Hepatocellular Cancer

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Gastrointestinal Cancers

Contents

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42.1 Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults. Even if improvements in prevention and diagnosis have been done in recent years, HCC still remains the third leading cause of cancer death [1].

It occurs in the setting of chronic liver inflammation, mostly linked to chronic viral hepatitis B or C. Exposure to toxins such as alcohol or aflatoxin could conceivably be causes of HCC. Also metabolic syndrome and nonalcoholic steatohepatitis (NASH) are increasingly recognized as risk factors for HCC. Hemochromatosis and α1-antitrypsin deficiency could increase the risk of developing HCC.

Often, but not always, HCC develops through a fibrotic degenerative process with the formation of nodules called cirrhosis. So far, HCC is the most common cause of death in people affected by cirrhosis [2].

Most patients affected by HCC have signs and symptoms of chronic liver disease (jaundice, ascites, abnormalities of blood coagulation, hyporexia, weight loss, abdominal pain, nausea, and vomiting). Sometimes they do not show any symptoms. In some cases, HCC patients could present worsening of the symptoms.

42.2 Epidemiology

In the US surveillance, epidemiology, and outcome (SEER) database program, HCC accounts for 65 % of all cases of liver cancer [3, 4]. The incidence rate of HCC increased from 1.4/100,000 cases/year in the 1980s to 6.2/100,000 cases in 2011 [3, 5]. HCC is more frequent in men than in women, with a ratio of about 2.4:1 [6]. It is generally diagnosed between 50 and 70 years of age [7], is predominant in Asian and African countries, and is not very common in Northern Europe and North America [4]. The main risk factors are hepatotropic viruses infection, such as HBV and HCV, and alcohol abuse. About 80–90 % of HCCs occur within the context of cirrhosis [8]. In recent years an increase in the number of cases associated with metabolic syndrome has been observed.

42.3 Physiopathology

Hepatitis B virus is the principal cause of hepatocellular carcinoma. There are clear evidences of such an association, accumulated from biological studies in patients with chronic liver disease degenerated into neoplastic disease and from prospective and retrospective epidemiological studies conducted on populations from Africa, Malaysia, Japan [9, 10], China [11], Europe [12], and the USA [13]. Hepatitis C is also strongly associated with the risk of primitive HCC [14, 15], with a relative risk estimated up to more than a 20%, which is a figure similar to the one of hepatitis B.

Alcohol abuse is another risk factor for the development of this tumor type.

In recent years it has been shown as in developed countries there is a correlation between the metabolic syndrome (NASH and NAFLD) and HCC. However, the above form is still poorly studied.

In the world, the principal liver carcinogen aflatoxin content in food is a product of the metabolism of the fungus *Aspergillus flavus* that contaminates foods (usually the produce of grain stored in hot and humid environment) in many tropical countries, particularly in Southern Africa and Southeast Asia. Experimentally, it is among the most potent liver carcinogen known for certain animal species, and it is likely that it is a potential carcinogen also for men. In addition, the incidence of primitive HCC in some areas of Southern Africa (where this cancer is particularly prevalent) is positively correlated with the content of aflatoxin in the diet [16]. In developed countries, food is less contaminated by *Aspergillus flavus*, and this fungus is not involved in the carcinogenesis of HCC.

There is also a difference in the incidence of hepatitis B infection between developed and developing countries. In developing countries infection with hepatitis B, it is more common, while in developed countries hepatitis C infection is more frequent. The hepatitis B virus is a direct carcinogenic, while the hepatitis C virus is an indirect carcinogen: hepatitis C exerts its carcinogenic action through the inflammatory process and the resulting cirrhosis that develops in the liver. These etiological differences are reflected in a different biological behavior of HCC: the majority of Caucasian patients have a slow-growing and expansive cancer [17], whereas South African patients have a rapid-growing cancer [18]. As a consequence, there are significant different etiologies between primary HCC in Africans and Europeans and North Americans.

In turn, even among Europeans there are pathway and genetic differences between patients with HCC related to hepatitis and HCC patients related to metabolic syndrome.

Being a major player in the inflammation in carcinogenesis of this tumor, the expression of hepatitis virus-related proteins very likely reflects the differences between the various types of HCC.

