Clinics and Research in Hepatology and Gastroenterology 45 (2021) 101590

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PRACTICE GUIDELINES

Hepatocellular carcinoma: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, AFEF, SIAD, SFR/FRI)

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Available online 26 March 2021

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https://doi.org/10.1016/j.clinre.2020.101590

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KEYWORDS
Hepatocellular carcinoma;
French Clinical Practice Guidelines

Abstract
Introduction: This document is a summary of the French Intergroup guidelines regarding the management of hepatocellular carcinoma (HCC) published in March 2019.
Method: It is a collaborative work under the auspices of most of the French medical societies involved in the management of HCC. It is based on the previous guidelines published in 2017. Recommendations are graded in 3 categories according to the level of evidence of data found in the literature.
Results: The diagnosis and staging of HCC is essentially based on clinical, biological and imaging features. A pathological analysis obtained by a biopsy of tumoral and non-tumoral liver is recommended. HCCs can be divided into 2 groups, taking into account not only the tumor stage, but also liver function. HCCs accessible to curative treatments are tumors that are in Milan criteria or with an AFP score ≤ 2, mainly treated by surgical resection, local ablation or liver transplantation. Intermediate and advanced HCCs with no liver insufficiency, accessible only to palliative treatments, benefit from TACE, SIRT or systemic therapy according to the presence or absence of macrovascular invasion or extrahepatic spread.
Conclusion: Such recommendations are in permanent optimization and each individual case must be discussed in a multidisciplinary expert board.

Introduction

These guidelines are a collaborative work under the auspices of most of French medical societies involved in the management of hepatocellular carcinoma (HCC). The aim was to develop practical recommendations using only methodologically established evidence-based guidelines or primary evidence, and to achieve an interdisciplinary consensus. A writing multidisciplinary committee (from 8 medical societies), including experts from different specialties involved in the management of HCC (hepatic surgeon, pathologist, radiation oncologist, medical oncologist and hepatogastroenterologists), reviewed recent literature until May 2020 and wrote a first document. which was modified after further interactive discussions. The last version was finally validated by the steering committee of the participating national societies. The present paper is a summary of the French intergroup guidelines published in March 2019 on the website of the SNFGE society https://www.snfge.org/tncd. Level of evidence was graded according to standard definition (grade A: large meta analysis or large randomized trial; grade B: small randomized trials; Grade C prospective non randomized study). When no scientific evidence was available, recommendations were based on an expert opinion (agreement or not).

Epidemiology

HCC usually develops in cirrhotic patients (75 to 80% of cases), more rarely on non-cirrhotic chronic liver disease and exceptionally on healthy liver. Prognosis and treatments are conditioned not only by the cancer, but also by the liver function.

In France, the incidence of HCC in 2012 was 12.1/100000 in men and 2.4/100000 in women (InVS report). As in other Western countries, there has been a significant increase in incidence of HCC over the past 20 years due to several factors: increasing number of hepatitis C virus (HCV) infections and non-alcoholic steatohepatitis (NASH) related cases, better diagnosis and management of other complications of cirrhosis.

A semestrial abdominal ultrasonography (US) for screening of HCC is recommended in patients with compensated cirrhosis. It enables the diagnosis of HCC at a curable stage in more than 70% of cases and improves overall survival (OS)

in virus-related cirrhotic patients based on the recent results of the French CIRVIR cohort [1].

Diagnosis — Assessment of disease extension

Diagnosis

Evaluation of non-tumoral liver

Cirrhosis can be suspected on clinical, biological (prothrombin ratio, platelets and albumin), endoscopic (esophageal varices) and morphological criteria (liver dysmorphism and signs of portal hypertension). In the absence of these criteria, a non-tumoral liver biopsy is required to prove cirrhosis. The value of non-invasive fibrosis tests (Fibrotest®, Fibrometer®, Hepascore®, Fibroscan®) is not known in the presence of liver tumor.

Diagnosis of HCC

After a craze for non-invasive diagnostic criteria, it is necessary to return to a more conventional attitude in oncology, using histological evidence as a reference for the diagnosis of HCC. Indeed, the systematic use of non-invasive criteria exposes to the risk of diagnostic error, especially in case of nodules less than 3 cm [2]. Intrahepatic cholangiocarcinomas (particularly tumors of 2 to 3.5 cm), may have the same enhancement kinetics as HCC in computed tomography scan (CT-scan) [3] and in magnetic resonance imaging (MRI) [4]. In addition, the absence of pathological diagnosis deeply penalizes research, all the more so as alternatives such as liquid biopsies are not validated. The diagnosis of HCC based on non-invasive criteria is only validated in cirrhotic patients and must be performed by expert radiologists respecting strict technical and interpretive conditions of imaging. If all these conditions are not fulfilled, a biopsy is mandatory.

Non invasive diagnosis. The characterization of nodules is based on their dynamic radiological behavior. Multiphase CT-scan and MRI with injection of contrast and triple arterial, portal and late acquisitions are the two imaging techniques recommended for non-invasive diagnosis of HCC. HCC radiological hallmark is defined by contrast uptake in the arterial phase and washout in the venous/late phase [5]. MRI seems to be superior to CT in terms of sensitivity for the detection and characterization of nodules, particularly to distinguish regeneration nodules from HCC [6]. Contrast-enhanced US (CEUS) is the most recent imaging technique developed to characterize vascular behavior of tumors. It has a better sensitivity than CT to detect hypervascularisation at the arterial phase. However, a recent study showed that cholangiocarcinomas can have the same vascular enhancement and washing dynamics than HCCs in CEUS [7]. Therefore, the role of CEUS is still debated for the non-invasive diagnosis of HCC; CT-scan or MRI should be preferred according to European recommendations [5,8].

