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# ADVANCEMENTS IN DIAGNOSIS AND TREATMENT OF LIVER CANCER: A COMPREHENSIVE REVIEW

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## ABSTRACT

Liver cancer, primarily hepatocellular carcinoma (HCC), represents a significant global health burden with high morbidity and mortality rates. This abstract provides a comprehensive overview of liver cancer and its management, focusing on key aspects such as etiology, diagnosis, treatment modalities, and prognosis. Chronic viral hepatitis B and C infections, alcoholic liver disease, non-alcoholic fatty liver disease, and aflatoxin exposure are major risk factors for developing HCC. Understanding the underlying etiology is crucial for both prevention and management strategies.

Diagnosis of liver cancer involves a combination of imaging modalities such as ultrasound, CT scans, MRI, and biopsy. Early detection through surveillance programs targeting high-risk populations can significantly improve treatment outcomes.

Treatment for liver cancer includes both surgical therapy as well as pharmacological therapy. Surgical therapy like surgical resection, liver transplantation, locoregional therapies (radiofrequency ablation, transarterial chemoembolization), systemic therapies (chemotherapy, targeted therapy, immunotherapy), and palliative care where as pharmacological therapy include Sorafenib, Lenvatinib, Regorafenib, Pembrolizumab, Doxorubicin, Cabozantinib, Combination therapy: Atezolizumab & Bevacizumab. The selection of treatment depends on the stage of the cancer, the patient's overall health, and the underlying liver function.

The prognosis of liver cancer varies widely based on the stage at diagnosis and the effectiveness of treatment. While early-stage HCC is potentially curable with surgical resection or transplantation, advanced-stage disease has a poor prognosis.

A multidisciplinary approach involving hepatologists, oncologists, surgeons, radiologists, and supportive care teams is essential for optimal management and improved patient outcomes. Further research and advancements in treatment modalities are needed to address the challenges posed by liver cancer globally.

**Keywords:** Liver cancer, Hepatitis B and C infections, Biopsy, Surgical therapy, Pharmacological therapy.

## INTRODUCTION

Hepatocellular carcinoma stands as the predominant type of primary liver cancer in the United States, accounting for three-quarters of all cases of primary and secondary liver cancer.[1] The incidence of both new diagnoses and deaths is on the rise, mirroring the geographical prevalence of underlying chronic liver disease or cirrhosis as the etiological factor.[2]

Numerous cellular mechanisms contribute to the development of liver cancer, including dysregulation of the cell cycle and apoptosis, as well as molecular pathways associated with inflammation and fibrogenesis. These mechanisms present important targets for the development of novel drug therapies. Currently, sorafenib, a multikinase inhibitor approved for liver cancer treatment, serves as the first-line therapy for advanced hepatocellular carcinoma (HCC). While sorafenib has shown significant improvement in overall survival, it is unable to fully counteract disease progression due to the development of resistance to anti proliferative therapies. Hence, there is an urgent need to develop new molecules with both pharmacological efficacy and safety.

Animal models have played a pivotal role in biomedical research, particularly in studying the pathogenesis of various liver diseases, including cancer, and in evaluating the effectiveness and safety of new drugs. There exists a wide array of experimental liver cancer models, each with its own limitations and applications. The choice of model depends on the specific research goals. An ideal animal model should closely mimic the natural history, pathophysiology, and biochemistry of human liver cancer.

This study aims to provide a comprehensive review of approved drugs for liver cancer treatment, outlining their advantages and limitations, the cellular signaling pathways involved in cancer pathogenesis, and the primary cellular targets of these therapies. Additionally, we will review the most commonly used experimental models for studying liver cancer, delving into their methodological foundations, similarities to human disease, and key characteristics. [3]

Chronic liver disease (CLD) is characterized by a progressive decline in liver function lasting more than six months, affecting processes such as the synthesis of clotting factors and other proteins, detoxification of metabolic byproducts, and bile excretion. It involves a continuous cycle of inflammation, tissue damage, and

regeneration within the liver parenchyma, ultimately leading to fibrosis and cirrhosis. The causes of CLD are diverse and include prolonged exposure to toxins, chronic alcohol abuse, infections, autoimmune disorders, and genetic or metabolic conditions. Cirrhosis represents the advanced stage of CLD, marked by significant architectural disruption of the liver, the formation of nodules throughout the tissue, changes in blood vessel patterns, new blood vessel formation, and the accumulation of extracellular matrix. The cellular processes underlying fibrosis and cirrhosis involve the activation of stellate cells and fibroblasts, leading to fibrosis, while the regeneration of liver tissue relies on hepatic stem cells. CLD is a prevalent clinical condition, and research efforts focus on understanding its common causes, clinical symptoms, and effective management strategies.[4]

The liver is a frequent destination for cancer metastasis, with approximately 25% of metastatic cases occurring there. Various primary tumors can give rise to liver metastases, but colorectal adenocarcinomas are particularly noteworthy due to their prevalence and extensive research focus. The liver's dual blood supply not only makes it vulnerable to metastasis from gastrointestinal cancers but also facilitates access for interventional therapies. Treatment approaches for liver metastases are rapidly advancing globally, with a growing emphasis on interdisciplinary collaboration to improve patient outcomes.[5]