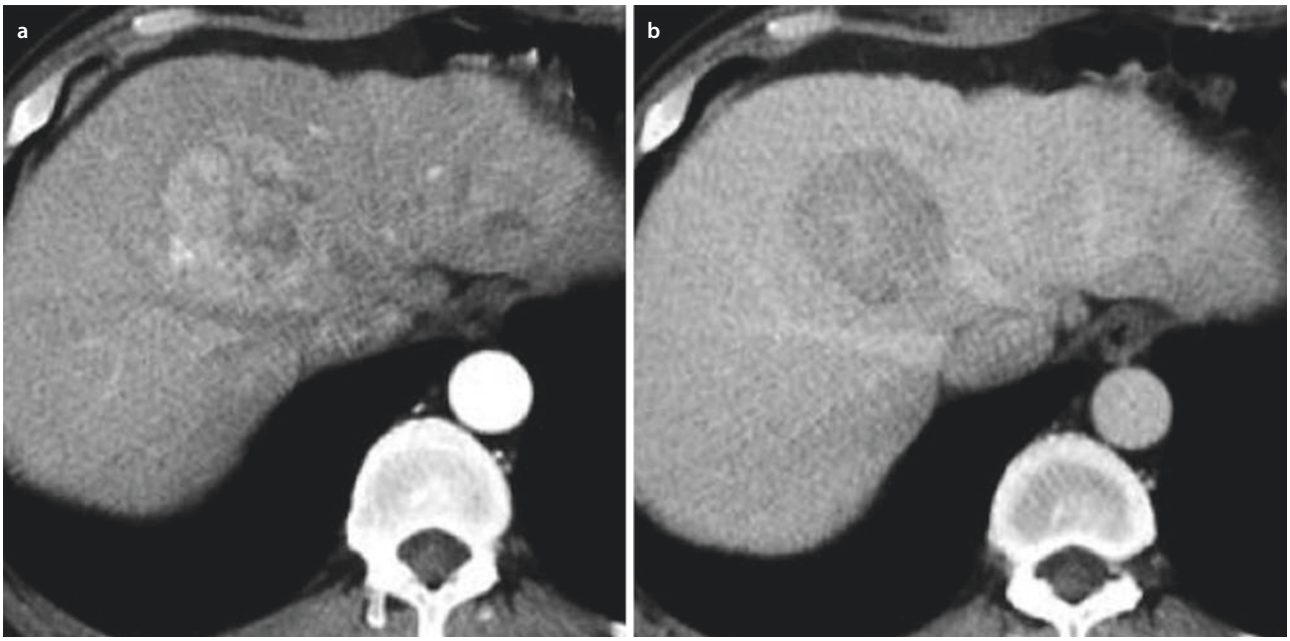


Fig. 42.1 HCC CT-scan. **a** Arterial phase sequence with wash in and **b** washout

42.4 Diagnosis

42.4.1 Radiological Criteria

The presence of small nodules in a cirrhotic liver is normal, making the differential diagnosis between regeneration nodules and neoplastic nodules often difficult. A "focal lesion," i.e., a lesion measuring at least 5 mm detected by ultrasound or another method is first identified [19]. Hepatic carcinogenesis occurs in stages in 90% of cases: the lesion progresses from regenerative micronodule to regenerative macronodule, with histological changes that lead from mild to severe dysplasia to carcinoma, extending to the entire nodule and beyond.

From a histological point of view, the transformations that occur during carcinogenesis are generally accompanied by a progressive formation of anomalous arterial vessels (tumor neoangiogenesis) and loss of the portal component [20]. The imbalance between the components of the vascular support gives HCC a unique behavior in the different contrast phases that enables imaging techniques to identify the tumor, i.e., an increase in the arterial phase signal in the lesion compared to the surrounding parenchyma (commonly called arterial hypervascularization or wash-in), followed by a reduction in the venous phase that makes the lesion appear moderately less contrast-enhanced than the parenchyma (appearance defined as premature washing or washout). In the presence of wash-in followed by washout, a 10-mm lesion in a cirrhotic liver can be fairly confidently diagnosed as HCC.

