
OBJECTIVES: The survival of treated, noncirrhotic patients with hereditary hemochromatosis is similar to that of the general population. Less is known about the outcome of cirrhotic hereditary hemochromatosis patients. The present study evaluated the survival of patients with hereditary hemochromatosis and cirrhosis.

METHODS: From an established hereditary hemochromatosis database, all cirrhotic patients diagnosed from January 1972 to August 2004 were identified. Factors associated with survival were determined using univariate and multivariate regression. Survival differences were assessed using the Kaplan-Meier life table method.

RESULTS: Ninety-five patients were identified. Sixty patients had genetic testing; 52 patients (87%) were C282Y homozygotes. Median follow-up was 9.2 years (range 0 to 30 years). Nineteen patients (20%) developed hepatocellular carcinoma, one of whom was still living following transplantation. Cumulative survival for all patients was 88% at one year, 69% at five years and 56% at 20 years. Factors associated with death on multivariate analysis included advanced Child-Pugh score and hepatocellular carcinoma. Patients with hepatocellular carcinoma were older at the time of diagnosis of cirrhosis (mean age 61 and 54.6 years, respectively; P=0.03). The mean age at the time of diagnosis of hepatocellular carcinoma was 70 years (range 48 to 79 years). No other differences were found between the groups.

CONCLUSIONS: Patients with hereditary hemochromatosis and cirrhosis are at significant risk of developing hepatocellular carcinoma. These patients are older when diagnosed with carcinoma and may have poorer survival following transplantation than patients with other causes of liver disease. Early diagnosis and treatment of hereditary hemochromatosis by preventing the development of cirrhosis may reduce the incidence of hepatocellular carcinoma in the future.

Key Words: Hemochromatosis; Hepatocellular carcinoma; Iron overload
17 patients, two with hepatocellular carcinoma, had a history of chronic hepatitis B or C in this group. Regarding alcohol intake, less than 20 g per day for men and 10 g per day for women. 

Patients and Methods

Methods

From an established database of hereditary hemochromatosis patients, all cirrhotic patients diagnosed from January 1972 to August 2004 were identified. The diagnosis of cirrhosis was based on clinical findings in 47 patients and histological findings in 48 patients. A clinical diagnosis of cirrhosis was established by an experienced hepatologist, and was based on a combination of physical examination and biochemical findings, as well as features of hepatic decompensation (ascites, portal hypertension and hepatic encephalopathy). The presence of histological cirrhosis was determined by a pathologist familiar with chronic liver disease and the formation of regenerative nodules. Patients with other medical conditions known to be associated with iron overload, such as hemolytic anemia and history of multiple transfusions, were excluded. There were no patients with liver structure by fibrosis and the formation of regenerative nodules. Cirrhosis was defined as widespread destruction of normal liver structure by fibrosis and the formation of regenerative nodules. Patients with other medical conditions known to be associated with iron overload, such as hemolytic anemia and history of multiple transfusions, were excluded. There were no patients with associated with iron overload, such as hemolytic anemia and history of multiple transfusions, were excluded. There were no patients with 

Figures and Tables

Table 1. The mean age of all patients was 57 years (range 28 to 82 years). The mean age at the time of diagnosis of hepatocellular carcinoma was 70 years (range 48 to 79 years). Fourteen patients (15%) were women and 81 (85%) were men. Median follow-up duration for the present study was 9.2 years (range 0 to 30 years).

Table 1. The main clinical and biological data of the patients are given in Table 1. The mean age of all patients was 57 years (range 28 to 82 years). The mean age at the time of diagnosis of hepatocellular carcinoma was 70 years (range 48 to 79 years). Fourteen patients (15%) were women and 81 (85%) were men. Median follow-up duration for the present study was 9.2 years (range 0 to 30 years).

