REVIEW ARTICLE

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Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide[1], with over four hundred thousand new cases and almost as many deaths each year[2]. The incidence ranges from <10 cases per 100,000 population in North America and Western Europe to 50-150 cases per 100,000 population in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths. Studies from the USA, UK, mainland Europe and Australia have shown a rising incidence of HCC[3-6], which probably relates to the increasing prevalence of hepatitis B and C due to immigration[7]. Improved care for individuals with cirrhosis has resulted in prolonged and a relatively greater opportunity for malignant changes to develop. HCC is a disease of multifactorial etiology; the development of a carcinoma in a given individual is a multi-step process and the result of an accumulation of risks. It is estimated that persistent infection with hepatotrophic viruses account for well over 80% of the world's liver cancer[8]. Hepatocellular carcinoma is the major cause of death in cirrhotic patients in Europe[9,10,11]. Once cirrhosis is present, up to 20% of patients will develop HCC over 10 years[12]. Genetic alterations are fundamental to the development of HCC by resulting in uncontrolled cellular proliferation and de-differentiation. Without treatment, the prognosis is dismal, with only a few months survival[13]. Several surgical and non-surgical therapeutic modalities have been used for the treatment of HCC. Surgical resection, liver transplantation and local ablation therapies demonstrate potentially curative treatment options that should always be considered when the tumor is restricted to liver.

Epidemiology

The incidence of HCC varies widely by geographic location. The distribution of HCC also differs among ethnic groups and regions within the same country[14]. High incidence regions (more than 15 cases per 100,000 populations per year) include sub-Saharan Africa, the People's Republic of China, Hong Kong, and Taiwan[14]. Over 40 % of cases occur in the People's Republic of China, with an annual incidence of 137,000 cases[15]. North and South America, most of Europe, Australia and parts of the Middle East are low incidence areas with fewer than three cases per 100,000 per year. The incidence in the US has increased during the past two decades. The overall age-adjusted incidence rates of HCC increased from 1.4/100,000 in 1975-1977 to 3.0/100,000 in 1996-1998 in the US, followed by a 25% increase in the years 1993-1995,more in 45 to 49 year-old group. These findings, reported in other low-rate areas as well[16], have been widely suggested to be related to increased prevalence of chronic HCV infection.

Intermediate incidence areas include several countries in Eastern and Western Europe, Thailand, Indonesia, Jamaica, Haiti, New Zealand, and Alaska[14].

Sex and age distribution: Men are at higher risk for HCC than women. The greatest difference occurs in high incidence regions, where males are

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affected 2.1 to 5.7 times more than females (3.7:1). The ratio decreases to 2.4:1 in intermediate incidence areas, and is lower in low incidence regions. There are, as yet, no satisfactory explanations for this phenomenon. It has been speculated that estrogens and androgens modulate hepatocarcinogenesis[17]. Several large prospective studies conducted in both Asia and Western Europe have noted a mean age at presentation between 50 and 60 years[19],decreasing in sub-Saharan Africa to a mean of 33 years[20]. Age probably represents length of exposure to underlying etiology. A prospective Spanish analysis of risk factors for HCC found a 4-fold greater risk for developing HCC in patients older than 54 years[21].

Risk factors

It has been recognized that the most important risk factor for HCC is cirrhosis. Furthermore, HCV and HBV are the major etiological agents that lead to the development of HCC[22]. Other risk factors include environmental toxins, hereditary hemochromatosis, and cirrhosis of almost any cause[23]. However, HCC can also occur in patients without known risk factors[24].

Hepatitis B infection- approximately 300-400 million people worldwide are chronically infected with HBV. Epidemiological studies have convincingly shown that HCC is closely associated with chronic HBV infection with increased risk of HCC while co-infection HBV/HDV or HBV/HCV[22]. The association between the hepatitis B carrier state and hepatocellular carcinoma has been demonstrated in several large population based studies (approximately 100-fold higher than uninfected)[25].

Chen CH et al. concluded the importance of perinatal transmission of HBV and maternal virus load as a risk factor in HBV carcinogenesis in a familial clustering of HCC[26]. The presence of viral replication (positive e antigen) increases the risk of HCC 62-fold, as well[27].