**ETIOLOGY**

Metastatic tumors in the liver are more prevalent than primary hepatocellular or biliary tumors, with adenocarcinomas being the most common subtype. However, other less common subtypes, such as squamous cell carcinoma, neuroendocrine carcinoma, lymphoma, sarcoma, and melanoma, also exist. Most of the literature on liver metastases focuses on the management of colorectal adenocarcinoma, which is the third most common primary malignancy globally. It's noteworthy that nearly 70% to 80% of cases with metastatic disease are localized to the liver.[6, 7]

Hepatocellular carcinoma typically arises from chronic liver disease caused by various risk factors. Notably, chronic hepatitis B and C virus (HBV and HCV) infections are strongly associated with its development. Other factors, such as coinfection with hepatitis D (HDV), alcohol consumption, cigarette smoking, and chronic hepatitis from different causes (e.g., hemochromatosis or alpha-1 antitrypsin deficiency), as well as cryptogenic cirrhosis, also elevate the risk of hepatocellular carcinoma.[8, 9] Environmental exposures, including aflatoxin, contaminated water containing blue-green algal toxin, and betel nut, are additional contributors. Ethanol abuse and metabolic syndrome are linked to liver cancer due to persistent liver damage leading to conditions like steatosis, steatohepatitis, cirrhosis, and ultimately hepatocellular carcinoma. Conversely, statins and coffee consumption have been associated with reduced risk. Managing chronic hepatitis, metabolic syndrome, and iron levels, along with alcohol cessation to prevent cirrhosis, can reduce the risk of developing hepatocellular carcinoma. Additionally, HBV vaccination and HCV screening have the potential to decrease its incidence globally. Surveillance guidelines for hepatocellular carcinoma are recommended for high-risk populations and typically include regular ultrasonography (US), with or without alpha-fetoprotein (AFP), every 6 to 12 months, although specific recommendations may vary among different societies and institutions.[1]

**EPIDEMIOLOGY**

Hepatocellular carcinoma ranks as the fifth most prevalent cancer and is the second leading cause of cancer-related deaths globally. The majority of cases stem from chronic hepatitis B and C viral infections. In the United States, data from the Surveillance, Epidemiology, and End Results (SEER) Database indicate an annual increase in incidence of 3.1%. Men exhibit an incidence rate of 11.5 per 100,000, while women have a rate of 3.9. Similarly, death rates from hepatocellular carcinoma have risen by 2.8% annually for males and 3.4% for females. Hepatocellular carcinoma typically occurs in older individuals with long standing chronic liver disease. The regional and racial/ethnic distribution of hepatocellular carcinoma correlates with specific exposure risk factors. Worldwide, hepatitis B virus (HBV) is more prevalent, whereas in the United States, hepatitis C virus (HCV) accounts for 30% of cases. Notably, HCV has a fivefold higher prevalence among individuals born in the United States between 1945 and 1965, contributing to the rise in liver cancer-related deaths within this demographic.[1] Around 20% to 25% of individuals diagnosed with colorectal cancer will develop liver metastases, with 15% to 25% of these cases being synchronous.[10] The most frequent origins of these metastases are colorectal primaries, followed by pancreatic and breast cancers. Among women under 50 years old, breast cancer is a more common source of metastatic liver disease. In contrast, in individuals over 70 years old, gastrointestinal sources predominate. Carcinomas account for 92% of metastatic hepatic lesions, with adenocarcinomas comprising 75% of these carcinomas. Overall, histologically confirmed hepatic metastases are more prevalent in males than females, and the majority of affected patients are over 50 years old.[11]

While cholangiocarcinoma comprises only 3% of all gastrointestinal malignancies, the United States Cancer Statistics estimate a staggering 52,450 new cases and 32,750 expected deaths when including cancers of the liver, intrahepatic bile duct, gallbladder, and other biliary sites. Collectively, these cancers account for 6% of all new cancer diagnoses, ranking as the fifth deadliest cancer. When categorized by anatomical site, intrahepatic, peripheral, and distal biliary tract cancers represent 5% to 10%, 50% to 60%, and 20% to 30% of cases, respectively. The incidence of cholangiocarcinoma generally rises with age, except in cases associated with primary sclerosing cholangitis, which tends to affect younger patients. Furthermore, cholangiocarcinoma is slightly more prevalent in males, except for gallbladder cancer, which shows a female predominance.[12]

Outside the United States, specific populations in regions like South America, India, Pakistan, Japan, and Korea have a high incidence of gallbladder cancer, largely due to the prevalence of gallstones and chronic gallbladder infections in these areas. In 2017, the American Cancer Society estimated 11,740 new cases of gallbladder cancer in the USA, resulting in 3,830 deaths, with a higher occurrence among females. While the overall incidence of gallbladder cancer has decreased in individuals over 50 years old, it has increased among younger people. Gallbladder cancer is more prevalent in White individuals, Southwestern Native Americans, and Mexican Americans, but less common in African Americans.[13]

