Therapeutic Strategies for Hepatocellular Carcinoma: New Advances and Challenges

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Opinion statement

Hepatocellular carcinoma (HCC) is the fastest growing malignancy in the USA, and its prognosis remains poor with a 5-year survival around 12 %. Clinical data demonstrate that 85 % of cases occur in individuals with underlying cirrhosis and only 15 % develop in non-cirrhotic livers. Therefore, American and European guidelines recommend routine HCC screening for high-risk individuals (patients with cirrhosis) with abdominal ultrasound every 6 months. Once a lesion is identified or suspected on ultrasound, dynamic imaging is then indicated. The diagnosis of HCC is established in a patient with cirrhosis when a lesion measures at least 1 cm in diameter and demonstrates arterial enhancement and portal venous washout on contrast-enhanced computerized tomography or magnetic resonance imaging. Indeterminate lesions should be followed with surveillance imaging or further investigated with biopsy according to the level of suspicion for malignancy. Given the clinical, pathological, and molecular heterogeneity of HCC, there are multiple therapeutic modalities available. These may be curative, such as surgical resection, liver transplantation, and local ablation, or palliative, such as catheter-directed therapies (transarterial chemo, radio, or bland embolization), and systemic therapy (sorafenib). Patients with a single lesion, good performance status, and preserved liver synthetic function should be offered curative surgical resection or ablation therapy. Patients with HCC and decompensated liver disease should be evaluated and listed for liver transplantation. For unresectable disease or tumor burden precluding transplantation or curative ablation, palliative therapeutic modalities should be offered. Sorafenib is indicated for patients with vascular invasion and/or extra-hepatic metastasis if the estimated life expectancy is more than 3 months. Systemic internal radiation therapy using yttrium-90

microspheres in cases of multifocal bi-lobar disease and/or portal vein occlusion is an emerging therapy. Best supportive care is recommended for patients who lack the hepatic reserve to tolerate therapy.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent malignancy and the second leading cause of cancer-related death in men worldwide [1]. It affects >700,000 lives/year worldwide and more than 20,000 Americans annually [2]. HCC is on the rise, and its incidence has almost tripled in the last three decades [3]. The majority of cases (~85 %) arises in a background of cirrhosis; only 15 % of HCC occurs in a non-cirrhotic liver, such as in patients with chronic hepatitis B virus (HBV) infection, hepatic adenoma, chemical exposures (e.g., aflatoxin B1), and, rarely, inherited liver diseases. For this reason, in clinical practice, cirrhosis is recognized as a high-risk preneoplastic condition, and national and international liver and oncology societies recommend HCC surveillance with abdominal ultrasound every 6 months for all patients with cirrhosis [4•, 5•, 6, 7]. The incidence of HCC among patients with underlying cirrhosis ranges 3–7 % per year [8]. Despite implementation of routine screening in high-risk individuals and improvement in early detection when treatment can be most effective, prognosis remains poor with a 5-year survival rate of just 12 % [2].

HCC is a clinically, pathologically, and molecularly heterogeneous disease and is one of the few solid organ malignancies resistant to conventional chemotherapy. Hence, while multiple locoregional modalities have sprung up in this vacuum, there is only one FDA-approved systemic therapy.

Diagnosis of Hepatocellular Carcinoma

According to the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines, the diagnosis of HCC can be established either by non-invasive imaging criteria or histologically. In fact, HCC is the only malignancy for which a definitive diagnosis may be reached in the absence of a tissue specimen. HCC is a highly vascular tumor that derives blood supply mainly from the hepatic artery rather than from the portal vein, resulting in a characteristic dynamic imaging pattern of arterial enhancement and portal venous washout. National and international liver societies agree that in patients with cirrhosis, diagnostic criteria are met by a single dynamic imaging study (contrast-enhanced computerized tomography or magnetic resonance imaging) that shows a hepatic lesion greater than or equal to 1 cm in diameter demonstrating this characteristic pattern [4•, 5•]. In all other circumstances, particularly in the setting of atypical imaging in any patient or the absence of cirrhosis, biopsy is indicated for diagnostic purposes. There are no robust data regarding the risk of seeding HCC along the needle track during biopsy; the risk in most small series is 0–1.6 % [9–11], but one often quoted meta-analysis reports a 2.7 % risk [12]. With newer biopsy techniques, the risk is considered trivial and biopsy should be obtained where clinically indicated.