The standardization of imaging (technique and interpretation) is an important issue that led to the creation of the Liver Imaging Reporting and Data (LI-RADS) system defining several categories of nodules from benign to HCC [9]. Criteria for HCC diagnosis include tumor size, arterial phase enhancement, washout in the portal phase, enhancing capsule and threshold growth. It could be useful to improve the diagnosis of HCC, especially for small nodules. This system is not yet widely used but should be encouraged to improve standardization of radiological reports and follow-up of patients.

There is no place for fluorine-18 deoxyglucose positron emission tomography (18-FDG PET) in the diagnosis of HCC. Indeed with FDG-PET, hypermetabolism is observed in less than 40% of cases [10] and most of well differentiated HCCs are negative. Another tracer, 11C-choline, could be useful to detect well differentiated tumors. However, the overall detection rate of PET is inferior to CT-scan and MRI [11].

Pathological diagnosis. Biopsy is helpful for the diagnosis of HCC. Indeed, it has been shown that a significant number of patients who were transplanted "for a highly probable HCC of less than 2 cm" diagnosed with non-invasive criteria, were found to have no tumor on the explant [2]. Moreover, some nodules are diagnosed after histological examination as benign nodules, non-hepatocyte lesions (hemangioma, cholangiocarcinoma) or mixed forms (hepatocholangiocarcinoma).

Biopsy is useful for characterization of tumors in a therapeutic goal. Indeed, more and more data show that HCCs are very heterogeneous tumors at a pathological and molecular level, leading to define histological subtypes and molecular classifications [12,13].

Biopsy using 14 to 18-gauge needles, providing good quality material for histological analysis, should be preferred. It must be performed through a significant thickness of non-tumoral parenchyma and with a protection of the parietal path (coaxial needle) to avoid the risk of dissemination (∼2%) [14]. It is now accepted that the risks (bleeding and needle track seeding) are uncommon, manageable, do not affect the course of the disease and should therefore not be considered as an argument against biopsy.

A prospective study evaluated the performance of biopsy for the diagnosis of single nodules less than 2 cm, detected by US. The diagnosis of HCC is confirmed with the first biopsy in 70% of cases and, in case of a first negative biopsy, the false negative rate is still of 39% with the second biopsy [15]. In practice, a "negative" biopsy does not exclude the diagnosis of HCC. In case of negative biopsy of a suspicious nodule, patients should be followed by US and/or CT-scan or MRI every 3 to 6 months. The strategy will be redefined according to the evolution of the nodule; if the size of the nodule increases and remains atypical, a new biopsy is recommended.

Diagnostic criteria.

Pretreatment investigations

Unlike other solid tumors for which therapeutic decision is made according to the TNM classification, there is no consensual prognostic classification for HCC. Many classifications have been proposed (Okuda, BCLC, CLIP, TNM-AJCC . . .) but studies comparing them yielded discordant results.

In practice, treatment of HCC must be discussed in multidisciplinary board; tumor extension, underlying liver function and patient's general condition should be considered.

Recommendations

- Diagnosis of HCC should be based on the pathological analysis of a tumoral and non-tumoral liver fragment ***(recommendation level: expert agreement)***.
- Elevation of alpha-fetoprotein (AFP), even greater than 400ng/mL, is not sufficient to assert the diagnosis of HCC.

Options

- The use of non-invasive criteria for diagnosis of HCC in cirrhotic patients is an option (Fig. 1). While one imaging technique (CT-scan or MRI) is required for nodules beyond 1 cm, a more conservative approach with 2 techniques is recommended in suboptimal settings.
- If the nodule is not typical, a biopsy should be performed.
- Nodules less than 1 cm should be monitored by US (and/or CT-scan or MRI) every 3 months. If there is no increase in diameter within a 2-year follow-up, the usual periodicity of surveillance can be used again ***(recommendation level: grade C)***.

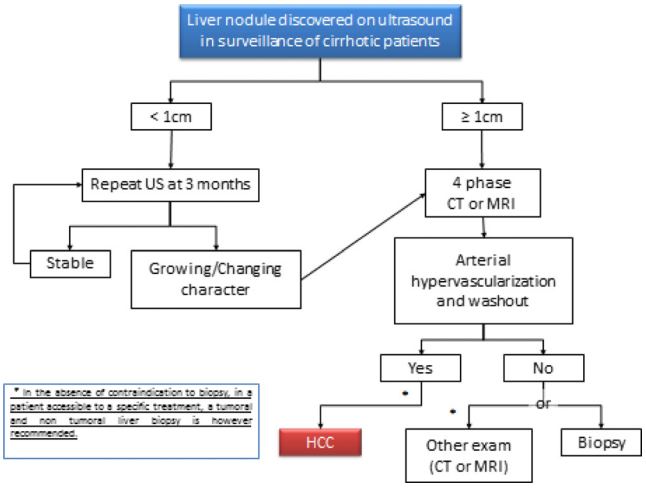


Figure 1 Hepatocellular carcinoma diagnosis algorithm.

Table 1 Child-Pugh score.

Child-Pugh Score			
	1 point	2 points	3 points
Encephalopathy	Absent	Grade 1-2	Grade 3-4
Ascites	Absent	Slight	Moderate
Bilirubin (μmol/L)	< 35	35 to 50	> 50
Albumin (g/L)	> 35	28 to 35	< 28
Prothrombin time (%)	> 50	40 to 50	< 40

Score	Class
5 to 6 points	A
7 to 9 points	B
10 to 15 points	C

Table 2 MELD score.

Model for End Stage Liver Disease (MELD) Score	
MELD =	3.78 x $\log_e$ bilirubin (mg/dL) + 11.20 x $\log_e$ INR + 9.57 x $\log_e$ serum creatinine (mg/dL) + 6.43 (constant for hepatic etiology)

http://www.mayoclinic.org/meld/mayomodel6.html

Assessment of tumor extension

Beyond physical exam and AFP dosing, tumor assessment should include an abdominal MRI combined with a chest CT-scan or a thoraco-abdominal CT-scan, in order to assess tumor morphology (location, number and size of nodules), portal vascularization, and identify pathological lymph nodes or visceral metastasis (lungs, bones, adrenal glands ...). Brain CT-scan and bone scintigraphy must only be performed in case of clinical suspicion of metastasis. Several studies showed that 18-FDG PET CT [16] and 11C-choline PET CT [17] may improve the detection of extrahepatic lesions. A recent publication suggested that 18-FDG PET could modify tumor staging and treatment allocation in patients with HCC [10]. Additionally, uptake on 18F-FDG PET seems to have a potential prognostic value and is associated with poor prognosis and vascular invasion. Therefore, it may facilitate the selection of patients for surgical resection or liver transplantation. However, these results have to be confirmed; PET CT has no place currently in clinical practice to assess tumor extension.