## PATHOPHYSIOLOGY

While genetic sequencing studies have identified numerous genes associated with hepatocellular carcinoma, many of the initial genetic triggers for this cancer remain unknown. Genomic instability, including chromosomal or single nucleotide polymorphism, is thought to drive tumorigenesis in liver cancer. Several recurrently mutated genes (such as TERT promoter, TP53,

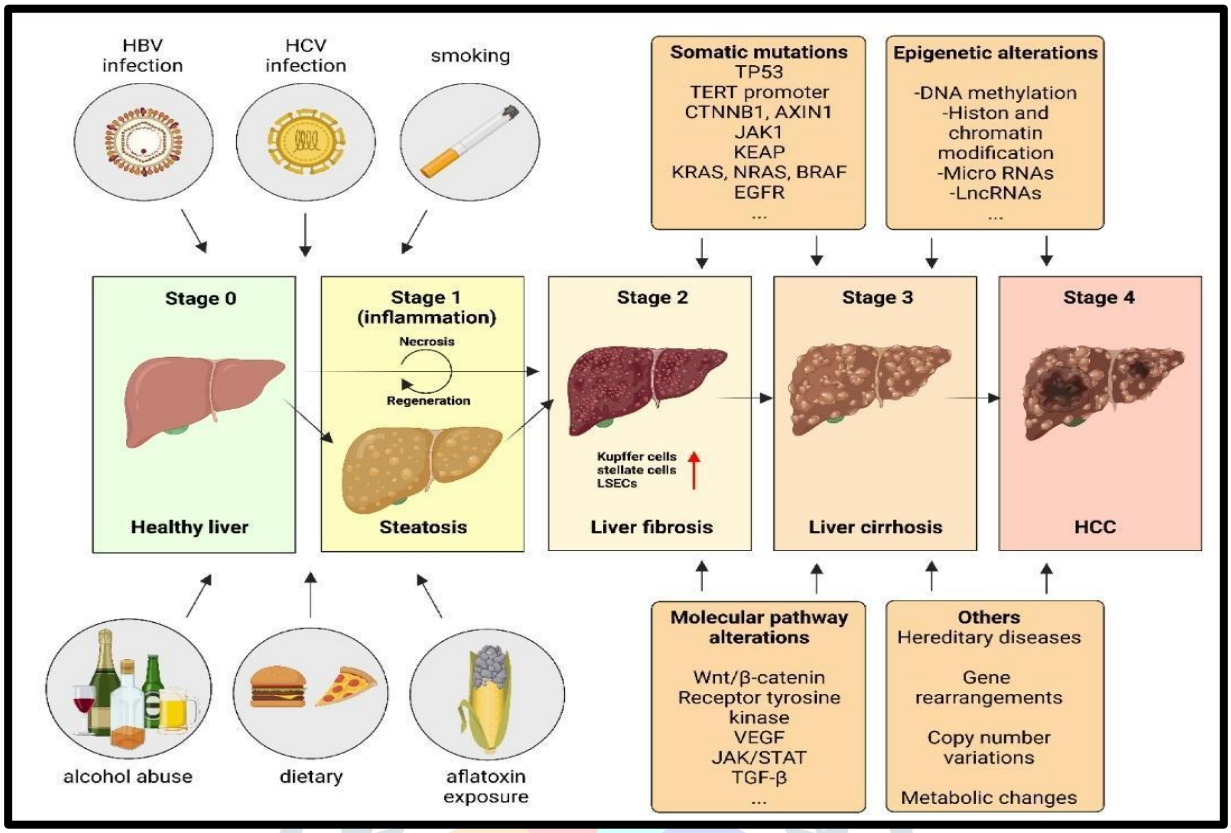


Fig.1 Adopted from Arias, Martínez et. al, 2018

CTNNB1, ARID1A, FGF) and their implicated signaling pathways (JAK/STAT, Wnt/β-catenin, PI3K-AKT-mTOR) have been identified as major drivers of hepatocellular carcinoma development.

However, the genomic heterogeneity of hepatocellular carcinoma has hindered the emergence of potential drivers or targeted therapies. Classical prognostic biomarkers for hepatocellular carcinoma include the expression of the Ki-67 protein and mutations in the TP53 gene, both of which have been consistently linked to poor prognosis.