Screening rates for HCC in the USA, even among specialists, are extremely low [13]. The only other US society to endorse routine screening for HCC in patients with cirrhosis is the National Cancer Clearinghouse Network (NCCN) [6]; therefore, patients who are not already under the care of a gastroenterologist or hepatologist are far less likely to be screened [14, 15]. Screening for HCC is

still a matter of considerable controversy and is far from gaining widespread acceptance in the fields of primary care and preventive health.

Management of Hepatocellular Carcinoma

Once the diagnosis of HCC is established, several factors need to be carefully considered in order to decide on the best plan of care. Multidisciplinary review of each patient's performance status, medical comorbidities, hepatic reserve (presence or absence of cirrhosis, presence or absence of hepatic decompensation), imaging (size, number, and location of lesions), and pathology if available is fundamental. A multidisciplinary conference or Liver Tumor Board should meet regularly with routine attendance of specialists involved in the treatment of HCC: hepatologists, hepatobiliary and transplant surgeons, diagnostic and interventional radiologists, pathologists, and oncologists. This multispecialty approach can be particularly valuable in attaining an expert consensus in uncommon clinical presentations where there is no clear evidence-based guidance [16•].

Unlike most malignancies, HCC largely arises in a diseased liver, so all therapies must be considered in the context of the patient's underlying liver function and performance status [17]. Specifically, when a patient is not a transplant candidate and has Child-Turcotte-Pugh (CTP) class C cirrhosis, best supportive care is recommended independently of tumor burden, since the patient's 1-year survival rate based exclusively on underlying advanced liver disease is less than 50 % [18]. Staging and treatment decisions are guided by the internationally validated Barcelona Clinic Liver Cancer (BCLC) staging system [19] as recommended by both AASLD and EASL. In brief, the BCLC staging system accounts for tumor size, extent of the primary tumor, underlying liver function, and Eastern Cooperative Oncology Group performance status and integrates the Okuda stage and CTP score.

Another unique aspect of HCC biology is the concept of recurrence. Since underlying cirrhosis predisposes to HCC development, two clear patterns of recurrence occur in HCC. A 2-year mark has been arbitrarily used to distinguish between early dissemination (<2 years) of the primary tumor versus late recurrences (>2 years) possibly due to new malignant clones. Further investigation using genetic and genomic approaches is needed to confidently distinguish between primary tumor recurrence versus de novo HCC. This molecular distinction, while likely relevant to clinical trial design, does not yet affect clinical decision-making.

Multiple treatment modalities are available for HCC (Figs. 1 and 2). They can be divided in two major categories: (I) therapies with curative intent and (II) therapies with palliative intent (summarized in Table 1).

Therapeutic Modalities With Curative Intent

Surgical Resection

Resection is the treatment of choice for single lesions in patients without cirrhosis or those with very well-compensated cirrhosis (normal bilirubin and
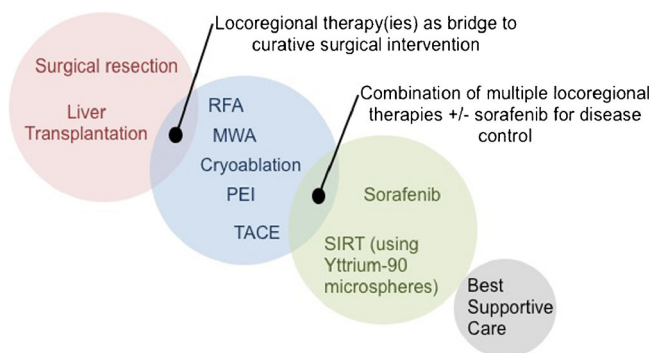
Fig. 1. Schematic outline of step-wise HCC management approach from surgical and ablative procedures to best supportive care, when all above therapeutic modalities have been exhausted and the patient is not a candidate for further interventions. *RFA* radiofrequency ablation, *MWA* microwave ablation, *PEI* percutaneous ethanol injection, *TACE* transarterial chemoembolization, *SIRT* systemic internal radiation therapy.

