شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

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# جامعة عين شمس

# التوثيق الإلكتروني والميكروفيلم

# قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

# يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

# INTRODUCTION

Hepatocellular carcinoma (HCC) shows an incre asing incidence and represents the third most common cause of cancer-related death ***(Cucchetti et al., 2016).***

The majority of HCC cases develop in chronically inflamed livers due to chronic viral hepatitis, alcohol abuse and, with rapidly increasing incidence, in patients with non-alcoholic steatohepatitis (NASH) ***(Welzel et al., 2011).*** However, the underlying mechanism of HCC has not been entirely elucidated. Surgical resection and orthotopic liver transplantation are the best curative tools for the long-term survival. However, surgical resection is not feasible in more than 80% of HCC patients because of tumor location, tumor size or severity of the underlying liver disease. Only 5%-15% of HCC patients are potentially resectable ***(Zhang et al., 2014).***

Loco-Regional therapy is considered among the important lines for treatment of HCC including radiofrequency ablation (RFA) that has become the most frequently used form of local ablation therapy. It is the best treatment alternative for patients with early stage HCC who are not eligible for surgical resection or transplantation. Several recent randomized trials of adequate quality have shown RFA to be more effective than the once-

conventional method of ethanol injection in treating patients with small hepatocellular tumors (2 to 3 cm in diameter), with lower rates of local recurrence and higher rates of overall and disease- free survival ***(Cho et al., 2009).***

Trans Arterial Chemo-Embolization (TACE) has been shown to improve survival among patients with preserved liver function, particularly those with Child–Pugh class A cirrhosis who do not have extrahepatic metastases, vascular invasion, or prominent cancer-related symptoms. TACE is also used as a neo-adjuvant therapy or as a means of down staging a patient's condition before liver transplantation, but whether these approaches provide a survival benefit is unclear ***(Xie et al., 2015).***

Current methods for HCC diagnosis are classified into the following main categories: imaging [abdominal ultrasonography, contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI)] and laboratory biomarker analysis [serum alpha-fetoprotein (AFP) levels]**.** However, the diagnostic performance of imaging technologies is unsatisfactory, particularly for the diagnosis of small lesions and early-stage HCC ***(Hung et al., 2015).***

AFP is the most commonly used tumor marker for HCC diagnosis and prognosis prediction, but the false negative rate using AFP level alone is as high as 40% for patients with early-stage HCC. AFP levels remain normal in 15%-30% of all the patients, even patients with advanced HCC ***(Zhang et al., 2014).***

Amphiregulin (AREG) is a ligand of the epidermal growth factor receptor (EGFR), a widely expressed transmembrane tyrosine kinase. AREG is synthesized as a membrane-anchored precursor protein, AREG is secreted and behaves as an autocrine or paracrine factor. Through EGFR binding AREG activates major intracellular signaling cascades governing cell survival, proliferation and motility. Physiologically, AREG plays an important role in the development and maturation of mammary glands, bone tissue and oocytes. Chronic elevation of AREG expression is increasingly associated with different pathological conditions, mostly of inflammatory and/or neoplastic nature. Consequently, Amphiregulin may represent a possible diagnostic target in HCC, which have raised interest as possible predictors of the presence and progression of HCC ***(Berasain & Avilla 2014).***

# AIM OF THE WORK

The aim of this work is to evaluate the diagnostic value of serum level of Amphiregulin for HCC and its prognostic value after transarterial chemo-embolization (TACE) or radiofrequency ablation (RFA).