An Italian study followed a cohort of 296 blood donors excluded from donation 30 years ago (157 HBV-negative blood donors at the time were controls) when HBV surface antigen screening became mandatory[28]. There was no difference in HCC as the cause of death for HBV carriers (2/296; 0.6%) and controls (1/157; 0.6%). This study confirmed that HBV carriers have a low rate of development of HCC. The incidence of HCC in children decreased in Taiwan after a universal hepatitis B vaccination program[29].

Hepatitis C infection- Globally 170 million people are infected chronically with HCV. It is a leading cause of chronic hepatitis, liver cirrhosis and HCC worldwide. The combination of HCV and HBV infection appears to augment the risk of HCC[30]. In contrast to hepatitis B virus infection, hepatocellular carcinoma in patients with hepatitis C occurs almost exclusively in those with cirrhosis[31]. HCV genotype 1b may be another risk factor.

Cirrhosis- Compensated cirrhotics have a 3 to 4% annual incidence of HCC, while chronic hepatitis has an approximate annual risk of 1%. Patients with chronic hepatitis and elevated serum alpha-fetoprotein concentrations have a higher risk of HCC than those with normal values (<20 µg/L). Among patients with hereditary hemochromatosis (HH), HCC is virtually limited to patients with cirrhosis[32]. In a cohort study of 667 patients with primary biliary cirrhosis, hepatocellular carcinoma was not seen in any of 394 patients who had stage I or II disease on their last liver biopsy. However, HCC developed in 16 of 273 patients (5.9%) with stage III or IV disease; more common in men than women (20 vs. 4 percent)[33].

Environmental risk factors- Besides etiology of liver disease, environmental risk factors have been shown to be important in the development of HCC. An association between diabetes mellitus and HCC has been reported[34], but the temporal relation remains unknown. The first population-based study assessing the risk of HCC based on the presence of diabetes followed a cohort of patients discharged from the Department of Veterans Affairs medical system of the U.S. up to 2000[35]. The study identified 173,643 patients with diabetes, and the incidence rate for HCC was 2.39 in diabetics vs. 0.87 in non-diabetics (P<0.0001), with a hazard rate ratio of 2.16 for the development of HCC.

Alcohol has been shown to be an important risk factor for the development of HCC, less common in Islamic population[36]. The annual incidence of HCC in alcohol related cirrhosis is 1-4%[37].

While some studies have shown cigarette smoking as a risk factor for HCC[38], others have not[39]. Heavy smokers have an approximately 50% higher risk than nonsmokers. The cytochrome P450 system is highly inducible by smoking. One study evaluated the interaction of alcohol, tobacco, diabetes and viral hepatitis in the causation of HCC[40]. Yuan JM et al. studied 295 cases with HCC and 435 age, gender and race-matched controls from Los Angeles and found that alcohol, tobacco, diabetes and viral hepatitis were independent risk factors for HCC. A synergistic interaction on HCC risk was observed between alcohol consumption and diabetes (OR = 4.2; 95% CI: 2.6-5.8), alcohol and viral hepatitis (OR = 5.5; 95% CI: 3.9-7), diabetes and viral

hepatitis (OR = 4.8; 95% CI: 2.7-6.9) but not with tobacco smoking. Another study from the U.S. showed that male gender, advanced age and non-Caucasian background were independent risk factors for HCC[41]. These studies indicate that viral hepatitis; diabetes; environmental (alcohol and tobacco), demographic (older age) and familial risk factors interact to increase the risk of HCC.

Aflatoxin- Aflatoxin is a mycotoxin that commonly contaminates corn, soybeans, and peanuts. High rates of dietary aflatoxin intake have been associated with HCC. In another study from Shanghai, the odds of developing HCC among individuals with HBV and exposure to aflatoxin were 59.4 times more than normal population[42]. Mutations of the p53 tumor suppressor gene have been demonstrated in patients with hepatocellular carcinoma who have chronically been exposed to aflatoxin[43].

Contaminated drinking water- Several studies in rural China have noted a higher mortality rate from HCC among people who drink pond-ditch water compared to those who drink well water (100 vs. fewer than 20/100,000 per year)[44]. The blue-green algal toxin microcystin commonly contaminates these ponds and is thought to be a strong promoter of HCC[45].

