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Epidemiologic Profile and Risk Factors for Hepatocellular Carcinoma in Qena City

Ahmed Mohamed Mahmoud Hany[1], Mohamed Mostafa Ali Wahman[2], Mona Gouda Maghrabi[3], Aliaa Mohamed Ali Eltaher[4*]

[1]Professor of Public health and community, Department of Public health and community, Faculty of Medicine - Assiut University
[2]Assistant professor of Clinical Oncology, Department of Clinical Oncology, Faculty of Medicine - South Valley University
[3]Lecturer of Radiology, Department of Radiology, Faculty of Medicine - Luxor University
[4]Assistant lecturer of public health and community, Department of public health and community, Faculty of Medicine - Luxor University
E-mail: aliaaeltaher1@gmail.com

Hepatocellular carcinoma (HCC) is the 6th most prevalent 1ry malignancy globally, with a greater frequency and occurrence within Asia and Africa. Over the recent few decades, the global frequency of hepatocellular carcinoma has varied, with some regions having a reduction in rates and others the opposite. The mass screening program that the public authority implemented to identify and manage hepatitis C virus may be a contributing factor to the increased identification of hepatocellular carcinoma within Egypt. Because of this study, numerous cases have been diagnosed and managed for hepatocellular carcinoma. The primary reason for malignant transformation in the case of hepatitis C virus (HCV) infection is the repeated occurrence of damage, regeneration, and inflammation. Every year, approximately 0.5% to ten percent of hepatitis C virus-correlated cirrhosis results in hepatocellular carcinoma. As a result of the unsafe IV therapy for schistosomiasis within the 1950s till the 1980s, Egypt had the greatest occurrence of hepatitis C virus globally. The objective of this investigation was to evaluate the epidemiological profile and risk factors of HCC in the city of Qena.

Keywords: HCC, HCV, cirrhosis.

1. Introduction

Unfortunately, the burden of this nearly always fatal illness is significantly higher in the less economically developed regions of Central America, sub-Saharan Africa, and Asia, as the frequency rates and age of diagnosis of hepatic tumors vary enormously on a worldwide basis (Oh, & Jun, 2023).

Within 2018, the combined age-standardized probability of death from hepatic tumor for males and females globally was 8.5 per 100,000, respectively. In the year 2018, hepatic tumor accounted for nineteen percent of completely recently diagnosed patients in both all ages, and genders, with a frequency rate of thirty-two percent and a death rate of thirty-one percent, as reported by the global cancer observatory. The Eastern Mediterranean and Europe are both World Health Organization regions that traditionally comprise the nations that are classified as part of the Middle East. The age-standardized rate of death of hepatic tumors within Egypt is the 2nd greatest globally, at 49.0 and 16.7 per 100,000 for males and females, respectively (Groopman, 2021).

The correlation among the hepatocellular carcinoma and HCV considered as a significant study area in Egypt. Initially, Egypt has an elevated documented hepatitis C virus transmission rate, with approximately 416,000 new infections annually (Ezzat et al., 2021).

Following that, it is recognized that there is a association among progression of hepatocellular carcinoma and HCV. Lastly, the government's implementation of a programmatic screening and monitoring process resulted in a rise in the number of people with the two illnesses.

The objective of the current research was to study the epidemiologic profile the HCC in relation to characteristics of patients, social habits, and environmental factors; to detect risk factors related to HCC, particularly viral infections, aflatoxin intake, and schistosomiasis; and to utilize data in the prevention and control of tumor incidence in Qena City.

2. Hepatocellular carcinoma

More than eight percent of hepatic tumor cases are hepatocellular carcinoma, which is the primary neoplasm of hepatic cells and originates from hepatocytes. The frequency of hepatocellular carcinoma is greater in China, at an average age of fifty-five to fifty-nine from diagnosis, and in Europe and North America, at sixty-five to sixty-three years. East and Southeast Asia, in addition to East and Western Africa, show elevated rates of hepatocellular carcinoma. In the year 2012, the most recent information reported to GLOBOCAN indicated that there were approximately 782,000 new cases and 745,000 mortalities of hepatic tumors globally. Consequently, the World Health Organization regards hepatocellular carcinoma as the 2nd most common reason for neoplasm-related mortality (Chidambaranathan-Reghupaty et al., 2021).

