Introduction

Hepatocellular carcinoma is the most common primary malignant tumour of the liver. HCC accounts for 90% of primary liver cancers and causes at least 1 million deaths worldwide per year **(March et al ., 1999)**. It is the 5th most common cancer in the world (5th in men and 8th in women), and the 4th in annular mortality rate. The annular mortality rate from HCC is virtually the same as its annular incidence, due to its rapid course, and grave prognosis **(El – Serage , 2002)**.In 2001, liver malignancies were the 3rd most common cancer in men and 6th in women in NCI, Cairo University **(El – Attar, 2002)**. **Sherif and Ibrahim (1987 a)** reported that the percentage of HCC compared to all cancer on Cairo Cancer registry was 1.5 in the period (1973 – 1982). The same authors, **Sherif and Ibrahim (1987 b)** reported that the percentage of HCC in Alexandria Cancer registry was 2%. **El – Zayadi (1989)** reported that the prevalence of HCC among liver disease patients in the period (1985 – 1989) was 2.95% he pointed out to the rise of prevalence of this tumour. National cancer registry reported that HCC is one of the most common three cancers in Egypt being, cancer bladder, breast cancer, and HCC also, NCI registered 10811 cancer cases from 1/1/2000 to 31/8/2001 including 130 (2%) HCC cases **(NCR, 2002)**. In Egypt , 4.7 % of chronic liver disease patients suffer from HCC. The development of HCC is mainly due to high rates of hepatitis B and C infections among Egyptian patients**(El – Zayadi et al., 2001)** .Worldwide , there is a clear predominance of males , ranging from 8 : 1 in countries with high incidence of HCC to approximately 2 : 1 to 3 : 1 in population with low frequency **(Crawfort , 1999).** In low incidence countries, the incidence of vHCC is very low before 40 years in increases

progressively between age 40 and 80 years. In high – incidence countries, HCC is seen frequently better the age of 40 years **(Parkin et al ., 1997).**

The incidence of HCC is quite variable worldwide, related to a variable distribution of the risk factors. High incidences (more than 20 cases per 100.000 populations) are found in Eastern and South Eastern Asia, Some of the western pacific islands, and eastern Africa). In these countries, HCC is the most common tumour. Intermediate incidences (10 – 20 cases per 100.000 populations) are seen in the Far East (Japan) southern Europe, the Caribbean and Central America. Low incidence (less than 5 cases per 100.000 populations) is found in England, North and South America, Scandinavia, India, Australia, Northern Africa , and Middle Asia. The highest recorded incidence rate is seen in Mozambique , where it is 113 in men per 100.000 populations.

The second most common incidence rate is in China 90 per 100.000 men **(Kew 2002).** The overwhelming majority of HCC case occur in patients with chronic liver disease **(Simontti et al., 1991)**. Approximately 80% have cirrhosis ,and most of the remainder have moderate to advanced Fibrosis.

Cirrhosis of any cause can result in HCC , but chronic viral hepatitis accounts for more than 80 % of cases worldwide **(Bosch et al ., 2004).** Among patients with cirrhosis due to hepatitis C , HCC is the first complication to develop in 27 % of patients; is the most common complication ; and is the main cause of death (44%) **(Sangiovanni et al ., 2006)**. The average annual risk of HCC in patients with cirrhosis from HCV is 3.2% **(Sangiovanni et al .,**

2006). The annual risk in Japan is approximately 6% to 7% **(Takano et al., 1995)**.

Among patients without cirrhosis , the annual risk increases as the stage of fibrosis increases **(Yoshida et al., 2004).** In patients with chronic hepatitis B the yearly risk is 0.02% to 0.2% among inactive HBsAg positive patients, 0.1 % to 1.0 % in persons with chronic hepatitis without cirrhosis, and 2.2 % to 3.2 % in patients with cirrhosis **(Fattovich et al., 2004)**. Loss of detectable virus with antiviral therapy decreases the risk of subsequent HCC but does not eliminate it **(Fattovich et al .,2004).** Thus any cause of liver disease that can result in cirrhosis should be considered a potential risk factor for HCC. Not surprisingly, the most common causes of cirrhosis (HBV , HCV , and alcohol) are also the most common causes of HCC. However , HCC is seen , albiet less commonly, in patients with cirrhosis or fibrosis due to other causes such as genetic hemochromatosis , autoimmune hepatitis, primary sclerosing cholangitis, NASH , alpha -1 antitrypsin deficiency, Wilson disease **(Davis et al ., 2008).**

The mechanisms by which viruses and /or hepatic fibrosis lead to HCC are not entirely clear. Recently, gene expression profiles of tumours were analysed in 103 HCV – related HCC **(Chiang et al., 2008),** three patterns were associated with pathway activation (Wnt/ beta – Catenin , tyrosine Kinase receptor activation , and interferon response over expression) while another was associated with over expression of several proliferative and tumour activation factors associated with chromosome 7 polysomy. Additionally , tumour cells may evade normal apoptosis mechanisms and facilitate angiogenesis.

