

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the fourth leading cause of cancer related death in the world. Although the survival of patients with HCC has been improved by advances in surgical and loco-regional techniques and perioperative management, long-term survival remains unsatisfactory owing to the high rate of recurrence and metastasis (*Llovet and Beaugrand, 2003; Tang et al., 2004*).

The dismal clinical outcome of HCC leads to an urgent need for in-depth understanding of the relevant factors affecting HCC prognosis after treatment. These may serve to guide decision-making for therapeutic strategies for HCC patients and improve their prognosis.

Diabetes mellitus (DM) is positively associated with risks of several common human malignancies, including cancers of the colon, breast, endometrium, pancreas and liver (*Strickler et al., 2001*).

Compared with their non-diabetic counterparts, patients with pre-existing DM have a higher risk for developing HCC, and it has been suggested as a potential risk factor for HCC (*El-Serag et al., 2004; Lai et al., 2006*).

Introduction

Many studies, including several case control studies (*Davila et al., 2005; Hassan et al., 2002; Rousseau et al., 2006*) and cohort studies (*Ogunleye et al., 2009; Torisu et al., 2007; Wang et al., 2009*) have reported a positive association between DM and HCC risk. A possible explanation for this association relates to the fact that diabetes often occurs as part of the metabolic syndrome itself characterized by a group of biochemical abnormalities and associated clinical conditions which include disturbed glucose and insulin metabolism resulting in hyperglycemia and hyperinsulinemia, dyslipidemia, and hypertension. The metabolic derangements associated with metabolic syndrome (hyperinsulinemia, hyperglycemia, and dyslipidemia) can lead to diabetes mellitus and/or atherosclerotic cardiovascular disease.

Moreover, these aforementioned metabolic abnormalities may contribute to the increasing risk of nonalcoholic fatty liver disease (NAFLD), including its most severe form, nonalcoholic steatohepatitis (NASH), and that HCC may be a late subsequent consequence of cirrhosis caused by NAFLD; however some studies have refuted this association (*Di Costanzo et al., 2008; Hung et al., 2011; Veldt et al., 2008*). Additionally, reverse causality is a major concern for causal inference in these case-control studies because in some cases diabetes might itself be a result of cirrhosis.

Introduction

Given the higher risk of HCC in patients with DM, investigation of how pre-existing DM may influence the prognosis of HCC after treatment is critical to decide the proper care of these patients. Recent researches have focused on the effects of comorbid conditions on the prognosis of HCC patients after treatment (***Amarapurkar et al., 2008; Komura et al., 2007***). But potential interactions between DM and HCC are so complex that a conclusion remains controversial (***Huo et al., 2004; Poon et al., 2002***).

The management of HCC is influenced not only by the tumor status and underlying liver function but also by comorbid illness in the patients.

Diabetes mellitus (DM) is one of the most common comorbid illnesses found in patients with HCC. The incidence of DM is higher in patients with cirrhosis, due to an altered carbohydrate metabolism, and DM may also be an independent risk factor for the development of HCC (***Kingston et al., 1984; Lai et al., 2006***).

Because of the frequent association of DM with HCC, studying the impact of DM on the management of HCC is of considerable clinical relevance.

AIM OF THE WORK

The aim of this prospective cohort study is to evaluate the impact of type 2 DM on the treatment outcome of HCC patients who underwent radiofrequency ablation (RFA) or trans-arterial chemoembolization (TACE).

HEPATOCELLULAR CARCINOMA (HCC)

Epidemiology

Liver cancer is the sixth most common cancer (749,000 new cases), the third cause of cancer-related death (692,000 cases), and accounts for 7% of all cancers (*Velazquez et al., 2003*). HCC represents more than 90% of primary liver cancers and is a major global health problem. Its incidence is increasing, ranging between 3% and 9% annually depending on the geographical location and variability in the incidence rates correspond closely to the prevalence and pattern of the primary etiologic factors (*Velazquez et al., 2003*).

HCC is the 5th among men and 8th among women; it is the 2nd among cancers of the digestive tract after stomach cancer (*Sangiovanni et al., 2004*).