Betel nut chewing- Case control trials have suggested that betel nut chewing, widespread in certain regions of Asia, may be an independent risk factor for cirrhosis and HCC[46].

Oral contraceptive- A positive association between OC use and hepatocellular carcinoma has been demonstrated in low-incidence countries in which there is no overriding risk factor[47].

Pathogenesis

Hepatocarcinogenesis is a multistep process involving different genetic alterations leading to malignant transformation of the hepatocyte. While significant progress has been made in recognizing the pathogenesis of other cancers, notably colorectal and certain hematopoietic malignancies, the molecular contribution of the multiple factors in hepatocarcinogenesis are still poorly understood. HCC is heterogeneous genetically, which is not unexpected because of the heterogeneity of etiological factors involved, hepatocyte functions and the late stage at which HCCs are usually detected and analyzed.

Malignant transformation of hepatocytes may occur regardless of the etiological agent through a pathway of increased liver cell turnover, induced by chronic liver injury and regeneration in a context of inflammation and oxidative DNA damage. This may result in genetic alterations, such as the activation of cellular oncogenes, inactivation of tumor suppressor genes, possibly in cooperation with genomic instability, overexpression of growth and angiogenic factors, and telomerase activation. Chronic viral hepatitis, alcohol consumption, metabolic liver diseases such as hemochromatosis and [alpha] 1-antitrypsin deficiency as well as non-alcoholic fatty liver disease may act predominantly through this pathway. Coexistence of etiologies, e.g. HBV and HCV infection, HBV infection and aflatoxin B1, HCV infection and alcohol, or HCV infection and liver steatosis, increases the relative risk of HCC development[48]. On the other hand, there is evidence that HBV - and possibly HCV - may play an additional direct role in the molecular pathogenesis of HCC.

New technologies may eventually lead not only to a better understanding of the cellular events involved in hepatocyte transformation, but to improve preventive measures and innovative therapies for one of the most devastating human malignancies in the world today, as well.

Clinical presentation and natural history

The growth of HCC is characteristically silent in nature, which may delay diagnosis for as long as 3 years from the time of development[49]. Patients generally present symptoms and signs of advancing cirrhosis such as pruritus, jaundice, variceal bleeding, cachexia, hepatic encephalopathy, increasing abdominal girth (portal vein occlusion by thrombus or tumor associated with rapid onset of ascites), right upper quadrant pain and physical findings such as: ascites, hepatomegaly, alcoholic stigmata (Dupuytren contracture, spider angiomata), asterixis, pedal edema, periumbilical collateral veins and enlarged hemorrhoidal veins. Non-cirrhotic patients are more likely to present signs and symptoms of long-standing malignancy such as weight loss, anorexia, malaise and abdominal distension[50]. A palpable abdominal mass with or without a hepatic bruit may be apparent on physical examination[51]. Extrahepatic manifestations of HCC may result from distant metastases or paraneoplastic syndromes. HCC can metastasize to any organ system via the lymphatic or hematogenous routes with a potential to produce a wide range of symptoms. Commonly, HCC spreads to lung, bone and adjacent abdominal viscera[52]. Osteoclastic destruction from bone metastases often produces pain while pulmonary metastasis has been reported to cause dyspnea[53]. Paraneoplastic phenomena, though rare, can cause symptoms

relating to hypoglycemia, hypercalcemia, polycythemia, and feminization syndrome[54]. Porphyria cutanea tarda and pityriasis rotunda, the Leser-Trélat sign (sudden appearance of multiple seborrhoeic keratoses) and dermatomyositis have been reported as well[55]. Trevisani et al. demonstrated extrahepatic manifestations to be significantly more common in non-cirrhotic patients[56].

Symptomatic hepatocellular carcinoma has a grave prognosis although in industrialized countries the tumor generally runs more indolent with longer survival[57]. Rare instances of spontaneous tumor regression have been reported.

The main reasons for the poor outcome are the extent of tumor burden when diagnosed and the presence of coexisting cirrhosis and more aggressive behavior such as poorly differentiated histology, lack of fibrous capsule, large size (>5 cm in diameter), and elevated serum levels of alpha-fetoprotein (AFP)[58]. An infiltrative type pattern of HCC is described more in hepatitis B patients, considered to progress more rapidly to multinodular disease than the encapsulated expanding type frequently noted in hepatitis C[59].

