INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with over 600,000 new diagnoses per year ***(Parkin et al., 2005).*** In Egypt, the annual incidence of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002 ***(El-Zayadi et al., 2005).***

HCC generally occurs in association with cirrhosis, particularly due to hepatitis C, hepatitis B, alcohol, hereditary hemochromatosis, and primary biliary cirrhosis ***(Bruix and Sherman, 2005).***

If left untreated, liver cancer has a poor prognosis with more than 90% of patients dying of the disease within 5 years of diagnosis ***(Jemal et al., 2006).***

Managements of HCC include, liver transplantation since the institution of the MELD (Model for End-Stage Liver Disease) score, HCC has become the primary indication in up to 22% of all liver transplantations in the United States ***(Sharma et al., 2004)***

If possible, surgical removal of the tumor is the standard treatment for liver cancer and gives the patient their best chance at long-term survival. Unfortunately, the majority of patients with liver cancer are not surgical candidates ***(Llovet et al., 2003).***

Percutaneous local ablative therapy (PLAT) is indicated for patients with small HCC (<5 cm) confined to the liver that is unresectable due to limited liver reserve or compromised liver function. It is usually done through the percutaneous route under ultrasound or computed tomography ***(Lau et al., 2003).***

Kuang et al. (2007) stated that Microwave (MW) and radiofrequency (RFA) are the currently widely used thermal ablation techniques.

RFA is the widely used and studied ablative technique worldwide. In RFA, a high frequency alternating electrical current is used to create ionic agitation, which produces frictional heat and heat conduction to achieve subsequent tissue necrosis ***(Dos Santos et al., 2009)***.

MW ablation is one of the most recent and exciting advances in the field of thermo ablative technology ***(Wright et al., 2005).***

Microwave ablation refers to the electromagnetic method of inducing tumour destruction by using devices with frequency C900 MHz ***(Goldberg et al., 2003).*** The rotation of the dipole Molecules accounts for the efficient amount of heat generated during microwave ablation ***(Diederich, 2005).***

With microwave ablation, one or more molecules are dipoles with unequal electrical charge distribution, and they attempt to reorient continuously at the same rate in the

microwave's oscillating electric field. As a result of the microwave transmission, the water molecules flip back and forth at a billion times a second leading to this vigorous movement to produce friction and heat, which leads to cellular death via coagulation necrosis. An additional mechanism responsible for heat generation in microwave ablation is ionic polarization, which occurs when ions move in response to the applied electric field of the microwave. The displaced ions cause collisions with other ions converting this kinetic energy into heat. However, this is the lesser of the two mechanisms that generate the efficient heat from microwave ablation. The current frequencies of the commercially available microwave ablation devices are at 915 or 2450 MHz. The benefit of the 915-MHz microwave is that it can penetrate deeper than the 2450-MHz microwave ***(Iannitti et al., 2007)*.**

Microwave ablation shares several theoretical advantages over RFA in consistently higher intra tumoural temperatures, larger ablation volumes, faster ablation times, less dependency on the electrical conductivities of tissue ***(Wright et al., 2005).***

However, only a few clinical studies have compared the response to RFA and PMC ***(Shibata et al., 2002).***

On the other hand, ***Ohmoto et al. (2009)*** stated that RFA is more useful than PMC for the treatment of small HCC because it is minimally invasive and achieves a low local

recurrence rate, high survival rate, and extensive necrosis after only a few treatment sessions.

So there is a need for a comparative evaluation of the potency of both techniques in ablation of tumours which are suitable for local ablative therapies.

Aim of the Work

The aim of this study is to compare the therapeutic efficacy and safety of percutaneous microwave coagulation (PMC) and radio frequency ablation (RFA) for treatment of hepatocellular carcinoma (HCC).

HEPATOCELLULAR CARCINOMA

Introduction and epidemiology:

Liver cancer is the sixth most common cancer (749,000 new cases/ year), the third cause of cancer related deaths (692,000 cases/ year), and accounts for 7% of all cancers. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem ***(Llovet et al., 2012).***

The development of HCC has emerged as one of the most important events during the evaluation of chronic liver disease. Several studies have shown that 5% of patients with compensated cirrhosis may be diagnosed as having HCC if they are properly evaluated, and that this percentage exceeds 15% among cirrhotics admitted because of variceal bleeding, ascitic decompensation or spontaneous bacterial peritonitis. Furthermore, the 5 years probability of the appearance of HCC in cirrhotics is as high as 20% ***(Bruix, 1997).***

In Egypt the annual proportion of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002 ***(El-Zayadi et al., 2005).*** About 4.7% of chronic liver disease patients suffer from HCC and the development of HCC is mainly due to the high rates of hepatitis B and C infections among Egyptian patients ***(El-Zayadi et al., 2001).***

Race: The relationship of race to HCC was also examined; population-based databases reveal that rates of HCC in blacks are more than twice that in whites***(Jemal et al., 2003).***

HCC has a strong male preponderance with a male to female ratio estimated to be 2:4 ***(Llovet et al., 2012)***.