A crucial pathological consideration is distinguishing the fibro lamellar variant, which typically presents with tumor encapsulation in younger individuals. These tumors are often more amenable to resection, less commonly associated with viral infections or cirrhosis, exhibit normal AFP levels, and generally have a better prognosis. In contrast, traditional hepatocellular cancer typically presents in older individuals with chronic disease, with less than 25% of cases being resect able.[1]

While hepatocytes receive their blood supply from the portal vein, the cholangiocytes of the biliary system are supplied by the hepatic artery. It is believed that metastatic liver tumors obtain their blood supply from the hepatic artery. This unique vascular arrangement creates an opportunity for liver-directed therapies that target tumor cells while sparing healthy hepatocytes. Furthermore, the liver has the remarkable ability to hypertrophy,

compensating for lost function. If the vascular supply and biliary drainage remain intact, up to 80% of the liver can be surgically removed. The remaining liver tissue can then undergo hypertrophy, restoring full hepatic function within weeks. This capacity for regeneration enables more aggressive surgical resections in cases of multiple metastases.[3]

Hepatic angiosarcoma is mainly composed of vessels or lymphatic endothelial cells, resulting in a tumor with abundant vasculature. Spindle or pleomorphic cells line or infiltrate the lumina of preexisting vascular spaces like sinusoids and terminal hepatic venules, leading to hepatocyte atrophy and the development of vascular channels. In some cases, it can form solid masses. Hepatic angiosarcoma should be considered in cases where a bleeding hepatic mass is encountered. Metastasis commonly occurs in the lungs and hilar lymph nodes but can also affect the spleen and bones.[14, 15]

## HISTOPATHOLOGY

Histologically, the malignancy comprises spindle-shaped and polyhedral cells, exhibiting various patterns of vascular channels. Solid areas resembling fibrosarcoma and polynuclear giant cells may also be present. Tumor invasion of portal and hepatic vein branches is common. Additionally, areas of infarction, atrophy, and fibrosis are frequently observed as parenchymal loss leads to scarring and occlusion of pre-existing vessels. Immunohistochemical markers such as CD31, CD34, Ulex europaeus agglutinin I, and factor VIII-related antigen can assist in diagnosis. Due to the highly vascular nature of the tumor, liver biopsy carries a significant risk of morbidity and mortality.[16, 17]

While most hepatocellular carcinomas (HCCs) exhibit characteristic imaging features, approximately 10% of tumors (and up to 30% of tumors measuring 1–2 cm in diameter) may present atypically, lacking these hallmark characteristics. The International Consensus Group for Hepatocellular Neoplasia has identified major histological features of HCC, including stromal invasion, increased cell density, intratumoral portal tracts, unpaired arteries, a pseudoglandular pattern, and diffuse fatty changes. When there is clinical suspicion of HCC but the imaging appearance is atypical, a biopsy or a second contrast-enhanced study is recommended. The sensitivity of a biopsy is around 70%, and it is even lower for tumors smaller than 2 cm due to the potential for missed lesions and the challenge of distinguishing well-differentiated HCC from dysplastic nodules. Some patients may require multiple biopsies for a definitive diagnosis, and those with a negative biopsy should continue to be monitored with serial contrast-enhanced imaging. If a lesion enlarges but maintains its atypical appearance for HCC, a repeat biopsy should be considered.[18]

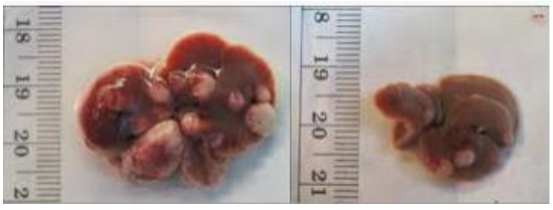

Figure 2 adopted from medical express

## PATIENT HISTORY

While most patients with hepatocellular carcinoma (HCC) are initially asymptomatic, they often develop related symptoms due to underlying chronic liver disease. These symptoms may include upper abdominal discomfort and distention, weight loss, fever, poor appetite, early satiety, and diarrhea. Any acute liver decompensating characterized by the onset of ascites, encephalopathy, jaundice, or hematemesis should raise suspicion for HCC. In rare cases, patients with HCC may present with unusual symptoms associated with a paraneoplastic syndrome, such as hypoglycemia, erythrocytosis, hypercalcemia, or severe watery diarrhea.

During a physical examination, signs of chronic liver disease or cirrhosis may be observed, including hepatomegaly, splenomegaly, ascites, jaundice, or engorgement of collateral veins (such as the caput medusae, also known as the palm tree sign, which refers to dilated superficial epigastric veins and can be a sign of cirrhosis).[1]

Hepatic angiosarcoma typically presents with nonspecific symptoms such as right upper quadrant abdominal pain, weight loss, distension, jaundice, and fatigue. Upon physical examination, jaundice, ascites, and hepatomegaly may be observed. In some cases, patients with hepatic angiosarcoma may be asymptomatic and the condition is discovered incidentally during imaging studies.[2]