The distribution of liver cancer varies by region and more than 80% of cases and deaths occur in developing countries (*Hall and Wild, 2003*) In Africa, liver cancer has been ranked as the fourth common cancer, and most of liver cancers are HCC (*Parkin et al., 2008*).

Moreover, there has been an alarming increase in incidence of liver cancer in Egypt, which is three times higher than that in the USA (*Lehman et al., 2008*).

The development of HCC is mainly due to the high rate of hepatitis B and C infections among Egyptian patients (*El-Zayadi et al., 2005*). In Egypt, there is a growing incidence of HCC (10-120/100,000), which represents the leading cause of death from all other cancer sites. HCC has nearly doubled over the last decade from 4.0% in 1993 to 7.2% in 2002 among patients with chronic liver disease (CLD)(*El-Zayadi et al., 2010*).

The estimated incidence of new cases is about 500 000-1 000 000 per year, causing 600 000 deaths globally per year (*Parkin et al., 2005*). Most cases of HCC occur in Asia where several countries, particularly in East Asia, have a very high incidence (over 20 cases/100 000 population) (*Montalto et al., 2002*). Hong Kong and Thailand also have similarly high rates (*Bosch et al., 2004*).

Areas with moderately high risk (11cases/100 000-20 cases/100 000) include Italy, Spain and Latin American countries, and those at intermediate risk (5 cases/ 100 000-10 cases/100 000) include France, the United Kingdom, and the Federal Republic of Germany. A relatively low incidence (less

than 5 cases /10 000) is found in the United States, Canada, and in Scandinavia (**Bosch et al., 2004**).

The incidence of HCC increases with age, reaching its highest prevalence among those aged over 65 years (**El-Serag, 2007**). However, HCC is rare before the age of 50 years in North America and Western Europe (**Bosch et al., 2004**).

Aetiology of HCC

Several factors have been identified as being related to the etiology of HCC. In some instances, several etiologic factors may be identified in the same patient, suggesting a synergistic role.

Cirrhosis:

Cirrhosis is a risk factor for HCC development, irrespective of the etiology of the cirrhosis. The annual risk of developing HCC in patients with cirrhosis is between 1% and 6%, and HCC has been identified as a relevant cause of death in these patients (**Donato et al., 2001**).

Cirrhosis is present in the vast majority of patients with HCC varying between 90% and 95% (**Grando-Lemaire et al., 1999**).

It is not clear if all diseases associated with cirrhosis present an equal risk for HCC. The best documented risk

appears to be in cirrhosis with chronic viral hepatitis, alcoholism, hemochromatosis, and alpha-1-antitrypsin deficiency. Conditions in which the risk is thought to be lower include Wilson's disease, primary biliary cirrhosis and autoimmune hepatitis; however, HCC has been well documented in all of these conditions in the presence of cirrhosis, and there may be other explanations for its apparent lack of frequency (*Chiaramonte et al., 1999*).

1- Hepatitis B virus infection:

This DNA virus is the most frequent etiology of liver cancer. There is strong epidemiological evidence correlating HCC to HBV infection (*Abdel-Hamid, 2009*). The hepatitis B replication status seems to play an important role in determining the risk of development of HCC, as analysis showed that the level of HBV DNA is a prognostic marker for HBV-related HCC (*Ohkubo et al., 2002*).

A high relative risk of HCC among HBs Ag compared to those without HBs Ag and the risk increased more when both HBs Ag and HBe Ag were positive (*Yang et al., 2002*).

The mechanisms by which HBV infection results in HCC are not clear. Certainly, it results in chronic liver injury (including inflammation, regeneration and fibrosis) which may predispose to HCC by itself. However, not all cases of HBV-related HCC have cirrhosis, which suggests that HBV may have

some intrinsic hepatocarcinogenic properties. Although the integration of hepatitis B virus (HBV) DNA into human liver DNA cells has been found to be associated with the development of hepatocellular carcinoma (HCC), the molecular mechanism remains unclear (***Wang et al., 2004***).