the absence of clinically significant portal hypertension, e.g., (HVPG) less than 10 mmHg [4•]). Patients without cirrhosis usually tolerate major liver resections with low morbidity; however, patients with cirrhosis need to be appropriately selected to diminish the risk of hepatic decompensation or liver failure, particularly if a right hepatectomy is considered. Moreover, in the era of curative hepatitis C virus (HCV) therapy, patients with HCV-related HCC should be carefully evaluated for curative resection and/or ablative therapy followed by
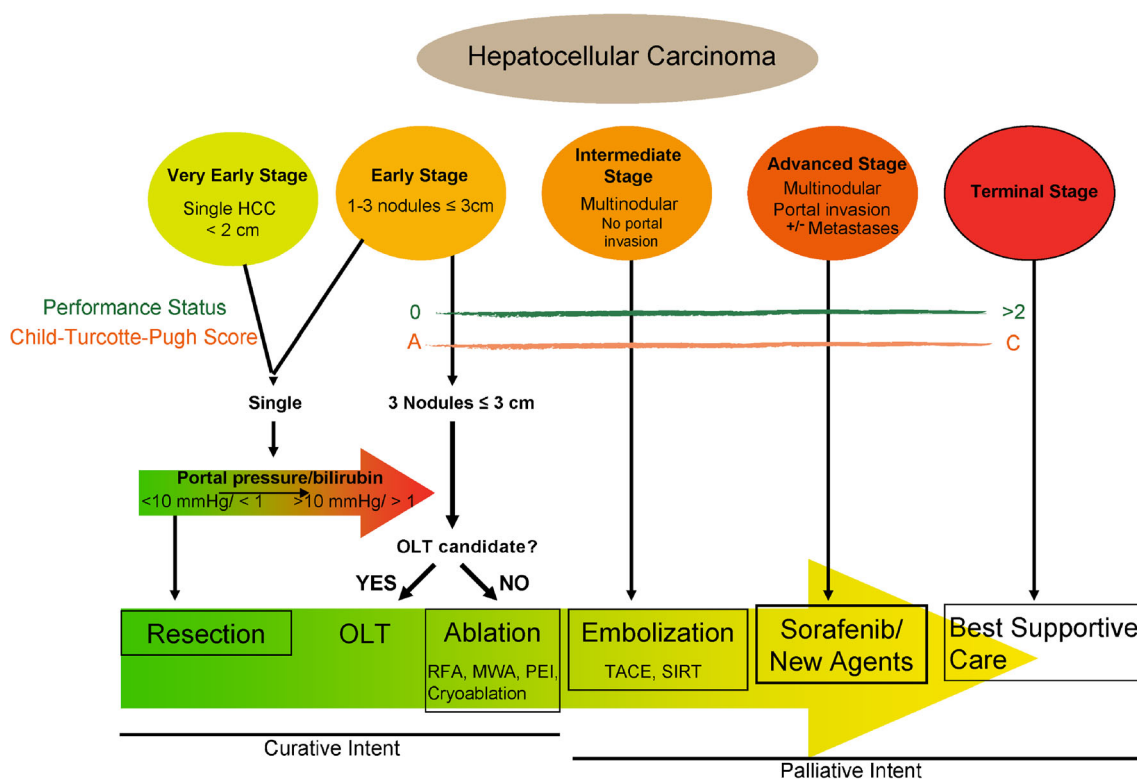

Fig. 2. Flowchart adapted from The Barcelona Clinic Liver Cancer (BCLC) staging algorithm [19]. *RFA* radiofrequency ablation, *MWA* microwave ablation, *PEI* percutaneous ethanol injection, *TACE* transarterial chemoembolization, *SIRT* systemic internal radiation therapy.

