REVIEW

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NOVELTIES IN LOCOREGIONAL, SYSTEMIC AND MULTIMODAL TREATMENT OF PRIMARY MALIGNANT LIVER TUMORS

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Abstract. *Hepatocellular carcinoma accounts for approximately 90% of all primary liver cancers and is a major cause of cancer-related mortality worldwide, ranking second among the most common causes of cancer death. Primary liver cancer is defined as a malignant neoplasm originating from cells in the liver, including hepatocytes, cholangiocytes, or their progenitor cells.* ***Objective:*** *to analyze the latest developments in locoregional techniques and systemic and multimodal treatment of primary liver tumors.* ***Materials and Methods:*** *systematic review of scientific publications through documentary analysis and content analysis of scientific publications selected by predefined key words.* ***Results and Discussion:*** *over the last decade, there has been a paradigm shift in the treatment of primary liver cancer. The integration of transarterial therapies, targeted agents, and immune checkpoint inhibitors has significantly prolonged survival and transformed the therapeutic landscape. These advances require complex, multidisciplinary decisions regarding the sequence of therapies and patient management. Advances in molecular biology have transformed therapeutic approaches, particularly in ICC, where treatment is now guided by biomarkers, and in HCC, where immunotherapeutic combinations have set a new standard of care.*

Key words: *hepatocellular carcinoma, intrahepatic cholangiocarcinoma, surgical treatment, locoregional treatment, targeted therapies, monoclonal antibodies, tyrosine kinase inhibitors*

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INTRODUCTION

Primary liver cancer is a significant clinical and global health challenge. Hepatocellular carcinoma (HCC) accounts for approximately 90% of all primary liver cancers and is a major cause of cancer-related mortality worldwide, ranking second among the most common causes of cancer death [1, 7]. Intrahepatic cholangiocarcinoma (ICC), the second most common primary malignant tumor of the liver, originates from the epithelium of the bile ducts and also significantly contributes to the severity of the disease [1, 6]. Understanding the definitions, classifications, and key differences between these two diseases is crucial for accurate diagnosis, prognosis, and selection of an appropriate therapeutic strategy. Primary liver cancer is defined as a malignant neoplasm originating from cells in the liver, including hepatocytes, cholangiocytes, or their progenitor cells [8]. Primary tumors arise de novo in the liver parenchyma, while metastatic tumors originate in other organs (e.g., colon, breast, lungs) and subsequently spread to the liver. Cholangiocarcinoma (CC) is defined as an aggressive cancer of the bile duct epithelium that can develop anywhere along the bile ducts, from the intrahepatic bile ducts to the duodenal ampulla. Over 95% of CCs are adenocarcinomas. Based on its anatomical origin, CC is classified into two main groups: intrahepatic (ICC) and extrahepatic, the latter being subdivided into perihilar (PCC) and distal (DCC). The minor bile ducts serve as an anatomical dividing point between ICC and extrahepatic forms [6, 9].

Understanding the epidemiology of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) is of strategic importance for public health. Global patterns of incidence, mortality trends, and the distribution of risk factors form the basis for developing effective primary prevention strategies, surveillance programs, and prioritizing clinical research. Primary liver cancer is the fifth most common cancer and the second most common cause of cancer-related death worldwide [1]. HCC has a markedly uneven geographical distribution, with very high incidence rates in East/Southeast Asia and Sub-Saharan Africa. In these regions, HCC often occurs at a younger age, which is due to the high prevalence of chronic hepatitis B virus (HBV) infection and exposure to aflatoxin B1 from early childhood. In contrast, in resource-rich regions, the main risk factors are chronic hepatitis C virus (HCV) infection and metabolic syndrome [7]. ICC is the second most common primary liver cancer, with data from the Surveillance, Epidemiology, and End Results (SEER) registry in the United States showing an incidence of 1.19 per 100,000 person-years for the period 2001-2017. Projections indicate that the burden of ICC will continue to increase, with incidence in 2029 expected to be almost double that observed in 2001 [6].

The distribution of the main risk factors for primary liver cancer varies considerably across geographical regions, which explains the differences in incidence. Chronic HBV infection is responsible for approximately 54% of cases worldwide, while chronic HCV infection accounts for 31% [1]. These factors, together with alcohol consumption, contribute differently in different parts of the world.