Evaluation of non-tumoral liver function

The evaluation of the underlying liver disease should include at least two parameters: the degree of fibrosis and presence of portal hypertension. In case of severe fibrosis (≥F3), clinical and biological assessment of liver function is necessary to establish the Child-Pugh (Table 1) and Model for end-stage liver disease (MELD) scores (Table 2). The severity of portal hypertension is screened biologically (platelet count) and endoscopically (hypertensive gastropathy esophageal varices).

When a surgical resection is considered, the remaining volume of the liver is evaluated by volumetry. Some teams add "functional" tests (indocyanine green retention rate at 15 min), evaluation of the hypertrophy of the future liver remaining after portal vein embolization, or, in the absence of clear endoscopic signs of portal hypertension, a measure of hepatic venous pressure gradient.

Evaluation of general condition of patient

General condition of patients must be evaluated with the performance status (PS) score (Table 3). Comorbidities and cancers related to the field should be checked for, especially in case of alcoholic cirrhosis and/or smoking: heart and respiratory failure, lung and upper digestive tract cancers.

Clinical features of metabolic syndrome (high blood pressure, diabetes, dyslipidemia) and its complications (in particular coronary disease) should be seeked because fre-

Table 3 Performance status (PS) score.

Performance status score	
Activity	Score
Fully active, capable to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature	1
Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of limited self care, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair	4

quently associated with HCC and to be considered when treatment modalities are proposed.

Recommendations

- Liver function should be evaluated
  - o Clinical and biological evaluation: **Child-Pugh score, MELD score**
  - o Biological and endoscopic signs of portal hypertension: **platelet count, esophageal varices**
- Tumor extension should be assessed ***(recommendation level: expert agreement)***
  - o **AFP**
  - o **Non injected Chest CT-scan and contrast enhanced abdominal MRI**

Options

- Contrast enhanced thoraco abdominal CT-scan if contraindication to MRI

Treatment

Curative treatments

Liver transplantation (LT)

Because LT treats both HCC and the underlying liver disease, it is considered as the best therapeutic option in cirrhotic patients with HCC. Internationally, the consensual indication for LT is HCC strictly localized to the liver, either single and measuring 2 to 5 cm, or 2 to 3 nodules not exceeding 3 cm, in the absence of macrovascular invasion (Milan criteria) [18]. Under these conditions, LT cures two thirds of patients, with results similar to LT for cirrhosis without tumor [19,20]. Retrospective studies have shown 5-year OS rates of 63 to 80% and recurrence rates of 4 to 20% [21]. However, this option suffers from many contraindications (age, physiological state, comorbidities, active alcoholism, refusal of a long-term treatment), as well as scarcity of grafts.

Table 4 AFP score.

AFP score		
Parameters	Class	Points
Tumor size	$\leq$ 3cm	0
	3-6 cm	1
	> 6 cm	4
Number of nodules	$\leq$ 3	0
	> 4	2
AFP (ng/ml)	$\leq$ 100	0
	100 - 1 000	2
	> 1 000	3

In France, HCC represents 30% of liver transplants performed each year. In practice, LT is discussed in 10% of patients with HCC and is performed in 3 to 4% due to mentioned limitations. Two trends have been observed to optimize the results of LT: the first is to encourage resection or percutaneous destruction for single HCCs; the second, on the contrary, is to carefully expand LT indications beyond Milan criteria. In France, this widening of the criteria was not associated with a worse prognosis, the 5-year OS seeming identical to other countries that retained restrictive criteria [22,23]. Consequently, in 2013, the graft attribution criteria changed in France, with the adoption of the AFP score by the French Agency of Biomedicine (Table 4). Indeed, it has been shown in a French cohort that in case of a score $\leq$ 2, results of LT for HCC are excellent [24]. These results were confirmed by a South American [25] and Italian [26] study. In practice, if the score is higher than 2, patient is not eligible for transplantation. If the score is $\leq$ 2, the patient can be registered on the national waiting list for ''HCC'' and in case of a single HCC < 2 cm the accessibility to transplant is only based on the MELD score.

Due to lengthening of waiting time for LT, reaching 12 to 18 months in 2014 in France, there is a risk of tumor progression, raising the problem of pre-transplant therapies. In practice, most centers perform a waiting treatment (using transarteriel chemoembolization (TACE)) or a "first curative treatment" (resection or percutaneous ablation). In case of recurrence after a first curative treatment with an AFP score $\leq$ 2, an accelerated access to a salvage transplant is possible under certain conditions.

LT with living donors may be considered if the waiting period seems excessive, but its place is currently very marginal in France. Down-staging sometimes offers an access to LT in patients with HCC initially beyond criteria, even if the place of down-staging in transplant strategy remains to be refined.

In summary, LT is part of a global strategy for the management of HCC. As a result, the choice of performing pre-transplant therapy and the type of treatment should be established in close partnership with the transplant center.

Surgical resection

In cirrhotic patients, resection of HCC should be considered in patients with preserved liver function (Child-Pugh class

A) and no evidence of portal hypertension [19,27]. The volume of the future remaining liver must exceed 40% of the total hepatic volume. Therefore, when right hepatectomy is considered, prior right portal vein embolization is often required; surgery is performed only if sufficient hypertrophy of the left liver is induced.

