Chapter Two

Literature Review

2. Literature Review:

2.1 Scientific background:

Hepatocellular carcinoma (HCC) is the main form of liver cancer, a part from chronic infections with hepatitis B and hepatitis C viruses, and the second most important type of liver cancer is cholangiocarcinoma, whose main known cause is infestation with the liver flukes, opistorchis viverrini and clonorchis sinensis (Shu-Chun, *et al*. 2009).

Hepatocellular carcinoma (HCC) remains a common malignant cancer worldwide, it is considered the fifth most common malignant cancer (Ibrahim, *et al.* 2015).

2.2 Anatomy and physiology of liver:

The liver is the largest gland in the body occupying 2.5% of total body weight and providing a host of functions necessary for maintaining normal physiological homeostasis. Despite the complexity of its functions, the liver has a homogenous appearance (Juza and Pauli, 2014).

It is located in the right upper quadrant of the abdominal cavity beneath the right hemi diaphragm, it is protected by the rib cage and maintains its position through peritoneal reflections, referred to as ligamentous attachments (Abdel-Misih and Bloomstonm, 2010).

The main function of the liver is to take up nutrients, to store them, and to provide nutrients to the other organs (Ramadori, *et al*. 2008).

2.3 Abnormalities of liver:

2.3.1 Inflammation of liver:

Primary liver cancer, mostly hepatocellular carcinoma (HCC), is a clear example of inflammation-related cancer as more than 90 % of HCCs arise in

the context of hepatic injury and inflammation. Chronic unresolved inflammation is associated with persistent hepatic injury and concurrent regeneration, leading to sequential development of fibrosis, cirrhosis, and eventually hepatocellular carcinoma (Bishayee, *et al*. 2014).

2.3.2 Precancerous lesion of liver:

Precancerous lesions that may be detected in chronically diseased, usually cirrhotic livers, include clusters of hepatocytes with atypia and increased proliferative rate (dysplastic foci) that usually represent an incidental finding in biopsy or resection specimens, and grossly evident lesions (dysplastic nodules) that may be detected on radiologic examination (Hytiroglou, *et al*. 2007).

2.3.3Benign lesions of liver:

2.3.3.1Hepatocellular adenoma:

Hepatocellular adenoma is an uncommon benign primary hepatic neoplasm consisting of sheets of normal-appearing hepatocytes but lacking the normal acinar architecture of the surrounding hepatic parenchyma (Jay, 2007).

2.3.3.2Hemangioma:

Hemangioma of the liver is the most common benign liver tumor and is usually of the cavernous hemangioma variety. Hemangioma is considered to be a developmental mal-formation that is usually of no clinical significance. It usually exhibits high echogenicity, but this is not a specific finding for diagnosis. Temporal changes of echogenicity, such as the wax and wane sign, the disappearing sign, and the chameleon sign, are relatively specific findings that are useful for diagnosing hemangioma (Takamichi and Masakatsu, 2014).

2.3.3.3Focal nodular hyperplasia (FNH):

FNH is a benign hypervascular tumor arising from the normal liver parenchyma. It occurs primarily in young women, is solitary in 75-80% of cases, and is often discovered incidentally on abdominal CT or ultrasound examinations (Carlson, *et al*. 2000).

2.3.3.4Angiomyolipoma:

It is a rare disease and consists of hypervascular tumor with a fat component. The fat component can be detected by computed tomography (CT) and ultrasonography. When the fat deposition is very minor. Other benign liver tumors with fat components are myelolipoma, pseudolipoma, and lipoma; these lesions are rare and are usually hypovascular (Takamichi, *et al*. 2014).

2.3.4Malignant lesions of liver:

2.3.4.1Primary lesions:

2.3.4.1.1 Hepatocellular carcinoma (HCC):

Primary neoplasms of the liver are composed of cells that resemble the normal constituent cells of the liver. Hepatocellular carcinoma, in which the tumor cells resemble hepatocytes, is the most frequent primary liver tumor, and is highly associated with chronic viral hepatitis and cirrhosis of any cause (Zachary, 2007).

HCC is one of the ten most commonly occurring solid cancers worldwide and is the second cause of death from malignancy (Ferlay , *et al*. 2015).