Suspicious nodules should be evaluated with contrast-enhanced MRI and/or CT scan to identify a diagnostic pattern typical of HCC (hypervascularization in the arterial phase and washout in the venous/late phase) and to carry out staging in order to define prognosis and the most suitable therapy if malignancy is confirmed (Fig. 42.1). The role of contrast-enhanced ultrasound (CEUS) in the diagnosis of HCC has been questioned due to its poor ability to differentiate intrahepatic cholangiocarcinoma from HCC [21].

In the case of a typical MRI and/or CT (with wash-in and washout) appearance of lesions exceeding 10 mm, a diagnosis of HCC can be considered confirmed. Conversely, for lesions with an atypical appearance (lack of arterial hypervascularization and/or washout), further evaluation with an alternative contrastographic technique (MRI or CT) or CEUS is performed, or it may be decided to proceed directly to biopsy, if technically feasible [21] (Fig. 42.2).

42.4.2 Role of Alpha-Fetoprotein

Alpha-fetoprotein is the most commonly used serum marker for HCC. Alpha-fetoprotein is no longer recommended as a diagnostic test because of the low sensitivity of its threshold value (about 20%), especially in small nodules, and also because of its lack of specificity when lower limits are used, e.g., >20 ng/dL). Thus, diagnosis of HCC is based on the results from typical imaging of malignancy in a cirrhotic liver or histological confirmation. High values of alpha-fetoprotein have a clear negative prognostic significance [21].

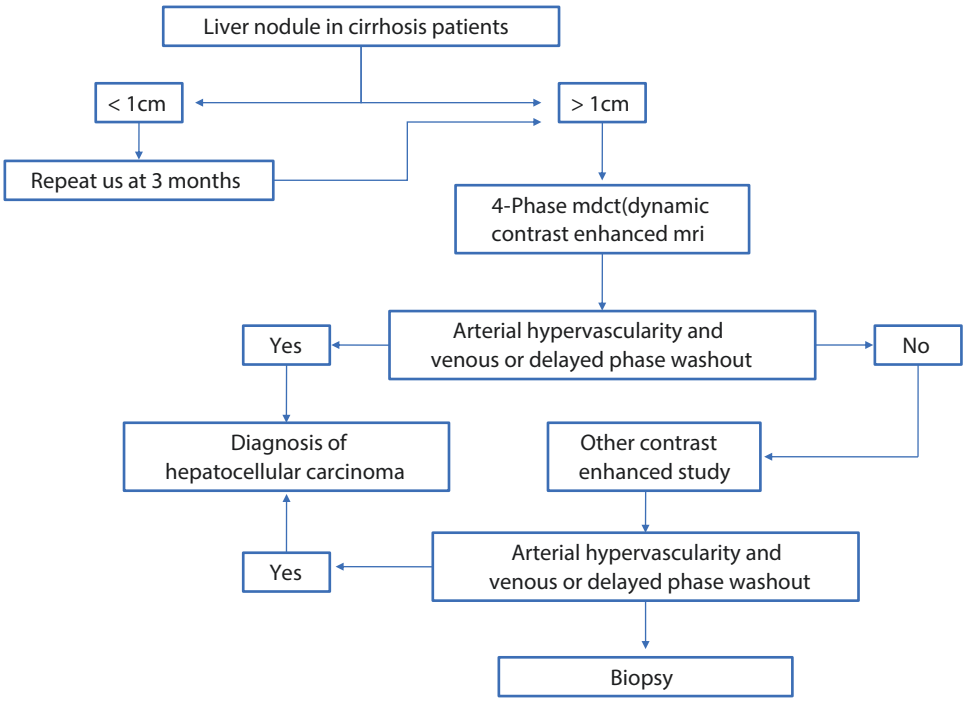


Fig. 42.2 Diagnostic flow chart

42.4.3 Histological Criteria and Classification

42.4.3.1 Liver Biopsy

Even if instrumental investigations could be able to achieve a diagnosis, sometimes HCC should be investigated by the histological examination of the lesion through ultrasound- or CT-guided percutaneous biopsy usually when radiological examinations lead to diagnostic doubts.

