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Preserved liver function, portal thrombosis and absence of oesophageal varices are risk factors for metastasis of hepatocellular carcinoma

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ABSTRACT

Background: Extrahepatic metastases represent a major obstacle for further improving prognosis of hepatocellular carcinoma.
Aim: To assess clinical predictors of extrahepatic metastases in a large cohort followed in a single centre.
Methods: We evaluated clinical files of 520 consecutive patients with hepatocellular carcinoma admitted from 1994 to 2002 to our Liver Unit. The following risk factors were assessed: age, gender, hepatitis viruses, alcohol, diabetes, size, number and differentiation of hepatocellular carcinoma, percutaneous biopsy, portal thrombosis, alpha-fetoprotein, Child-Pugh, Cancer Liver Italian Program and Model for End-stage Liver Disease scores, Barcelona Clinic Liver Cancer classification, varices, hepatocellular carcinoma treatment.
Results: Extrahepatic metastases were detected in 55/520 patients (10.5%) after 0–72 months (median 15, CI 3–20) from initial evaluation. Lower bilirubin, INR, Child-Pugh and Model for End-stage Liver Disease scores, higher alpha-feto protein levels, portal thrombosis and absence of oesophageal varices were all associated with distant metastases at univariate analysis. Absence of oesophageal varices and portal thrombosis resulted as independent predictors ($P = 0.0003$ and $P = 0.004$, respectively) on multivariate logistic regression. Patients with metastases showed poorer survival (3 months) than total hepatocellular carcinoma population (26 months).
Conclusions: Extrahepatic metastases of hepatocellular carcinoma are rare but significantly impair prognosis. Extrahepatic metastases were more frequent in patients with well preserved liver function. Absence of oesophageal varices and presence of portal thrombosis were the strongest risk factors.

1. Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, representing the third cause of cancer related death [1]. Although this disease typically affects elderly males, in recent years there has been a shift towards relatively younger age groups [2]. Hepatitis viruses and alcohol abuse explain more than half of the observed increase in HCC. In a variable but significant proportion of cases, the insulin resistance syndrome, is considered a potential risk factor [2,3].

Technological advancements and screening programs have allowed to detect HCC at earlier stages when tumour size is small and effective treatments such as surgical resection, liver transplantation and percutaneous ablation can be applied [4]. Despite effective treatment, though, a large number of patients develop HCC recurrence during follow-up [4]. The prognosis of patients with HCC depends mainly on residual liver function, grade of portal hypertension and tumour extension [5,6].

Intra-hepatic recurrence and extrahepatic metastases (EM) are major obstacles for further improving survival and prognosis of HCC patients. Risk factors and prognostic significance of EM in HCC are not well defined, as well as characteristics, prevalence and incidence of this complication. Although accurate prediction of the risk of EM would be helpful to select the best therapeutic options in particular with regard to liver transplantation, a widely accepted protocol to detect distant metastases in HCC is lacking. The aim of this study was to investigate the prevalence and incidence of EM, as well as to identify predictors of EM, in a large cohort of patients with liver cirrhosis and HCC observed and treated for HCC in a single centre.

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2. Patients and methods

This historical cohort observational study was approved by our Institutional Review Board and complies with the standards of Declaration of Helsinki and current ethical guidelines.

2.1. Population

The medical records of all consecutive cirrhosis patients with HCC observed from March 1994 to December 2002 at the Liver Unit of the "A. Cardarelli" Hospital, Naples were reviewed. Patients who had recent (<5 years) history or presence of other concomitant malignancy were excluded from the analysis.

Patients were systematically evaluated for hepatitis virus infection, alcohol abuse or other causes of liver damage. Child-Pugh [7], Cancer Liver Italian Program (CLIP) [6], the Model for End-stage Liver Disease scores (MELD) [8] and the Barcelona Clinic Liver Cancer (BCLC) staging classification [9] were calculated. All patients underwent chest X-ray, abdominal ultrasonography, chest and abdominal CT scan and upper gastrointestinal endoscopy.

2.2. Diagnosis of HCC

HCC was diagnosed when at least two of the following tests were positive: ultrasonography, serum alpha-feto protein (AFP) higher than 200 ng/mL [10], typical features on dynamic computed tomography scan (arterial hypervascularization and rapid "wash-out" of the contrast medium on portal-venous phase). When only one of the above criteria was present, magnetic resonance imaging or hepatic angiography or histopathological confirmation were required. Histopathological differentiation of HCC was graded according to the criteria of Edmondson and Steiner [11].