Under these circumstances, postoperative mortality is < 5%, and 5-year OS and non-recurrence rates approximately 50% and 30%, respectively [19]. Due to improved selection of patients, perioperative management and surgical technique, recent series have reported a 5-year recurrence-free survival rate of 65% or more [28,29].

It is currently admitted that the best candidate for resection has a single nodule less than 5 cm. Yet, good results in terms of survival after resection of larger and/or multiple tumors have been published by expert centers [30,31]. The presence of homolateral tumor-related portal vein extension may be discussed in an expert center for resection when the contralateral main trunk is free from disease [32]. However, French cohorts showed that surgery does not provide OS benefit compared to sorafenib in this setting [33].

Ideally, resection of HCC should consist in an anatomical resection with margins of 2 cm [34,35].

In the absence of advanced liver fibrosis, resection is the gold standard and the possibilities are greater than in cirrhotic patients, even for large tumors [36].

Local ablation

Percutaneous ablation is an alternative to surgery, usually well tolerated, without significant amputation of non-tumoral parenchyma. Radiofrequency ablation (RFA) and microwave ablation are the most performed techniques and are possible if the tumor is accessible to puncture guided by US or CT and located away from the hilum and large bile ducts. Biliodigestive anastomosis or significant ascites are contraindications to local ablation.

Local ablation represents an effective alternative to surgery for small HCCs under certain conditions. To date, 6 randomized studies [37—42] and 6 retrospective studies [43—48] with propensity score analysis compared surgery with RFA. Most of these studies have limited statistical power because of the small number of patients. Among the randomized studies, only 2 studies were positive in OS and 3 in survival without recurrence in favor of surgery. Of the retrospective studies, two studies were positive for OS in favor of surgery. The majority of studies showed a significant lower number of major complications after RFA compared to surgery. Importantly, the two techniques providing quite similar results, for tumors less than 3 cm, the choice of the best approach for the patient must be done according to the size, the location of the tumor and liver function (Table 5) [49].

New methods as multipolar RFA and irreversible electroporation are being evaluated. The use of multipolar probes may be intended to treat larger tumors, from 3 to 5 cm, but as they do not represent a standard of care, the decision should be based on a multidisciplinary expert board decision, and after considering more appropriate options [50,51]. In practice, percutaneous destruction of HCCs larger than 3 cm remains to be evaluated and should be carefully discussed in multidisciplinary meetings, with expert interventional radiologists and liver surgeons.

Adjuvant treatments

After a curative treatment there is a high risk of recurrence, raising the question of adjuvant therapy. Several trials conducted in Asia, mainly in patients with HCC developed on hepatitis B-related cirrhosis, suggest the benefit of adoptive immunotherapy, but this strategy remains difficult to implement [52]. Sorafenib as adjuvant therapy has been tested in several studies with negative results [53]. There is therefore no evidence of the benefit of adjuvant therapy after a curative treatment of HCC.

However, the management of chronic liver disease improves prognosis and may reduce the risk of recurrence. This concerns the treatment of the underlying liver disease (including HCV), management of comorbidities and prevention of complications related to portal hypertension in case of cirrhosis. In 2016, a retrospective cohort study lead to controversy by suggesting an increased risk of HCC recurrence in patients treated with direct acting antivirals (DAAs) [54]. In a cohort of 58 patients with a median follow-up of 5.7 months, 16 patients (27.6%) developed a recurrence. Following this publication, many teams reported their experience showing discordant results with methodological limitations. However, the analysis of 3 French cohorts including more than 6000 patients with HCV-related cirrhosis, did not find an increased risk of HCC recurrence after DAA treatment [55]. These reassuring results have been confirmed by several other large cohorts and meta-analyses [56,57]. In these patients it is therefore recommended to perform a cross-sectional imaging before DAA treatment, since there is currently no robust enough data to determine the role of DAAs on the evolution of HCC.

External radiotherapy

Stereotactic radiotherapy (6 to 20 Gy/session) has been studied in phase I and II studies with good local control rates at 1 and 2 years (between 90 and 100%), high survival rates (80-90% and 70% at 1 and 2 years respectively) and low complication rates [58—60]. This treatment is offered in certain experienced French centers, with adequate equipment. Stereotactic radiotherapy is preferably intended in patients with single or paucinodular HCC not accessible to surgical resection, LT or local ablation. It applies to HCCs less than 5 cm, because beyond there is a significant risk of hepatitis radiation.

Interesting results have been reported with high-dose focused conformal radiotherapy ($\leq$ 5 Gy / session) in Child-Pugh A patients [61]. High doses of radiation are delivered to the tumor while sparing non tumoral parenchyma. It should only be discussed in patients with single or pauci-nodular HCC less than 5 cm who cannot benefit from other curative options. For larger HCCs (5-10 cm), conformal radiotherapy is possible, but cohort studies and meta-analysis show that it is preferable to associate it with TACE [62].

The best indication would be a unique HCC, 4 to 10 cm, not eligible for surgical resection, local ablation or LT.

Table 5 Criteria for choice between local ablation and resection.

Choice of treatment between local ablation and surgical resection for small HCC			
		Local ablation	Resection
Number and size of nodules	Unique nodule	≤ 3 cm	3 to 5 cm
	≥ 2 nodules	2 or 3 nodules	2 or 3 nodules Same hepatic segment
Localization of nodules		Deep	Superficial
Liver function		Good [a]	Excellent [b]
Portal hypertension		Yes	No

[a] Child-Pugh A.
[b] Criteria to define.

Palliative treatments

Transarterial chemoembolization (TACE)

Two phase III trials and one meta-analysis reported an increased survival (+20% at 2 years) in patients treated with TACE [63]. However the benefit of TACE in HCC remains controversial especially for tumors developed on alcoholic cirrhosis as suggested by the negative results of the FFCD 9402 trial [64]. Two more recent meta-analysis suggest a moderate or very low benefit despite significant objective response rates confirmed by pathology [65].