The correlation among the hepatocellular carcinoma and HCV defined as an essential field of study in Egypt. At first, Egypt has an elevated reported hepatitis C virus transmission rate, with approximately 416,000 new infections annually. Subsequently, it is recognized that there is a association among progression of hepatocellular carcinoma and HCV. Finally, the

government's implementation of a programmatic screening and monitoring process resulted in a rise in the number of people with the two illnesses (Baraka et al., 2023).

2.1. Epidemiology of Hepatocellular Carcinoma

Within the two male and female groups, the worldwide frequency of hepatic tumor has not decreased since 2000, with the most significant alteration occurring from 2001 to 2004 (annual percentage change (APC) −8.90, 95% confidence interval −10.0 to −7.70). Nevertheless, the worldwide frequency of hepatic tumors appears to have reached a plateau in the past few years (Fig. 1) (Amini et al., 2022).

There is additionally epidemiological data that suggests a correlation among exposure to environmental factors, including smoking, air pollution, and aflatoxin, and an elevated risk of hepatocellular carcinoma. Consequently, the epidemiology of hepatocellular carcinoma is indicative of the occurrence of these etiological risk factors. Consequently, the trends in hepatocellular carcinoma frequency worldwide have changed over the years as a result of the initiation of national vaccination programs against hepatitis B virus, the introduction of direct-acting antiviral agents (DAAs) for the management of hepatitis C virus infection, and the increasing occurrence of alcohol consumption and obesity, which respectively affect the occurrence of alcohol-related liver disease and metabolic dysfunction-associated steatotic liver disease (Lu et al., 2022).

2.2. Hepatocellular carcinoma frequency regarding etiological risk factor

Due to heterogeneity in research design (prospective vs. retrospective), variable factors and severity of cirrhosis, such as competing risks of mortality and transplantation of the liver, there is a significant amount of variation in the recorded annual frequency rates of hepatocellular carcinoma in groups of cases with metabolic dysfunction-associated steatotic liver disease and alcohol-related liver disease. Within a systematic review of eighteen investigations that included 470,404 cases with metabolic dysfunction-associated steatotic liver disease, those who did not have cirrhosis developed hepatocellular carcinoma at a yearly rate of 0.03% (95% confidence interval 0.01–0.07%) (Orci et al., 2022).

The risk of death of cases with cirrhosis is elevated, and it is dependent upon the cause. The risk for mortality is greatest in cases with alcohol-related liver disease, then in cases with metabolic dysfunction-associated steatotic liver disease, followed by cases with hepatitis B virus-correlated or hepatitis C virus-correlated cirrhosis. The risk of death was greater for cases with alcohol-related liver disease (subdistribution HR 1.4, 95% confidence interval 1.12–1.77) and lesser for cases with viral hepatitis (subdistribution HR 0.83, 95% confidence interval 0.64–1.07) in a group investigation including 2,609 cases with cirrhosis of various causes as comparing with cases with metabolic dysfunction-associated steatotic liver disease (Jepsen et al., 2020).

2.3. Global variation in the epidemiology of hepatocellular carcinoma

Due to variations in the distribution of etiological risk factors and in the availability of screening and therapies for underlying hepatic disorders, the frequency of hepatocellular carcinoma ranges in different regions of the globe. The frequency of hepatocellular carcinoma is greatest in Africa and Asia, while it is lesser in Europe, the Middle East, and the Americas (Zhang et al., 2022).

Asia is the site of over seventy percent of all hepatocellular carcinoma cases. Based on the GLOBOCAN 2020 database, Mongolia has the greatest age-standardized frequency rate of liver cancer (85.6 cases per 100,000 people), which is a minimum of four times greater than that of any other country. However, China accounts for most of the patients in Asia (62.4%), then Vietnam (4.0%), Japan (7.0%), Thailand (4.2%), and India (5.3%), in that order. With the exception of Japan, in which over seventy percent of hepatocellular carcinoma cases are associated with hepatitis C virus infection, hepatitis B virus infection is responsible for most of the hepatocellular carcinoma cases in most Asian nations, with proportions more than sixty to eighty percent in endemic areas (Sung et al., 2021).