2.3. Treatment of HCC

Resective surgery, percutaneous alcohol injection (PEI) and, after 2001, radiofrequency ablation (RFA) were considered as first choice treatment in patients with compensated cirrhosis. Liver transplantation (LT) was considered in decompensated patients without contraindications. After 1996, Mazzaferro criteria were adopted [12]. Transarterial chemoembolization (TACE) was performed in patients not suitable for the above treatments and in patients listed for liver transplantation.

2.4. Extrahepatic metastases (EM)

The diagnosis of EM was histological in 33/69 metastases while in the remaining it was based on imaging modalities: including CT scan, magnetic resonance imaging, bone or brain scintigraphy. Diagnosis of abdominal lymph node metastasis was always histologically confirmed. Positron emission tomography (PET) scan was used when biopsy was unsuccessful or not technically feasible.

2.5. Follow-up

All patients were followed until death or December 31, 2008. Follow-up protocol consisted of physical examination, blood testing, AFP monitoring and ultrasonography every 3 months. Dynamic chest and abdominal CT scans were performed every 6 months. All treated HCC patients underwent a CT scan 1 month after treatment, before entering the surveillance protocol. CT scans were systematically collected and reviewed by specialized members of the HCC workgroup. Brain and/or bone scintigraphy were performed when indicated by clinical examination.

Loco-regional re-treatment was applied in cases of residual or recurrent tumour after surgery or initial loco-regional therapy. Patients with uncontrolled tumour spread associated with worsening liver function were given only supportive treatment.

2.6. Risk factors

The following potential risk factors for extrahepatic spread of HCC were evaluated: age, gender, hepatitis viruses (HCV, HBV ± HDV), alcohol, number and size of HCC nodules, degree of tumour differentiation, percutaneous liver biopsy, serum levels of AFP, bilirubin, albumin INR/prothrombin time, presence of diabetes (defined as use of insulin or oral glucose lowering drugs), the degree of liver dysfunction/tumour progression (Child-Pugh, CLIP, MELD and BCLC), portal vein thrombosis, presence of oesophageal varices, and HCC treatment (treated vs. untreated).

2.7. Statistical analysis

Survival of patients with or without EM was assessed using the Kaplan–Meier method. Differences in continuous variables were evaluated by the Mann–Whitney ranked sum test. Chi-square test was used for categorical data. Logistic regression was used for multivariate analysis. Differences were considered statistically significant when the P-value was less than 0.05. Values are expressed as median (95% confidence interval of median) if not otherwise indicated. Statistical analysis was performed using SPSS version 12.0 (MJ Norusis, Chicago, IL, USA).

3. Results

A total of 520 consecutive cirrhosis patients with HCC and complete medical profile were retrieved and analysed. Mean (±SD) age was 65.3 (±8.2) years (range 37–85), with male gender accounting for 393 (75.6%) of the cases. The aetiology of liver disease was HCV in the majority of patients (66.9%). Forty-six percent of the patients (239/520) were in BCLC class A. Detailed clinical characteristics of studied population are outlined in Table 1.

One hundred and twelve patients (21.5%) had histological confirmation of HCC through needle biopsy. The mean tumour size was 36 ± 17 mm (range 7–110). Globally, 63 (12.1%) patients underwent surgical treatments, including partial hepatectomy (N = 44) or LT (N = 19). A total of 351 (67.3%) patients underwent loco-regional therapy, while 106 (20.4%) were left untreated and received merely supportive therapy. This group included 16 patients with EM at the time of initial observation (Table 2) Among 19 patients who received LT, 12 (63%) are still alive, 3 died for recurrence, and only one for metastatic disease.

Follow-up was complete in all but 4 patients. Three of these drop out patients underwent LT and one liver resection in foreign countries. During a mean follow-up period of 33 ± 29 months (median 26, range 1–153) a total of 69 extrahepatic metastases were detected in 55 (10.5%) patients. Among these patients, 17 had EM at the time of initial observation (prevalence 3.3%), while 38 cases developed EM during follow-up (incidence rate 27/1000 patient-year). In the latter group, the median time from the first evaluation to the diagnosis of EM was 15 months (95% CI 3–20). No significant modification in the occurrence rate of EM was found along the observation period. The sites of extrahepatic metastases are listed in Table 3. Abdominal pain was the most frequent symptom of peritoneal metastases. Brain lesions appeared as coma in one case, Bell's palsy in another and dizziness in the remaining one. Three patients presented with skin lesions (subcutaneous masses), one of them after surgery (seeding). The single patient with gingival metastasis had oral bleeding as first manifestation. Lymph nodes were the most frequent metastatic site, with a diameter ranging from 1.5 to 4.0 cm.