Table 1. Summary of therapeutic modalities for HCC with curative versus palliative intent

HCC therapeutic modalities	
Curative intent	Palliative intent
Surgical resection	Systemic therapy: sorafenib
Liver transplantation	External beam radiotherapy
Locoregional ablation	Catheter-directed locoregional therapies
Radiofrequency ablation (RFA)	Transarterial embolization (TAE)
Microwave ablation (MWA)	Transarterial hemoembolization (TACE)
Cryoablation	Selective internal radiation therapy (SIRT, using Yttrium-90 microspheres)
Percutaneous ethanol injection (PEI)	Best supportive care
	Palliative care
	Hospice

HCV treatment, which may ultimately arrest the progression of hepatic fibrosis and mitigate the risk of HCC recurrence, similar to what has been observed in HBV-associated HCCs after the introduction of HBV antiviral therapy [20••].

Neo-adjuvant or adjuvant therapies have not shown any benefit and therefore are not recommended. A phase III randomized, double-bind, placebo-controlled trial of adjuvant sorafenib after resection or ablation to prevent recurrence of HCC (STORM trial) showed no benefit in recurrence-free survival to patients who received sorafenib after a curative intervention with surgical resection or ablation.

Tumor recurrence is the major complication (5-year recurrence risk is as high as 70 %), in which case the patient should be re-assessed and re-treated accordingly.

Liver Transplantation

HCC is the only solid organ malignancy for which transplantation offers a cure. In 1996, Mazzaferro and colleagues reported the first prospective cohort study describing a group of HCC patients for whom liver transplantation resulted in excellent outcomes (>85 % 5-year recurrence-free survival), establishing the Milan Criteria: a single HCC no greater than 5 cm or up to three tumors none greater than 3 cm with no vascular or extrahepatic tumor burden on pre-transplant imaging [21]. For the last 18 years, these results have been replicated worldwide [22], and the Milan Criteria remain the standard for patient selection for liver transplantation. The biological heterogeneity of HCC, with some tumors being indolent and others more aggressive, has led many investigators to consider expanded criteria for liver transplantation, the most notable of which is the San Francisco Criteria [23]. These criteria, also showing excellent recurrence-free survival rates, have been adopted in parts of the USA and have also led to the acceptance of "downsizing/downstaging criteria" for tumors that can be treated to within acceptable limits for transplantation [24].

Locoregional Ablation

Less than 40 % of patients with HCC are surgical candidates. Percutaneous locoregional ablative therapy is an excellent alternative approach in many cases. Radiofrequency ablation (RFA) is the most commonly used ablative technique.

For small tumors, three randomized clinical trials (RCTs) showed no significant difference in overall or recurrence-free survival when comparing RFA to surgical resection [25, 26, 27•]. However, a more recent RCT suggests that percutaneous RFA is more likely to be incomplete in certain locations within the liver, and laparoscopic RFA or surgery may be a better option [27•].

High-frequency microwave ablation (MWA) is another form of tumor ablation and has been used in China and Japan for several years. A single RCT comparing MWA and RFA in small HCCs showed equivalent complete response rate, 2-year local recurrence rate, complication, and residual disease rates [28]. However, tumors were fully ablated with fewer sessions of RFA compared to MWA. No long-term survival data were reported.

Other forms of ablation such as ethanol injection (PEI) and cryoablation have been abandoned as first-line treatment in favor of RFA, which is associated with a significantly lower local recurrence [29–31]. PEI and cryoablation are reserved for lesions in anatomic areas with higher risk of local thermal complications (e.g., abutting the diaphragm, gallbladder, or other viscera).

Therapeutic Modalities With Palliative Intent

When a patient is not a candidate for curative therapies, other therapeutic modalities that focus on prolonging life or bridging the patient to transplantation should be considered. These include bland particle and chemoembolization, systemic internal radiation therapy (SIRT), external beam radiotherapy, and systemic therapy with sorafenib.

Transarterial Bland Particle Embolization and Chemoembolization

Because HCC derives blood supply mainly from the hepatic artery rather than from the portal vein, embolization of the feeding hepatic artery can eliminate the tumor's blood supply leading to tumor necrosis. Transarterial embolization is indicated for palliation and often as a bridge to liver transplantation in the treatment of unresectable (non-metastatic) HCC not suitable for local ablation.