TACE was initially recommended in patients Child-Pugh A or B7 [16,41] with multinodular HCC, without vascular invasion or extrahepatic spread and in good general condition [27]. However, the most recent recommendations restrain the use of TACE to patients with preserved liver function, Child A without ascites [5]. Segmental portal vein tumor invasion is not an absolute contraindication to TACE but results in this situation are disappointing, without benefit compared to sorafenib [66]; such indications should be discussed in multidisciplinary team sessions.

Several scores have been developed to better identify good candidates for TACE. None of these scores are clearly validated and consensual. Nonetheless, some criteria are associated with a poor efficacy of TACE as hypovascular and/or infiltrative HCC, multinodular bilobar HCCs (more than seven nodules), elevated AFP or increased CRP. In these patients the choice between TACE and systemic therapy must be discussed.

TACE modalities including the chemotherapeutic agent, the type of drug carrier using lipiodol emulsion or drug-eluting beads (DEB), the embolization method and the post-treatment monitoring are not consensual. The current attitude is to encourage selective or supra-selective chemoembolization. A retrospective study suggests that supra-selective embolization is more effective than conventional TACE in terms of tumor necrosis in patients waiting for LT [67]. This may be an option for small HCCs when surgical or percutaneous treatment is not possible, even if the results remain inferior to local ablation techniques [68]. The selectivity of TACE is important to avoid liver damage; in the recent ESMO recommendations, TACE is restricted to tumors less than 10 cm and accessible to supra-selective catheterization [8]. Other TACE modalities using DEB are available with the advantage of a better standardization of the technique. However, despite a better pharmacokinetic systemic profile, the superiority over conventional TACE using lipiodol has not been demonstrated in terms of survival [69]. Moreover, DEB induce higher liver toxicity than lipiodol [70,71].

Considering the availability of several effective systemic therapies and the risk of liver deterioration after TACE, the right time to switch from TACE to a systemic treatment is a crucial issue which remains unresolved. TACE failure can be defined by the occurrence of macro-vascular invasion or extrahepatic spread, an increase of AFP after TACE, a lack of complete radiological response after two TACE or the occurrence of new lesions less than six months after TACE.

There is a scientific rationale for the association of TACE and antiangiogenic agents. However, association with sorafenib [72] or brivanib [73] failed to show an increase in OS in phase II and III studies and therefore should not be used in clinical practice.

Selective internal radiation therapy (SIRT)

This new treatment is defined as the infusion of a radioactive substance such as yttrium-90 (Y90) microspheres or similar agents into the hepatic artery. Because of the minimally embolic effect of Y90, treatment can be safely used in patients with portal vein thrombosis.

In the first retrospective study comparing TACE and SIRT, ORR was 40 to 50%, time to progression (TTP) 13 months, and OS 20 months [74]. It determined the contraindications (Child-Pugh > B7, hyperbilirubinemia > 35 μmol/L, clinical ascites, digestive shunt that could not be embolized) and the bad indications (major hepatic invasion > 50%, significant extrahepatic disease, truncal portal thrombosis).

Results from 4 randomized phase III trials have been reported in patients progressive after TACE or not eligible to TACE. The French SARAH trial comparing SIRT to sorafenib included 459 patients [75]. The main objective (improvement in OS) was not achieved (8 months with SIRT vs 9.9 months with sorafenib, HR = 1.15, p = 0.18). Similarly, there was no improvement in PFS (4.1 vs 3.7 months). Even if AEs are less frequent with SIRT (76% versus 94%), this negative study does not allow to consider radioembolization as an alternative to sorafenib. In a sub-analysis, the dose of radiation delivered to the tumor was associated with prognosis and is important to consider in further trials. The SIRveNIB trial, with a similar design to the SARAH trial, was conducted in Asia [76]. 360 patients were included, 30% with portal

vein thrombosis. OS was not significantly increased in the radioembolization group (8.54 vs 10 months), TTP was 5.88 vs 5.36 months (HR 0.93) and PFS was 5.29 vs 5.06 months (HR 0.94). The added value of sorafenib in patients treated with SIRT has been evaluated in the SORAMIC trial comparing the association SIRT and sorafenib versus sorafenib alone [77]. The intent to treat population analysis was negative, with a median OS of 12.1 months with the combination compared to 11.5 months with sorafenib monotherapy (HR: 1.01; p = 0.93). Finally, the STOP-HCC study is evaluating SIRT prior to sorafenib vs sorafenib alone in the treatment of patients with unresectable HCC [78].

In view of these negative studies, the place of SIRT in the therapeutic strategy is not yet defined. Despite these negative results, the French authorities approved the use of SIRT with Therasphere® in HCC with portal vein thrombosis, in patients with a good PS, Child-Pugh A and ineligible (or after failure) to sorafenib. This decision is based on retrospective data suggesting a benefit of SIRT in HCC with vascular invasion excluding truncular portal invasion [79]. The opportunity to use SIRT in this indication must be discussed in a multidisciplinary meeting, keeping in mind the availability in second line of validated systemic therapies.

Medical treatments

Several systemic agents have shown survival benefits in phase III studies carried out in patients with compensated cirrhosis (Child-Pugh score A), in good general condition (PS 0-2), and advanced HCC (BCLC C or B not eligible for TACE).

a. First line treatments

The efficacy of **sorafenib** (inhibitor of VEGFR-2, VEGFR-3, PDGFR-β, CRAF, BRAF, V600E BRAF, c-KIT receptor and FLT-3) was proven in a phase III randomized study (SHARP trial) comparing sorafenib and placebo in patients with advanced HCC [80]. Despite low response rates, sorafenib showed a significant increase in OS (10.7 vs 7.9 months) and TTP (5.5 vs 2.8 months). Most common severe adverse events (AEs) grade $\geq$ 3 included diarrhea and hand-foot syndrome. Based on these findings, sorafenib was approved in October 2007 for ''the treatment of HCC". The consensual indication of sorafenib considered by the French PRODIGE-AFEF working group was "the palliative treatment of HCC in patients in good general condition (PS 0 to 2), conserved liver function (Child-Pugh A) not eligible for LT, surgical resection, local ablation or TACE), or recurrence after one of these treatments" [81]. A recent phase II study, comparing sorafenib to best supportive care in Child Pugh-B patients confirmed the lack of benefit of sorafenib in patients Child-Pugh B8 or B9 and a weak benefit in Child-Pugh B7 patients [82]. In these patients the decision to use sorafenib should take into account general condition, age and comorbidities to properly assess the risk benefit ratio.