2.4. Future projections in hepatocellular carcinoma epidemiology

The yearly number of new cases of hepatic tumor will rise by fifty-five percent from 2020 to 2040 on the worldwide level, with 1.4 million individuals expected to be diagnosed by 2040. Additionally, it is projected that hepatic tumors will take the lives of 1.3 million individuals globally in 2040, a 56.4% increase from 2020. The rises are primarily due to the developing and ageing global population, in addition to the consistent frequency and death rates of hepatocellular carcinoma. Nevertheless, these estimations may be overestimated, as they include hepatocellular carcinoma and other hepatic tumors, including cholangiocarcinoma (Rumgay et al., 2022).

2.5. Risk factors for hepatocellular carcinoma in Egypt

2.5.1. Hepatitis C virus

Progression of hepatocellular carcinoma is mainly the consequence of the expression of hepatitis C virus protein in infected cells of the liver, which leads to mutation and malignant transformation. The primary reason for malignant transformation is thought to be the repeated processes of inflammation, damage, and regeneration. The probability of developing hepatocellular carcinoma is increased by more than twenty times when hepatitis C virus is present. yearly, approximately 0.5% to ten percent of hepatitis C virus-correlated cirrhosis results in hepatocellular carcinoma (Borgia et al., 2021).

Genotype 4 is the predominant genotype in Egypt, accounting for more than 92.5% of infected cases, with genotype 1 following at 3.6%. An investigation has shown that the lymphotoxin alpha gene mutation could contribute to the susceptibility to hepatitis C virus infection and the subsequent development of clinical manifestations, at minimum in Egypt (Roudot et al., 2021).

2.5.2. Hepatitis B virus

DNA viruses may integrate into a host genome, promoting malignant transformation by downregulating tumor inhibitors genes and activating oncogenes. The annual frequency of hepatocellular carcinoma is 0.42%, and it varies depending on the presence of hepatitis B virus infection or cirrhosis. The overall risk of hepatocellular carcinoma development between hepatitis B virus carriers ranges from ten percent to twenty-five percent. As a result of antiviral management for hepatitis B virus, liver function and histology may be enhanced, as hepatitis B virus-DNA concentrations may be reduced. A growing body of data suggests that nucleos(t)ide analogs reduce the probability of developing hepatocellular carcinoma; however, they can't completely prevent it (Nahon et al., 2021).

2.5.3. Environmental toxins

Metabolizing chemical agents is the primary function of the liver. Liver plays a role in numerous metabolic and excretory processes and has a particular blood supply. This results in liver damage, including fatty liver, cirrhosis, hepatocellular carcinoma, and hepatocellular injury (Cohen, 2020).

Aflatoxins are recognized as a significant factor in the progression of hepatocellular carcinoma in Egypt. Aflatoxins recognized carcinogenic metabolites of molds, particularly parasites, and Aspergillus flavus, which contaminate a variety of agricultural products, including seed of cotton, maize, and peanuts (Rashed, 2021).

In addition to molds, an investigation carried out on desserts in Egypt revealed which aflatoxin B1 has been identified at levels exceeding permissible thresholds of two parts per billion in seventy percent of samples of one of the dairy desserts. Additionally, aflatoxin M1 exceeded the limits in ten percent of every type of sample. Egyptians with hepatocellular carcinoma showed elevated serum concentrations. Aflatoxin B1 defined as the most mutagenic, carcinogenic, and teratogenic metabolite and is a primary metabolite produced. In individuals who presented with multiple hepatic focal lesions exceeding five centimeters in diameter, it was detected at elevated levels. Anwar et al. discovered that the development of liver illness to G3S3 is associated with the presence of aflatoxins and hepatitis C virus, which suggests the presence of hepatocellular carcinoma. In an investigation carried out by Sharaf-Eldin et al., it was discovered that the concentrations of aflatoxin were significantly greater in hepatocellular carcinoma cases compared to cirrhotic people and controls (Daou et al., 2020, Ezzat et al., 2021).