These geographic variations are closely related to the prevailing etiology. In resource-limited regions, such as Sub-Saharan Africa and parts of Asia, chronic HBV infection and exposure to the dietary carcinogen aflatoxin B1 are the dominant risk factors. In resource-rich regions, such as Western Europe, North America, and Japan, chronic HCV infection, alcohol abuse, and metabolic syndrome are more significant causes. Men are more frequently affected by HCC in all populations, reflecting the higher prevalence of risk factors such as HBV infection, alcohol consumption, and smoking in this group. Significant changes in epidemiological trends have been observed in recent decades. Countries such as the United States have reported an increasing incidence of HCC, mainly due to the growing prevalence of chronic HCV infection among the aging population and the obesity epidemic leading to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). NAFLD is becoming an increasingly important cause of HCC in developed regions [1, 6].

The prognosis for ICC is also worrying. Analysis of SEER data shows that the annual percentage change in ICC incidence increased significantly between 2007 and 2017 [6]. Projections indicate that by 2029, the

Table 1. Geographic distribution of major risk factors for primary liver cancer (Adapted from EASL Clinical Practice Guidelines [159])

Region	Alcohol (%)	HBV (%)	HCV (%)	Other (%)
Europe				
Western	32	13	44	10
Central	46	15	29	10
Eastern	53	15	24	8
North America	37	9	31	23
Andean Latin America	23	45	12	20
Asia				
East Asia	32	41	9	18
Asia-Pacific region	18	22	55	6
Southeast Asia	31	26	22	21
Africa				
North Africa, Middle East	13	27	44	16
Southern (Sub-Saharan)	40	29	20	11
Western (Sub-Saharan)	29	45	11	15

incidence of ICC may reach 2.13 cases per 100,000 people, which is almost double that of 2001. These increasing trends highlight the urgent need for a better understanding of risk factors and the development of strategies for prevention and early diagnosis.

The World Health Organization (WHO) classification describes the main histological types of primary liver cancer, with HCC and ICC being the main entities. Pathological diagnosis is the gold standard for defining these tumors, especially in cases where imaging studies are inconclusive or in patients without cirrhosis [1]. In addition to classic HCC, there are several histological variants. Fibrolamellar HCC is a rare subtype that usually occurs in younger patients without underlying liver disease. Combined hepatocellular-cholangiocarcinoma (combined HCC/CC) is a malignant tumor with mixed characteristics of both HCC and CC. The diagnosis of this mixed tumor is made when there is clear differentiation to cholangiocarcinoma or when there are unambiguous signs of mixed differentiation in a significant part of the tumor, which requires careful pathological evaluation [1].

From a clinical point of view, it is crucial to distinguish whether HCC occurs in the context of cirrhotic or non-cirrhotic liver. In the Western world, up to 90% of HCC cases develop in patients with cirrhosis [1, 4]. This distinction has important implications for surveillance, diagnostic criteria, and treatment selection. Patients with cirrhosis undergo regular surveillance, which allows for earlier detection, while diagnosis in patients without cirrhosis is often delayed. Furthermore, non-invasive imaging criteria for diagnosing HCC have only been validated in patients with cirrhosis.

Macroscopic growth patterns also provide important information for staging and treatment planning. HCC can present as unifocal (single nodule), multifocal (multiple nodules), or diffuse (infiltrative) forms. On the other hand, HCC usually presents as a mass-forming tumor or as a periductal infiltrating type [1]. These anatomical characteristics influence the possibilities for resection and the choice of locoregional therapies.

Understanding the etiology is the cornerstone of prevention and surveillance of primary liver cancer. Identifying the various risk factors for hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) is crucial for determining high-risk populations that would benefit most from screening programs and primary prevention strategies. Knowing the causes allows for targeted interventions to reduce the burden of these diseases.

OBJECTIVE: to analyze recent advances in locoregional techniques and systemic and multimodal treatment of primary liver tumors. **MATERIALS AND METHODS:** systematic review of scientific publications through documentary analysis and content analysis of scientific publications selected by predefined key words.

RESULTS: approximately 90% of HCC cases are associated with a known underlying etiology. The main risk factors include liver cirrhosis, chronic viral hepatitis, alcohol abuse, metabolic diseases, and exposure