It occurs more commonly in males in the fourth and fifth decades of life, among all cancers, HCC is one of the fastest growing causes of death. Chronic liver disease due to hepatitis B virus or hepatitis C virus and alcohol accounts for the majority of HCC cases. Incidence of nonalcoholic fatty liver disease has been on the risem and it has also been associated with the development of HCC. Carcinogenesis of HCC includes angiogenesis,

chronic inflammation, and tumor macroenvironment and microenvironment (Yezaz, *et al*. 2017).

2.3.4.1.2 Cholangiocarcinoma (CCA):

CCA is an epithelial cancer originating from the bile ducts with features of cholangiocyte differentiation. CCA is the second most common primary hepatic malignancy. The only curative therapy is surgical extirpation or liver transplantation, but unfortunately the majority of patients present with advanced stage disease, which is not amenable to surgical therapies (Boris and Gregory, 2008).

2.3.4.1.3 Adenocarcinoma:

Primary adenocarcinoma that arises from a bile duct, is second in frequency. It is associated with inflammatory disorders and malformations of the ducts, but most cases are of unknown etiology (Goodman, *et al*. 2007).

2.3.4.2 Secondary liver lesions (metastatic):

The liver is one of the most common sites for metastatic disease, accounting for 25% of all metastases to solid organs. In the adult oncology patient, most are metastatic carcinomas, of which adenocarcinomas are the predominant subtype, followed by squamous cell carcinomas and neuroendocrine carcinomas. Other tumor types that metastasize to the liver include melanomas, lymphomas, and rarely sarcomas (Centeno, *et al*. 2006).

2.4 Signs and symptoms of liver cancer:

The occurrence of multiple symptoms in HCC patients is common, and may include pain, fatigue, weight loss, and obstructive syndromes such as ascites and jaundice. Because of the limitations in the efficacy of current treatment options for HCC, aggressive symptom management is key to preserving physical functioning in this cancer population (Virginia, *et al*. 2008).

2.5 Risk factors of liver cancer:

2.5.1Cirrhosis:

Approximately 80% of HCCs develop in cirrhotic livers. The high rate of co-existing cirrhosis in HCC patients and the emergence of HCC in prospectively followed cirrhosis patients have led to the assumption that pre-existing cirrhosis is an important prerequisite for hepatocarcinogenesis, although some HCCs do arise in the absence of cirrhosis (Ashraf, *et al*. 2013).

2.5.2Alcoholism:

It is an important risk factor for HCC because it causes fatty liver, necro-inflammation, fibrosis, liver cirrhosis and malnutrition, especially when it is associated with HCV infection (Roberto, *et al*. 2016).

2.5.3 Hemochromatosis:

It is the most common genetic defect and it leads to the accumulation of iron in the body, causing heart, joint, endocrine and liver diseases (Roberto, *et al*. 2016).

2.5.4Hepatitis B virus (HBV) infection:

It is known to cause genomic integration in the liver tissue resulting in chromosomal deletions and in turn metaplasia (Premashis, 2014).

2.5.5Hepatities C virus (HCV) infection:

It is now considered an important etiologic factor in HCC. HCV-related carcinogenesis is possibly related to chronic inflammation and cirrhosis (Premashis, 2014).

2.5.6Obesity:

Excess body mass is associated with a higher risk of developing all cancers, including liver cancer. Those patients who were overweight had a 17% increase in risk of developing HCC (Ashraf, *et al*. 2013).

2.5.7 Diabetes mellitus (DM):

Diabetes mellitus directly affects the liver because of the essential role the liver plays in glucose metabolism . Diabetes is an independent risk factor for HCC (Julius, *et al*. 2016).

2.5.8 Other risk factors:

HCC in non cirrhotic livers can also occur as a result of contamination of food stuffs with aflatoxin B1. Another risk factor for developing HCC is including primary biliary cirrhosis, silent chronic liver disease, Non alcoholic fatty liver disease and autoimmune hepatitis (Arun, *et al*. 2010).

2.6 Diagnosis of liver cancer:

2.6.1Ultrasound (US) :

Suspicion for HCC is raised when any lesion more than 1 cm in size is seen in the background of liver cirrhosis (Bhosale, *et al*. 2006).

2.6.2 Computed tomography (CT) and magnetic resonance imaging (MRI):

Imaging plays a crucial role in early detection, accurate staging, and the planning of management strategies , dynamic MRI and CT are regarded as the best imaging techniques available for the non invasive diagnosis of HCC (Lee, *et al*. 2012).

