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Hepatocellular carcinoma: A comprehensive review of epidemiology, diagnosis, and treatment

Hepatocellular carcinoma: A comprehensive review

Mehmet Mutlu KİDİ[1]

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Abstract: Hepatocellular carcinoma (HCC) is a primary liver cancer predominantly arising in individuals with chronic liver diseases such as cirrhosis or chronic hepatitis B virus (HBV) infection. Accounting for approximately 75% of primary liver tumors, HCC's global epidemiology is significantly influenced by HBV and hepatitis C virus (HCV) infections, alcohol and tobacco use, metabolic syndrome, diabetes, obesity, and aflatoxin B1 exposure. Preventive measures, including HBV vaccination and direct-acting antivirals for HCV, have reduced incidence rates, particularly in younger populations. Early diagnosis through surveillance in high-risk groups is critical, employing imaging modalities like ultrasound, CT, and MRI, alongside biomarkers such as alpha-fetoprotein (AFP). Prognostic assessments utilize scores like Child-Pugh and ALBI. Treatment strategies for HCC are multifaceted, involving surgical resection, locoregional therapies (e.g., transarterial chemoembolization), and systemic therapies, including targeted and immunotherapies. Despite advancements, treatment efficacy remains a challenge, necessitating ongoing research into novel therapeutic approaches and predictive biomarkers to enhance personalized treatment and improve outcomes for HCC patients.

Keywords: Hepatocellular carcinoma, Chronic liver disease, Treatment options

Cukurova University Faculty of Medicine, Department of Medical Oncology, Adana, Türkiye
email: mehmetmutlu_01@hotmail.com
ORCID iD: 0000-0002-4750-720X

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Epidemiology of Hepatocellular Cancer

Hepatocellular carcinoma (HCC) is a type of liver cancer that usually occurs in individuals with chronic liver disease, especially those with cirrhosis or chronic hepatitis B virus infection. HCC accounts for around 75 percent of primary liver tumors, whereas cholangiocarcinoma makes up the majority of the remaining instances (1).

1. **Hepatitis B Virus (HBV):** HBV is a DNA virus that causes HCC by triggering chronic necroinflammatory disease in liver cells (2). It is responsible for 33% of HCC cases worldwide (3). The lifetime risk of developing HCC in HBV carriers is between 10-25%. Risk factors include male gender, advanced age, high viral load and HBV genotype (4-6).
2. **Hepatitis C Virus (HCV):** HCV, an RNA virus, causes tumor development through repetitive damage, regeneration and fibrosis. Chronic HCV infection increases the risk of HCC by 10-20 times (7) and is responsible for 10-25% of HCC cases worldwide. Risk factors include advanced age, male gender, HCV genotype and co-infections (8).
3. **Alcohol and Tobacco Use:** Chronic alcohol consumption (≥3 drinks/day) increases the risk of HCC by causing fatty liver, alcoholic hepatitis, fibrosis and cirrhosis. The annual incidence of HCC is 1-2% in patients who develop cirrhosis (9). Alcohol may have a synergistic effect with other risk factors (10). Tobacco use also increases the risk of HCC; the risk is 70% in current smokers compared to 40% in people who have quit smoking (11).
4. **Metabolic Syndrome, Diabetes and Obesity:** These factors increase the risk of HCC. Treatment of type 2 diabetes with metformin reduces the risk of HCC, while treatment with insulin and sulfanilurea increases the risk (12, 13).
5. **Non-Alcoholic Fatty Liver Disease (NAFLD):** NAFLD is one of the major reasons for the recent increase in the incidence of HCC(35). 20-30% of people with NAFLD develop non-alcoholic steatohepatitis (NASH) and 10-20% of these cases progress to cirrhosis(38,39). 70-80% of HCCs developing on the background of NAFLD develop on the background of cirrhosis and 20-30% develop without cirrhosis (14).
6. **Aflatoxin B1:** Aflatoxins produced by Aspergillus fungi, especially B1 (AFB1), increase the risk of HCC. According to a meta-analysis published in 2011, AFB1 alone increases the risk of HCC by 6 times, HBV alone by 11 times, and AFB1 and HBV together by 54 times (15).
7. **Other Factors:** Excessive iron buildup significantly elevates the risk of HCC. Notably, a higher ferritin concentration in the bloodstream is associated with a 49% increase in HCC risk. Factors such as hemachromatosis, alpha-1 antitrypsin deficiency, glycogen storage diseases, porphyrias, tyrosinemia and Wilson's disease also increase the risk of developing HCC (16).