The male predominance may be due to specific genetic and hormonal profiles together with a higher prevalence of risk factors such as viral infections, alcoholism and smoking ***(Bruix and Sherman, 2005b)***.

It was also concluded that hepatocyte necrosis induced by diethylnitrosamine leads to hepatocarcinogenesis via kupffer cell IL-6 production, which is suppressed by higher concentrations of estrogens in females, and therefore results in lower rates of chemical-induced tumor genesis***(Walzer and Kulik, 2008).***

Age: The age at which HCC appears also varies according to gender, geographic area, and risk factors associated with cancer development. In most areas female age is higher than male ***(Bosch et al., 2004).***

In high-incidence areas where HBV is the main etiologic agent, the peak age appears after 40 years, while in low-incidence areas such as the USA, the peak age appears beyond 75 years ***(Bosch et al., 2004).***

HCC in Egypt

In Egypt, about 7.2% of chronic liver disease patients develop HCC. 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).***

The number of deaths per year from HCC exceeds 250,000, placing it as the sixth cause of death from cancer world-wide***(Steel et al., 2004).***

Time trends in the incidence of HCC in Egypt:

The annual proportion of HCC showed a significant rising trend from 4.0% in 1993 to 7.2% in 2002. A significant increase in male proportion from 82.5% to 87.6%; M/F from 5:1 to 7:1 and a slight increase of the predominant age group (40-59 years) from 62.6% to 66.8%, reflecting a shift to younger age group. There was a significant decline of HBsAg from 38.6% to 20.5% and a slight increase of HCV-Ab from 85.6% to 87.9%. HBV conferred a higher risk to develop HCC more than HCV but the relative contribution of HBV for development of HCC declined ***(El-Zayadi et al., 2005).***

Hepatitis C virus genotype 4 (HCV-4) is the most common variant of the hepatitis C virus (HCV) in the Middle East and Africa, particularly *Egypt*. Egypt has the highest prevalence of HCV worldwide, with more than 90% of infections due to genotype 4 ***(Kamal and Nasser, 2008).***

In another study that was conducted between 2009 and 2011 by ***(Shaker et al., 2013)*** the proportion of HCV-related cases was 91.32% and that of HBV-related was 2.51%.

Etiology:

The incidence of HCC varies in different countries, mainly depending on the prevalence of chronic liver disease, particularly chronic viral hepatitis. The proportion of cases of HCC attributable to hepatitis B or hepatitis C varies in different geographical areas, with most cases occurring in China, South - East Asia, Philippines and in Sub-Saharan Africa. The etiological agents of HCC are known in more than 90% of cases ***(Sherlock and Dooley, 2011).***

I. Hepatitis B virus infection:

The annual incidence of HCC is 0.4% - 0.6% in HBV-infected non-cirrhotic patients, 2% in HBV-infected cirrhotic patients ***(Bruix and Sherman, 2005a).***

The WHO has reported HBV to be second only to tobacco as a known human carcinogen ***(Gomaa et al., 2008).***

Hepatitis B virus (HBV) infection affects 400 million people worldwide and is the main risk factor for HCC in Eastern Asia and Africa. Approximately 54% of HCC cases worldwide can be attributed to HBV infection ***(Llovet et al., 2012).***

The association of HBV and HCC is confined to chronic HBV infection. The period from acquisition of the virus to tumor development can be as short as 4 years and as long as 80 years ***(Johnson and Williams, 2006).*** Evidence of infection with HBV may include serologic markers of active current infection, such as HBsAg or HBV DNA in serum, or the presence of antibodies to HBV antigens, such as anti-HBc and anti-HBs ***(Pan and Zhang, 2005).*** In some instances, HBV DNA can be isolated from liver or tumor tissue in patients with HCC who have no serologic evidence of HBV infection (occult HBV infection) ***(Marrero and Lok, 2004)***.

The entire nucleotide sequences of HBV genomes have been classified into 8 genotypes (A-H), with predominance of genotypes A and D in Western countries, and B and C in Southeast Asia and the Far East ***(Arauz-Ruiz et al., 2002).*** 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 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).***

High levels of HBV replication associated with increased HCC risk, providing the rationale for early treatment of patients with high viremia, with the aim of reducing the HCC risk. Indeed, either spontaneous or treatment induced seroconversion from hepatitis B e antigen (HBeAg) to anti-hepatitis B e antigen (anti-HBe) is associated with improved clinical outcomes and a reduced HCC risk, particularly in patients with limited hepatic fibrosis ***(Camma et al., 2001)***.