Several studies from the Far East evaluated the association between distinct genotypes and severity of liver disease. Genotype C was shown to be associated with the development of liver cirrhosis and HCC in Taiwan (***Kao et al., 2000***). China (***Ding et al., 2001***) and Japan (***Orito et al., 2001***), whereas genotype B was shown rarely to be associated with the development of HCC in China and Japan. In contrast, in Taiwan genotype B is the predominant type in patients with HCC who are younger than 35 years (***Kao et al., 2000***).

2- Hepatitis C virus infection:

Investigations in Egypt have also shown the increasing importance of HCV infection in the etiology of HCC, now estimated to account for 40-50% of cases (***El-Zayadi et al., 2005***). Markers of HCV infection are found in a higher proportion of HCC patients than that in most of the Asian countries; ranging from 44% to 66% in Italy, 27% to 58% in France, 60% to 75% in Spain. Japan, unlike other Asian countries, also has a high proportion of HCC caused by HCV

infection accounting for 80% to 90% of all the cases (***El-Serag and Rudolph, 2007***).

The natural history of chronic hepatitis C infection is characterized by a predominantly asymptomatic course and a variable clinical outcome. For these reasons it is difficult to define the rate of progression to cirrhosis and HCC. The risk of cirrhosis in chronic hepatitis C is less than 10% in women infected at a young age and >30% in men infected after the age of 40 over a 20 year period (***Poynard et al., 1997***). In patients with hepatitis C, there is an increased risk of HCC coinciding with the establishment of cirrhosis with yearly incidence between 3-8% (***Bolondi et al., 2001; Degos et al., 2000***).

However, the possibility that HCV may also operate through other pathways (other than causing chronic inflammation, cell death, proliferation and cirrhosis) in promoting malignant transformation of hepatocytes as HCC without cirrhosis in HCV-infected patients, though rare, have been reported. The transforming potential of NS3 protein and core protein has been described (***But et al., 2008***).

An alternative mechanism of HCV-induced hepatocarcinogenesis may be that HCV has a direct oncogenic action. Viral replication might cause inappropriate expression of two growth factors that may be implicated in hepatic

carcinogenesis: transforming growth factor- α and insulin-like growth factor II (*Michielsen et al., 2005*).

3- Alcohol:

Heavy alcohol intake, defined as ingestion of > 80 g/d ethanol for at least 5 years increases the risk of HCC by nearly fivefold (*Donato et al., 2002*). It is unclear whether risk of HCC is altered significantly in those with low or moderate alcohol intake. In addition to a daily dose response, persistent alcohol consumption appears to have a long-term effect on the risk of HCC occurrence (*El-Serag and Rudolph, 2007*).

Cirrhosis and HCC may follow episodes of hepato-ellular injury and regeneration. Alcohol-mediated enzyme induction increases the conversion of co-carcinogens to carcinogens and may also promote carcinogenesis through depression of immune responses (*Sherlock and Dooley, 2002*).

4- Mycotoxins:

Aflatoxin is produced by contaminating mold and *Aspergillus flavus*. It is highly carcinogenic to the mouse, guinea pig and monkey. Aflatoxin can contaminate food such as corn, legumes, ground nuts or grains, especially when stored in tropical conditions. Estimated aflatoxin intake from foods in various areas of Africa correlates with frequency of HCC. Aflatoxin may act as a co-carcinogen with HBV.

Mutations in P53 have been found in human cancer from South Africa and China and have been linked to increased intake of aflatoxin (***Sherlock and Dooley, 2002***).

Of the aflatoxins, AFB1 is the most prevalent, the most occurring and also the most potent. Acute dietary exposure to AFB1 has been implicated in epidemics of acute hepatic injury (***Sudakin, 2003***).

In Egypt, the AFB1 could have a contributory role to HCC as it confers two times higher risk of getting HCC when compared to healthy control (***El-Zayadi et al., 2001***).

Furthermore, Aflatoxin is an additive factor in development of HCC through detecting its metabolite Aflatoxin. ***Mokhles et al.,*** in ***2007***, found that, there is high significant value of M1 concentration in urine of upper Egypt residents compared to those of lower Egypt and its concentration among females of the HCC group was significantly higher than that among males (***Mokhles et al., 2007***).