2.5.4. Non-alcoholic fatty liver disease (NAFLD)

Abnormal fat accumulation in the liver is the result of non-alcoholic fatty liver disease, which is not caused by significant alcohol consumption. Non-alcoholic fatty liver disease encompasses a wide range of liver diseases, including steatosis and cirrhosis. This disorder is the most prevalent liver illness associated with obesity and has the potential to develop into hepatocellular carcinoma (Michelotti et al., 2021).

2.5.5. Lifestyle causes (smoking, dietary factors, and alcohol consumption)

It is widely recognized that extreme alcohol drinking is a risk factor for the development of hepatocellular carcinoma. ALCD is the 2nd most prevalent reason for transplantation of liver in the European Union, which represents around forty percent of all primary liver transplants. Excessive drinking is responsible for between sixty and eighty percent of liver-related deaths. Egypt has a minimal risk of this. The probability of hepatocellular carcinoma is elevated by over sixteen percent as a result of heavy alcohol consumption. Heavy ethanol consumption for a period exceeding ten years results in a five- to sevenfold rise in risk (Taniai, 2020).

2.5.6. Obesity

Approximately 600 million are obese and 1.9 billion individuals worldwide are overweight. Obesity is associated with progression of numerous metabolic conditions, such as diabetes mellitus and hypertension, which in turn contribute to the greater prevalence of hepatocellular carcinoma. Premorbid obesity is correlated to a death risk associated with hepatocellular

carcinoma that is greater than twice. It was proposed that the probability of hepatocellular carcinoma increases by thirty-nine percent for each five-unit rise in BMI. According to another investigation, the death rate associated with hepatocellular carcinoma in obese males (BMI, 30-34.9 kilograms per square meter) was 1.9 times that of males with a normal BMI (BMI, 18.5-24.9 kilograms per square meter) (Hamed et al., 2019).

2.5.7. Genetic factors

It has been suggested that certain hereditary liver illnesses with genetic mutations are associated with an increased risk of developing hepatocellular carcinoma. Wilson's illness, glycogen storage illnesses, hemochromatosis, tyrosinemia, alpha-1 antitrypsin deficiency, and porphyrias comprise these conditions. The same is correct for polymorphisms that elevate the probability of hepatocellular carcinoma. Risk was stated to be significantly correlated with polymorphisms in interlukin-1B MnSOD, and UGT1A7. The probability of gene mutation, which results in the progression of hepatocellular carcinoma, has been observed to be elevated by hepatitis C virus and hepatitis B virus infection (Toh et al., 2023).

2.6. Pathology of Hepatocellular Carcinoma

HCC, or malignant hepatoma, is a main liver malignancy. The majority of hepatocellular carcinoma cases are caused by either cirrhosis (alcoholism is the most frequent reason for hepatic cirrhosis) or viral hepatitis infection (hepatitis C or B) (Zajkowska et al., 2022).

2.7. Gross morphological features

The macroscopic morphology of HCC may be categorized as nodular, large, or diffuse. The nodular form might manifest as a single nodule or several nodules that vary in size and are clearly delineated (Torbenson et al., 2021).