Prevention and screening

Prevention of chronic liver disease is crucial in reducing hepatocellular carcinoma (HCC) risk. Effective strategies include hepatitis B virus (HBV) vaccination programs, which have significantly reduced HCC incidence in younger populations, and direct-acting antivirals for hepatitis C virus (HCV) elimination (17). For early detection, international guidelines recommend surveillance of high-risk populations using six-monthly abdominal ultrasound, with or without alpha-fetoprotein (AFP) testing. However, controversies persist regarding AFP's value due to varying sensitivity and specificity (18, 19).

In conclusion, while significant progress has been made in HCC prevention and early detection, continued research and public health efforts are necessary to address emerging risk factors and improve screening efficacy.

Diagnosis of hepatocellular cancer:

Early diagnosis of HCC is important. While the 5-year survival rate is 70% in patients diagnosed at an early stage and treated, this rate drops to 18% in

patients diagnosed late (20, 21). High-risk patients Cirrhosis, chronic hepatitis B and chronic hepatitis C patients with advanced fibrosis are high-risk patients in terms of HCC development. Regular surveillance is recommended in high-risk patients (22). Ultrasonography (USG) and alpha-fetoprotein (AFP) are generally used for surveillance. The Liver Imaging Reporting and Data System (LI-RADS) is used for the diagnosis of HCC. LI-RADS classifies lesions according to the likelihood of malignancy (23).

Three main imaging modalities are used in the diagnosis of HCC: Contrast-enhanced US (CEUS), triphasic contrast-enhanced CT, and dynamic contrast-enhanced MRI.Typical findings for HCC on imaging are: contrast staining in the arterial phase, contrast material excretion in the venous phase, and capsule visualization.Biopsy is recommended in lesions without typical HCC findings (LI-RADS-4) (22, 24-26).

Clinical and biochemical biomarkers in hepatocellular carcinoma:

Hepatocellular carcinoma prognosis depends on tumor characteristics and underlying liver disease. Higher serum AFP levels correlate with increased mortality and recurrence risk after resection or transplantation (27). Child-Pugh and ALBI scores evaluate liver function as prognostic factors, with post-hoc analyses confirming their role during systemic therapy (28). Molecular signatures classify HCC into proliferation and non-proliferation classes, but have limited clinical use. HCC typically has low-moderate tumor mutational burden. Liquid biopsy approaches show potential for non-invasive diagnosis and monitoring. Angiogenesis biomarkers are associated with poor prognosis but don't predict treatment response. Inflammatory markers may predict survival benefit with systemic therapy. These biomarkers collectively contribute to our understanding of HCC biology and patient outcomes, though their clinical application remains an area of ongoing research and development (29).

Treatment:

Guidelines at national and international levels provide a clear picture of the treatment options available for patients diagnosed with hepatocellular carcinoma. The Barcelona Clinic of Liver Cancer (BCLC) algorithm is the predominant staging system for hepatocellular carcinoma. It categorizes patients into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D) (30).

Surgery:

Treatment of patients with HCC requires a multidisciplinary approach. Surgical resection is one of the curative treatment modalities and can provide a 5-year survival of more than 50% in well-selected patients (31). The stage of the disease, patient performance, liver reserve and risk factors should be evaluated when selecting surgical candidates. Methods such as Child-Pugh classification, MELD score and ICG test are used to evaluate liver reserve (32). The presence of portal hypertension and high bilirubin levels are indicators of poor prognosis. Child A patients without portal hypertension and with normal bilirubin levels are the best candidates for surgery (33). Postoperative morbidity ranges between 33-55% and mortality between 1-24%. The main complications include liver failure, bile leakage and pleural effusion [30,39,48].Tumor size, number, vascular invasion, extrahepatic involvement and liver function are the main factors affecting postoperative results (34,35).

Locoregional Therapies in Hepatocellular Cancer:

Locoregional therapies, which are usually performed by interventional radiologists, are basically divided into two groups: transcatheter embolizations (transarterial embolization [TAE], transarterial chemoembolization [TCE]), which are characterized by the delivery of chemotherapeutics or radiotherapeutics to the targeted area via the arterial route, transarterial radioembolization [TARE]) and

local (usually percutaneous) ablations (percutaneous ethanol injection [PEE], radiofrequency ablation [RFA], microwave ablation [MDA], cryoablation [KA], laser-induced thermotherapy [LITT] and irreversible electroporation [GDE]) (36).

