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REVIEW

Hepatocellular Carcinoma: Essentials Interventional Radiologists Need to Know

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Epidemiology, Predisposing Factors, Pathology

Liver cancer is a leading cause of death worldwide and the second most common cause of death for cancer at global level. The most common type of liver cancer is hepatocellular carcinoma (HCC) that accounts for more than 85% of primary liver malignancies [1, 2]. Other types are cholangiocarcinoma and rare tumors such as angiosarcoma or hepatoblastoma.

The incidence of HCC is highest in Africa and East Asia. These regions comprise more than 80% of all cases. Northern Europe and the USA are countries with low incidence, while Southern Europe has an intermediate incidence. Most HCCs occur in patients with cirrhosis. The main causes are chronic hepatitis B and C virus infection, alcohol abuse, non-alcoholic steatohepatitis related to the metabolic syndrome, alpha-1 antitrypsin deficiency or hemochromatosis. Exposure to the food contaminant aflatoxin is a major causative factor in rural African areas. Obesity, diabetes and tobacco may also contribute to the development of HCC [3–5]. The incidence of HCC has increased in the last decades in most Western countries, while it is decreasing in Southeast Asia and eastern sub-Saharan countries as a consequence of hepatitis B virus vaccination campaigns [6, 7]. The incidence in all countries is expected to decrease due to extensive cure of hepatitis C infection with the newest direct antiviral agents.

HCC histopathology may resemble the normal hepatic architecture (trabecular pattern) or show acinar or solid patterns. A distinct macrotrabecular massive HCC subtype has recently been defined and associated with a more aggressive behavior [8]. Other histopathological variants include fibrolamellar, scirrhous, sarcomatoid and lymphoepithelioma-like HCC, combined HCC–cholangiocarcinoma and undifferentiated carcinoma. Fibrolamellar HCC usually occurs in young patients without cirrhosis. The histopathological subtype usually has no impact on therapeutic decisions. However, most clinical trials testing systemic therapies in recent years have excluded patients with fibrolamellar, sarcomatoid and mixed tumors.

Edmonson and Steiner's histopathological classification identifies four grades of differentiation, from well to poorly differentiated tumors. The degree of tumor differentiation has a prognostic influence after transplantation, resection or ablation [9].

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Ten most important points of the cancer

1. Chronic infection with hepatitis B and C viruses, alcohol abuse, fatty liver disease and aflatoxin exposure are the main causes
2. 80–90% of the patients have cirrhosis of different etiologies
3. Regular screening should be offered to individuals at high risk of developing HCC to improve the detection of curable tumors
4. Liver transplantation is the only therapy available for patients with decompensated cirrhosis
5. Liver resection is limited by the amount and the quality of the future liver remnant
6. Percutaneous ablation may be an alternative to resection or transplantation for very early tumors
7. Transarterial chemoembolization is the mainstay of the treatment of unresectable or multinodular tumors that have not expanded beyond the liver
8. Selective internal radiation therapy or radioembolization may have a role as an alternative to TACE in selected cases, particularly in large tumors or when an ablative dose of radiation can be delivered
9. Several tyrosine-kinase inhibitors are now in the toolbox of systemic therapies used in the advanced stages
10. Immune checkpoint inhibitors are being tested alone and in combinations across tumor stages

Five most important numbers of the cancer

Six cases per 100,000 patients-year are the estimated incidence in Western countries

10% is the 5-year rate of tumor recurrence after liver transplantation following Milan criteria

40% of patients receive intra-arterial therapies as first treatment

Seven drugs have proven antitumor activity in the advanced stages

Seventy clinical trials listed in clinicaltrials.gov are testing immuno-oncology agents blocking PD-1, PD-L1 or CTLA4, alone or in combination

Three major pivotal studies for the last 5 years

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CELESTIAL. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. N Engl J Med. 2018 Jul 5;379(1):54–63

CHECKMATE 040. El-Khoueiry A, Sangro B, Yau T, Crocenzi T, Kudo M, Hsu C, et al. Lancet. 2017; 389(10088):2492–2502

Two messages about the cancer

- Cirrhosis of different etiologies is present in around 90% of the patients with a large impact on treatment selection and outcome
- Prognosis has improved over the last decades due to early diagnosis by means of screening of high-risk patients and development of more effective therapies

One prediction for the 5 future years

- The incidence of HCC worldwide will decrease in the future due to hepatitis B virus vaccination and hepatitis C virus cure

Diagnostic and Initial Workup

Recognition of chronic liver disease as the main cause of HCC allows running screening programs for death prevention through early detection. Surveillance is universally recommended for patients with cirrhosis or with chronic hepatitis B infection at high risk of HCC development [2, 10, 11]. Several scores can help evaluate the risk of HCC in patients with chronic hepatitis B [12–14]. The recommended screening procedure is liver ultrasound examination every 6 months. No strong evidence supports the practice of measuring serum levels of the biomarker alpha-fetoprotein (AFP) for screening purposes.