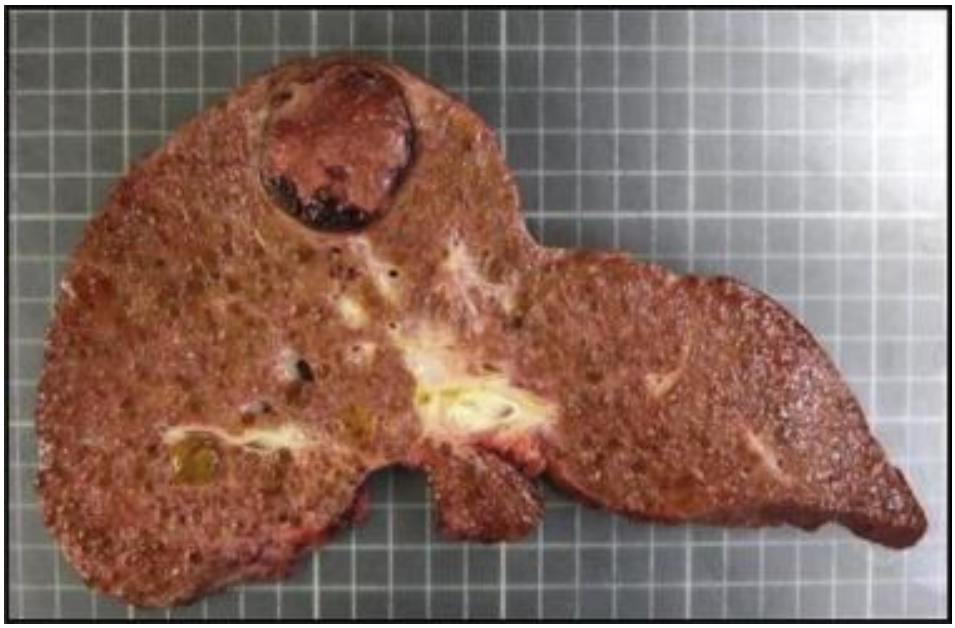

Fig. 1: HCC and micronodular cirrhosis (Vij et al., 2023)

2.8. Microscopic features

Typically, the tumor is trabecular, with liver plates varying in thickness from two to several cells and being divided by sinusoids, with minimal intervening stroma. The pseudo-glandular pattern is believed to be caused by the disintegration of thick trabeculae, and the degenerative voids left behind contain debris that has been replaced with eosinophilic material. Another pattern, compact, is often seen after radiation or chemotherapy and may be related to compression artefact. Hepatocellular carcinoma cells are typically polygonal and have variable levels of nuclear enlargement and atypia. There may also be pleomorphic large cells, transparent cells, and sarcomatoid patches. Oncocyte-like cells may be seen; however, the fibrolamellar variety of hepatocellular carcinoma is more prevalent (Mouleeswaran et al., 2023).

2.9. Preventive measures: Hepatitis C virus control in Egypt

At that time, approximately 5.5 million individuals, or ten percent of people worldwide, tested positive for hepatitis C virus antibodies in 2015. Egypt's government started a nationwide campaign to identify and manage hepatitis C virus in response to the World Health Assembly's 2016 choice for remove virus, which is a significant reason for hepatocellular carcinoma in the country. By 2018, the campaign had managed over two million people, with a cure rate of ninety percent. The Egyptian government's implementation of a reduction in the cost of direct-acting antiviral medications was primary factor in the successful removal of the illness. The initial application of this process was to chronic cases that had been detected (Shiha et al., 2020).

2.10. HCC Screening

Screening programs for noncirrhotic hepatitis B virus patients for hepatocellular carcinoma development have shown benefits, including improved survival rates, well treatment, and improved early detection. A study in Japan compared the survival probabilities of hepatocellular carcinoma in Hong Kong and Japan, highlighting the importance of intensive screening programs. Despite potential psychological or financial harm, advantages outweigh the harm. The annual risk of hepatocellular carcinoma development in cirrhotic cases is two to four percent, which is why screening is strongly suggested for all cirrhotic cases, irrespective of the cause (Ezzat et al., 2021).

2.11. Screening procedures

Ultrasound is the most frequently utilized imaging method for the routine screening of hepatocellular carcinoma. It is non-invasive, cheap, easily accessible, and simple, which are among its numerous benefits. Ultrasound has a sensitivity of not higher than forty-five percent in the detection of hepatocellular carcinoma, particularly in lesions that are fewer than one centimeter in diameter. It’s influenced by the operator, the case's capacity to maintain their breath throughout the nodularity and the examination of the liver, that complicates the identification of new lesions. Certain regions, such as the dome of the liver, are inaccessible. The effectiveness of the technique is reduced as a result of the difficulty of examination caused by NASH and obesity. In these cases, computed tomography scanning and magnetic resonance imaging may act as substitutes for ultrasound. However, they aren't cost-effective and aren't

considered as primary screening techniques for hepatocellular carcinoma (Marrero et al., 2020).

2.12. Surveillance of Hepatocellular Carcinoma

The effect of early identification of hepatocellular carcinoma on the cure rate and overall survival (OS) is the subject of conflicting reports. On a global scale, hepatocellular carcinoma surveillance encompasses measuring of alpha fetoprotein (AFP) levels and ultrasound (Rashed et al., 2020).