## EVALUATION

Patients suspected or confirmed to have hepatocellular carcinoma (HCC) typically undergo a comprehensive laboratory workup to assess the severity of liver disease. This evaluation includes testing for hypoalbuminemia, hyperbilirubinemia, and hypoprothrombinemia, along with clinical assessments for ascites and encephalopathy, which are used to categorize patients according to the Child-Pugh assessment scale. The American Association for the Study of Liver Disease (AASLD) has established diagnostic algorithms for solid liver lesions based on their size. Surveillance using ultrasound (US) often identifies high-risk patients and is further characterized by dynamic contrast-enhanced magnetic resonance imaging (MRI) or four-phase computed tomography (CT). Negative findings on MRI are typically followed by serial ultrasounds every three months. Biopsy is not required for patients with an increased risk of HCC if MRI or CT findings are diagnostic. Alpha-fetoprotein (AFP) levels, especially above 500 mcg/L, raise suspicion for HCC. Other tumor markers such as Lens culinaris agglutinin-reactive AFP (AFP-L3) and Des-gamma-carboxy prothrombin (DCP) may be used in combination with AFP, but they can miss HCC in a small percentage of cases. If the diagnosis remains uncertain, a biopsy may be necessary. Staging imaging with CT is required to evaluate for metastasis in diagnosed cases of HCC.

Several prognostic staging systems exist for liver cancer, with the Barcelona Clinic Liver Cancer system being one of the most commonly used. This system divides HCC into four stages (A to D) based on performance status, constitutional symptoms, and the Okuda criteria. The Okuda criteria include tumor size, presence of ascites, albumin and bilirubin levels, with each factor correlating with different stages and median overall survival. Treatment strategies vary based on the stage, ranging from radical therapies for early-stage patients to systemic palliative therapy for terminal-stage disease. Very early and early stages may be considered for resection or liver

transplant, with a curative rate of 30% and a 5-year survival rate of 40% to 70%. After complete resection, the TNM staging system can further benefit from prognostic survival evaluation using the Cancer of the Liver Italian Program (CLIP) score, which takes into account various factors to predict survival outcomes.[1]

High-quality imaging plays a crucial role in evaluating suspected liver metastases, aiding in both diagnosis confirmation and identification of the primary disease. Common imaging modalities include triple-phase CT and MRI scans. Triple-phase CT scans consist of non-contrast, arterial, and venous phases. In these scans, liver metastases and primary liver tumors typically exhibit the strongest attenuation in the arterial phase and are hypo attenuating in non-contrast studies. CT imaging is advantageous for tumor localization, aiding in the planning of liver-directed therapies. It assesses metastatic tumor size, morphology, degree of liver disease, and the predicted future liver remnant. Identifying the potential resectability of liver tumors is critical, as lesions near major vascular structures may be inoperable. MRI is another useful modality, especially when characterizing liver lesions is challenging. Liver metastases appear hypo-intense on T1-weighted imaging and hyperintense on T2-weighted imaging. Gadolinium contrast-enhanced T1-weighted images can show total or rim enhancement, depending on the size of the lesion.

Additional contrast agents such as gadoxetate disodium (Eovist) and gadobenate dimeglumine (Multihance) are designed to enhance MRI sensitivity. However, several benign conditions can mimic liver metastases on imaging. Fluorodeoxyglucose-18 (FDG) PET/CT can aid in detecting hepatic metastases and identifying primary and extrahepatic metastases. However, it has poorer anatomical resolution than CT and is insensitive in detecting lesions smaller than 1 cm. PET/CT has been particularly useful in detecting metastatic neuroendocrine carcinomas, such as with gallium-68 DOTATATE PET imaging. Ultrasonography, while less sensitive, can also be used in certain cases. However, it is not routinely used in diagnostic workups. The workup for suspected liver metastases should also include basic liver function tests, a complete blood count, esophagogastroduodenoscopy (EGD), and colonoscopy.[19]

**TREATMENT AND MANAGEMENT**

In most patients, the curative approach for hepatocellular carcinoma (HCC) is surgery, either resection or transplantation. Unfortunately, the majority of patients (about 70%) are not suitable candidates for surgery. Resectable candidates typically have early-stage HCC (less than stage IIIB) and Child-Pugh stage- A liver disease. Resection can result in a relapse-free survival of 40% and a 5-year overall survival (OS) of 90%, but it carries a mortality rate of 5% to 10% in patients with cirrhosis. Transplant candidates are assessed based on the Milan criteria (single tumor smaller than 5 cm or two to three tumors, none exceeding 3 cm, with no vascular invasion or extrahepatic spread) and a high MELD-Na score to prioritize organ allocation according to urgency. Liver transplantation can achieve a relapse-free survival of 80% and a 4-year OS of 75%. However, the waiting time for a transplant can be prolonged, leading to the use of bridging therapies such as chemoembolization, radiofrequency ablation, or partial hepatectomy. Neoadjuvant therapy is not standard, and adjuvant therapy with sorafenib in the Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial

did not show benefit. Patients should be considered for enrollment in clinical trials when available. If chronic viral hepatitis is present, treatment should be part of the multidisciplinary discussion.

