggressive type of cancer than anti-HCV-positive subjects. Not only do they develop HCC at a younger age, but HCC is significantly more often already incurable or diffuse at presentation. This aggressive behaviour is in agreement with other data from our group which show that HBsAg-positive subjects develop variant oestrogen receptors more often than anti-HCV-positive subjects, which is a molecular marker of rapidly progressing HCC [19,20]. While intervals between ultrasonographic testing shorter than 6 months would be impossible from an economical and organisational point of view, when applied to all patients, a special strategy could be devised for HBsAg-positive patients, who represent, even in countries like Italy where HBV is still an important aetiological factor of chronic liver disease, not more than 20% of all cirrhotic patients.

Despite the advanced stage of disease at presentation, median survival in our series was 18 months. This figure is similar to that reported in a Northern American population by Sutton and colleagues [14] and Stuart and associates [15]. Other studies [7,21–25] have reported much shorter survivals with medians of 3–4 months. These differences have been partly ascribed to different pathological characteristics associated with ethnic origin: Okuda and associates [7] studied Japanese subjects, Falkson and colleagues [22] a mixed population from North America and South Africa, Calvet and coworkers [24] and Attali and colleagues [21] studied Northern European populations. However, in our series, the main factor influencing survival was not geographical origin (Northern or Southern Italy), but characteristics of the disease at diagnosis, survival being significantly longer in patients with less compromised liver function (24 months survival in Child–Pugh A patients versus 6 months in Child–Pugh C patients: $P = 0.0001$) and having well differentiated tumours (differentiated versus poorly differentiated: $P = 0.0333$). There was instead no statistically significant differences in the survival according to the number and size of the lesions, as already reported by others [14,15]. Analysis of data by multiple regression analysis indicated that the only independent risk factors were either factors related with degree of impairment of liver function (low serum albumin, high bilirubin) or with the pathological characteristics of the tumour (abnormal AFP, the presence of untreatable lesions; the presence of PVT).

Comparison of the different treatment options shows better survival curves in patients treated with PEI or TACE (surgery was excluded from the analysis because of the very few patients treated surgically). This has also been shown by others [7,14]. However, as our patients were not randomised to the different forms of treatment, a selection bias may have affected the results, as it is likely that treatment was offered to patients with a better life expectancy.

Epidemiologically, the Italian patients of our series with HCC are intermediate between the Orientals and Africans and the Northern Europeans and North Americans [1,26,27]. Liver cirrhosis was the prevalent pathological lesion in the HCC patients accounting for approximately 96% of cases, while only a few had chronic active hepatitis. This is in agreement with other Italian series [28], and also with most other series in the world [4,15,24,25,27,29–31]. Cirrhosis, whatever the aetiology, therefore, represents the principal risk factor for the development of liver cancer [16,30,31]. The most represented aetiological factors in our series were HCV infection associated with other risk factors (alcohol abuse or HBV infection) in approximately 23% of patients. If we compare this percentage with that of non A, non B (NANB) infection in patients observed in the same institution approximately 12 years ago [28], we find that the incidence of HCV infection is apparently much higher than it was. However, it is likely that in those patients, classified at that time as "HBV antibody positive", the aetiological agent of liver disease was in fact HCV: this means that the relative proportion between HBV and HCV 12 years apart has not changed much. For example, 12 years ago, our data confirm a definite biological disadvantage for the male sex in HCC: not only was the male/female rate 3.5:1, but also HCC developed at a younger age in the males than in the females and survival was significantly shorter, independent of the Child–Pugh score. This recalls the importance of the molecular characteristics of the tumour in males, in whom the more frequent presence of modified oestrogen receptors in comparison with females is associated with a more aggressive clinical course and shorter survival, especially in HBsAg-positive subjects [19,20].

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