There are numerous screening guidelines accessible to great-risk populations, such as cases who have been diagnosed with HBV/HCV infection and/or cirrhosis (whether or not they have cirrhosis). The main variances among these guidelines are the surveillance intervals and screening techniques. Despite the significant impact of these guidelines on medical practice, the global incidence of hepatocellular carcinoma death is on the rise as a result of inadequate adherence to screening (Ferraz et al., 2020).

2.13. Biomarkers

The biomarker that is utilized most frequently in the screening process for hepatocellular carcinoma is alpha fetoprotein. While it is easily accessible, cheap, and simple to use, its inclusion in the guidelines along with ultrasonography is a contentious problem. The American Association for the Study of Liver Diseases suggests the application of ultrasound, with the clinician determining the appropriate utilization of alpha fetoprotein based on the case's condition. Nevertheless, European guidelines suggest that ultrasound can be utilized without a requirement for alpha fetoprotein (Luo et al., 2020).

2.14. Treatment Management of HCC in Egypt

2.14.1. Diagnosis

The detection of a suspicious lesion in the cirrhotic liver through ultrasound surveillance is then confirmed by diagnostic confirmation through contrast-advanced helical computed tomography or dynamic magnetic resonance irradiation. Additionally, the alpha-fetoprotein testing, in conjunction with the noted imaging methods, provides non-pathological evidence of the hepatocellular carcinoma diagnosis (Renzulli et al., 2022).

2.14.2. Role of PET-CT diagnosis in hepatocellular carcinoma

Positron-emission tomography (PET) appears to be a more efficient and noninvasive method compared to traditional radiography methods of scanning every part of the body. The application of PET-CT for the diagnosis of hepatocellular carcinoma has made significant advancements in the past few years, despite the poor sensitivity of 2-deoxy-2-(18F) fluoro-D-glucose (18F-FDG) positron-emission tomography, which ranges from thirty-six percent to seventy percent for identifying hepatocellular carcinoma (Lu et al., 2019).

2.14.3. Role of histopathology in diagnosis

The current diagnostic method for hepatocellular carcinoma is predicated on imaging investigations, which limits the application of histopathology to specific conditions. The diagnostic criteria for hepatocellular carcinoma have been modified by the clinical guidelines of the American Association for the Study of Liver Disease, the Asian-Pacific Association for

the Study of Liver, and the European Association for the Study of the Liver (EASL). In considering the remarkable advancements in methods that have resulted in extremely good specificity and sensitivity for hepatocellular carcinoma diagnosis, radiology is now recommended (Rastogi, 2018).

2.14.4. Histopathology and Immunohistochemistry for the Prognostication and Diagnosis of Hepatocellular Carcinoma

Tumor histopathology is a critical diagnostic tool that also acts in a variety of other critical functions, including the ability to differentiate between other lesions, prognosis, and therapy decisions. These functions are essential and can't be replaced by cancer indicators or imaging methods. The evaluation of histological variables in tumor resection specimens was demonstrated for predicting recurrence and metastatic potential, thereby indicating the necessity of salvage transplantation (Ayyad et al., 2021).