For non-surgical candidates, several local treatment options are available. Radiofrequency ablation can achieve complete remission in 80% of cases for tumors smaller than 3 cm and 50% of tumors larger than 3 cm. It is suitable for tumors smaller than 4 cm and Child-Pugh A/B liver disease severity. Transarterial chemoembolization is often used for large or multifocal disease not suitable for local ablation, offering a survival benefit in selected patients with smaller tumors and low CLIP1 scores. Absolute contraindications for transarterial chemoembolization include portal vein thrombosis, encephalopathy, and biliary obstruction. Combining transarterial chemoembolization with radiofrequency ablation may yield better outcomes, with a five-year OS of 44% compared to 20% with transarterial chemoembolization alone or 28% with radiofrequency ablation alone. Percutaneous ethanol injection is considered for patients with poor Child-Pugh B/C liver stage. Other thermal ablation therapies include cryoablation or microwave ablation. Various radiation therapy modalities are available, but there are no clear guidelines or consensus on their use.[1]

Primary hepatic angiosarcoma is characterized by its aggressive clinical course and poor prognosis in inoperable cases. Most patients succumb to the disease within six months of diagnosis, and even with treatment, the survival rate beyond two years is only around 3%. Complete hepatic resection or radical tumor resection is the most effective treatment for single lesions, but it may not always be feasible in cases of metastatic disease. Liver transplant is generally not recommended due to the high recurrence rate and rapid disease progression, resulting in a survival period of less than seven months post-transplant. Currently, there is no established effective chemotherapy for hepatic angiosarcoma, although some reports have shown potential benefits from using 5-FU-carboplatin with doxorubicin or ifosfamide in unresectable cases with distant metastasis. Studies with large patient populations have demonstrated a significant survival advantage for stage I hepatic angiosarcoma patients who underwent surgical treatment compared to those who received non-operative treatment. Transcatheter arterial chemoembolization (TACE) can be employed for palliative purposes or to control bleeding. However, there are no established guidelines for the optimal treatment modalities, including surgery, chemotherapy, and radiation, due to varying study outcomes.[20, 21]

## DRUGS USED IN THE THERAPY

Certainly, here are some medicines commonly used in the treatment of liver cancer and their actions illustrated in Table no. 01. These medicines are used in the treatment of liver cancer to either directly target cancer cells or to modulate the tumor microenvironment to inhibit tumor growth and spread. The choice of medication depends on various factors including the stage of the cancer, the patient's overall health, and the specific characteristics of the tumor. [22]

**Drugs and their Mechanism of action**

| S. No. | Drugs | Mechanism |
|---|---|---|
| 1. | Sorafenib (Nexavar) | It is a multi-kinase inhibitor that works by targeting multiple proteins involved in tumor cell proliferation and angiogenesis (the formation of new blood vessels that supply the tumor). It inhibits the Raf/MEK/ERK signaling pathway, which is important for cancer cell survival and growth. Sorafenib also inhibits the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), which are involved in angiogenesis. |
| 2. | Lenvatinib (Lenvima) | It is another multi-kinase inhibitor that targets VEGFR1-3, fibroblast growth factor receptors (FGFR) 1-4, PDGFRα, KIT, and RET. By inhibiting these receptors, lenvatinib suppresses tumor angiogenesis and tumor cell proliferation. |
| 3. | Regorafenib (Stivarga) | It is also a multi-kinase inhibitor that targets several kinases involved in angiogenesis (VEGFR1-3, TIE2), oncogenesis (KIT, RET, RAF-1), and the tumor microenvironment (PDGFR, FGFR). Its mechanism of action is similar to sorafenib and lenvatinib, inhibiting tumor growth and angiogenesis. |
| 4. | Pembrolizumab (Keytruda) | It is a PD-1 inhibitor that works similarly to atezolizumab by blocking the interaction between PD-1 on T cells and PD-L1 on cancer cells, thus enhancing the immune response against cancer cells. It may be used in some cases of liver cancer, particularly if the cancer has specific genetic characteristics |
| 5. | Doxorubicin | It is a cytotoxic chemotherapy drug that works by intercalation with DNA, thereby disrupting DNA replication and RNA synthesis. It also generates free radicals that cause DNA damage, leading to cell death. |
| 6. | Cabozantinib (Cabometyx): | It is a tyrosine kinase inhibitor that targets VEGFR2, MET, AXL, and RET. It is used as a second-line treatment for patients with advanced HCC who have previously been treated with sorafenib. |
| 7. | Nivolumab (Opdivo) | It is another PD-1 inhibitor that works similarly to pembrolizumab. It is used as a second-line treatment for |

| | | |
|---|---|---|
| | | patients with advanced HCC who have previously been treated with sorafenib. |
| 8. | **Combination therapy**<br>Atezolizumab<br>(Tecentriq)<br>&<br>Bevacizumab<br>(Avastin) | Atezolizumab is a programmed death-ligand 1 (PD-L1) inhibitor that enhances the body's immune response against cancer cells. Bevacizumab is a monoclonal antibody that inhibits VEGF, thereby blocking angiogenesis. The combination of atezolizumab and bevacizumab works by both activating the immune system against cancer cells and inhibiting the blood supply to the tumor. |