to environmental factors. Cirrhosis, regardless of the cause, is the most important risk factor for HCC. Approximately one-third of patients with cirrhosis will develop HCC during their lifetime [1]. The annual risk of developing HCC in patients with cirrhosis ranges from 1% to 8% depending on the etiology, being higher in patients with chronic viral hepatitis [1]. Chronic infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common causes of HCC worldwide. Globally, 54% of cases are due to HBV infection and 31% to HCV infection. Chronic HBV infection is the leading cause in Africa and East Asia, while chronic HCV infection is more prevalent in the Western world. It is important to note that HCC can develop in patients with chronic HBV infection even in the absence of cirrhosis [1, 7]. Antiviral therapy that suppresses HBV replication or leads to a sustained virological response (SVR) in HCV significantly reduces the risk of developing HCC. However, the risk is not completely eliminated, especially in patients who already have established cirrhosis, and they should continue to be monitored [1]. Chronic alcohol abuse is a significant risk factor. Consuming more than 80 g of alcohol per day for more than 10 years increases the risk of HCC approximately fivefold [1]. Alcohol often acts synergistically with other risk factors, such as viral hepatitis [7]. Non-alcoholic fatty liver disease (NAFLD), associated with metabolic syndrome, obesity, and diabetes, is becoming an increasingly important cause of HCC in developed countries. An alarming aspect of NAFLD is that in a significant proportion of cases, HCC can develop even in non-cirrhotic livers. Exposure to the food mycotoxin aflatoxin B1, which contaminates staple foods in tropical and subtropical regions, is a potent cofactor for the development of HCC, especially in combination with chronic HBV infection [15, 16]. Certain hereditary and metabolic disorders also increase the risk of HCC, including genetic hemochromatosis and alpha-1-antitrypsin deficiency, as they lead to chronic liver damage and cirrhosis [1, 7].

Unlike HCC, no known risk factors have been identified in many patients with ICC [8]. However, several established risk factors have been identified, most of which are associated with chronic inflammation and damage to the bile ducts. These include: primary sclerosing cholangitis (PSC); hepatolithiasis (intrahepatic gallstones); choledochal cysts. These conditions lead to chronic bile stasis, inflammation, and damage to cholangiocytes, creating an environment conducive to malignant transformation [8].

Risk stratification is essential for identifying patients who need regular monitoring for early detection of HCC. According to the guidelines of the European Association for the Study of the Liver (EASL), monitoring is recommended for the following high-risk groups [1]: Patients with cirrhosis, Child-Pugh stages A and B; Patients with cirrhosis, Child-Pugh stage C, who are on the liver transplant waiting list; patients with chronic HBV infection without cirrhosis who are at moderate or high risk of developing HCC. Various scoring systems have been developed to refine the risk assessment in patients with HBV without cirrhosis. For example, the PAGE-B scale is used to assess risk in Caucasian patients treated with nucleos(t)ide analogues and helps identify those at low risk, in whom monitoring may not be necessary, and those at moderate to high risk, in whom it is strongly recommended [1].

Understanding the molecular pathogenesis of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) reveals the fundamental biological processes that drive these cancers. This knowledge forms the basis for the development of targeted therapies, the identification of prognostic biomarkers, and the creation of personalized treatment approaches aimed at improving patient outcomes. **The cirrhosis-carcinoma sequence is the dominant pathway for the development of HCC**, with approximately 80% of cases occurring in patients with cirrhosis. This process is characterized by chronic inflammation, cell death, compensatory regeneration, and replicative stress [5]. The constant cycle of hepatocyte damage and regeneration increases the likelihood of accumulating genetic and epigenetic abnormalities, which ultimately lead to malignant transformation. This process usually goes through histologically defined stages, starting with dysplastic nodules that can progress to early and then advanced HCC. HCC can also develop in a non-cirrhotic liver, although less frequently, often associated with HBV infection or NAFLD [1]. The origin of ICC is more heterogeneous. It is believed that tumors may originate from different cells, including mature cholangiocytes (epithelial cells of the bile ducts), hepatic progenitor cells (HPCs), or even transdifferentiated mature hepatocytes. This cellular plasticity contributes to the histological and molecular diversity observed in ICC [8]. Genomic studies have identified several **key oncogenic drivers and altered pathways in HCC**. Mutations in the TERT (telomerase reverse transcriptase) promoter are the most common genetic event, occurring in approximately 60% of tumors [5]. These mutations are considered a "gatekeeper“ event, as they are often found in pre-neoplastic dysplastic nodules and contribute to cellular immortality by maintaining telomere length [5]. Other common changes include activating mutations in the CTNNB1 gene (encoding β-catenin)

and inactivating mutations in the tumor suppressor gene T*P53*.