A systematic review of cohort and randomized studies showed no survival benefit of transarterial chemotherapy (TACE) as compared to bland particle embolization alone [32], reporting a trend towards increased survival with TACE. AASLD guidelines recommend TACE rather than bland particle embolization for the treatment of HCC, but the overall evidence is weak. TACE theoretically provides both the cytotoxic effect of local chemotherapy with the obliteration of vascular flow to the tumor. The goal is to eliminate the arterial blood supply to the tumor as highly selectively as possible, in order to avoid compromising blood supply to the adjacent liver parenchyma, thus diminishing the risk of hepatic decompensation or failure. Contraindications to TACE include portal vein and/or biliary obstruction, encephalopathy, and CTP class C cirrhosis.

SIRT and External Beam Radiotherapy

HCC is a radiosensitive tumor, but the use of external beam radiotherapy has been limited by the intrinsic radiosensitivity of the liver. An alternative to avoid injury to the background parenchyma is to infuse radioactive isotope-tagged microspheres, such as yttrium-90 (Y90), selectively into the tumor via the hepatic artery and its branches. SIRT has been called radioembolization, but it is

a misnomer because no vessel is embolized. While Y90 has an acceptable safety profile, studies comparing Y90 to other palliative locoregional therapies are lacking. Hence, there is still no evidence-based consensus as to the optimal use of this therapy. In clinical practice, it is used in patients with unresectable bilobar HCC and a life expectancy greater than 3 months [33]. Another clinical scenario in which SIRT maybe preferred is where TACE is contraindicated due to the presence of portal vein occlusion [4•, 34, 35]. Y90 therapy does not involve vascular obliteration of the feeding hepatic artery and therefore would not cause hepatic infarction in an area lacking portal vein supply. An absolute contraindication to Y90 therapy is the presence of shunts to the lung or flow to the gastrointestinal tract that cannot be corrected by catheter techniques. Relative contraindications include prior radiation involving the liver and persistent hyperbilirubinemia as a marker of poor hepatic reserve.

Recent phase I and II clinical trials using stereotactic body radiotherapy (SBRT) for locally advanced HCC provided data to consider SBRT for sustained local control in patients for whom curative local treatment options are not available [36]. These studies led to the design of the ongoing randomized phase III study (RTOG1112: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1112) of sorafenib versus SBRT followed by sorafenib in BCLC intermediate (B) or advanced (C) patients.

Systemic Therapy: Sorafenib

Sorafenib, a multi-tyrosine kinase inhibitor, is the only FDA-approved systemic therapy for advanced HCC and has a modest 2-month survival benefit based on the SHARP and Asia-Pacific trials [37, 38]. A retrospective subgroup analysis of the SHARP trial identified a greater survival benefit for HCV-related HCC patients (5 months instead of 2 months). Most of the data generated by these trials was observed in CTP class A patients.

Sorafenib in the clinic: who and when to treat? It is well accepted that sorafenib should be offered to patients with unresectable disease, good performance status, and preserved liver reserve. Our personal experience suggests that starting sorafenib at lower doses than the recommended 800 mg daily with careful titration to a tolerable dose minimizes side effects and maximizes compliance. Common side effects include hand-foot-skin reaction, diarrhea, hypertension, and fatigue, which can be mitigated with urea cream application and antidiarrhea and antihypertensive medications, respectively.

Sorafenib has a broad inhibitory profile in the following pathways: Raf1, B-Raf, vascular endothelial growth factor receptor (VEGFR)-2, platelet-derived growth factor receptor (PDGFR), and c-kit. In clinical practice, a wide spectrum of tumor responses to sorafenib is described, but unfortunately no reliable biomarkers are available to accurately predict a patient's response. Hence, response can only be assessed with interval imaging following a trial of the drug.

Sorafenib as an adjuvant therapy is not currently recommended due to lack of evidence-based data. However, the linear approach currently recommended for HCC treatment, resorting to sorafenib after local therapies, seems antithetical to current multimodal practices in oncology. The personalized medicine achieved for breast and lung cancers relies on a thorough understanding of the molecular and genetic bases of those malignancies. While this investigation is ongoing and increasing exponentially in the field HCC, few treatment targets have emerged.