Lenvatinib (inhibitor of VEGF receptors 1 to 3, FGF receptors 1 to 4, PDGF α receptor, RET and KIT) showed comparable efficacy to sorafenib in a non-inferiority phase III study, in patients with BCLC stage B or C (without truncular portal invasion) HCC, Child-Pugh A and PS $\leq$ 1 (OS 13.6 vs 12.3 months) [83]. PFS was significantly increased in the lenvatinib arm (7.4 vs 3.7 months; HR 0.66), as well as the objective response rate (ORR) according to modified RECIST criteria as determined by investigator (24.1% vs 9.2%) and masked independent imaging review (40.6% vs 12.4%). The most common AEs were hypertension (42%), diarrhea (39%), decreased appetite (34%), weight loss (31%) and fatigue (30%). Lenvatinib was approved by the European Medicines Agency (EMA) (but non refunded in France) and is therefore an alternative to sorafenib as first-line treatment.

The results of the combination of **atezolizumab** (immune checkpoint inhibitor (CPI) blocking PD-L1) and **bevacizumab** (monoclonal antibody targeting VEGF) have very recently been published [84]. In the phase III IMbrave150 study, the association of atezolizumab and bevacizumab significantly improved OS and PFS compared to sorafenib in first line treatment of advanced HCC; median OS with the combination was not reached vs 13.2 months with sorafenib (HR 0.58). Median PFS was also significantly increased (6.8 vs 4.3 months, HR 0.59). Time to deterioration of quality of life was lengthened. In light of these results, this combination is now the reference for the first line treatment of advanced HCC.

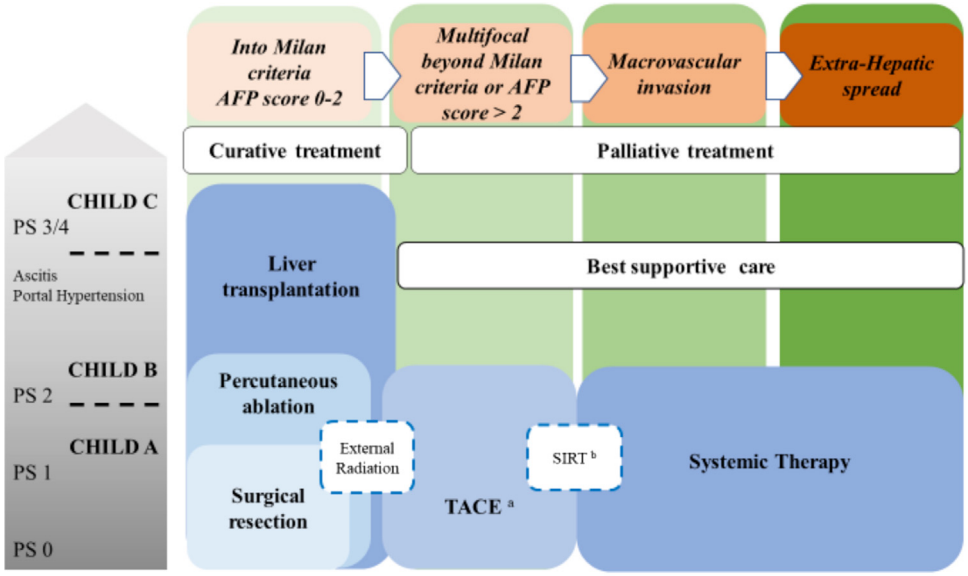
b. Second line treatments

Several phase II and III clinical trials have evaluated the benefit of second-line treatment after failure (or intolerance) of sorafenib. To date, three phase III studies are positive in second line.

The randomized, placebo-controlled, double-blinded RESORCE trial, showed efficacy of **regorafenib** (inhibitor of VEGFR1 to 3, c-KIT, TIE-2, PDGFR-b, FGFR-1, RET, RAF-1, BRAF and p38 MAP kinase), at a dose of 160 mg/day three weeks out of four, in patients with Child-Pugh A score, PS 0-1, after failure of sorafenib [85]. Patients intolerant to sorafenib were excluded from the study (the tolerability of prior sorafenib was defined as the administration of $\geq$ 400 mg daily for at least 20 of the last 28 days of treatment). Regorafenib significantly increased OS compared to placebo (10.6 vs 7.8 months). The most common AEs were high blood pressure, hand-foot syndrome and diarrhea.

The results of the double-blinded randomized CELESTIAL trial comparing **cabozantinib** (inhibitor of VEGFR 1 to 3, MET, AXL, KIT and RET) to placebo in second or third-line treatment were published in July 2018 [86]. Patients in good condition (PS 0-1), with preserved liver function (Child-Pugh A) after failure or intolerance to prior sorafenib were included. The median OS was 10.2 months with cabozantinib versus 8 months with placebo (HR 0.76). Median PFS was doubled, reaching 5.2 months with cabozantinib compared to 1.9 months with placebo (HR 0.44). Cabozantinib was approved by EMA in November 2018 and is therefore a new option in second- or third-line setting.