The incidence of HCC in inactive HBV carriers without liver cirrhosis is less than 0.3% ***(Manno et al., 2004).***

II. Hepatitis C

The natural history of chronic hepatitis C infection is characterized by a predominantly asymptomatic course and a variable clinical outcome. 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 persons infected at a young age and >30% in men infected after the age of 40 over a 20 years period ***(Poynard et al., 1998).*** In patients with hepatitis C, there is an increased risk of HCC coinciding with the establishment of cirrhosis with a yearly incidence between 3–8% ***(Bolondi et al., 2001).***

In Egypt, HCV appears to play a major role in the evolution of chronic liver disease to HCC. Both HBV and HCV

are implicated in the development of HCC in 95% of patients, emphasizing the unavoidable need for antiviral therapy and prophylaxis especially in endemic areas for HCV and HBV ***(El-Zayadi et al., 2005).***

Nash et al. (2010) recorded six patients (five males, one female) with chronic hepatitis C infection without cirrhosis presented to a single center with HCC over a 2-years period. Five patients were treated by surgical resection and one patient underwent liver transplantation.

Co infection of HBV and HCV

Co infection of HBV and HCV seems to result in more severe liver disease than either infection alone ***(Sato et al., 1994).*** The risk of developing HCC in subjects with both infections has been investigated in a meta-analysis of 32 epidemiological studies between 1993 and 1997**.**

Coinfection of HBV and HCV with HIV

Coinfection of HBV and HCV with HIV is common because these diseases share the same routes of transmission. A series of HCC in HIV-HCV co infected patients was published, indicating an unusually rapid development of HCC in these patients ***(Garcia-Samaniego et al., 2001).***

III. Alcohol:

Alcohol has no direct carcinogenic effects on the liver, but the hepatic carcinogenic effect of alcohol is potentiated by confection with HCV and HBV.

The risk for HCC appears when alcohol intake exceeds 60 g/day and beyond this cut-off it increases linearly ***(Bagnardi et al., 2001)***. Also alcohol consumption above 80 g/day for more than 10 years is associated with a fivefold increased risk. The risk of HCC development is further increased on development of cirrhosis and the annual incidence increases beyond 2% in decompensated cirrhosis ***(Morgan et al., 2004).***

IV. Cirrhosis:

Cirrhosis is associated with an increase in fibrous tissue and a destruction of liver cells, which provides the soil for development of cancerous nodules ***(Caillot et al., 2009).***

Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis, alcohol, inherited metabolicdiseases such as hemochromatosis or alpha-1-antitrypsin deficiency, and non-alcoholic fatty liver disease. All etiologic forms of cirrhosis may be complicated by tumor formation, but the risk is higher in patients with hepatitis infection. Overall, one-third of cirrhotic patients will develop HCC during their lifetime ***(Llovet et al., 2012).***

The risk varies according to the degree of liver function impairment. There is a steady increase in incidence from early cirrhosis without portal hypertension (PHT) to decompensated cirrhosis fitting into Child–Pugh class C ***(Sangiovanni et al., 2004).***

V. Aflatoxin exposure:

Aflatoxins are mycotoxins generated by the fungi Aspergillus flavus and Aspergillus parasiticus. These mycotoxins are among the most potent naturally occurring carcinogens known ***(Johnson and Williams, 2006).***

Humans can be exposed to aflatoxin by ingesting contaminated foodstuff (i.e., peanuts, wheat, soybeans, ground nuts, corn, and rice) or products of animals fed cereals contaminated with aflatoxin. Aflatoxin B1 is a frequent contaminant of grains and legumes, particularly in tropical and subtropical regions (i.e. Asia and sub-Saharan Africa), where a hot climate and methods of food storage cause high quantities of aflatoxins in the food supply ***(Koike and Shiratori, 2001).***

In Far East and Africa, the dietary exposure to aflatoxin-contaminated foodstuff likely accelerates the natural history of HBV-related HCC ***(Kulkarni et al., 2004).***

VI. Nonalcoholic Fatty Liver Disease:

A relevant proportion of patients with HCC and cryptogenic cirrhosis have demographic and clinical features of nonalcoholic steatohepatitis (NASH) ***(Sangiovanni et al., 2004).***

VII. Obesity:

In a large prospective study evaluating more than 900,000 individuals in the United States followed for 16 years, liver cancer mortality rates were exceedingly higher in men

with greater than 35 baseline body mass index than in persons with a normal body mass index ***(Calle et al., 2003).***

VIII. Diabetes Mellitus:

Diabetes often occurs as part of the metabolic syndrome, which increases the risk of non-alcoholic steatohepatitis (NASH), and that HCC can be a late complication of NASH ***(Bugianesi et al., 2002).*** Diabetes mellitus is more prevalent among patients with chronic hepatitis C than in the general population ***(Mehta et al., 2000).***

There are two potential ways in which HCC may develop among patients with both chronic hepatitis C and diabetes mellitus: by the metabolic pathway and by the carcinogenic effect of the HCV. Also, it is proved that diabetes mellitus, obesity, hyperlipidemia and hypertension are independent risk factors for pathogenesis of HCC especially in non B non C patients. Also, these factors are incorporated in progression and prognosis of HCC ***(Takamatsu et al., 2008).***

IX. Tobacco: is causally associated with liver cancer ***(Boyle and Ferlay, 2005).*** In a meta-analysis on smoking and cancer ***(Gandini et al., 2008)*** concluded an overall odds ratio (OR) of 1.56 comparing current-smokers to never-smokers and of 1.49 comparing former smokers to never-smokers.