Interestingly, there are studies suggesting that locoregional therapies may stimulate cytokine production, such as VEGF, known to drive tumor angiogenesis and metastasis. Given the antiangiogenic effects of sorafenib, its use is conceivable at any point along the treatment paradigm and clinical trials should be designed to incorporate sorafenib in combination therapies [39•].

Best Supportive Care

When all above therapeutic modalities have been exhausted and the patient is not a candidate for further interventions, including potential clinical trials using experimental agents, best supportive care should be provided by the patient's primary hepatologist and/or oncologist with the goal of minimizing the side effects of hepatic decompensation and tumor progression. Palliative care services that integrate symptom management with a holistic approach to defining goals of care and planning the end of life should be integrated into the treatment plan as early as possible to maximize quality of life and minimize patient and caregiver anxiety.

Radiological Criteria for Diagnosis and Surveillance of Hepatocellular Carcinoma

As discussed above, HCC is the only malignancy for which a definitive diagnosis may be reached exclusively by a single dynamic imaging study. Thus, radiologists have developed systems of standardized terminology and criteria to interpret and report CT and MR imaging findings of the liver, with the goal of reducing inter-radiologist variability and errors and facilitating quality assurance, physician communication, and patient-oriented research. Here, we briefly review three of the most commonly used imaging criteria: the Liver Imaging Reporting and Data System (LI-RADS) [40], the Organ Procurement and Transplantation Network (OPTN) criteria [41] (http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_273.pdf), and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [42].

LI-RADS

When assessing a liver nodule in patients with cirrhosis or at risk of HCC, LI-RADS criteria include arterial phase hyper-, iso-, and hypo-enhancement characteristics, diameter (<10, 10–19, and >20 mm), and the presence or absence of portal venous phase washout, "capsule," and/or growth. By combining these factors, LI-RADS delineates the following eight categories: LR-1, definitely benign; LR-2, probably benign; LR-3, intermediate probability for HCC; LR-4, probably HCC; LR-5, definitely HCC; LR-5V, definitely HCC with tumor in vein; LR-M, probably malignant, not specific for HCC; and LR-treated, treated observation. In addition, the updated LI-

RADS 2014 version describes a subcategory designated LR-5g for lesions with ≥50 % diameter increase in ≤6 months which dovetails with the OPTN 5A-g definition (see below for details).

OPTN Criteria [41]

As previously mentioned, HCC is the only solid organ malignancy for which transplantation offers a cure. Thus, the OPTN/United Network for Organ Sharing (UNOS) developed and approved the OPTN imaging criteria (http://optn.transplant.hrsa.gov/PublicComment/pubcommentPropSub_273.pdf) to bring uniform standards to the diagnosis and staging of HCC among patients on the liver transplant waiting list. UNOS requires all cross-sectional imaging in liver transplant patients to be reviewed at a transplant center where radiologists designate an OPTN classification in their CT and MR liver imaging reports. In summary, the OPTN system for nodules identified in cirrhotic livers are divided in two major classes: class 0, which denotes an incomplete or technically inadequate study, and class 5 which refers to adequate studies that reveal lesions which meet radiologic criteria for HCC. OPTN class 5 nodules are classified into five subgroups:

1. Class 5A, a lesion ≥1 and <2 cm measured on late arterial or portal venous phase images; with increased contrast enhancement on late arterial phase, washout during the later contrast phases, and peripheral rim enhancement (capsule/pseudocapsule)

2. Class 5A-g, a lesion ≥1 and <2 cm measured on late arterial or portal venous phase images; with increased contrast enhancement on late arterial phase showing growth by ≥50 % documented in ≤6 months

3, Class 5B, a lesion with maximum diameter between 2 and 5 cm, increased contrast enhancement on late arterial phase, and either washout on portal venous/delayed phase or peripheral rim enhancement (capsule/pseudocapsule) or growth by ≥50 % documented in ≤6 months (OPTN class 5B-g)

4. Class 5T, refers to any residual lesion or perfusion defect at the site of a prior HCC that has undergone regional treatment