Table no. 01: Drugs used in the treatment of liver Cancer

**DIAGNOSIS**

1. Differential Diagnosis
2. Surgical Oncology
3. Radiation Oncology
   I. Stereotactic Body Radiotherapy( Sbrt)
4. Hyper Ablation
   I. Radiofrequency Ablation (Rfa)
   II. Microwave Ablation (Mwa)
5. Collision Trial,

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for hepatic lesions is extensive. While imaging and patient history can help narrow down the possibilities to more common causes, some differential diagnoses include primary hepatocellular carcinoma, cholangiocarcinoma, adenoma, hemangioma, hematoma, focal nodular hyperplasia, abscess, and secondary masses from metastatic diseases such as carcinoma, lymphoma, or sarcoma.[3]

**SURGICAL ONCOLOGY**

Surgical resection followed by adjuvant chemotherapy has been linked to improved survival rates and decreased morbidity and mortality in patients with hepatic metastases. Since colorectal adenocarcinoma is the most common cause of hepatic metastasis, much of the literature is focused on this condition. However, treatment for other specific clinical scenarios is tailored to individual needs.

For anatomically resectable colorectal hepatic metastases, surgical resection remains the preferred treatment. Clinical guidelines recommend that the future liver remnant should be at least 20% of its original volume in a healthy liver, 30% in cases of mild to moderate hepatic dysfunction, and 40% in cases of hepatic cirrhosis.

Strategies to increase the likelihood of successful resection include neoadjuvant chemotherapy, portal vein embolization to augment the future liver remnant, or a two-stage resection as opposed to a combined one-stage resection of the primary tumor and hepatic lesions.[3]

**RADIATION ONCOLOGY**

Stereotactic Body Radiotherapy( SBRT)

Highly precise short-course radiotherapy at ablative doses has been extensively studied across various contexts, particularly in the treatment of metastatic cancer. Recent clinical trials, like SABR COMET, have demonstrated improved survival outcomes in patients with a limited number of metastases (oligometastatic, <5 metastases) who received radiotherapy. The use of Stereotactic Body Radiation Therapy (SBRT) for liver metastases has shown promising results, providing excellent local control with minimal invasiveness and acceptable toxicity compared to alternatives like hepatic resection, radiofrequency ablation, and Transarterial Chemo/Radioembolization (TACE/TARE). One-year local control rates were 87%, dropping to 68% at three years, with an overall survival of 84% at one year and 44% at three years. Severe (Grade 3+) toxicities were observed in less than 5% of patients. While dose and fractionation strategies vary, evidence suggests that higher biological equivalent doses exceeding 100 Gy lead to superior local control. Although there is currently a lack of prospective comparisons between SBRT and other liver-directed therapies, SBRT remains a viable, effective, and minimally invasive treatment option for patients with liver metastases.[3]

**HYPER ABLATION**

The use of high temperatures (>60°C) to ablate liver tumors can be achieved through two techniques: Radiofrequency Ablation (RFA) and Microwave Ablation (MWA). Both methods work by heating tumor cells, leading to protein denaturation, destruction of the cell membrane, and coagulative necrosis.

Radiofrequency Ablation (RFA) employs uninsulated electrodes through which alternating electrical current is passed at a frequency of 375 to 500 kHz. This creates ionic friction, generating heat. However, RFA is less effective near major heat sinks like large vessels and carries a risk of thermal injury to structures such as the bile ducts, diaphragm, and bowel. There can also be interference with cardiac pacemakers. Local recurrence rates range from 10 to 31%, varying based on the size and location of the metastasis. RFA is generally well-tolerated, with few complications. Post-ablation syndrome, characterized by fever, chills, nausea, and vomiting, occurs in about 30-40% of patients but is typically self-limiting.

Microwave Ablation (MWA) heats tumors through dielectric hysteresis of water molecules using frequencies between 0.915 and 2.45 GHz. Local recurrence rates for MWA range from 5 to 13%, although it is currently unclear which method is superior. MWA offers theoretical advantages such as less heat sink effect due to its heating mechanism and the ability to achieve higher intratumoral temperatures. The procedure can be performed using open, laparoscopic, or percutaneous approaches, with image guidance (CT, MRI, or ultrasound) used to localize the tumor. Operator experience and tumor size significantly impact outcomes. MWA is generally limited to treating fewer than five tumors, each measuring less than 3 cm. Local control rates decline substantially for

tumors larger than 3 cm (85% vs. 39%). Ongoing research, such as the COLLISION Trial, is comparing the effectiveness of thermal ablation versus surgical resection in patients with colorectal metastases ≤ 3 cm, with an estimated study completion date of December 2022.[3]

**MEDICAL ONCOLOGY**

Systemic chemotherapy has shown objective response rates, although achieving a complete pathological response is uncommon. There is no consensus in the literature regarding the optimal duration of chemotherapy, but it is generally recommended to continue a selected regimen for a minimum of three to six months before considering a change in agents. When considering non-first-line chemotherapy agents, including biologic medications, it is essential to balance the potential benefits with the associated morbidity of side effects, especially in consideration of the patient's clinical status. Close monitoring is crucial due to mixed data on the success rates of these treatments in managing hepatic metastases.[3]