The diagnosis of HCC in nodules < 1 cm cannot be confirmed using imaging techniques alone and may prove elusive after biopsy even for trained pathologists [15, 16]. Such small nodules should therefore be followed up every 4 months to assess the growth pattern. If the lesion does not grow after 12 months, the patient can resume the standard surveillance program. Most HCC tumors larger than 1 cm show arterial hypervascularity, with an early enhancement on the arterial phase and an early washout in the delayed phases of contrast-enhanced techniques. When tumors with these characteristics and > 1 cm are detected on a cirrhotic liver, the diagnosis of HCC can be accurately established without the need for histopathological confirmation. For any lesion in a non-cirrhotic liver and for non-specific nodules > 1 cm in a cirrhotic liver, a liver biopsy should be obtained regardless of the radiological appearance and AFP levels [2, 11].

Contrast-enhanced CT or MRI can be used for diagnostic purposes. Contrast-enhanced US lacks good specificity in differentiating HCC from cholangiocarcinoma [17, 18]. MRI using extracellular contrast agents has a better performance for small lesions (1–2 cm) than CT [19, 20]. The use of hepatobiliary contrast agents like gadoxetic acid increases the sensitivity of MRI for the detection of small nodules [21] but its benefit has not been proven yet in adequately powered studies.

Liver imaging reporting and data system (LI-RADS) provides a standardized framework for classification of liver nodules detected by CT and MR in cirrhotic patients on screening programs [22]. The degree of suspicion for malignancy increases from LR1 to LR5 nodules. However, recommendations for follow-up or biopsy should not be made based on LI-RADS class. LR2, LR3 and LR4 nodules have an increasing risk of harboring HCC but the presence of the tumor cannot be ruled out in any of these classes and biopsy is therefore recommended whenever it is technically feasible [2]. ^{18}FDG-PET scan is not recommended for HCC staging.

Since most HCCs occur in patients with chronic liver disease, prognosis depends on both tumor burden and liver function. Liver dysfunction negatively impacts on the outcome of any treatment able to induce liver damage, from resection to drug therapy. The TNM system is therefore not suitable for HCC. A number of staging scores and systems have been proposed [23–25] although the most generally accepted is the one proposed by the Barcelona Clinic Liver Cancer (BCLC) group [26] and endorsed by most scientific societies particularly in Western countries (Table 1). Five stages are defined based on tumor characteristics (number of nodules, vascular invasion and metastasis), liver dysfunction and performance status. The BCLC system provides treatment recommendations for each stage although this is a more controversial issue.

Approved/Recommended Treatments

Treatment allocation in HCC depends on the amount and distribution of the tumor burden and the degree of liver dysfunction as summarized in Fig. 1.

Single tumors that develop on patients with absent or compensated cirrhosis (very early and early BCLC stages 0 and A) should be considered for surgical resection. The risk of postoperative decompensation and survival depends on the quantity and quality of the liver remnant and can be estimated using the extent of resection (minor vs. major hepatectomy), functional liver reserve (ALBI (albumin–bilirubin) grade [27], Child–Pugh class [28], MELD (Model for End Stage Liver Disease) score [29, 30], indocyanine green clearance [31, 32]) and/or portal hypertension (hepatic venous pressure gradient [33]). Patients with normal functional liver reserve and no portal hypertension can tolerate major hepatectomies (usually defined as the resection of 3 or more liver segments). Minor hepatectomies can be performed in the presence of mild portal hypertension or slightly impaired functional liver reserve. Any resection is contraindicated in front of marked portal hypertension or impaired liver function. Resection of multiple tumors results in worse outcomes and is generally not recommended, although individual patients may achieve long-term survival [34]. Tumors with vascular invasion are resected in some Asian centers albeit with poor outcomes [35].

Liver transplantation should be considered for oligonodular tumors when resection is not an option based on the above-mentioned criteria. Donor scarcity demands excellent outcomes for transplanted patients. Besides a relatively young age (< 65–70 years old) and lack of significant comorbidities, Milan criteria (single nodule < 5 cm or up to three nodules up to 3 cm) are the backbone of transplant indication [36] and allow a 5-year survival rate above 75%. Different proposals to set the limits slightly beyond the Milan criteria are frequently used but with less strong levels of evidence [37–39]. Macroscopic vascular invasion and extrahepatic spread are an absolute contraindication for liver transplantation.