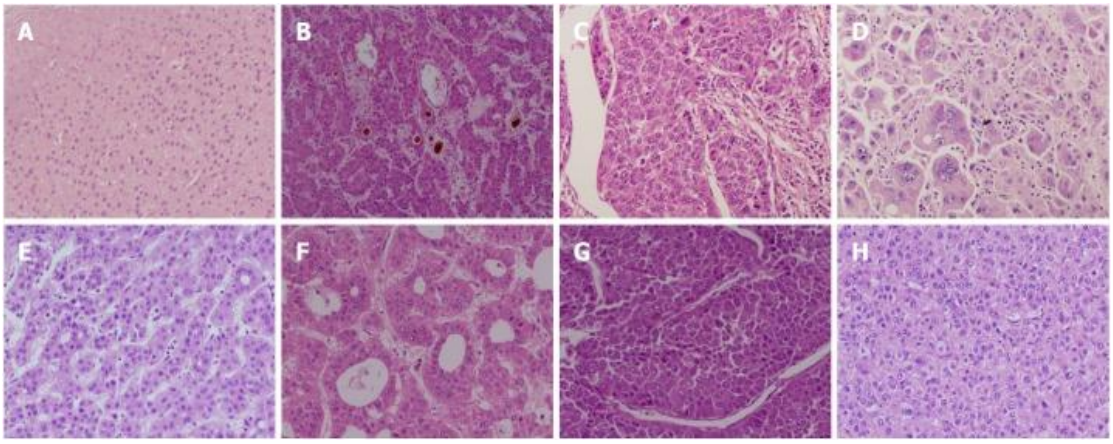

Fig. 4: Hepatocellular carcinoma Edmondson and Steiner grading. Grade 1 (A); grade 2 (B); grade 3 (C); and grade 4 (D). The most frequently observed histopathological patterns in hepatocellular carcinoma are pseudoglandular (F), microtrabecular (E), and compact (H) macrotrabecular (G). (Hematoxylin and eosin stain) (Rastogi, 2018).

2.14.5. Surgical intervention

Cancer resection or liver transplantation are among the surgical procedures that are utilized to treat hepatocellular carcinoma. Liver transplantation is the optimal option, as the whole organ will be substituted with a new one, permanently resolving the underlying pathology. Nevertheless, this isn't practicable within wholly patients. The Milan criteria have been established to determine whether a case is a viable candidate for liver transplantation. Surgical resection of hepatocellular carcinoma is the subsequent step if transplantation is not possible. Resection is the optimal therapy option for cancers below five centimeters in non-cirrhotic cases from an oncological perspective (Kow, 2019).

Cases in and beyond the Milan criteria didn't show statistically insignificant variance in their overall survival time. The lobar distribution, cancer grade, total tumor burden, and size of the largest nodule in the explanted liver were the causes that influenced recurrence. In an investigation conducted by Galal et al., the investigators determined that alpha fetoprotein has

the potential for predicting the recurrence of hepatocellular carcinoma following living donor liver transplantation (area under the curve = 0.806) at cutoff values of over sixty-six nanogram per milliliter. The research revealed a 94.3% specificity, 60% sensitivity, 97.1% negative predictive value, and 42.9% positive predictive value (Galal et al., 2019).

2.14.6. Local ablation methods

The utilization of thermal ablation for hepatic focal lesions offers numerous benefits, including the capacity to replicate the procedure, minimal morbidity, and minimal complications. Microwave ablation is more effective in regions with near vessels or high blood flow due to its immunity to the heat sink impact. Egyptian research was conducted to evaluate the effectiveness of microwave ablation in high-risk regions, including those near the diaphragm, near blood vessels and close to other organs. Within the research group, microwave ablation achieved ablation rates of 75%, 100%, and 87.5% for lesions located in close proximity to the perivascular lesions, gall bladder, and subcapsular lesions, respectively (Badawy et al., 2020).

2.14.7. Transarterial chemoembolization

The therapy preferred for cases with intermediate-stage hepatocellular carcinoma is transarterial chemoembolization, regarding BCLC. It is additionally the standard therapy for non-resectable hepatocellular carcinoma. It is regarded as a palliative therapy that has a beneficial effect on quality of life and survival. Many intravascular methods were developed since Seldinger's 1953 description of his method. This has been succeeded by percutaneous selective angiography and arterial infusion of vasopressin via catheterization to regulate gastrointestinal bleeding. The debate regarding the utilization of chemotherapy for supporting transarterial chemoembolization over transarterial embolization persisted for over a decade (Prince et al., 2020).

2.14.8. Transarterial radioembolization

The standard line of therapy for Barcelona clinic liver cancer stages B is transarterial chemoembolization, as recommended by guidelines; however, the outcomes remain not fully satisfactory. Radiation from external beams to the liver is ineffective in delivering lethal doses due to the radioresistance of hepatocellular carcinoma. A catheter-based therapy for hepatocellular carcinoma that has been newly applied is radioembolization with Yttrium-ninety microspheres. It’s safe to carry out in cases with portal vein thrombosis because of it’s minimal embolic impact. Transarterial radioembolization offers the benefits of a short hospitalization, an extended duration till development, and a long progression-free survival (Müller et al., 2021).

