

## Introduction

**H**epatocellular carcinoma (HCC) is the sixth most common neoplasm in the world. (*Rhee et al., 2012*)

HCV-related cirrhosis and HCC became a serious health problem 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*), Transarterial chemoembolization (TACE) was introduced as a palliative treatment in patients with unresectable HCC, it has become one of the most common forms of interventional therapy (*Takayasu et al., 2006*).

On the other hand, curative treatments of HCC such as liver resection, liver transplantation or percutaneous ablation [percutaneous ethanol injection (PEI) and radiofrequency ablation (RF)] are applicable in only 30%-40% of cases (*Llovet et al., 2004*).

Nowadays TACE is often performed by selective catheterization of the hepatic segmental arteries nourishing the HCC lesions, to limit as much as possible the injury to the surrounding non tumorous liver. The procedure involves the application of iodide in the form of iodized oil as a

radiopaque contrast medium, for example lipiodol mixed with a chemotherapeutic agent (*Miraglia et al., 2007*).

HCC exhibits intense neo-angiogenic activity during its progression, as the tumor grows the blood supply becomes progressively arterialized, so that even well differentiated HCC is mostly dependent on the hepatic artery for blood supply acute arterial obstruction induces ischemic tumor necrosis. Hepatic artery obstruction is performed during an angiographic procedure and is known as transarterial, or transcatheter arterial embolization (TAE). When TAE is combined with the prior injection into the hepatic artery of chemotherapeutic agents, usually mixed with lipiodol, the procedure is known as transarterial chemoembolization (TACE). Chemotherapy has to be injected prior to arterial obstruction, It is usual to suspend chemotherapy in lipiodol, an oily contrast agent used for lymphographic studies. Lipiodol is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy (*Bruix et al., 2010*).

Lipiodol and related compounds are products of the addition (not substitution) of iodine to double bonds of the unsaturated fatty acids of certain plant oils most of which have a very high percentage of unsaturated fatty acids, is an

oily contrast medium and has been used for lymphangiographic studies (*Guerbet, 2001*).

Although required for thyroid hormone synthesis, excess intra-thyroid iodide can paradoxically decrease the organification of iodide and subsequent hormone synthesis, a phenomenon first described in vivo in the rat by Wolff and Chaikoff in 1948 and termed the "acute Wolff-Chaikoff effect" (*Braverman, 1990*). The iodide-induced decrease in hormone synthesis is transient and thyroid hormone synthesis resumes in spite of continued excess iodine administration. This latter phenomenon apparently serves to defend the thyroid from iodine-induced hypothyroidism and goiter and has been termed the "adaptation or escape" from the "acute Wolff-Chaikoff effect" (*Wolff et al., 1949*).

## **Aim of the Work**

**E**valuation of the thyroid dysfunctions after the TACE procedure for patients with HCV related hepatocellular carcinoma.

## Chapter (1)

# Epidemiology and diagnosis of HCC

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and represents approximately 85-90% of primary malignant tumors of the liver (**El Serag, 2011**).

It is the sixth most common neoplasm in the world (**Llovet et al., 2008 a**), With a 5 year survival rate of less than 5% and an incidence of at least one million new patients per year (**Bruix and Sherman, 2010**).

HCC is the 4th commonest cause of death due to cancer, after cancers of the respiratory system, stomach, and colon/rectum. Liver cancer ranked 3rd for male subjects and 5th for women (**Seeff and Hoofnagle, 2006**).

Each year, hepatocellular carcinoma is diagnosed in more than half a million people worldwide, including approximately 20,000 new cases in the United States (**Ferlay et al., 2008**), (**SEER program, 2009**).

Most of the burden of disease (85%) is borne in developing countries, males are predominantly affected, with a

3:2 male/female ratio ,with the highest incidence rates reported in regions where infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is endemic, Southeast Asia and sub-Saharan Africa (*World Health Organization, 2008*).

The major risk factor for the development of HCC is cirrhosis of the liver, by different risk factors such as, viral (chronic hepatitis B and hepatitis C), toxic (alcohol and aflatoxins), metabolic (diabetes and non-alcoholic fatty liver disease, hereditary haemochromatosis) and immune-related (primary biliary cirrhosis and autoimmune hepatitis) (*Parikh and Hyman, 2007*). More than 95% of HCC patients present underlying hepatopathy in particular of viral etiology (*Liu and Kao, 2007*), ( *Shariff et al., 2009*).