Ramucirumab is a human antibody inhibiting the activation of VEGF-2 receptor, tested in second line treatment of HCC in a randomized, placebo-controlled, phase III trial (REACH trial) [87]. Although median OS was not significantly increased compared to placebo (9.2 vs 7.6 months), a benefit was observed in the pre-defined subgroup of patients with AFP > 400 ng/ml. The results of a second phase III study (REACH-2) specifically dedicated to patients with AFP > 400 were reported; ramucirumab significantly improved OS (8.5 vs 7.3 months; HR 0.710) and PFS. [88]. Additionally, the safety profile of ramucirumab appears more favorable than tyrosine kinase inhibitors (TKI) and the time to clinical deterioration is significantly delayed in patient receiving ramucirumab [89]. Ramucirumab is approved by EMA and FDA for the treatment of advanced HCC previously treated



[a] TACE: transarterial chemoembolization; [b] SIRT: selective internal radiation therapy; PS: performance status

Figure 2 French therapeutic algorithm.

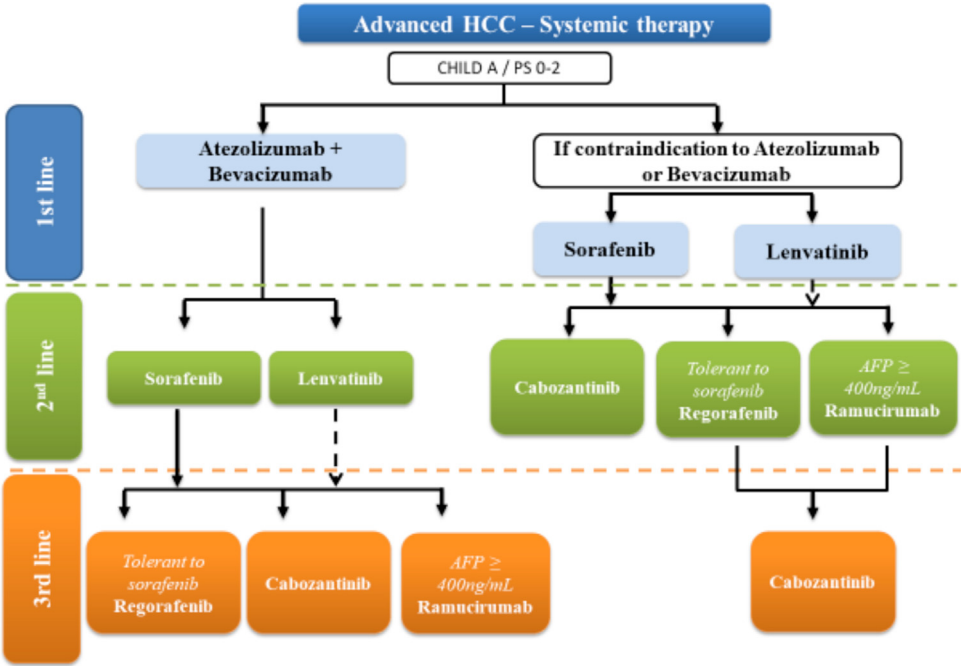


Figure 3 Algorithm for management of advanced HCC.

with sorafenib and baseline AFP over 400 ng/mL, but is not refunded in France for the moment.

c. Treatments in development

Immunotherapies are being developed. Encouraging results in phase I and II studies were published for **nivolumab** and **pembrolizumab** with interesting ORR of respectively 20% and 17% [90,91]. However, in phase III trials, both nivolumab and pembrolizumab failed to demonstrate a significant improvement in OS and PFS as single agents in first and second line, respectively [92,93].

The combination of **nivolumab** and **ipilimumab** in patients who progressed on frontline therapy was evaluated in the phase I/II CheckMate-040 study; ORR was 31% [94]. An accelerated FDA approval was granted to the combination in March 2020 for the treatment of patients with advanced HCC previously treated with sorafenib. Frontline international phase III trials of anti-PD1/PDL1 and anti-CTLA4 combination versus sorafenib are underway (**nivolumab/ipilimumab** (CheckMate 9DW); **durvalumab/tremelimumab** (HIMALAYA study)).

For the moment, no CPI is approved in second line in Europe for the treatment of advanced HCC.

Other first line phase III trials combining anti-PD1/PDL1 and anti-angiogenic agents are ongoing (**atezolizumab/cabozantinib** (COSMIC trial), **pembrolizumab/lenvatinib** (LEAP-002 trial)). Results should be available in 2021.

Therapeutic indications: recommendations, options

HCC developed on cirrhotic liver

Treatment strategy is guided by tumor extension, Child-Pugh score, and presence of portal hypertension; it is summarized in Fig. 2. Three situations are schematically possible:

- For HCC without vascular or extrahepatic extension, with an AFP score $\leq$ 2 and/or in the Milan criteria, a curative treatment should be considered. The choice of treatment is influenced by the Child-Pugh score and general conditions of patients.
- For HCC with macroscopic vascular invasion and/or extrahepatic spread, palliative treatment should be considered and discussed according to the Child-Pugh score and PS status.
- In other cases, in patients Child-Pugh A, the curative or palliative option may not be obvious and requires a multidisciplinary discussion in order to benefit from the expertise of teams of transplantation, and interventional radiology (recommendation level: expert agreement). For example, patients with multinodular HCCs beyond criteria of transplantation could benefit from a down-staging strategy. The respective place of TACE and systemic treatments should also be discussed for every patient in order to allow an optimal use of all therapeutic lines.

HCC accessible to curative treatment. It concerns HCCs that are potentially eligible for LT (at diagnosis or after down staging), defined by AFP score $\leq$ 2.

a. Child-Pugh A cirrhosis

Recommendations:

- **Liver transplantation should systematically be discussed, in the absence of obvious contraindications *(recommendation level: B)***. Contraindications include age over 70, extrahepatic spread including lymph nodes, severe extra-hepatic disease, macroscopic vascular extension. On waiting list, a bridging treatment can be proposed according to tumoral characteristics and expected time to transplantation ***(recommendation level: grade C)***.
- **Resection or percutaneous ablation should be considered in first intention, either in a transplant project at the time of recurrence (salvage transplantation) or in case of contraindication to liver transplantation *(recommendation level: grade B,* Fig. 2)**.
- In case of contraindication to resection or percutaneous destruction, hyperselective TACE or stereotactic radiotherapy should be discussed ***(recommendation level: expert opinion)***.

b. Child-Pugh B and C cirrhosis

Recommendations:

- **LT is the reference** for severe cirrhosis and should be discussed with a referral center ***(recommendation level: grade C)***.
- In case of contraindication to LT, reference is RFA for patients Child-Pugh $\leq$ B7 in the absence of significant ascites (***recommendation level: grade C)***.
- Otherwise, palliative care is the only option.
- When an etiological treatment is possible (alcohol withdrawal, treatment of viral hepatitis B or C...), liver function can improve and therapeutic discussion regarding HCC reevaluated.