Table 2. Key oncogenic drivers in hepatocellular carcinoma (Adapted from Llovet et al. [5])

Altered pathway	Key altered genes and frequency
Telomere maintenance	*TERT* promoter mutation (~60%)
Cell cycle regulation	*TP53* mutation (~25%)
Wnt/β-catenin signaling	*CTNNB1* mutation (~30%)
Chromatin remodeling	*ARID1A* mutation (~8%)
Ras/PI3K/mTOR signaling	*PIK3CA* mutation (~2%)
Oxidative stress	*NFE2L2* mutation (~4%)

The molecular landscape of ICC is significantly different from that of HCC. Frequent mutations in metabolic genes such as *IDH1/2* (isocitrate dehydrogenase 1/2) are characteristic of iHCC and are found in 16-29% of cases [8, 12]. These mutations lead to the production of the oncometabolite 2-hydroxyglutarate (2-HG), which alters cell differentiation and promotes tumorigenesis [8]. Mutations in genes involved in chromatin remodeling, such as *ARID1A* and BAP1, are also common [8, 12]. A distinctive feature of ICC is the presence of *FGFR2* (fibroblast growth factor receptor 2) gene fusions, which occur in 10-15% of patients. These fusions lead to constitutive activation of *FGFR2* kinase and represent a key therapeutic target for which specific inhibitors have been developed [6, 8]. Other less common but potentially treatable genetic alterations include *BRAF V600E* mutations and *HER2 (ERBB2)* amplifications [14].

As in HCC, **the tumor microenvironment plays a critical role in tumorigenesis** in ICC. The chronic inflammation characteristic of cirrhotic liver creates an immunosuppressive environment that allows tumor cells to evade immune surveillance [5]. This environment is rich in various immune and stromal cells that can promote tumor growth, angiogenesis, and metastasis. Intrahepatic spread often occurs through satellite nodules or microvascular invasion, which is an important prognostic factor. Extrahepatic spread can occur through direct invasion into adjacent structures or through hematogenous and lymphogenous metastases to regional lymph nodes, lungs, bones, and other organs [1].

A precise understanding of tumor morphology, location, and extent of spread, classified using standardized staging systems, is essential for determining prognosis and selecting the most appropriate therapy. Pathoanatomy and staging represent a critical bridge between diagnosis and clinical decision-making, allowing the multidisciplinary team to stratify patients and recommend an individualized treatment plan. Planning surgical and locoregional therapies requires a thorough understanding of liver and vascular anatomy, including segmental division, the portal vein, hepatic veins, and the hepatic artery. Macroscopic growth patterns of primary liver tumors are important for staging. As mentioned, HCC can present as a unifocal (single), multifocal (multiple nodules), or diffuse infiltrative tumor. ICC most often presents as a mass-forming tumor or as a periductal infiltrating type [1]. These patterns directly influence resectability and choice of therapy.

Several microscopic characteristics are crucial for determining the prognosis and risk of recurrence after curative treatment: **degree of differentiation:** well-differentiated tumors have a better prognosis than poorly differentiated tumors; **microvascular invasion (MVI):** the presence of tumor cells in small intrahepatic vessels is a strong predictor of early recurrence and poorer survival [1]; **satellite nodules:** the presence of small tumor nodules in close proximity to the main tumor is also associated with a higher risk of recurrence; **resection margin status:** achieving clear surgical margins (R0 resection) is essential for reducing the risk of local recurrence. R1 resection (microscopic presence of tumor in the margin) is associated with poorer outcomes.

Unlike most solid tumors, HCC staging systems must take into account three key components: tumor status (size, number, vascular invasion), liver function, and the patient‘s general condition. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely accepted and recommended system. Its strength lies in its unique integration of tumor burden, liver function (Child-Pugh), and the patient‘s functional status (ECOG PS), which provides a framework that not only predicts prognosis, but also directly guides therapeutic recommendations – a feature that is lacking in traditional TNM staging systems for this disease [10].

The BCLC system classifies patients into five stages:

- **BCLC 0 (very early stage):** single tumor <2 cm, preserved liver function (Child-Pugh A), PS 0. The recommended treatment is resection, ablation, or transplantation. The expected survival is >5 years.
- **BCLC A (early stage):** single tumor or 2-3 nodes, each <3 cm, preserved liver function, PS 0. Treatment includes resection, transplantation, or ablation. Expected survival is >5 years after transplantation or resection and >2.5 years after ablation.
- **BCLC B (intermediate stage):** multinodular tumor, unresectable, no vascular invasion or ex-

trahepatic spread, preserved liver function, PS 0. Standard treatment is transarterial chemoembolization (TACE). Expected survival is ≥10 months.