Statistical analysis

Statistical analysis was performed by logistic regression using the MedCalc software package (version 6.0, Mariakerke, Belgium). Values were considered significant at P<0.05. The independent effect of significant variables from univariate analysis (P<0.05) was assessed using multivariate regression analysis. Survival differences were assessed using the Kaplan-Meier life table method (Winstat 3.0, Kalma, USA).

Results

Patients

The main clinical and biological data of the patients are given in Table 1. The mean age of all patients was 57 years (range 28 to 82 years). The mean age at the time of diagnosis of hepatocellular carcinoma was 70 years (range 48 to 79 years). Fourteen patients (15%) were women and 81 (85%) were men. Median follow-up duration for the present study was 9.2 years (range 0 to 30 years).

Regarding the diagnosis of hereditary hemochromatosis after 1997, 60 patients underwent genetic testing and of these, 52 patients (87%) were C282Y homozygotes. In the remaining 52 patients (87%) were C282Y homozygotes. In the remaining 19 (20%) had a diagnosis of hepatocellular carcinoma while 76 (80%) were free of hepatocellular carcinoma. In all cases, a diagnosis of hereditary hemochromatosis was made based on liver biopsy with a hepatic index greater than 1.9 and was supported by pedigree studies. Of 95 patients, 19 (20%) had a diagnosis of hepatocellular carcinoma while 76 (80%) were free of hepatocellular carcinoma.

Of 95 patients, 19 (20%) had a diagnosis of hepatocellular carcinoma while 76 (80%) were free of hepatocellular carcinoma. In all cases, hereditary hemochromatosis was diagnosed before the diagnosis of hepatocellular carcinoma. The diagnosis of hepatocellular carcinoma was confirmed by histological findings on percutaneous biopsy, surgical resection or autopsy. Of patients with hepatocellular carcinoma, only one was alive at the end of follow-up, having undergone orthotopic liver transplantation (OLT) for this indication. Ten patients underwent regular screening with ultrasound and alpha-fetoprotein. Four patients had hepatocellular carcinoma diagnosed during screening. Alpha-fetoprotein level was only minimally elevated (16 µL) in one patient who successfully underwent OLT and was living at the time of the present study. Alpha-fetoprotein was significantly elevated in these patients.
elevated in the remaining patients (386 µg/L to 2109 µg/L). A second patient was offered chemoembolization and declined. The remaining two patients were too ill for surgery or other treatment modalities. Of those not screened for hepatocellular carcinoma, two patients had incidentally diagnosed tumours. One patient underwent three sessions of percutaneous ethanol injection and survived 18 months following diagnosis. The second patient received chemoembolization and survived 25 months. Both patients eventually died secondary to tumour progression.

**Univariate analysis**
Clinical and laboratory features were evaluated to determine which, if any, correlated with patient survival. Univariate analysis was performed for each variable (using logistic regression for continuous variables and linear regression for frequency data). Factors significantly associated with death on univariate analysis included male sex, ferritin level, transferrin saturation, alanine aminotransferase level, bilirubin level, creatinine level, international normalized ratio, hepatic iron index, Child-Pugh score and the presence of hepatocellular carcinoma (P<0.05).

**Multivariate analysis**
The independent effects of factors found to be significant in univariate analysis were assessed by multivariate analysis (stepwise linear regression). Using the multiple regression model, the presence of hepatocellular carcinoma (P=0.0273) and Child-Pugh score (P=0.00025) were found to be associated with shorter survival duration. The parameters from this analysis are given in Table 2.

**Kaplan-Meier survival curve**
The survival curve of 76 nonhepatocellular carcinoma patients was compared with 19 hepatocellular carcinoma-affected patients (Figure 1). The rate of survival was lower in patients with hepatocellular carcinoma (P=0.0193, log rank test). Cumulative survival for all patients was 88% at one year, 68% at five years, 63% at 10 years and 55% at 20 years.