5, Class 5X, lesions ≥5 cm with increased contrast enhancement on late arterial phase and either washout on portal venous/delayed phase or peripheral rim enhancement (capsule/pseudocapsule), describing HCC lesions beyond Milan criteria

mRECIST

In clinical medicine, imaging studies are the routine objective method used by medical providers to assess tumor response to a variety of anticancer treatments. RECIST classification is widely used for solid tumors, whereas mRECIST criteria apply exclusively to HCC. In contrast to other solid malignancies, most of the therapies used for HCC treatment are locoregional and they frequently cause morphological changes and persistent scars. For that reason, mRECIST quantifies the size of viable tumor (the portion of the tumor that continues to show increased contrast

enhancement on late arterial phase after treatment) instead of measuring the size of the entire hepatic lesion, which may or may not contain residual and/or recurrent disease.

Ongoing Clinical Trials and New Systemic Agents

To date, with the exception of sorafenib, all phase III studies testing other molecular therapies failed to show any survival benefit for patients with HCC [43]. These negative results highlight the unique toxicity profile of patients with underlying liver dysfunction and the complexity of clinical trial design in this heterogeneous cancer.

For simplicity, systemic therapies can be divided in three main groups: (1) immunotherapies; (2) hormonal manipulation; and (3) molecular therapies [17].

Cancer immunotherapy manipulates the immune system to fight cancer, using cytokine-based therapies, antibody therapies, cell-based therapies, and oncolytic vaccines [44–47].

Cytokines

Immunomodulator, antiproliferative, and antiangiogenic effects of interferon alpha have been explored in the treatment and prevention of recurrence of HCC, but no clear benefit was achieved [48–50]. Modulation of the tumor immune response has been investigated using other cytokine-based therapies without significant success.

Antibody Therapies

Antitumor activity has been demonstrated by several monoclonal antibodies against many different solid tumors. However, to date, monoclonal antibodies have failed to show any benefit in the treatment of HCC. Phase I dose escalation of nivolumab (anti-PD1) in patients with advanced HCC with or without chronic viral hepatitis (clinical trial: NCT01658878) [51] illustrates one of many ongoing studies exploring the potential role of monoclonal antibodies in HCC therapy.

Cell-Based Therapies

These therapies include the use of either expanded effector immune cell subsets [52] or dendritic cells pulsed with HCC tumor antigens to augment antitumor responses [53, 54]. These therapeutic modalities are still experimental with limited clinical data.

Oncolytic Vaccines

These vaccines were developed based on a few reports relating viral infections to solid tumor regression [55], and they target tumor-restricted signaling pathways for viral replication and tumor necrosis. A phase II study using JX-594, an oncolytic and immunotherapeutic vaccinia virus, in patients with advanced HCC showed promising results in tumor response and overall survival [46].

In the past, hormonal manipulation was explored in the treatment of HCC; however, antiestrogen [56–59], antiandrogen [60], and long-acting somatostatin analog (octreotide) [61] therapies showed no benefit in patients with advanced HCC.

Over 250 early phase clinical trials of molecular targeted therapies for HCC are currently ongoing, and approximately 50 have been tested. These include antiangiogenic agents, epidermal growth factor receptor (EGFR) inhibitors, MEK inhibitors, mTOR inhibitors, and histone deacetylase inhibitors, among others [62]. In the treatment of advanced HCC, sunitinib (VEGFR, KIT, and PDGFR inhibitor); brivanib (fibroblast growth factor receptor (FGFR) and VEGFR inhibitor); linifanib (VEGFR and PDGFR inhibitor); and erlotinib (EGFR inhibitor) have recently failed to demonstrate any survival benefit when used as first-line treatment. As second-line treatments for advanced HCC, regorafenib (VEGFR, TIE2, and PDGFR inhibitor), ramucirumab (VEGFR inhibitor), and tivantinib (MET inhibitor) are currently being tested [63], whereas everolimus (mTOR inhibitor) has recently shown a lack of benefit (EVOLVE-1 trial) [64].

HCC is a genetic disease that largely results from somatic mutations as well as epigenetic modifications. In the era of massively parallel sequencing, the HCC mutational landscape has been characterized by several groups [65–71], but this knowledge has not yet translated to advances in diagnosis, management, or prognosis of patients suffering from HCC. Thus, clinical trials designed with HCC molecular profiling have been recently suggested [63], where patients will be selected according to their individual HCC genomic signature and enrolled in the corresponding specific molecular-based targeted therapy.