Thermal radiofrequency ablation (RFA) may result in complete necrosis of most tumors < 3 cm [40]. It is indicated in patients with such small tumors that are not suitable for surgery. For tumors < 2 cm, RFA can even be considered an alternative to resection [41]. Percutaneous ethanol injection is inferior to RFA [42–44] but may be an alternative for tumors ≤ 2 cm in contact with large vessels, bile ducts, or the gallbladder [45–47]. Microwave ablation has no benefit over RFA in randomized trials [48]. However, it is preferred in some centers due to faster ablation times and no requirement for grounding pads.

The arterial vascularization of HCC provides the rationale for intra-arterial therapies. They are the mainstay of the treatment of BCLC stage 0 and A tumors not suitable for resection, transplantation or ablation, and for BCLC stage B tumors that can be targeted superselectively, based on two randomized trials [49, 50]. In conventional transarterial chemoembolization (TACE), doxorubicin or other chemotherapeutic drugs are mixed with the oily contrast Lipiodol and the feeding artery is then obstructed

Table 1 BCLC staging system [26]

	Tumor stage				
	0 Very early	A Early	B Intermediate	C Advanced	D Terminal
Tumor burden	Single < 2 cm	Single or 2–3 nodules < 3 cm	Multinodular, unresectable	Any	Not transplantable
Vascular invasion or metastasis	Absent	Absent	Absent	Present*	Any
Performance status	0	0	0	1–2*	3–4*
Liver function	Preserved	Preserved	Preserved	Preserved	End stage*

All criteria should be fulfilled for stages 0 to C while any of* could be met in stages C and D. Preserved liver function usually means Chil-Pugh A without ascites

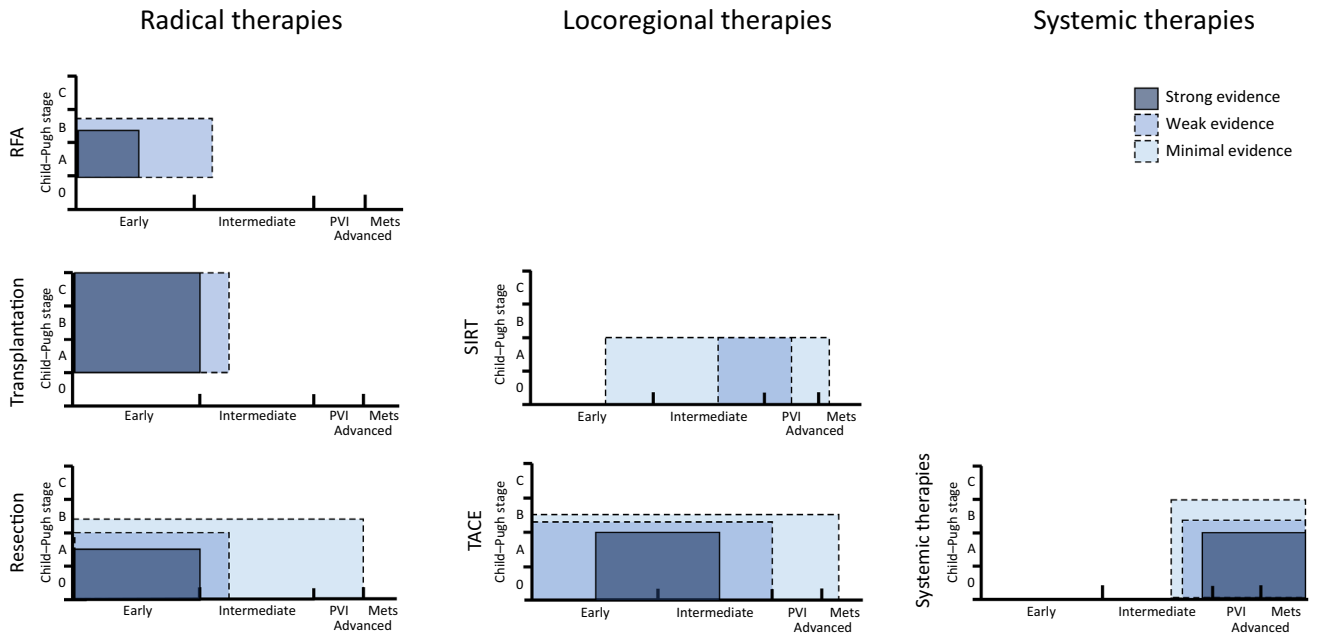

Fig. 1 Patient profile for the different treatment options in HCC according to the strength of the supporting evidence. *SIRT* selective internal radiation therapy or radioembolization, *TACE* transarterial chemoembolization, *PVI* portal vein invasion, *Mets* metastasis