Tumor growth rates vary even among patients of the same region, regardless of disease stage. Doubling times range from 1 to 19 months (mean 4-6)[60]. A recent study by Kubota et al. found mean doubling time of small HCC to be 93.5 days using serial multiphasic contrast enhanced computed tomography scanning[61]. Different rates provide a further challenge in a universally accepted screening interval protocols[62]. The serum AFP level generally does not necessarily correlate with growth rate although Ebara et al. showed that sudden acceleration can coincide with exponential growth on ultrasound imaging[58].

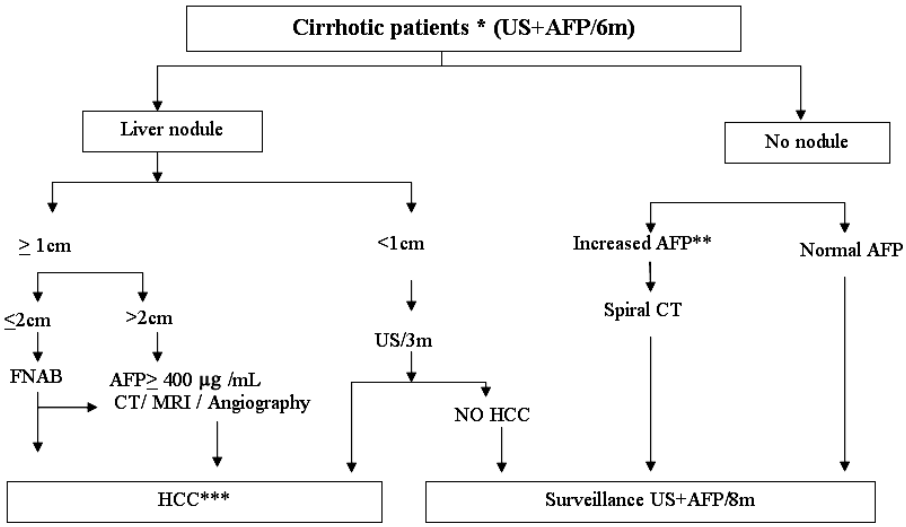
The development of liver cell dysplasia is a well-recognized premalignant finding in patients with cirrhosis of any etiology[63]. Efferent vessels of portal origin have been described to create arterioportal or arteriovenous (A-V) shunts which serve as low resistance path for tumor thrombi fragments to spread within the portal network[64]. In a large autopsy study from Sweden, 56% of HCC tumors had microvascular invasion, while other studies showed the invasion to be 92%[65]. Yuki et al. demonstrated less lymphogenous and hematogenous invasion in tumors smaller than 5 cm in diameter[66].

Diagnosis

The diagnosis of HCC can be difficult, and often requires serum markers, one or more imaging modalities, and histologic confirmation. HCC is frequently diagnosed late because of the absence of pathognomonic symptoms and the liver's large functional reserve[67]. As a result, many patients have untreatable disease when first diagnosed. The mean survival following diagnosis is approximately 6 to 20 months[68]. Large tumor size, vascular invasion, poor functional status, and nodal metastases are all associated with a poor outcome[69]. Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who develop decompensation such as ascites, encephalopathy, jaundice, or variceal bleeding. For non-cirrhotic patients, the diagnosis of HCC should be considered for any hepatic mass that is not clearly a hemangioma or focal nodular hyperplasia, especially if it is hypervascular. The approach to a liver nodule depends on its size. The European Association for the Study of the Liver (EASL) expert panel has proposed the following diagnostic strategy (Fig. 1)[70]. Nodules that are greater than 2 cm are more than 95% likely to be HCC[71]. In this situation, the diagnosis of HCC can be confirmed by two further imaging techniques (CT, MRI or angiography) showing arterial hypervascularity of the lesion. If the AFP concentration is greater than 400 m g/ml, then a single imaging technique showing hypervascularity will suffice. The lesion should undergo biopsy if diagnostic difficulties persist. A lesion between 1 cm and 2 cm, has a 75% likelihood of being an HCC[72]. Biopsy is required to confirm the diagnosis. Directed core biopsies are more useful than fine needle biopsy because of the increased amount of tissue obtained and the ability to obtain uninvolved hepatic parenchyma[73]. The potential risk of spreading tumor along the biopsy tract should always be considered while deciding, especially in patients in whom surgical resection or liver transplantation might be performed. Nodules less than 1 cm in size must be followed-up with imaging every 3 months because they are malignant in less than 50% of cases. If an elevated AFP is detected in the absence of a liver nodule on ultrasound, further radiological evaluation is required.