TAE: Provides occlusion of the arteries supplying the tumor with embolic agents. Provides tumor control in BCLC class B and C patients. It can also be used for downstaging before liver transplantation (37).

TAKE: It uses a combination of chemotherapeutic and embolic agents. It is the first-line treatment in unresectable HCC (BCLC stage B). It can also be used as a bridge to surgical methods (38).

TARE: Provides delivery of radioactive microspheres to the tumor. Recommended for BCLC stage 0 or A single HCC smaller than 8 cm. Protects quality of life in patients with portal vein invasion (39).

PEE: Cell death is achieved by injecting ethanol into the tumor. It shows similar efficacy to RFA in small HCCs (<1.5 cm) (40).

RFA: Creates coagulation necrosis in tumor tissue with high frequency current. It is indicated in early stage HCC (≤3 cm, ≤3 nodules) (41).

MDA: Provides cell death by heating the tissue with microwave energy. It has similar indications to RFA, but may be more effective in larger tumors (3-5 cm) (42).

KA: Cell death is achieved by applying extremely low temperatures. It can be used safely in subcapsular high-risk HCCs Other methods such as LITT and GDE are also available, but their role in HCC treatment has not yet been fully determined (43, 44). These locoregional therapies have an important role in the management of HCC and are expected to be used more frequently as monotherapy or combination therapies in the future.

Targeted Therapies and Immunotherapy in Hepatocellular Cancer:

Surgical resection is the mainstay of treatment in HCC, but most patients are not suitable for surgery. There have been many developments in the treatment of patients with HCC (figure-1) (29). Until 2008, there was no effective treatment for advanced HCC (45, 46). Sorafenib became the standard of care in first-line treatment, showing a survival benefit in the SHARP and Asia-Pacific trials (47, 48). Lenvatinib was also an alternative to sorafenib in subsequent studies (49). In second-line treatments, regorafenib (50), cabozantinib (51) and ramucirumab (52) were found to be effective. In the IMbrave150 study, the combination of atezolizumab plus bevacizumab was superior to sorafenib in first-line treatment in Child-Pugh A patients (53). In the Himalaya study, durvalumab plus tremelimumab showed an overall survival benefit over sorafenib (54). Other targeted therapies (linifanib, tivantinib, axitinib) have been evaluated in various studies but have not entered standard treatment. In the Imbrave 050 study, atezolizumab plus bevacizumab showed a recurrence-free survival benefit in adjuvant treatment in patients with high-risk HCC (55). HCC treatment is complex and requires a multidisciplinary approach. Patients should be carefully evaluated for available treatment options.

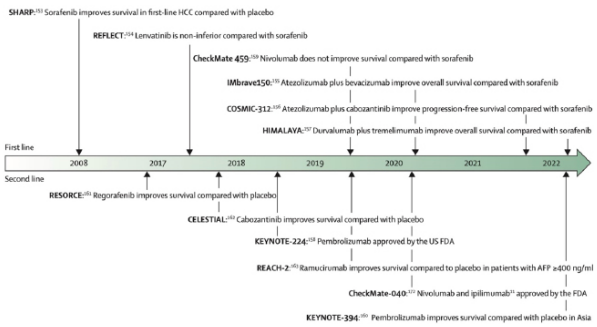

Figure 1: Milestones in the development of systemic therapy for HCC AFP=alpha-fetoprotein. FDA=Food and Drug Administration. HCC=hepatocellular carcinoma.

Conclusion:

The epidemiology of liver cancer is changing and increasingly non-viral causes are becoming dominant. Innovative approaches and preventive strategies are needed to address the increasing incidence of hepatocellular carcinoma in patients with fatty liver disease. Despite significant advances in locoregional and systemic therapy, the majority

of patients do not respond and ultimately treatment failure is likely. Consequently, there is still a need for more effective systemic therapies as well as predictive biomarkers that enable personalized and cost-effective treatment stratification. The dynamic interaction between locoregional and systemic therapy is also under investigation. Despite being one of the cancers with the worst prognosis, the coming years will be dedicated to studies that will contribute to survival leading to better outcomes.

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