2.14.9. Systemic therapies

Currently, the management for progressing hepatocellular carcinoma focuses on systemic treatment, which includes immunotherapy, anti-angiogenesis agents, and TKIs. There was no medication accessible prior to the progression of sorafenib that would provide this enhanced overall survival in cases of this nature (Qing et al., 2021).

Sorafenib is an oral multi-kinase suppressor that possesses anti-proliferative and anti-angiogenic characteristics. Sorafenib functions by suppressing vascular endothelial growth factor receptor-2 and -3 tyrosine kinases, rapidly accelerating fibrosarcoma kinases and

platelet-derived growth factor receptor-β tyrosine kinases. Sorafenib has been initially used in cases where liver function was excellently preserved. However, the Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its management with sorafenib revealed a comparable safety profile, regardless of Child-Pugh staging. It isn't suggested to administer sorafenib to cases that have underlying liver dysfunction on a regular basis (Huang et al., 2021).

2.15. National population-based tumor registry program

In year 2008, the Egyptian National Cancer Registry Program has been established to act as a reliable source for tumor frequency data in Egypt. Egypt was divided into three geographical regions by the NCRP: middle, lower, and upper. Information is routinely obtained from specialized tumor therapy centers that are scattered throughout the nation. Hepatocellular carcinoma was the most commonly detected tumor in lower and middle Egypt, and it was the second most commonly noticed tumor in upper Egypt, according to the Egyptian National Cancer Registry Program research findings (Ezzat et al., 2021).

2.16. Hepatocellular carcinoma screening after hepatitis C virus treatment with DAAs

Following the national campaigns of screening and combating hepatitis C virus, a significant breakthrough was observed, as all populations were screened for hepatitis C virus, and basic laboratory findings and ultrasounds were conducted. Numerous hepatocellular carcinoma cases were identified and offered alternatives to therapy. In spite of the excellent safety profile of DAA treatment, which allowed for the therapy of severe cases and was predicted to lower the incidence rate of hepatocellular carcinoma following therapy, there were some contradictory findings regarding hepatocellular carcinoma frequency rates following SVR (Shahid et al., 2021).

3. Aflatoxins

Aflatoxins are secondary metabolites that are naturally produced by the fungi Aspergillus parasiticus and Aspergillus flavus. These Di furanocoumarin derivatives are prevalent contaminants of numerous staple foods, such as ground nuts, maize, sorghum, and rice, and are generated in a variety of substrates and under particular environmental conditions. The toxins are highly mutagenic, carcinogenic, toxic, and teratogenic, and they are widely distributed in nature, posing significant public health risks to humans (Khan et al., 2021).

As a result, rural residents in resource-limited regions are exposed to aflatoxins at a significantly higher rate and under more severe conditions compared to their urban dwellers. The toxin is additionally susceptible to a significant seasonal variation in exposure. Two types of aflatoxin poisoning are noted. There are two types of exposure: acute severe intoxication, which results in direct liver damage, subsequent disease, and mortality, and chronic symptomatic exposure (Mollay, 2022).

Aflatoxin B1 is the most potent of these toxins and has the greatest hepatocarcinogenic potential. It is the aflatoxin that is commonly found in contaminated human foods. The liver is the primary site of aflatoxin metabolism, and the primary human cytochrome P450 enzymes included in its metabolism are CYP 3A4, 3A5, 3A7, and 1A2 (Chain et al., 2020).

3.1. Aflatoxins as a Reason for Hepatocellular Carcinoma

Aflatoxin B1 is the most powerful experimental hepatocarcinogen discovered to date and is directly associated with the progression of hepatocellular carcinoma in humans. Presently, no animal model that has been subjected to the toxin has been unable to acquire hepatocellular carcinoma. Because the number of new tumors globally increases annually, hepatocellular carcinoma is responsible for around 9.2% of the total. It is the 7th most prevalent tumor in women and the most prevalent in men, and it is diagnosed at a relatively young age in resource-limited regions. These regions account for around eighty-four percent of all new cases of hepatocellular carcinoma, with an occurrence that is sixteen to thirty-two times greater in sub-Saharan Africa and the Asia-Pacific region compared to resource-rich regions (Blidisel et al., 2021; Erkekoglu & Sabuncuoğlu, 2021).

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