- **BCLC C (advanced stage):** portal invasion or extrahepatic spread, preserved liver function, PS 1-2. Treatment is systemic therapy (e.g., atezolizumab plus bevacizumab). Expected survival is ~10 months with sorafenib, but longer with newer regimens.
- **BCLC D (terminal stage):** end-stage liver disease (Child-Pugh C) or poor general condition (PS 3-4), unsuitable for transplantation. Treatment is best supportive care (BSC). The expected survival is ~3 months.

Other staging systems, such as TNM and Hong Kong Liver Cancer (HKLC), are also used, but BCLC remains the preferred system for clinical practice and clinical trials [1].

The main staging system for ICC is the TNM classification. However, clinical decision-making is based on the concept of resectability, which is determined by a multidisciplinary team. The disease is classified as: **resectable**: a tumor that can be completely removed surgically with clear margins while preserving sufficient volume of the future residual liver (Future Liver Remnant, FLR); **borderline resectable**: tumors with close vascular involvement that may become resectable after neoadjuvant therapy or procedures to increase FLR; or **unresectable**: tumors with extensive vascular invasion, bilateral spread, or distant metastases.

Liver transplantation is the optimal treatment for HCC in patients with cirrhosis, as it treats both the cancer and the underlying liver disease [1]. Strict selection criteria are used to ensure excellent results after transplantation. **The Milan criteria** are the conventional standard and include: single tumor ≤5 cm or up to 3 nodes, each ≤3 cm. Patients who meet these criteria have a 5-year survival rate after transplantation comparable to that of patients transplanted for non-oncological reasons. Expanded criteria (e.g., UCSF, Up-to-7) have also been developed, allowing transplantation of carefully selected patients outside the Milan criteria. Biomarkers such as alpha-fetoprotein (AFP) are increasingly used to refine selection, as high AFP levels are associated with a poorer prognosis [1].

Recognizing the diverse clinical picture of primary liver cancer is essential for a timely diagnosis. Presentation ranges from incidental discovery in asymptomatic patients undergoing surveillance to acute decompensation in those with advanced disease. The manner of presentation directly influences the diagnostic process and prognosis, with surveillance and early detection programs being essential. The most common scenario for early diagnosis of HCC is the incidental discovery of a liver nodule during a routine ultrasound examination in an asymptomatic patient with compensated cirrhosis [1]. In these cases, patients usually have no symptoms related to the tumor, and the discovery is the result of the successful implementation of a surveillance program. This is the ideal scenario, as it allows for radical treatment. In contrast, in patients with decompensated cirrhosis, the appearance of new or worsening symptoms may be the first sign of underlying HCC. Symptoms such as new or worsening ascites, jaundice, weight loss, or episodes of hepatic encephalopathy should raise suspicion of a malignant process that destabilizes the already fragile liver function [11].

When primary liver cancer becomes symptomatic, it is usually a sign of advanced disease. The most common symptoms are nonspecific and include [11]: abdominal pain: usually localized in the upper right quadrant and may be dull or constant; unexplained weight loss: significant and unintentional weight loss; loss of appetite and early satiety: feeling full after eating a small amount of food. These constitutional symptoms are often associated with a large tumor volume that causes stretching of the liver capsule or compression of adjacent organs. Although there is overlap in symptoms, there are some typical differences in the presentation of HCC and ICC. HCC most often occurs in the context of known cirrhosis, so patients are often already under medical supervision [1]. In contrast, a significant proportion of patients with ICC do not have underlying chronic liver disease [8]. Since ICC originates in the biliary tract, it may more often present with symptoms related to biliary obstruction, even with smaller tumors. These symptoms include: jaundice: yellowing of the skin and whites of the eyes; itching (pruritus): generalized itching of the skin. These symptoms are less common as an initial manifestation of HCC, unless the tumor is centrally located and compresses the major biliary tract.

There are several common diagnostic pitfalls. In patients with cirrhosis, regenerative or dysplastic nodules may be mistaken for HCC on imaging studies, requiring careful evaluation and sometimes biopsy for confirmation [1]. Another challenge is distinguishing ICC from metastatic adenocarcinoma in the liver, especially when the primary source of the metastasis is unknown. This often requires detailed immunohistochemical analysis of the biopsy material to determine the origin of the tumor [6]. The suspected diagnosis based on the clinical picture must be confirmed and staged through a systematic evaluation that includes imaging studies, tumor markers, and often biopsy to determine the final treatment plan.