Other serum markers -Several other serum markers, used alone or in combination with the serum AFP have been evaluated for diagnosis or determining prognosis in HCC :

- Tumor-associated isoenzymes of gammaglutamyl transpeptidase[74]
- Urinary transforming growth factor-beta-1[75]
- Serum levels of circulating intercellular adhesion



*Available for curative treatments if diagnosed with HCC
**AFP levels to be defined.
***Pathological confirmation or non-invasive criteria (Table1)

Figure 1. European Association for the Study of the Liver (EASL) surveillance and recall strategy for HCC[70].

molecule-1[76]
- Serum alpha-L-fucosidase activity[77]

However, none of these diagnostic tests have demonstrated superior accuracy compared to the serum AFP.

Staging and Prediction of Survival

The life expectancy of patients with newly diagnosed HCC has classically been measured in weeks to months with a mortality/incidence ratio close to 1[78]. Llovet et al. prospectively followed patients with non-surgical HCC and showed overall 1, 2 and 3 year survivals of 54%, 40% and 28%, respectively[79]. Furthermore, since the prognosis of HCC is strongly linked to the degree of hepatic impairment, application of TNM cancer staging system has been limited as it strictly classifies tumors based on anatomical extent. The Child-Pugh classification, which was designed to predict survival in cirrhotic individuals, has been used successfully to evaluate survival in cirrhotics with HCC, but excluding tumor morphology reduces its usefulness. On the other hand, the first widely accepted staging system which incorporates tumor biology and hepatic function (Okuda et al.)[80] does not properly identify patients who may be amenable to certain therapeutic interventions, limiting its use in the clinical setting.

The Cancer of the Liver Italian Group Programme (CLIP) staging system and the Barcelona Clinic Liver Group (BCLG) staging system which effectively selects patients for aggressive treatments is quite useful in the clinical setting[81], but further prospective studies are required to set one staging system.

Screening for Hepatocellular carcinoma

Periodic surveillance of patients at risk for HCC, remains contentious[82]. The efficacy of screening for HCC in patients who are chronic HBV carriers has generally been disappointing[83]. Using AFP and ultrasound, is practiced widely and recommended by a consensus conference[84]. However, there are no data that surveillance improves overall survival. The importance of surveillance for HCC was highlighted in several articles recently. One study evaluated the cost-effectiveness of surveillance with ultrasound and AFP in patients with HCV-related cirrhosis using a Markov decision model[85]. The second article evaluated an Italian cohort of 312 patients with cirrhosis (254 HCV positive) who were followed for a mean of 93 months (range 14-94 months)[86]. A third study evaluated a total of 417 compensated Italian cirrhotics who were followed for a mean of 148 months (range, 1-213 months) with biannual ultrasound and AFP[87]. A fourth study evaluated the prognostic value of gene expression profile in 91 patients with HBV-related HCC[88]. To conclude, despite the relative lack of clear evidence, surveillance for HCC in patients

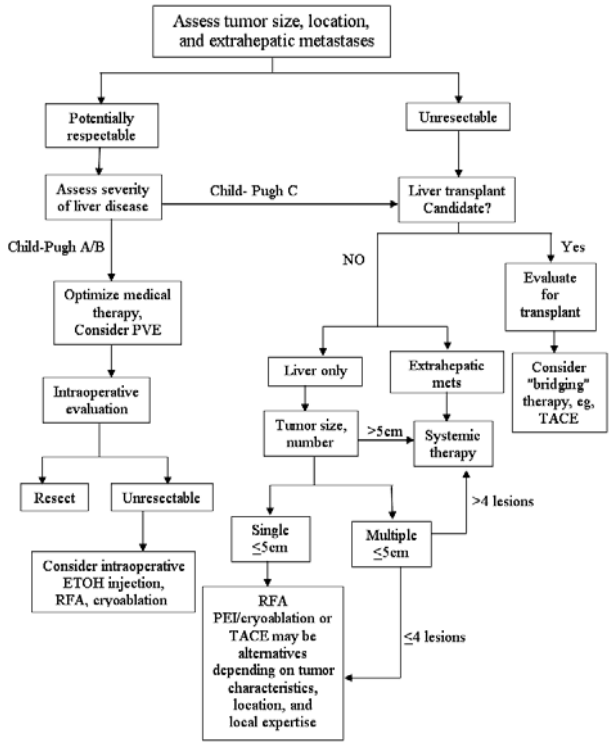
with cirrhosis has become accepted by most hepatologists[89].