Chapter 1

# HEPATOCELLULAR CARCINOMA

liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally, with 854, 000 new cases and 810, 000 deaths per year. Hepatocellular carcinoma (HCC) occupies around 90% of primary liver cancers and constitutes a major global health problem ***(Akinyemiju et al., 2017).***

The incidence of HCC increases progressively with advancing age. The HCC incidence is higher in men, with a male to female ratio2-2.5: 1 ***(White et al., 2017).***

The difference in exposure to hepatitis viruses and different environmental pathogens affects the geographical distribution of HCC, so the incidence is highest in East Asia, and Sub-Saharan Africa, with 80% of the total number of cases, while in most industrialized countries the incidence is low, except in the South of Europe. Use of the high number of people infected with HCV ***(Pascual et al., 2016)***

Growing evidence from retrospective investigations suggests an increased HCC incidence in patients with NAFLD associated with metabolic syndrome, diabetes, and

obesity. Moreover, metabolic syndrome has an additive risk effect in those patients with chronic viral hepatitis ***(Yu et al., 2017).***

## Etiology and risk factors:

About 90% of HCCs are caused by known underlying etiologies, most frequently chronic viral hepatitis (C and B), alcohol intake and aflatoxin exposure.The largest attributable fraction, in East Asia and Africa, is caused by hepatitis B (60%). In the Western world only 20% of cases can be attributed to HBV infection, but chronic hepatitis C appears to be the major risk factor ***(Akinyemiju et al., 2017).***

Worldwide, about 55% can be attributed to HBV infection (which affects 400 million people globally) while 30% can be attributed to HCV infection (which affects 170 million people) and 15% due to other causes. However, these calculations are rough estimations which do not reflect co-morbidities and are likely to underestimate the impact of NASH/ metabolic syndrome ***(Akinyemiju et al., 2017).***

### *1. Cirrhosis:*

Cirrhosis is a significant risk factor for HCC, and may be caused by chronic viral hepatitis, chronic alcohol abuse, acquired and inherited metabolic diseases such as NAFLD,

as well as genetic haemochromatosis, or in some cases alpha-1-antitrypsin deficiency. All etiologic forms of cirrhosis may be complicated by hepatocellular carcinoma, however the risk is higher in patients with chronic viral hepatitis ***(Lok et al., 2009).***

Overall, one-third of cirrhotic patients will develop HCC during their life. Long-term follow- up studies have reported that about 1–8% of patients with cirrhosis develop HCC per year. Generally, features of liver disease severity (platelet count less than $10^9$x100/L, presence of oesophageal varices) as well as male gender and older age correlate with development of HCC between patients with cirrhosis. Studies have found that liver cancer incidence increases in parallel to portal pressure or linked to the degree of liver stiffness as measured by transient elastography ***(Wong et al., 2014).***

## *2. Hepatitis B infection:*

Hepatitis B virus (HBV) contributes to hepatocellular carcinoma (HCC) development through direct and indirect mechanisms. HBV DNA integration into the host genome occurs at early steps of clonal tumor expansion and induces both direct insertional mutagenesis of diverse cancer-related genes and genomic instability. Prolonged expression of the

viral regulatory protein HBx and/or altered versions of the preS/S envelope proteins dysregulates cell transcription and proliferation control and sensitizes liver cells to carcinogenic factors ***(Levrero and Zucman-Rossi, 2016).***

Several studies have reported HBV-related factors as key predictors of HCC development in patients with chronic hepatitis B infection. The independent predictors of HCC development are Hepatitis B virus e antigen seropositivity, genotype C and high viral load ***(Kim et al., 2015).***

The relative risk is reduced by about 50 to 60 percent after treatment with nucleos (t) ide derivatives or interferon. However, patients who developed nucleos (t) ide resistance did not benefit and treatment does not completely reduce the risk ***(Singal et al., 2013).***

### *3. Hepatitis C virus:*

In contrast to developing countries in the Sub-Saharan Africa and Asia-Pacific regions, where hepatitis B virus (HBV) is the major risk factor for HCC, chronic infection with hepatitis C virus (HCV) has been a leading cause of HCC in developed countries ***(El-Serag, 2011)***. In the United States, chronic HCV infection is the first indication for liver transplantation for patients with HCC ***(Wong et al., 2014).***

Worldwide, 3% of the world's population has been infected with HCV and that more than 170 million people are currently chronic carriers of HCV, according to the World Health Organization (WHO) estimations ***(Galbraith et al., 2014).***