Incidence of HCC in Egypt is currently increasing which is now three times higher than that in the USA and became the second most frequent cause of cancer incidence and mortality among males and the fifth in female (*Lehman et al., 2008*). Hospital based studies from Egypt have reported an increase in the relative frequency of all liver-related cancers in Egypt (>95% as HCC), from 4.0% in 1993 to 7.3% in 2003. Which may be the result of a shift in the relative importance of HBV and HCV as primary risk factors. Over a decade (1993-2002),

there was nearly a twofold increase of the proportion of HCC among chronic liver disease (CLD) patients in Egypt (*El-Zayadi et al., 2005*).

There was strong evidence that HBV was the major cause of HCC in Egypt, but more recently, HCV has become the predominant factor with the more recent epidemics of HCC, it has been well documented that Egypt has one of the highest prevalence rate of HCV in the world, up to 90% of HCC cases were attributed to HCV infection. (*Shepard et al., 2005*), (*Lehman and Wilson, 2009*).

Recent population study suggested that environmental factor might contribute to the incidence of HCC in Egypt, occupational exposure, farming, industrial exposure, and cigarette smoking , may increase the risk of HCC among HCV-sero-positive individuals. (*Chu et al., 2010*).

## **Diagnosis of HCC**

### **CLINICAL PRESENTATION**

The clinical picture is very variable; the patient may be completely asymptomatic with no physical signs other than those of cirrhosis. The tumor may be diagnosed incidentally. Alternatively the presentation may be so florid and liver failure so great that the picture resembles a liver abscess (*Sherlock and Dooley, 2002*).

#### ***Symptoms:***

The various clinical presentations generally relate to the extent of hepatic reserve at time of diagnosis. Cirrhotic patients tend to have less tolerance for malignant infiltration within the liver and frequently present with nonspecific signs and symptoms of hepatic decompensation such as jaundice, hepatic encephalopathy, and anasarca, Ascites, Approximately 10% of patients have gastrointestinal bleeding at presentation (variceal bleeding) resulting from portal vein invasion and elevated portal pressure (*Johnson, 2000*) Symptoms are often related to long-standing malignancy and tumor growth including malaise, anorexia, wasting, right upper quadrant abdominal pain, and distension (*Omata et al., 2002*).

Obstructive jaundice can be caused by compression of major intrahepatic bile ducts by the primary tumor or the common bile duct from nodal metastases in the porta hepatis. Bone pain from osseous metastases can be localized to the vertebrae, sacrum, ribs, femur, or skull. Dyspnea is most frequently related to the presence of a pleural effusion, although occasionally a markedly elevated right hemidiaphragm or extensive pulmonary metastases is the cause (*Sass and Chopra, 2005*).

Watery diarrhea has been shown to be significantly more common with cirrhosis and HCC than with cirrhosis alone and can be an initial presenting symptom. Increased production of intestinal secretory substances, such as gastrin and vasoactive intestinal peptide (VIP), has been suggested as a possible cause (*Steiner et al; 1986*), (*Bruix et al., 1990*).

### ***Signs:***

Hepatomegaly is the most frequent physical finding in both high- and low-incidence areas. Liver tenderness is frequent and may be severe, arterial bruit is detectable over the liver in 5 to 25% of patients. The presence of a bruit reflects the highly vascular nature of HCC and may be attributable to turbulence in dilated tumor vessels or

indicative of arterio-venous communications, Splenomegaly related to portal hypertension, A palpable spleen in HCC patients has been reported in 15 to 48% of cases (*Kuntz and Kuntz, 2006*). Painless obstructive jaundice can indicate tumor encroachment onto adjacent extrahepatic biliary structures (*Murata et al., 2003*).

Ascites is related most frequently to portal hypertension secondary to coexisting cirrhosis, or to tumor invasion of the portal vein. Tumor invasion of hepatic veins is found in 14% of HCC patients at necropsy (*Okada, 2000*), (*Sass and Chopra, 2005*).

Muscle wasting related to anorexia and weight loss is noted in up to 25% of patients. The presence of a persistent temperature elevation of 37.5° to 38.5°C is noted in 10 to 40% of patients, which is related to the tumor necrosis and release of pyrogenic compounds (*Ryder, 2003*).

Extra hepatic manifestations of HCC are well described and may relate either to distant metastases or paraneoplastic phenomena. Advanced HCC can metastasize to any organ system via hematogenous or lymphatic routes, and most commonly spreads to bone (bone pain), lung

(dysapnea,cough), and abdominal viscera (*Si Ms, 2003*), (*Sass and Chopra, 2005*).

