PRIMEVIEW

HEPATOCELLULAR CARCINOMA

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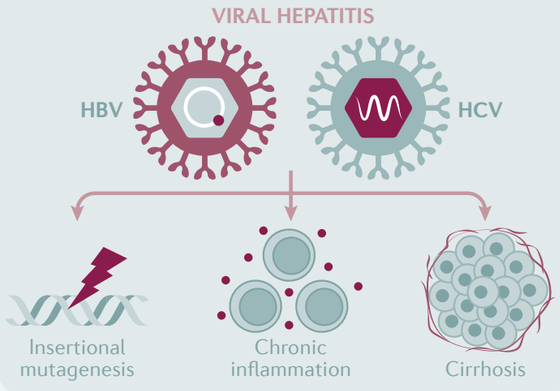
Hepatocellular carcimoma (HCC) accounts for 85–90% of all primary liver cancers. Each year, 850,000 new cases of liver cancer are reported, making it the second leading cause of cancer-related deaths worldwide.

MECHANISMS

HCC can arise in mature hepatocytes or their progenitor cells. The molecular pathogenesis of HCC has been well-studied, and tumours typically contain ~40 genetic alterations, of which only a few are considered driver mutations. Processes that commonly contribute to HCC initiation and development include re-expression of fetal genes, changes in cell cycle control, dysregulation of protein folding, constitutive activation of the oxidative stress pathway and the activation of the WNT–β-catenin, RAS–RAF–MAPK and PI3K–AKT–mTOR signalling pathways. In addition, enhanced telomere maintenance through telomerase activation contributes to uncontrolled hepatocyte proliferation by inhibiting cellular senescence. An altered microenvironment is fundamental to liver carcinogenesis, and HCC usually develops on a background of liver damage (most commonly cirrhosis). Indeed, HCC can be considered a classic inflammation-associated cancer, with most cases linked to prolonged hepatitis due to viral infection or excessive alcohol intake.

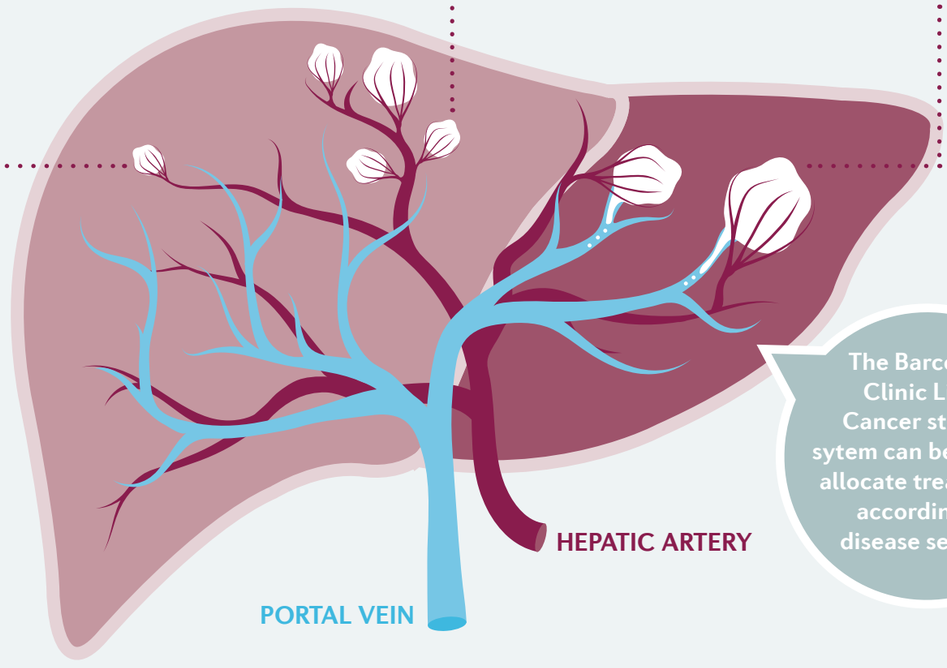


MANAGEMENT

Early-stage HCC is characterized by one or a few small nodules without portal vein invasion and by preserved liver function. Treatment involves liver resection, transplantation or local ablation.

Intermediate-stage HCC involves multiple nodules, preserved liver function and no portal vein invasion or symptoms. Treatment is commonly transcatheter arterial chemoembolization, which delivers chemotherapy directly to the tumour using drug-eluting beads.

Hallmarks of advanced disease are portal vein invasion, metastases and/or symptoms. Treatment with the multikinase inhibitor sorafenib increases survival by approximately 3 months.



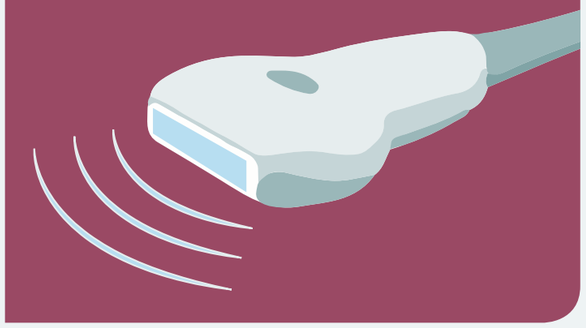
The Barcelona Clinic Liver Cancer staging sytem can be used to allocate treatments according to disease severity

PREVENTION

The risk factors for developing HCC include cirrhosis, alcohol abuse, infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), and ingestion of the fungal metabolite aflatoxin B1, which is associated with mutations in the tumour supressor gene *TP53*. In addition, metabolic syndrome has been linked to HCC that develops on a non-cirrhotic background. Prevention or treatment of hepatitis B using vaccines or antivirals has reduced the incidence of HCC. With the advent of improved drugs against HCV, it is hoped that similar improvements will be made in populations with high rates of hepatitis C.

DIAGNOSIS

HCC can be diagnosed using either invasive (biopsy) or non-invasive (radiological) methods. Patients with cirrhosis can be diagnosed radiologically (usually with CT and/or MRI) alone, whereas those who do not have cirrhosis or whose imaging results are inconclusive require a biopsy. HCC symptoms usually do not occur until the disease is advanced, by which time potentially curative treatments are no longer an option. As such, screening of at-risk populations using ultrasonography is important for early diagnosis.



OUTLOOK

Despite detailed knowledge of driver genes in HCC, few of these have proven to be druggable targets. Consequently, only one systemic treatment (sorafenib) is currently available for treating this cancer, which improves survival by a few months. Moreover, first-line treatment for early-stage disease remains surgical removal of the affected liver, and no adjuvant therapy has been shown to be effective in this setting. Future progress in these areas will probably involve improved clinical trial design and greater understanding of tumour heterogeneity, which together will enable targeting of treatments to specific subsets of patients.

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