The diagnostic and staging evaluation of primary liver tumors is a multimodal process that aims not only to confirm the diagnosis, but also to accurately determine the extent of tumor spread, assess underlying liver function, and evaluate the patient‘s suitability for treatment. This comprehensive approach is essential for determining the optimal therapeutic strategy within a multidisciplinary team (MDT). In high-risk patients (e.g., those with cirrhosis), the diagnostic process often begins with the detection of an abnormality during a routine ultrasound examination for surveillance. The detection of a new nodule >1 cm in size in a cirrhotic liver triggers a strategy for follow-up investigations (recall strategy), which includes more definitive imaging methods to characterize the lesion. This proactive strategy is key to detecting HCC at an early, treatable stage.

Multiphase contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) play a central role in the non-invasive diagnosis of HCC in patients with cirrhosis. The pathognomonic imaging feature for HCC is the combination of arterial phase hyperenhancement (APHE), followed by washout in the portal venous or late phase. This characteristic pattern reflects tumor neoangiogenesis and allows for a definitive diagnosis without the need for biopsy in patients with cirrhosis for nodules ≥1 cm in size. In general, MRI is considered a more sensitive method than CT, especially for detecting smaller lesions. The specificity of both methods varies between 85% and 100%, but sensitivity decreases significantly for tumors smaller than 2 cm. The use of hepatobiliary contrast agents in MRI (e.g., gadolinium acid) may increase the sensitivity for detecting nodules, as most HCCs do not take up this contrast in the hepatobiliary phase and appear hypointense. This characteristic helps to distinguish them from benign nodules [1].

The Liver Imaging Reporting and Data System (LI-RADS) provides a standardized framework for reporting and classifying liver lesions in patients at risk of HCC, thereby improving communication and consistency. CEUS can be used to characterize liver nodules. Refined criteria for HCC on CEUS include APHE, followed by late (>60 seconds) and mild washout. These criteria help to distinguish HCC from other malignant tumors, such as ICC, which typically show earlier and show a more pronounced washout [1].

Liver biopsy remains the gold standard for diagnosis when non-invasive criteria are not met or are not applicable. According to EASL guidelines, biopsy is indicated in the following cases: mandatory in cases of suspected HCC in a non-cirrhotic liver, as imaging findings are less specific; necessary in patients with cirrhosis when imaging studies are atypical or inconclusive; necessary in all cases of suspected ICC to confirm the diagnosis and enable molecular profiling to identify therapeutic targets [6].

Immunohistochemical markers, such as glypican-3 (GPC3), heat shock protein 70 (HSP70), and glutamine synthetase (GS), are used to aid in the differential diagnosis between well-differentiated HCC and dysplastic nodules.

Serum alpha-fetoprotein (AFP) has suboptimal sensitivity and specificity for surveillance, but may be useful for diagnosis and prognosis in certain cases, especially at high levels. Other markers such as des-gamma-carboxy prothrombin (DCP) are also tested, but are not part of routine monitoring practice.

Assessment of liver function (Child-Pugh scale, MELD score, albumin, bilirubin) and the patient‘s general condition (ECOG/WHO performance status) are critical components of staging systems, such as BCLC, and are essential for determining the patient‘s suitability for different types of treatment [1].

Fluorodeoxyglucose positron emission tomography (FDG-PET/CT) has a high false-negative rate in well-differentiated HCC and is not recommended for early diagnosis. However, it can be useful for detecting extrahepatic spread, especially in ICC, and has a prognostic value.

The final assessment of resectability, transplant eligibility, and overall treatment strategy should be made within a multidisciplinary team (MDT). This team, which usually includes a hepatologist, surgeon, oncologist, radiologist, and pathologist, integrates all radiological, pathological, and clinical data to make the best decision for each individual patient.

For patients with early-stage disease (BCLC 0-A HCC or resectable ICC), radical treatment offers the best chance for long-term survival. The choice between liver resection, transplantation, and local ablation is a complex decision guided by tumor characteristics, underlying liver function, and the patient‘s overall condition. A multidisciplinary approach is essential to determine the most appropriate strategy for each individual patient.

Liver resection is the preferred treatment in several key scenarios: HCC in patients with non-cirrhotic liver; single HCC in patients with cirrhosis and well-preserved liver function (Child-Pugh A, without clinically significant portal hypertension); resectable ICC with adequate future liver reserve (FLR) [1, 12].

Before performing resection in patients with cirrhosis, a multiparametric assessment is mandatory, including liver function (MELD, indocyanine green clearance), assessment of portal hypertension, and

calculation of FLR volume. In patients with ICC who require major hepatectomy, methods to increase FLR, such as portal vein embolization (PVE), can be used to reduce the risk of postoperative liver failure. Minimally invasive approaches (laparoscopic/robotic resection) are an option for selected cases and may reduce hospital stay and complications [1, 13].