**DISCUSSION**
In the present retrospective study of the long-term follow-up of patients with hereditary hemochromatosis and cirrhosis, a diagnosis of hepatocellular carcinoma was established in 19 of 95 patients (20%). The prevalence at the authors’ centre is in keeping with the literature, where the published incidence of hepatocellular carcinoma in patients with hereditary hemochromatosis ranges from 12.4% to 45% (10-12). It is possible that this is a slight underestimation of the true prevalence of hepatocellular carcinoma because not all patients were screened for hepatocellular carcinoma or underwent autopsy, at which time small tumours may have been discovered with careful hepatic sectioning. Also, because the authors’ centre is a referral centre for patients with hemochromatosis, a referral bias cannot be excluded.

Patients who undergo iron depletion therapy before the development of cirrhosis have a survival rate comparable with the general population (5,13). The development of genetic testing for hemochromatosis has led to earlier diagnosis in patients with possible iron overload and has led to screening of family members, allowing the diagnosis to be made at a presymptomatic stage (14-16). The widespread availability of genetic testing may lead to early diagnosis and treatment. This could, in the future, lead to a decreasing incidence of hepatocellular carcinoma in patients with hereditary hemochromatosis.

Before 1995, patients at the authors’ centre did not receive routine surveillance for hepatocellular carcinoma. Thus, the majority of patients in the current study were not screened. In recent years, serial ultrasound and alpha-fetoprotein measurements have been widely adopted as surveillance measures. However, this practice remains controversial because definite evidence is lacking that show that surveillance improves patient outcomes (17-19). Had each patient undergone regular, biannual ultrasounds and alpha-fetoprotein measurements, a total of 2894 investigations would have been performed, resulting in significant cost (20,21).

Before the publication of the Milan criteria (22) in 1996, few patients at the authors’ centre underwent transplant for hepatocellular carcinoma. The majority of tumours in the present study (13 of 19) were diagnosed in patients before this time and would not have been transplanted. As well, although there is no absolute age when transplantation is contraindicated, with increasing age, the risks associated with transplantation begin to exceed an acceptable level (23-25). It has also been shown that older transplant recipients, particularly those older than 60 years, have poorer long-term post-transplant survival. Malignancy accounts for the majority of deaths in this patient group (26,27). An acceptable upper limit for age at many centres, including the authors’, is approximately 70 years. Among the hepatocellular carcinoma patients in the present study, 11 of 18 would have been excluded from consideration for transplantation as a result of advanced age at the time of diagnosis. In addition, with an average wait for transplant of two to three years, many of the remaining patients who would have been considered candidates...
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may have become ineligible. It is also likely that in some cases during this waiting period, tumour progression may have resulted in the patient becoming ineligible for transplant.

In contrast with hemochromatosis, the development of hepatocellular carcinoma in patients with viral hepatitis appears to occur at a younger age. A mean age of 63 years for the diagnosis of hepatocellular carcinoma has been reported in patients with hepatitis C virus-associated cirrhosis (28,29). Therefore, early diagnosis in this group of patients may allow for more definitive treatment of lesions with transplantation or hepatic resection in those who are candidates. Despite concerns regarding recurrent infection, many appropriately selected patients with viral hepatitis and hepatocellular carcinoma generally do well following liver transplantation. Patients with hereditary hemochromatosis and iron overload have been shown to have poorer survival following liver transplant (30,31). This outcome is not explained solely by the concomitant presence of hepatocellular carcinoma. Increased rates of infection and late cardiac complications have been found to be the most common causes of post-transplant deaths in hereditary hemochromatosis patients (32,33). One- and five-year post-transplant survival rates of only 64% and 34% have been documented in hereditary hemochromatosis patients (34). These are significantly worse than the generally accepted rates of 80% and 70% seen for most other causes of chronic liver disease (35).

**SUMMARY**

Hepatocellular carcinoma occurs in approximately 20% of hemochromatosis patients with cirrhosis and is one of the most common causes of death. The role of surveillance for hepatocellular carcinoma in these patients needs to be further evaluated.