What Surveillance Test Should Be Used and Who Should Be Surveyed?

HCC usually occurs with a background of cirrhosis and chronic liver dysfunction. It is now recognized that the degree of liver function impairment is a major determinant for treatment outcome[90]. Therefore, only patients with well-compensated cirrhosis (Child-Pugh stages A and B) receiving treatment should enter surveillance. Measurement of AFP and ultrasonography every six months is commonly performed in patients with compensated cirrhosis. The stratification of these patients at higher risk of HCC would improve the efficacy and cost-effectiveness of surveillance program. Elevated AFP is not specific for HCC, and can occur in flares of hepatitis and changes in HBV replication[91] not expressed in 10-20% of HCCs. A systematic review showed that AFP threshold of 400 μg/ml had 0% to 64% sensitivity, while AFP threshold of 10-19 μg/ml had 45-100% sensitivity[92]. The sensitivity of ultrasound for detecting HCC varied from 11% to 99%, with a specificity of 95-100%[93]. The combination of AFP and ultrasound improves the efficacy. Many serological and urinary markers have been investigated including soluble interleukin-2 (IL-2) receptor, des-gamma carboxyprothrombin (DCP), and urinary transforming growth factor-[beta]1 (TGF-[beta]1). None are yet in routine clinical use. Long-term active carriers of HBV in the absence of cirrhosis should be considered to be at risk of developing HCC and surveillance is suggested in patients older than 40 years. In contrast to HBV, HCC in HCV rarely occurs in those without cirrhosis[94]. There are no data indicating that abstinence reduces this risk. In hemochromatosis, the risk falls if iron levels are reduced[95]. Interestingly, there is a low risk of HCC in autoimmune cirrhosis. The reason remains unclear. Wilson's disease is also associated with a low incidence of HCC.

Treatment

Choosing the best treatment approach for patients should be based on an individual discussion by a multidisciplinary team, including surgeons, hepatologists, oncologists and interventional radiologists. Several surgical and non-surgical therapeutic modalities have been used for the treatment of HCC (Figure 2). Surgical resection, liver transplantation and local ablation therapies demonstrate potentially curative treatment options that should always be considered when the tumor is restricted to the liver. However, the therapy is not only determined by the extent of tumor but also by the underlying liver disease and general condition of the patient, as well[96].



PVE: Portal vein embolization
RFA: Radiofrequency ablation
PEI: Percutaneous ethanol injection
TACE: Transcatheter arterial chemoembolization

Figure 2. Treatment algorithm for hepatocellular carcinoma

Role of Surgical Resection

Liver resection should always be considered in the absence of extrahepatic disease. Improvements in diagnosis and surgical techniques, anesthesia and postoperative complications management have greatly reduced mortality and morbidity rates[97]. However, the morbidity rate after liver resection remains high and is primarily related to liver dysfunction and coexisting liver disease.

Partial hepatectomy- Curative partial hepatectomy is the optimal treatment for HCC. Patients ideal for resection have a solitary HCC confined to liver, which shows no invasion to hepatic vasculature, have well preserved hepatic function, and have no portal hypertension[98]. Unfortunately, most patients are not in this category. In high-incidence regions of the world,

only 10 to 15% of newly diagnosed patients are candidates for standard resection whereas in low incidence areas, between 15 and 30% of patients are potentially resectable[99]. Furthermore, only one-half of patients referred to surgeons actually have resectable tumors. The reasons are multifocal intrahepatic disease, extrahepatic extension, inadequate functional hepatic reserve, inability to obtain appropriate (1 cm) tumor-free margins, or involvement of the confluence of the portal or hepatic veins[100, 38].