Advanced HCC. a. Child-Pugh A cirrhosis

b. Child-Pugh B and C cirrhosis

Recommendations:

- **In the absence of vascular or extrahepatic extension: TACE *(recommendation level: grade A)***. The size, the number and the localization of HCC should be taken into account and supra selective TACE should be preferred. Liver function after TACE has to be carefully checked.
- **In case of extrahepatic metastasis, abnormalities of the portal flow, or failure of TACE, in patients in good general condition (PS $\leq$ 2): systemic therapy** (Fig. 3)
  - o In first-line:
    - ■ **Atezolizumab / bevacizumab *(recommendation level: grade A)***
    - ■ **If contraindication to atezolizumab or bevacizumab**
      - Sorafenib ***(recommendation level: grade A)***
      - Lenvatinib ***(recommendation level: grade A)***
  - o In second-line:
    - ■ **After atezolizumab / bevacizumab**
      - Sorafenib or lenvatinib ***(recommendation level: low)***
    - ■ **After sorafenib or lenvatinib**
      - Regorafenib in patients previously tolerant to sorafenib ***(recommendation level: grade A after sorafenib, low after lenvatinib)***
      - Cabozantinib ***(recommendation level: grade A after sorafenib, low after lenvatinib)***
      - Ramucirumab ***(recommendation level: grade A after sorafenib, low after lenvatinib)***
  - o In third-line:
    - ■ **After atezolizumab — bevacizumab and then sorafenib or lenvatinib :**
      - Cabozantinib or regorafenib ***(recommendation level: low)***

Options:

- In the absence of significant extrahepatic disease: SIRT (*recommendation level: expert agreement)*

Recommendation:

- Best supportive care (recommendation level: grade C).

HCC without cirrhosis

Recommendations:

- **Surgical resection *(recommendation level: grade C)***. Histology of the non-tumoral liver is essential and must be available at the time of the discussion in multidisciplinary meeting. The results of resection are good when there is no portal invasion.
- If a resection is not possible: discussion of other treatments according to the same criteria as when there is cirrhosis ***(recommendation level: expert agreement)***.

Surveillance

There is no data available in literature to recommend an optimal surveillance schedule; MRI is the best imaging technique (because non-irradiating) for liver monitoring. When MRI is not available, an injected CT must be performed. Chest CT is the modality of choice to monitor lungs. Radiologists must use RECIST 1.1 or modified RECIST criteria for evaluation of loco-regional and systemic treatments [95,96].

The normalization of AFP (if elevated before treatment) after curative treatment is important to evaluate.

After transplantation

The surveillance modalities will be discussed with the transplant center. Patients should be closely monitored during the first 2 years during which tumor recurrence rate is highest. Extrahepatic sites (particularly lungs) are the most frequently affected by recurrence. Surveillance methods should be adapted according to individual risk of recurrence (size and number of tumors, vascular invasion, degree of tumor differentiation, AFP).

After resection

Recommendations:
The high recurrence rate supports close monitoring:

- Clinical and biological evaluation (liver tests and AFP) every 3 months the first year then every 6 months
- Chest CT-scan every 6 months for 2 years
- Liver imaging: MRI (or CT-scan if MRI is not possible) and liver US alternately every 3 months for 2 (to 3) years. After this monitoring, screening of new HCCs may be done by MRI or hepatic US every 6 months all life. ***(recommendation level: low)***

After percutaneous destruction

Recommendations:
The follow-up should ideally be done in the center that performed the procedure

- MRI (or CT-scan) and US according to the habits centers every 3 months for 2 to 3 years, then every 6 months. ***(recommendation level: low)***

After radiotherapy / SIRT

Recommendations:
MRI is the best technique but should not be programmed too early (rather 3 months after the end of radiation). The radiological semiology must be defined because it is often difficult to distinguish persistence of viable tumor tissue with post-radiation peri-lesional hepatitis reaction. Further monitoring is not standardized but could be identical to the recommendations after percutaneous destruction ***(recommendation level: expert opinion)***.

After TACE

Recommendations:
Control 6 weeks after TACE

- Clinical and biological evaluation (liver tests and AFP)
- Liver MRI (+ CT scan without injection in case of TACE with lipiodol®).

Given the heterogeneity of practices, monitoring procedures will be adapted on a case-by-case basis and according to the rhythm of the sessions. ***(recommendation level: expert opinion)***.

With systemic therapies

Recommendations:

- Clinical monitoring and blood tests (liver tests and AFP) every month
- Imaging every 2 to 3 months by thoraco-abdomino-pelvic CT-scan or hepatic MRI and chest CT. ***(recommendation level: expert opinion)***

Conflicts of interest

JF Blanc: Personnal fees and Advisory Board for AstraZeneca, Bayer, BMS, ESAI, IPSEN, ROCHE, AMGEN.

Acknowledgement

We thank the review committee: A Abergel (Clermont-Ferrand), E Buc (Clermont-Ferrand), JF Cadranel (Creil), T de Baere (Villejuif), A Heurgue (Reims), A Landau (Dreux), M Lapeyre (Toulouse), JY Mabrut (Lyon), B Menahen (Caen), I Ollivier-Hournaud (Caen), JM Peron (Toulouse), L Quintane (Valence), F Darloy (Douai), JM Regimbeau (Amiens), C Silvain (Poitiers), B Suc (Toulouse).

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