with gelatin foam or calibrated beads. Doxorubicin-eluting beads are not more effective but provide a more standardized way of performing TACE and reduce the systemic side effects of doxorubicin [51]. However, there is no TACE platform that can be considered highly standardized. Based on the same rationale, radiation can be selectively delivered to the tumor using microbeads loaded with radioactive isotopes such as ^{90}Yttrium. This selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE) has not been compared to TACE in large randomized trials in good TACE candidates (BCLC stage A or B) although small randomized trials and large cohort series suggest that similar outcomes may be expected [52–56]. SIRT can be safely administered to patients with large tumors or in the presence of portal vein thrombosis, where TACE carries a higher risk of complications [57, 58].

Systemic therapies have recently joined the armamentarium against HCC (Table 2). HCC is a highly chemoresistant tumor, and no cytotoxic drug, alone or in combination, has shown significant activity. Sorafenib was the first agent that showed the ability to prolong survival of patients at BCLC C stage or at BCLC B stage after progression to TACE [59, 60]. The activity of sorafenib seems to be limited to this population with fairly advanced tumors. When used in combination with TACE or after TACE, sorafenib failed to prolong time to progression or overall survival [61, 62]. Very recently, a Japanese trial has shown a prolongation in progression-free survival among patients receiving sorafenib in combination with TACE versus TACE alone [63]. However, an innovative endpoint of progression-free survival was described in this trial as the time to death or untreatable progression (defined as the time to the date of a state when TACE continuation is not possible due to untreatable tumor progression, deterioration to Child–Pugh C or appearance of vascular invasion or extrahepatic metastasis) and survival data have not been reported yet. Sorafenib is unable to prolong time to recurrence compared to placebo in patients with confirmed disease-free status after resection or RFA [64].

After almost a decade of failing clinical trials, four agents have joined sorafenib in the systemic agents toolbox based on positive randomized trials. Lenvatinib proved to be non-inferior to sorafenib in prolonging the survival of patients who were naïve to systemic treatment [65]. Regorafenib prolonged the survival compared to placebo of patients that were able to stably tolerate a relevant dose of sorafenib and progressed radiologically [66]. Cabozantinib prolonged the survival of patients that were intolerant or had progressed to up to two lines of systemic therapy including sorafenib [67]. Ramucirumab initially failed to show a benefit in patients that were intolerant or had progressed to sorafenib but after a post hoc analysis a subsequent trial showed that this intravenous drug prolonged the survival of the subgroup of patients with serum AFP $>$ 400 UI/ml [68].

Finally, immunotherapy has irrupted in the field of liver cancer as in many other tumor types. Nivolumab and pembrolizumab have been tested in single-arm trials. They consistently produce very durable objective remissions that

Table 2 Systemic agents for the treatment of HCC

Agent	Mechanism of action	Main molecular targets	Indication	Source of evidence
Sorafenib	Anti-angiogenic Anti-proliferative	VEGFR, PDGFR, c-raf, b-raf, RET	1L in advanced stage	2 RCT versus placebo 1 RCT versus doxorubicin
Lenvatinib	Anti-angiogenic Anti-proliferative	VEGFR, PDGFR c-kit, FGFR, RET	1L in advanced stage (no main PVT or tumor involvement > 50%)	1 RCT versus sorafenib (non-inferiority)
Regorafenib	Anti-angiogenic Anti-proliferative	VEGFR, TIE2 c-kit, FGFR, b-raf	2L post-sorafenib (progressors tolerant to ≥ 400 mg/d sorafenib)	1 RCT versus placebo
Cabozantinib	Anti-angiogenic Anti-proliferative	VEGFR c-met, AXL, RET	2L post-sorafenib (intolerants or progressors to 1–2 lines)	1 RCT versus placebo
Ramucirumab	Anti-angiogenic	VEGFR 2	2L post-sorafenib (intolerants or progressors with AFP > 400 UI/ml)	1 RCT versus placebo
Nivolumab	Immune stimulant	PD-1	2L post-sorafenib (intolerants or progressors to 1–2 lines)	1 single-arm trial
Pembrolizumab	Immune stimulant	PD-1	2L post-sorafenib (intolerants or progressors to 1–2 lines)	1 single-arm trial

result in prolonged overall survival in around 15% of sorafenib-experienced patients [69, 70]. Nivolumab has been approved as second-line treatment in several countries based on these data, and pembrolizumab has recently been approved by the US Food and Drug Administration.