Finally, there are also precarcinogenic mechanisms that are specific to a particular etiology **(Chiang et al., 2008)**.

Alpha – fetoprotein (AFP) has been used as a serum marker for HCC for decades. In the year prior to sensitive imagining techniques such as US, CT , and MRI , AfP was felt to be both sensitive and specific for HCC. However, it is now apparent that this is not the case. The test has limited specificity, and the presence of chronic inflammatory liver diseases such as hepatitis can raise the levels to more than 200 ng / ml. even more problematic, however, is the limited sensitivity of the essay , in the range of 40% to 60% **(Daniele et al ., 2004).**

Any focal lesion in a patient with cirrhosis should be suspected of being HCC.

The ability of abdominal imaging to detect HCC has improved dramatically over the last 2 decades. Despite this progress, however , US , CT, and MRI remain variably insensitive for detecting HCC , particularly with tumors < 2 cm in diameter **(Snowberger et al., 2007 ; Taouli & Keinsky, 2006 & colli et al ., 2006)**. Furthermore , much of the older radiological literature overestimated the sensitivity of imaging methods since no correlation with whole organ explants pathology was available **(Snowberger et al ., 2007 ; Taouli & Krinsky, 2006 & Colli at al ., 2006)**. New hardware and software technology that was introduced for CT and MRI in 2000 improved the sensitivity of both modalities. MRI is the most sensitive study and identifies almost 80% of tumours , including 63% of tumours < 2 cm **(Snowberger et al ., 2007)** . CT scanning identifies about 70% and US about 60% **(Snowberger et al ., 2007)**. All three imaging methods are quite good at estimating tumour size. On the other hand, none are

very accurate in documenting the total number of lesions present; this is likely related to size, different imaging characteristics of tumour , and location **(Davis et al., 2008).**

The role of biopsy in confirming HCC is controversial **(Bialeckti et al. 2006)**. the risk of tumour seeding of the biopsy track is extremely low **(Schotman et al., 1999).**

Without specific treatment the prognosis is poor , with a medium survival of 1 to 2 month for patients with advanced tumors and 6 to 9 months for those with HCC in early stages **(OKuda et al ., 1985).**

Several therapeutic approaches have been developed as invasive or noninvasive strategies for HCC treatment **Liver Resection** Over the past recent years , clinical implementation of early detection strategies for HCC has significantly increased the number of patients under going liver resection **(Hu et al ., 2003).**

Advances in preoperative management, in combination with new surgical techniques and better patient selection, have significantly lowered the operative morbidity and mortality after resection of HCC as compared with historical experience **(Jamagin et al., 2002).** Liver transplantation is in principle optimal of therapeutic option for HCC because it simultaneously removes the tumor and the underlying cirrhosis , **(Shetty et al., 2004).**

Percutaneous interventions are the best options for small unresectable HCCs.

Tumor ablation can be achieved chemically by Percutaneous **ethanol injection** or **Acetic acid** injection or **Hot Saline** or **thermally** by **Radiofrequency** thermal ablation, **Microwave** – **Heat** induced

Thermotherapy, **Laser** induced thermotherapy, or **cryoablation**. A part from percutaneous interventions.

These techniques can be applied also laparoscopically or with open laparotomy **(Liveraghi et al., 2004)** .Transarterial embolisation and chemoembolization are the most widely used treatments for HCCs that are unresectable or can not be effectively treated by percutaneous interventions.**(L lovet and Bruix . , 2004) Drugs Systemic Chemotherapy** For a number of reasons , systemic chemotherapy may appear to be ineffective against HCC. Inherent drug resistance may be present , or the underlying hepatic dysfunction or the drug delivery to the tumor may be compromised due to portal hypertension or blood shunting **(Fong et al., 2002).Interferon and Combinations with Interferon** Interferon alpha has antiviral , antiangiogenesis , and antitumor activities and has been shown significantly to reduce the rate of HCC in patients with viral hepatitis **(Leung and Johnson , 2001). Hormonal Therapy**HCC cells have been shown to express estrogen receptors in 35% , tamoxifen in combination with etoposide or with cytotoxic drugs to treat advanced HCC **(Schaschschol et al ., 2000) .Viscum** The liquid extract from mistletoe plant has been used for over 75 years to treat tumours with active ingredients being viscotoxins , lectins and other **(Baudina , 1987).Targeted Immunotherapy** involves the use of monoclonal antibodies against tumour cells as I131 labeled antiferritin and Alpha – fetoprotein antibodies **(Williams et al ., 1987)**