A strong association between HCC and chronic HCV infection has been detected, but the mechanisms involved in carcinogenesis remain unclear. A significant clinical observation is that HCC in patients with HCV occurs almost exclusively in patients with advanced stages of hepatic fibrosis or cirrhosis. However, in up to 10 percent of patients with HCV infection who undergo resection for HCC, only mild degrees of fibrosis are found ***(Mahale et al., 2017).***

The advent of the new direct-acting antivirals (DAA) has been a major breakthrough because of their adequate safety profile and their high efficacy, which enabled their use in patients with advanced liver disease, in whom interferon-based regimens were not recommended ***(Nahon et al., 2017).***

### *4. Environmental toxins:*

Aflatoxin produced by Aspergillus species (molds) found on corn, grains, peanuts, or soybeans stored in warm humid conditions is a strong hepato-carcinogen. The risk of

HCC with aflatoxin is determined by the dose and duration of exposure. Aflatoxin exposure is more predominant in rural United States. Aflatoxin exerts a synergistic effect on hepatitis C- and B-induced liver cancer, the risk being 35 times higher with chronic hepatitis B plus aflatoxin exposure than with aflatoxin exposure only. The most effective aflatoxin, AFB1, when removed from the environment has resulted in a decrease of the incidence of HCC ***(Chen et al., 2013).***

### *5. Tobacco and alcohol abuse:*

Cigarette smoking has been shown to be a risk factor for HCC in some studies ***(Koh et al., 2011).*** Alcohol intake has been linked to HCC in many reports, although the duration of use and the threshold dose are unclear. The relationship between ethanol and HCC could be a direct toxic effect, or an indirect one, since alcohol represents an important risk factor for cirrhosis, a predisposing factor for HCC. In various reports, the risk of HCC increased by concomitant heavy alcohol intake, diabetes mellitus, and obesity ***(Loomba et al., 2013).***

### 6. Diabetes mellitus & Nonalcoholic fatty liver disease:

Epidemiologic studies suggest a possible link between HCC and diabetes mellitus. Multiple systemic reviews and meta-analyses have also shown an association ***(Wang et al., 2012).***

There is growing evidence that NAFLD represents an increasingly frequent underlying liver disease in patients with HCC. It is likely that NAFLD causes HCC via cirrhosis, while the exact pathogenesis has not yet been determined. One study observed that HCC in NASH was associated with diabetes, obesity, hypertension and male sex. Other studies found that HCC can occur in patients with NAFLD who do not have cirrhosis ***(Mittal et al., 2016).***

## Pathology of HCC:

Macroscopically, hepatocellular carcinoma can grossly be classified into the three macroscopic groups: massive, nodular, and diffuse. The nodular type can either consist of a single or multiple nodules. Single nodules are usually encapsulated and may show extracapsular growth in the vicinity of the primary nodule. The multinodular type is defined as an aggregation of a varying amount of small

nodules. The massive type is a large tumor with irregular demarcation. This morphologic appearance can also be seen in advanced stage of nodular HCC. The diffuse type is described to have many small nodules in a liver lobe or the whole organ ***(Kojiro, 2009).***

Microscopically, there are 4 architectural and cytological types (patterns) of hepatocellular carcinoma: fibro-lamellar, pseudo-glandular (adenoid), pleomorphic (giant cell) and clear cell ***(Goodman et al., 2012).***

The classical histomorphologic features of well-differentiated HCC are well vascularized tumors with wide trabeculae (> 3 cells), prominent acinar pattern, small cell changes, cytologic atypia, mitotic activity, vascular invasion, absence of Kupffer cells and the loss of the reticulin network. In poorly differentiated forms, malignant epithelial cells are pleomorphic, discohesive, anaplastic, giant. The tumor has a scant stroma and central necrosis because of the poor vascularization ***(Shafizadeh and Kakar, 2011).***