Neoadjuvant strategies prior to liver resection- The remnant liver in patients with a normal liver should not be less than 25% while the volume in those with signs of significant liver disease must be higher than 40% to prevent postoperative liver insufficiency[101]. Despite potentially curative surgery, local recurrence develops in majority of patients, which may be related to preexisting clinically occult microscopic tumor foci. This suggests neoadjuvant therapies to eradicate the disease prior to definitive resection.

Several types of therapy have been evaluated, including TACE[102], systemic chemoimmunotherapy[103], hepatic artery infusion of radiolabeled lipiodol[104], and regional irradiation with or without chemotherapy or TACE[105]. Although many of these can decrease the size of previously unresectable tumors, they have not translated provided benefit in survival. The small size of many studies and the heterogeneity in the patients under study limits the results[106].

Adjuvant therapy- The high recurrence rate following curative resection for HCC has prompted a search for effective postoperative adjuvant therapy[106].

Liver transplantation- For patients with HCC and decompensated cirrhosis, liver transplantation remains the only curative option. Transplantation may be considered for patients who have a single lesion < or = 5 cm, up to three separate lesions, none larger than 3 cm, no evidence of gross vascular invasion, and no regional nodule or distant metastases. In non-cirrhotic patients, liver transplantation may be considered as an alternative only when resection is not feasible. In compensated cirrhosis, the best treatment remains controversial. Overall survival in carefully selected patients undergoing orthotopic liver transplantation (OLT) for HCC is similar or only slightly worse than survival for patients undergoing OLT for non-malignant causes[107].

Expanding the morphological criteria for liver transplantation- Yao et al. demonstrated that survival after liver transplantation was not affected by extending the criteria to solitary tumors £6.5 cm, or three or fewer nodules with the largest lesion £4.5 cm and a total tumors diameter £8 cm [108]. Tamura et al. reported 3 year survival rates of 62.5% and 0% for well-to-moderately and poorly differentiated HCC, respectively, for patients with large tumors (>5 cm)[109].

Bridging procedures to liver transplantation- Transarterial chemoembolization (TACE) and local ablative techniques may be beneficial prior to liver transplantation but large RCTs are needed to standardize the best treatment option[109]. In patients with compensated cirrhosis and where the waiting time is probably too long, elective surgical resection followed by liver transplantation can be applied. If patients are not suitable or if the waiting time is likely to be short, TACE or percutaneous ablation therapies should be considered[110]. Alternatives to 'conventional' cadaveric transplantation such as split liver and living donation may help in selected cases.

Living donor transplantation- In recent years, there has been a growing interest in adult-to-adult LDLT for the treatment of HCC to reduce the death rate during the waiting time for liver transplantation. Successful transplants have been described in case reports of carefully selected patients. Ethical issues are still debated. The advantages of LDLT are better overall status of the recipients, better liver function of the graft and shorter waiting time to liver transplantation.

Downstaging of large hepatocellular carcinoma- Patients with large HCC who respond to any of the adjuvant interventions could return to meet the accepted morphological criteria, and therefore, become suitable candidates for liver transplantation[111]. However, liver resection as a bridge to liver transplantation increases the risk of recurrence and impairs the patient's transplantability. In addition, pre-transplant TACE in patients with advanced-stage HCC failed to show any beneficial effect on survival. Further development in neoadjuvant and adjuvant therapies, based on the molecular biology of liver tumors, is needed to reduce the risk of recurrence and to improve long-term disease-free survival.

Non-surgical Therapies for Localized Hepatocellular Carcinoma

Ablation techniques- Tumor destruction techniques are accepted alternative therapies for unresectable hepatic malignancies. These techniques may be used either alone or in combination with liver resection when tumors are not amenable to

resection alone.

Percutaneous ethanol injection- Before the advent of RFA, PEI had been the most widely accepted minimally invasive method for treating HCC. This approach is recommended for small unresectable lesions and for patients who are at adverse risk for surgery due to co-morbidity. Although ethanol injection is easy to perform with low costs, several sessions must be performed and is associated with high recurrence rates. Injection of 95 percent ethanol into a tumor can induce tumor necrosis and shrinkage, microvasculature thrombosis and tissue ischemia and may also improve survival[112]. Some clinicians accept ethanol injection as an alternative to surgery for resectable disease.