Liver transplantation is considered the ideal treatment for HCC in patients with cirrhosis, as it simultaneously treats both the cancer and the underlying liver disease that is responsible for its development [1]. As already mentioned, the Milan criteria (single tumor ≤5 cm or up to 3 nodes, ≤3 cm each) play a central role in the selection of candidates. Compliance with these criteria ensures excellent long-term survival after transplantation, comparable to that in non-oncological indications.

While patients are on the waiting list, bridging therapy (e.g., TACE, RFA) is used to control tumor growth and prevent removal from the list. Downstaging is a strategy in which patients with tumors that initially exceed the criteria undergo locoregional treatment to reduce the tumor burden to levels acceptable for transplantation. Successful downstaging is an indicator of favorable tumor biology [1]. The role of LT in ICC is more limited and controversial. However, studies show that in selected patients with unresectable ICC who have shown disease stability after neoadjuvant therapy, transplantation may be a viable option. A prospective study by Lunsford et al. demonstrated encouraging results in this regard [6, 13].

Local ablation aims to destroy tumor tissue *in situ* by applying chemical or physical agents. Radiofrequency ablation (RFA) is the standard of care for patients with early-stage HCC (BCLC 0-A) who are not suitable candidates for surgical resection. In very early HCC (<2 cm) located in a favorable site, RFA can be used as first-line treatment with results comparable to those of resection. Microwave ablation (MWA) is a newer thermal ablation technique that shows promising results, with similar or potentially higher efficacy compared to RFA, especially in larger tumors [1, 6]. Percutaneous ethanol injection (PEI) is an older technique that is still an option when thermal ablation is not technically feasible, especially for tumors <2 cm [1]. Stereotactic body radiation therapy (SBRT) is an emerging non-invasive locoregional method that delivers high doses of radiation with great precision to the tumor. Although convincing evidence for its role as a first-line treatment is still being gathered, SBRT can be used as a bridge therapy to transplantation or to treat patients who are not suitable for other locoregional therapies [1]. Patients with more advanced disease or those who are not candidates for radical treatment require a different set of multimodal and systemic treatments aimed at controlling the disease and prolonging survival.

Over the past decade, there has been a paradigm shift in the treatment of intermediate and advanced primary liver cancer. The integration of transarterial therapies, targeted agents, and immune checkpoint inhibitors has significantly prolonged survival and transformed the therapeutic landscape. These advances require complex, multidisciplinary decisions regarding the sequence of therapies and patient management.

Transarterial therapies exploit the dual blood supply to the liver, as liver tumors are primarily supplied by the hepatic artery, unlike normal parenchyma. Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate-stage (BCLC B) HCC. The procedure involves selective injection of a chemotherapeutic agent followed by embolization of the tumor-feeding arteries, resulting in a potent cytotoxic and ischemic effect. Multiple studies have demonstrated the survival benefit of TACE in this patient group [1]. Transarterial radioembolization (TARE/SIRT), also known as selective internal radiation therapy (SIRT), is another transarterial option in which microspheres containing a radioactive isotope (Yttrium-90) are delivered to the tumor. Multimodal applications: these therapies are also used in multimodal settings, such as bridging therapy or downstaging prior to liver transplantation, or in combination with RFA for larger tumors to improve local control [1].

Systemic therapy is the standard for patients with advanced (BCLC C) HCC.

First-line – standard of care: the combination of **Atezolizumab (anti-PD-L1) plus Bevacizumab (anti-VEGF)** is the current standard for first-line treatment. This is based on the IMbrave150 study, which demonstrated a significantly better overall survival compared to sorafenib [2, 5, 15].

Tyrosine kinase inhibitors (TKIs): Sorafenib, the first TKI to show survival benefit in the SHARP study, and **lenvatinib** remain alternative first-line options, particularly in patients with contraindications to immunotherapy or bevacizumab (e.g., high risk of variceal bleeding, autoimmune disorders) [5].

Second-line therapies: for patients who progress on sorafenib, several second-line agents are approved, including **regorafenib** and **cabozantinib** [1, 5]. **Ramucirumab**, a monoclonal antibody against VEGFR-2, is an option for patients with AFP levels ≥400 ng/mL [5].

Systemic therapy for advanced ICC is also evolving rapidly, shifting from standard chemotherapy to immuno- and targeted therapies based on the molecular profile of the tumor.

First line – standard care: the combination of **durvalumab (anti-PD-L1) plus gemcitabine-cisplatin chemotherapy** is the new standard of care. The TOPAZ-1 study showed that adding durvalumab to standard chemotherapy improves overall survival [3, 12].