What are the New Treatments on the Pipeline and Their Possible Molecular Drivers

The landscape of molecular derangements in HCC is increasingly well known [71]. Molecular subgroups are defined by whole-genome-based analysis of DNA aberrations or gene expression. Several activated oncogenic signaling routes have been identified. Unfortunately, some of them cannot be targeted by available drugs and those that can be targeted seem to be less relevant or redundant. Yet, agents targeting fibroblast growth factor and TGF-β are under investigation.

The enthusiasm prompted by immunotherapies needs confirmation. We await the results of two randomized trials comparing nivolumab versus sorafenib as first-line therapy and pembrolizumab versus placebo as second-line therapy after sorafenib. A recent press release reported that the latter failed to meet the two co-primary endpoints of overall and progression-free survival although both endpoints were significantly improved in the pembrolizumab-treated cohort. Dual blockade of different immune checkpoint molecules is also being compared to sorafenib as first-line treatment. In less advanced patients, immune checkpoint inhibitors, alone and in doublets, are being tested in phase 3 trials in combination with TACE and as adjuvant therapy after resection or ablation in patients at high risk of recurrence. The focus is now in testing combination therapies. There is little overlap between the toxicities of multikinase inhibitors or antiangiogenics and immune checkpoints inhibitors. Preclinical evidence of synergistic activity is lacking but at least an additive effect could improve the efficacy of systemic therapies. Early data are available from two of these combinations, lenvatinib in combination with pembrolizumab [72] and bevacizumab in combination with the anti-PD-L1 inhibitor atezolizumab [73]. An encouraging 32% overall response rate using RECIST 1.1 criteria has been reported for the latter.

Role of Interventional Radiology

Interventional radiology plays a pivotal role in management of HCC. Regarding therapy, in the setting of early HCC, interventional radiology may offer valid therapeutic alternatives for patients with liver cirrhosis and early tumors not suitable for surgical approaches. Local ablation of small nodules may be achieved through a variety of techniques from the most traditional techniques, such as alcohol ablation and radiofrequency ablation, to the newest, such as cryoablation, microwave or laser ablation or nonthermal energy ablation (irreversible electroporation). Most of these innovative strategies are still under

investigation, and comparative studies between the different techniques are not available yet.

As discussed above, the availability of different minimally invasive techniques places the interventional radiology as the first therapeutic resource for the treatment of intermediate-stage HCC (transarterial therapies) [2]. Transarterial therapies may be delivered in a superselective fashion, targeting specific liver area or single nodules and sparing the surrounding non-tumoral parenchyma [74, 75]. This may have a critical importance especially in patients with liver cirrhosis where it is essential to preserve the non-tumoral liver. Most of these transarterial therapies may be repeated several times when incomplete response is achieved or in case of tumor recurrence with an excellent safety profile, in expert hands [76].

In tertiary centers, different endovascular procedures may be also used in the setting of early tumors suitable for resection or in the setting of liver transplantation. Indeed, portal vein embolization may be used in selected cases to increase the volume of remnant liver, in an attempt to allow the resectability of large tumors. Similarly, SIRT may induce spared hemiliver hypertrophy at the same time of achieving tumor control and can be considered, in selected candidates, as an alternative to portal vein embolization [77]. In the setting of waiting list, locoregional therapies, TACE and SIRT, may be also used as bridging therapies, aiming to prevent tumor progression while waiting [78]. However, no RCT has analyzed the effects of TACE or SIRT in this setting and the risk–benefit ratio of transarterial procedures in candidates for liver transplantation is not completely known and its implementation needs to be evaluated case by case.

Suggested Readings

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http://www.hcc-olt-metroticket.org/#calculator_pre

Compliance with Ethical Standards

Conflict of interest Delia D'Avola has received consulting fees from Alnylam and Novartis. Bruno Sangro has received consulting and/or lecture fees from Adaptimmune, Astra Zeneca, Bayer, Bristol-Myers-Squibb, BTG, Eli Lilly, Onxeo, Sirtex Medical and Terumo. Jose I Bilbao has received consulting and/or lecture fees from Sirtex Medical, Terumo, Gore, Cook, Boston Scientific, iVascular.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, informed consent is not required.

Consent for Publication For this type of study, consent for publication is not required.

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