5- Hepatic venous disease:

Hepatic vena cava disease (HVD), a form of Budd-Chiari syndrome, is caused by the obstruction of hepatic portion of the inferior vena cava, which in turn cause increased regenerative activities of hepatocytes related to the recurrent ischemic loss of

hepatocytes probably led to the development of HCC in HVD. The development of complications [liver cirrhosis (LC) and hepatocellular carcinoma (HCC)] was related to the frequency or severity of acute exacerbations (*Shrestha, 2009*).

6- Hereditary hemochromatosis:

Hereditary hemochromatosis is an autosomal recessive condition characterized by excessive iron deposition in hepatocytes due to an increased intestinal absorption. Thus, liver disease is the commonest cause of death in patients with hereditary hemochromatosis (*Fracanzani et al., 2001*). Among hemochromatotic patients, 6% of men and 1.5% of women are at absolute risk of liver cancer (*Elmberg et al., 2003*).

However, a cross-sectional study showed that progression to HCC among hemochromatotic patients is mostly variable from one population to another, depending mainly on exposure to environmental factors that synergize the current underlying gene mutation (*Willis et al., 2005*).

7- Congenital disorders:

Alpha-1-antitrypsin deficiency and tyrosinemia might be complicated by the development of HCC (*Montalto et al., 2002*). Thus, dietary or pharmacological management of hereditary tyrosinemia might offer a strategy for prevention of HCC in these cases (*Ashorn et al., 2006*).

On the other hand, alpha-1- antitrypsin is an acute-phase protein that is produced by liver cells. Hereditary deficiency of this protein is mostly due to liver production of the abnormal protein that cannot be released into the plasma. Accumulation of the protein in hepatocytes can lead to liver damage. This can trigger hepatitis in neonates, end-stage liver disease, cirrhosis and HCC in adults (*Kok et al., 2007*).

8- Diabetes Mellitus, non alcoholic fatty liver disease (NAFLD) and Obesity:

Diabetes mellitus (DM) has been suggested as a potential risk factor for HCC in some published studies (*Davila et al., 2005; El-Serag et al., 2004*). However, it is very difficult to study the possible association between diabetes and HCC (*Gao and Yao, 2009*).

Diabetes is a risk factor for NAFLD including the most severe form, non-alcoholic steatohepatitis (NASH) (*Bugianesi et al., 2002*), which can lead to liver fibrosis, cirrhosis, and subsequently to HCC (*Shimada et al., 2002*).

Moreover, studies have proposed that non-alcoholic fatty liver disease (NALFD), and more specifically, NASH, confers an elevated risk of developing HCC (*Caldwell and Crespo, 2004*).

Obesity can lead to insulin resistance and steatosis, which is associated with the release of inflammatory mediators such as tumor necrosis factor- alpha (TNF- α) in kupffer cells, which in turn enhances the production of cytokines including interleukin-6 (IL-6) and IL-8, leading to steatohepatitis. In addition, NASH can result in some typical histologic characteristics, including parenchymal inflammation, hepatocyte necrosis, and ballooning hepatocyte degeneration (*Yuan et al., 2004*).

Other mechanisms concerns obesity, DM, and NAFLD in HCC have been suggested like insulin resistance which leads to a state of hyperinsulinaemia which, via interaction with the insulin receptor, promotes increased phosphorylation and activation of the downstream serine/threonine kinase and extracellular signal regulated kinase pathways. These have been shown to play important roles in tumorigenesis by decreasing apoptosis and increasing mitogenesis (*Dellon and Shaheen, 2005*).

Also, mechanism involves the insulin-like growth factor (IGF) which acts through separate binding proteins and receptors; it has the same downstream intracellular mediators as the insulin receptor pathway (*Wolf et al., 2005*).

Therefore, diabetes and obesity can cause hepatic inflammation, leading to oxidative stress and lipid peroxidation of the phospholipid constituents of hepatocyte and intracellular