2.6.3 Serological markers:

They are important for early diagnosis, as well as monitoring of tumer aggressiveness, treatment responsiveness , reocurrence and survival. The three most common markers are total alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive AFP (AFP-L3) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) (Yuen and Lai, 2005).

2.6.4 Liver biopsy:

It should only be considered when diagnostic imaging results are doubtful. In addition, clinical criteria have been developed that can be designed for prioritising patients with any suspicion of HCC prior to liver transplantation without confirming the diagnosis with a biopsy (Magdy and Shahira, 2015).

2.6.5 Immunohistochemistry:

Metastatic tumors are widespread in the liver, with metastatic adenocarcinoma (MA) constituting the greatest part, therefore differentiation of HCC from MA is a frequent problem facing the pathologist. Evaluating the diagnostic value of HepPar-1 immunostaining in differentiating hepatocellular carcinoma from metastatic tumors in liver (Ibrahim, *et al.* 2015).

A panel of immunohistochemical stains including glypican-3 (GPC-3), heat shock protein 70, and GS are useful in distinguishing HCC from non-malignant dysplastic nodules. Immunohistochemistry is also useful to determine whether a liver tumor is of primary hepatocellular or metastatic origin. Markers useful for this purpose include arginase-1, GPC-3 and bile salt export pump (Anne, *et al*. 2015).

The most commonly used markers include hepatocyte paraffin 1 (HepPar-1), alpha-fetoprotein (AFP), CD10, and polyclonal carcinoembryonic antigen (p-CEA) (Borscheri, *et al*. 2001).

2.6.6 Hepatocyte paraffin-1(HepPar-1):

HepPar-1 is an antibody to carbamoyl phosphate synthetase 1, a urea cycle enzyme in hepatocellular mitochondria, which is expressed predominantly in the liver, but also in other organs such as small intestine (Butler, *et al*. 2008).

It developed in 1993 from a failed liver allograft, this antibody has been found to be relatively sensitive (70%, although some authors report higher sensitivity) and specific (84%) for hepatocellular differentiation, in both normal tissue and HCC, as well as hepatoblastoma. Caveats with this marker include the reported loss of sensitivity as tumors become less differentiated and frequent negativity in the scirrhous variant (Anne, *et al*. 2015).

The histological differentiation of Hepatocellular carcinoma (HCC) from cholangiocarcinoma (CC) and metastatic adenocarcinoma (MA) of the liver is difficult in some cases and immunohistochemistry (IHC) is necessary for the diagnosis. HepPar-1 is available antibody which seems to be very specific and sensitive for the diagnosis of HCC (Geramizadeh, 2007).

Previous comparative cross-sectional study in 2014 where done by Hanif and Mansoor they study Hepar-1 as a novel immunohistochemical marker for differentiating hepatocellular carcinoma from metastatic carcinoma. They evaluate the diagnostic utility of Hepar-1 in differentiating hepatocellular carcinoma from metastatic carcinoma .It was performed on 60 cases of liver carcinoma, 30 cases each of metastatic and hepatocellular carcinoma. 25 out of 30 cases of hepatocellular carcinoma (83%). Out of 30 cases of metastatic carcinoma, only one case expressed staining in < 5% tumour cells and remaining 29 cases showed no reactivity (Hanif and Mansoor, 2014).

2.7 Staging of liver cancer:

HCC usually occurs on a background of a liver disease, making the level of management complexity unique among all malignancies. It is well known that the functional impairment of the underlying liver disease has a significant impact on prognosis, irrespective of the tumour stage. For this reason, systems that include the anatomical characteristics of the tumor only,

such as the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system that stratifies patients using a tumor-node-metastasis (TNM) classification, do not have a good predictive capability (Marcello, *et al.* 2014).

2.8 Management of liver cancer:

The prognosis and treatment of HCC depend on the tumor burden in addition to patient's underlying liver disease and liver functional reserve (Akiyoshi, *et al*. 2015).

Management of HCC patients depends on the stage of their tumor. Liver resection remains the first choice for very early-stage HCC. Liver transplantation still offers a better outcome however, local ablative therapy can be a substitute when transplantation is not feasible (Lin, *et al*. 2012).