Other differential diagnosis

- Angiosarcoma
- Cirrhosis
- Cholangiocarcinoma
- Epithelioid hemangioendothelioma
- Embryonal sarcoma
- Hepatoblastoma
- Hepatocellular carcinoma
- Hemangiomas
- Hamartoma (1)

**CLINICAL SIGNIFICANCE**

Due to the rarity of hepatic angiosarcoma, definitive therapeutic guidelines have not been established. Diagnosing this condition is challenging due to nonspecific symptoms like weight loss and abdominal pain, as well as the non-specificity of laboratory cancer markers and the difficulty in identifying the tumor on radiological imaging. Biopsy carries the risk of bleeding due to the tumor's highly vascular nature. A collaborative effort involving primary care doctors, hepatologists, radiologists, and pathologists is essential for an accurate diagnosis. Once hepatic angiosarcoma is diagnosed, the prognosis remains poor, and treatment options include surgery or palliative care. Surgeons, oncologists, and palliative care providers should be involved in determining the best course of action based on the patient's wishes and prognosis [Level IV]. Specialty care nurses in oncology and hospice play a crucial role in patient care, providing monitoring, education, and updates to the healthcare team [Level 5].[2]

## PROGNOSIS

The literature has predominantly focused on colorectal metastases, revealing a notable prognosis for patients with synchronous disease. Without intervention, the five-year survival rate stands at 5%. However, after the curative resection of hepatic lesions, the five-year survival rate significantly increases to about 58%, a stark contrast to a median survival of only 6 months without treatment.[23, 24] For neuroendocrine liver metastases eligible for partial hepatectomy, survival rates slightly surpass those of colorectal carcinoma, reaching 61% at five years.[25]

## COMPLICATIONS

Following hepatectomy, patients might experience various postoperative complications such as abscess formation, biliary leaks, recurrent disease, bleeding, sepsis, injury to nearby structures, and the necessity for additional surgical procedures. Additionally, complications could be associated with preoperative systemic chemotherapy, encompassing steatohepatitis, sinusoidal obstruction, leukopenia, systemic infections, fever, fatigue, weight loss, poor wound healing, and potential side effects. Radiation-induced liver disease (RILD) might manifest if the entire liver is exposed to doses surpassing established toxicity thresholds, contingent on volume, dosage, and fractionation. Furthermore, external beam radiotherapy can lead to complications like bowel perforation and spinal cord injury. Notably, post-embolization syndrome, characterized by fatigue, nausea, vomiting, and abdominal pain, is a frequent complication of transarterial radioembolization (TARE).[3]

Liver angiosarcoma is a rapidly fatal tumor often leading to mortality within six months, primarily due to liver failure or hemorrhage. In some cases, tumor rupture may occur, causing hemoperitoneum. When this happens, the first intervention is typically transarterial embolization, aimed at stabilizing the patient and halting the bleed. However, due to the rarity of liver angiosarcoma, there is no definitive recommendation for treating acute bleeding. Additionally, some patients may develop features of disseminated intravascular coagulation.[2]

## PATIENT COUNSELING

Managing liver cancer requires a collaborative team approach involving specialists such as oncologists, hepatobiliary surgeons, pathologists, radiologists, gastroenterologists, palliative care nurses, dietitians, and internists. However, surgery is often not an option for many patients. While various local treatments exist, they typically only extend life expectancy by a modest amount (6-18 months). Although biological agents are available, they are often expensive and generally do not significantly improve survival rates. Palliative care is often beneficial and should be integrated early in the treatment process. Surgeons and radiologists may also play a role in managing complications arising from metastatic liver disease. Overall, the prognosis for liver cancer patients is typically poor.[1]

Diagnosing metastatic liver disease presents challenges due to its stage IV classification from an originating primary site, with a poor prognosis in the absence of treatment. Effective management necessitates an interprofessional collaboration involving medical, radiological, and surgical oncologists to devise a patient-

centric treatment strategy, potentially incorporating chemotherapy and surgical resection to improve overall survival. While there's agreement on chemotherapy agents, surgical plans depend on individual patient factors. While metastases can't be prevented, regular annual screenings by a primary care provider, including physical examinations, colonoscopies, and blood tests, are crucial.[3]

## CONCLUSION

In conclusion, liver cancer, particularly hepatocellular carcinoma (HCC), poses a significant challenge in terms of its diagnosis and management. While advances in imaging technologies and treatment modalities have improved outcomes for some patients, there is still a critical need for early detection strategies and effective therapies, especially for advanced-stage disease. The multidisciplinary approach involving hepatologists, oncologists, surgeons, radiologists, and supportive care teams remains crucial in providing comprehensive care for patients with liver cancer. Continued research efforts aimed at understanding the underlying molecular mechanisms, identifying novel therapeutic targets, and improving treatment strategies are essential to further enhance the prognosis and quality of life for individuals affected by this complex disease.

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## CONFLICT OF INTEREST

Authors do not have any Conflict of interest with any individual.

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