Chemopreventive Strategies

Even when HCC is successfully treated and cure is achieved, most patients have underlying liver cirrhosis and face a 70 % 5-year recurrence risk. Thus, in addition to routine surveillance, it is very important to incorporate chemopreventive strategies in patient care as appropriate (Table 2). When possible, prevention is the optimal approach.

Antiviral Hepatitis Therapies

Anti-HBV and anti-HCV therapies are effective in primary and secondary prevention of HCC [72•, 73, 74••]. However, the cost of antiviral therapy is substantial and the use of these therapies should be considered in the context of tumor burden and overall prognosis.

Metformin

According to population-based studies, in diabetic patients, the use of metformin is associated with a decreased risk of developing HCC after

Table 2. Summary of the HCC chemopreventive strategies available in clinical practice

HCC chemopreventative strategies Underlying risk	The following intervention should be considered:
Chronic HBV infection	Anti-HBV therapy
Chronic HCV infection	Anti-HCV therapy
Diabetes	Metformin as first-line therapeutic agent
Metabolic syndrome-associated features	Statins, aspirin

	adjusting for age, gender, HBV and HCV infections, liver cirrhosis, end-stage renal disease, length of diabetes mellitus type II diagnosis, glycemic control, and other diabetic agents [75, 76].
Statins	
	Based on meta-analysis, statin use is associated with a reduced risk of HCC, most predominantly in Asian but also in Western populations [77].
Aspirin	
	A prospective cohort study shows that aspirin is associated with reduced risk of developing HCC (relative risk (RR)=0.59; 95 % confidence interval (CI)=0.45–0.77) [78].
Coffee	
	Interestingly, a meta-analysis incorporating a mix of 16 case-control and case-cohort studies suggested an inverse relationship between coffee consumption and risk of HCC (RR=0.60; 95 % CI=0.50–0.71) [79]. RCTs would be ideal to firmly establish the efficacy of chemoprevention using metformin, statins, and aspirin, but such trials are logistically and ethically challenging [72●]. According to our current knowledge, antiviral therapy should be initiated in patients with chronic HBV and/or HCV on the basis of AASLD guidelines. Statins should be considered in patients with non-alcoholic liver disease and associated features of metabolic syndrome, and metformin should be used as a first-line antidiabetic oral agent in individuals with chronic liver disease and diabetes. In the absence of portal hypertension, aspirin should be considered in patients with advanced liver disease on the basis of The United States Preventive Services Task Force guidelines for prevention of cardiovascular disease [72●].

Conclusion and Future Directions

In summary, the management of HCC has changed substantially in the past few decades, and the five following therapeutic modalities are accepted in clinical guidelines: (1) surgical resection; (2) liver transplantation; (3) RFA; (4) TACE; and (5) systemic therapy with sorafenib. Intra-arterial Y90 therapy is used in clinical practice for patients with multifocal bi-lobar HCC and no extrahepatic disease, but it is not yet

integrated in the clinical guidelines for treatment of HCC due to lack of RCT data.

To date, all the phase III clinical trials evaluating new systemic therapies have been negative. Thus, sorafenib, a multi-tyrosine kinase inhibitor, has remained the only systemic agent for HCC since its FDA approval in late 2007. Biomarker-driven strategies with individual molecular targets are most likely the future for clinical trial design in this field. Further studies targeting fibrosis, and potentially *TERT* promoter mutation, a somatic alteration recently reported in one fourth of cirrhotic preneoplastic nodular lesions [80], are needed in the arena of chemoprevention [81].

Efforts that focus on the implementation of personalized medicine approaches in HCC will probably be a major focus of research in the next decade, and since tissue biopsy in many cases is not clinically required, incorporation of biopsy into trial design coupled with advances in our understanding of circulating tumor DNA [82] and circulating neoplastic cells [83] will also inform the field.

Compliance with Ethics Guidelines

Conflict of Interest
Sílvia Vilarinho declares no conflict of interest.
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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• 	Of importance
•• 	Of major importance

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