Targeted therapies (second and subsequent lines): After progression on first-line chemotherapy, treatment is guided by the results of molecular profiling of the tumor (Table 3). Several targeted therapies are approved for specific genetic abnormalities:

Table 3

***FGFR2* fusions/rearrangements:** FGFR inhibitors such as **Pemigatinib, Futibatinib**, and **Infigratinib** are approved for patients with these abnormalities [6, 14].
***IDH1* mutations: Ivosidenib**, an inhibitor of mutant IDH1, has been approved based on the ClarIDHy study, which showed improved progression-free survival [6, 14].
***BRAF V600E* mutations:** The combination of **Dabrafenib** (BRAF inhibitor) and **Trametinib** (MEK inhibitor) is effective in patients with this rare mutation [14].
***HER2* amplification:** Regimens based on **trastuzumab** and newer agents such as **zanidatumab** show activity in tumors with HER2 overexpression [6].

The principle of migration between treatment stages is important in clinical practice. For example, a patient in BCLC stage B who is not eligible for or progresses on TACE may receive systemic therapy, which is usually reserved for stage C [1].

The sequence of therapies, the selection of the most appropriate regimen for each patient, and the management of treatment-related toxicities require the ongoing involvement of a multidisciplinary team to optimize outcomes and quality of life. Enhanced recovery after surgery (ERAS) is a standardized and evidence-based multimodal, perioperative strategy. It includes a series of measures aimed at reducing the physical and psychological stress responses to surgery and improving postoperative outcomes, reducing complications, reducing hospital length of stay (LOS) and the associated financing costs [16].

Palliative care is an integral part of overall cancer management, not just end-of-life care. For patients with advanced HCC and ICC, effective symptom control, realistic counseling about prognosis, and structured follow-up are crucial to maintaining quality of life. This approach provides comfort, dignity, and support for both the patient and their loved ones. Symptom management in patients with advanced liver disease requires special attention due to impaired liver function. Pain is one of the most common symptoms in advanced HCC [11]. For mild pain, acetaminophen (paracetamol) is recommended in doses up to 3 g per day. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with cirrhosis due to the risk of gastrointestinal bleeding and renal toxicity. Opioids may be used for moderate to severe pain, but with great caution and proactive management of constipation to prevent precipitating hepatic encephalopathy [1]. Management of symptoms associated with hepatic decompensation, such as ascites, requires diuretics and sometimes paracentesis. Other symptoms such as loss of appetite, fatigue, and nausea should also be actively managed [11]. Palliative radiotherapy is effective in relieving pain from bone metastases, which may occur in advanced disease.

DISCUSSION

Despite significant progress, several major challenges remain. According to key sources such as the EASL guidelines and the reviewed articles, „unmet needs“ include [1, 5, 17]:

1. Better tools for surveillance and early diagnosis: current ultrasound-based methods have their limitations. The development of more sensitive biomarkers or imaging techniques, including liquid biopsies, is essential for detecting tumors at an earlier and more treatable stage; 2. effective adjuvant therapies: the risk of recurrence after curative treatment (resection or ablation) remains high, reaching 70% at five years. Studies of adjuvant therapy to date have not shown a benefit. The development of effective adjuvant strategies to prevent recurrence is a major priority; 3. Predictive biomarkers: despite the availability of multiple systemic therapies for advanced HCC, there are no reliable predictive biomarkers to guide the choice and sequence of treatment for individual patients [5]. The identification of such markers would enable true personalized medicine. 4. Precision oncology: the full integration of molecular data into clinical decision-making is the next frontier. This requires mandatory biopsy and molecular profiling, especially in ICC, but also in the context of HCC clinical trials; 5. Biomarker-based clinical trials: future clinical trials should be designed to test new therapies in molecularly defined patient subgroups. This will increase the likelihood of success and accelerate the development of effective targeted treatments. 6. Combined and multimodal approaches: the investigation of new combinations of systemic therapies, as well as the integration of sys-

temic treatments with locoregional approaches (e.g., neoadjuvant therapy), has the potential to improve outcomes at all stages of the disease.

Conflict of interest: *The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

Ethical statements: *The authors declare that no clinical trials were used in the present study.*

The authors declare that no experiments on humans or human tissues were performed for the present study.

The authors declare that no informed consent was obtained from humans, the donors or donors' representatives participating in the study.

The authors declare that no experiments on animals were performed for the present study.

The authors declare that no commercially available immortalized human and animal cell lines were used in the present study.

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