Paraneoplastic manifestations occur rarely in HCC and include hypoglycemia, hypocalcemia and feminization syndrome, erythrocytosis which is related to ectopic production erythropoietin by the tumor (*Luo, 2002*), (*Kew, 2002*).

## **Laboratory Diagnosis of hepatocellular Carcinoma**

### ***Bio chemical changes:***

Biochemical changes may be only those of cirrhosis, serum alkaline phosphates is markedly elevated, serum transaminase level increase, Hypoglycemia can be found in 30% of patients, hypercholesterolemia in up to 38% of patients with HCC , The leucocyte count is usually raised to about  $10000/\text{mm}^3$  with 80% polymorphs. Eosinophilia is an occasional finding. (*Sherlock and Dooley, 2002*).

### ***Serum Markers for HCC:***

- ***Alpha-fetoprotein (AFP):***

Serum alpha-fetoprotein (AFP) has been used as a standard biological tumor marker of HCC since the 1970s. However, AFP can be elevated in patients with chronic hepatitis and/or cirrhosis in the absence of HCC, and can be elevated in intrahepatic cholangiocarcinoma (ICC), And in some metastases from colon cancer making AFP inadequate alone as a surveillance test. (*Colli et al., 2006*), (*Lok et al., 2010*).

Therefore, Western guidelines consider AFP as inadequate alone to survey patients at risk of HCC and recommend the use of ultrasound (US) ,or other radiological methods, in combination (*Bruix and Sherman, 2011*), (*EASL-EROTC, 2012*).

The positive predictive value of AFP in HCC patient with viral etiology will not reach 100% unless serum concentration is greater than 400 ng/ml. (*Soresi et al., 2003*), (*Gomaa et al., 2009*).

It has been confirmed on numerous occasions that AFP serum concentration increases in parallel with HCC tumor size. For this reason AFP has to be considered ‘the golden standard’ for HCC serum markers, HCC patients with a high AFP concentration ( $\geq 400$  ng/mL) tend to have greater tumor size, bi-lobar involvement, massive or diffuse types, portal vein thrombosis, and a lower median survival rate (*Tangkijvanich et al., 2000*), (*Li et al., 2005*) furthermore,80% of small HCC show no increase of AFP concentration so, sensitivity of AFP decreases from 52% to 25% when tumor size  $>3$ cm and  $< 3$ cm respectively (*Saffroy et al., 2007*).

- ***Des-γ-Carboxy Prothrombin (DCP):***

Serum DCP was found to have a HCC diagnostic sensitivity and specificity of 48-62% and 81–98%, respectively, in several large case-control studies. (*Marrero et al., 2003*), (*Grizzi et al., 2007*) DCP has been reported to be more sensitive and specific than AFP, especially in East Asian countries and North America (*Gomaa et al., 2009*).

According to a study by *Nakamura* and colleagues, the efficacy of DCP was lower than that of AFP in the diagnosis of small tumors, although higher than that of AFP for large tumors (*Nakamura et al., 2006*). Several studies have also shown that DCP can be a useful indicator of vascular invasion of HCC and in monitoring the recurrence of HCC after treatment (*Hagiwara et al., 2006*), (*Shirabe et al., 2007*).

- ***Gamma-glutamyl transferase (GGT):***

Sensitivities of GGT-II have been reported to be 74.0% in detecting HCC and 43.8% in detecting small HCC ,Furthermore, the simultaneous determination of GGT-II, DCP, and AFP can significantly improve the sensitivity over AFP alone (*Cui et al., 2003*).

- ***Squamous cell carcinoma antigen (SCCA):***

(*Pontisso et al., 2004*) first reported a high SCCA expression in HCC tissues, which seems very interesting, as liver does not possess squamous epithelial cells. Hepatocytes, however, share a common embryogenic origin. The sensitivity and specificity for SCCA in HCC diagnosis are 84% and 46% respectively.

The complementary strengths high sensitivity/low specificity) and total AFP (low sensitivity/high specificity) suggest that the combination of the 2 markers should be of more value for screening, and in fact it leads to a diagnostic accuracy of 90% ( *Giannelli and Antonaci., 2006*).

- ***Markers (AFP, SCCA, DCP) in immunocomplexes with immunoglobulins of the IgM class (AFP-IgM IC, SCCA-IgM IC, DCP-IgM IC):***

A new step for HCC testing is represented by forming known antigens (AFP, SCCA, DCP) into immunocomplexes (IC) with immunoglobulins of the IgM class. Monitoring of SCCA-IgM IC, AFP-IgM IC and DCP-IgM IC appears to be a much more advantageous approach for detecting patients with small HCC changes in patients displaying low levels of