Radiofrequency ablation- Local application of radiofrequency thermal energy to the lesion, in which a high frequency from the tip of an electrode into the tissue surrounding is a method of treating HCC. As the temperature within the tissue becomes elevated beyond 60°C, necrosis happens[113]. RFA can be performed by percutaneous, surgical, or laparoscopic approaches. No comparing article has been published yet. Although RFA has a lower recurrence rate than ethanol injection in cirrhotic patients with small HCC, no difference in survival was found. The role of ablation techniques in surgical treatment of HCC remains unclear.

Cryosurgery ablation- CryoA can be used alone or in combination with resection either as adjunct treatment to destroy unresectable tumor or to clear resection margins from infiltrating tumour (edge-cryosurgery). CryoA usually needs a laparotomy to be performed. CryoA can be complicated by postoperative hemorrhage and is also associated with a significant risk of recurrence for HCC.

Laser thermal ablation- Thermal ablation can also be accomplished with lasers[114]. In 74 patients with small primary HCC, a 5.0 watt laser was coupled to one to four fibers, directed percutaneously into the liver through a 21 gauge needle, and tumors treated for 6 to 12 minutes per session[114]. There were no major complications during 117 sessions.

Transarterial chemoembolization- TACE is injection of a chemotherapeutic agent, with or without lipiodol or a procoagulant material, into the hepatic artery. Lipiodol is an oily contrast agent that promotes intratumural retention of chemotherapy drugs. Stagnation of blood flow to tumor occurs and may result in greater antitumor efficacy than chemotherapy alone.

Radiotherapy- HCC is radiosensitive, but located in an extremely radiosensitive organ. Another drawback is difficulty in tumor localization.

Hormonal therapy- Several hormones have been studied in patients with advanced HCC including tamoxifen, megestrol, octreotide, and lanreotide.

Systemic chemotherapy- Chemotherapy has not been used routinely for patients with advanced HCC for some reasons: being refractory to chemotherapy, background of hepatic dysfunction and less efficacy in patients with significant cirrhosis. Despite these limitations, several single agents and chemotherapy combinations have been studied.

Prevention- Because HCV and HBV are the leading etiological agents for HCC, treating them may reduce HCC, but its true effectiveness is unknown. A recent study randomized 651 individuals with HBV who had cirrhosis or advanced fibrosis to receive lamivudine 100 mg per day (n = 436) while others received placebo (n = 215) (115). HCC occurred in 3.9% of those receiving lamivudine and 7.4% in the control group (P = 0.04, hazard ratio 0.49). Another study showed interferon alfa to reduce the risk of HCC (Relative Risk 0.084; 95% CI: 0.09-0.75). Prevention of HBV-related HCC is best accomplished by vaccination programs[116]. Further studies are needed to understand which patients with chronic HBV infection will benefit from antiviral therapy for the prevention of HCC.

Hepatocellular Carcinoma in Middle East and Iran

There are a few data available about HCC in Iran. In a recent study designed in southern Iran, the predominant cause for HCC was hepatitis B, and a progressive increase in HCC was observed as age increased[36]. The high relative frequency of liver carcinoma in Middle East is directly related to endemicity of hepatitis B and possibly hepatitis C infection[117] whose spread has been referred to as "new epidemic"[118]. Besides, Middle East has been reported as a region where majority (70%) of HCC cases present with intermediate or advanced stages of the disease[119].

According to author's personal experiences, it seems that prolonged life expectancy and HBV infection prevalence have resulted in several cases of HCC even with complications such as FHF and bone metastasis.

Conclusions

The incidence of HCC continues to rise. Even though patients with cirrhosis are at risk for developing HCC, it is now understood that viral

hepatitis infection, tobacco, alcohol, diabetes, obesity, familial and etiologic factors interact to increase the risk of HCC. Surveillance for HCC in patients with cirrhosis may lead to an improved survival. There is an urgent need to standardize the diagnostic criteria for HCC which may lead to better care for those affected with this tumor and for future research.

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