42.4.3.2 Pathology

Macroscopic Features

Macroscopic characteristics of HCC are related to both the size of the tumor and the presence or absence of liver cirrhosis. In fact, HCCs associated with liver cirrhosis show fibrous capsule and intratumoral septa, while the ones without cirrhosis tend to be massive and nonencapsulated (Fig. 42.3). HCC could occasionally present itself as a pedunculated lesion. Surrounding intrahepatic metastases are frequent in advanced phases.

Due to its significant angiogenesis features (Longo et al.), macrovascular invasion of portal vein could be present in more than 70% of advanced HCC. Furthermore, intrahepatic metastases are caused mostly by tumor spread in the portal vein branches. Less frequently, tumor invades the major bile ducts. Extrahepatic metastases are mostly hematogenous (i.e., liver, lung and less frequently bone). Regional lymph node metastases are frequent.

Microscopic Features

Neoplastic cells resemble polygonals with distinct cell membranes and abundant granular eosinophilic cytoplasm with a nucleus/cytoplasm ratio which is higher than normal. Moreover, the nucleus is round with coarse chromatin and a thickened nuclear membrane. The presence of sinusoidal vessels surrounding tumor cells is an important diagnostic feature. Common characteristics are portal vein thrombosis and microvascular invasion with presence of mitotic figures. The presence of abundant fat or bile canaliculi, copper, intracellular hyaline bodies, and intranuclear pseudoinclusions could be less frequent (Fig. 42.4). HCC is immunohistochemically positive for HepPar-1 and AFP, even if these markers may be negative in high-grade tumors. Also glypican-3 may be positive in both cytoplasm and membrane. Unlike the sinusoidal endothelial cells in normal liver tissue, those in HCC are immunohistochemically positive for CD34 and factor-VIII-related antigen.

A variable number of macrophages with similar features of well-differentiated tumors Kupffer cells are present in the sinusoidal blood spaces. They bear an immunohistochemical positivity for CD68 and antilysozyme [22].

Different Histological Patterns

The trabecular (plate-like) pattern is the most common in well- and moderately differentiated HCCs. Neoplastic cells are grouped in cords of variable thickness which are separated by sinusoid-like blood spaces. Sinusoid-like blood spaces often show varying degrees of dilata-

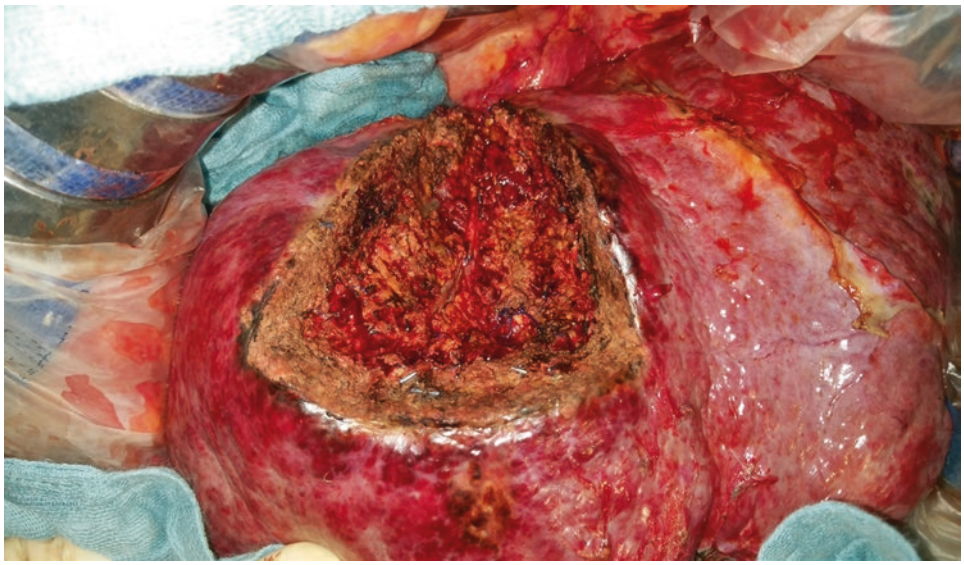


Fig. 42.3 Macroscopic aspect of hepatocellular carcinoma on cirrhotic liver

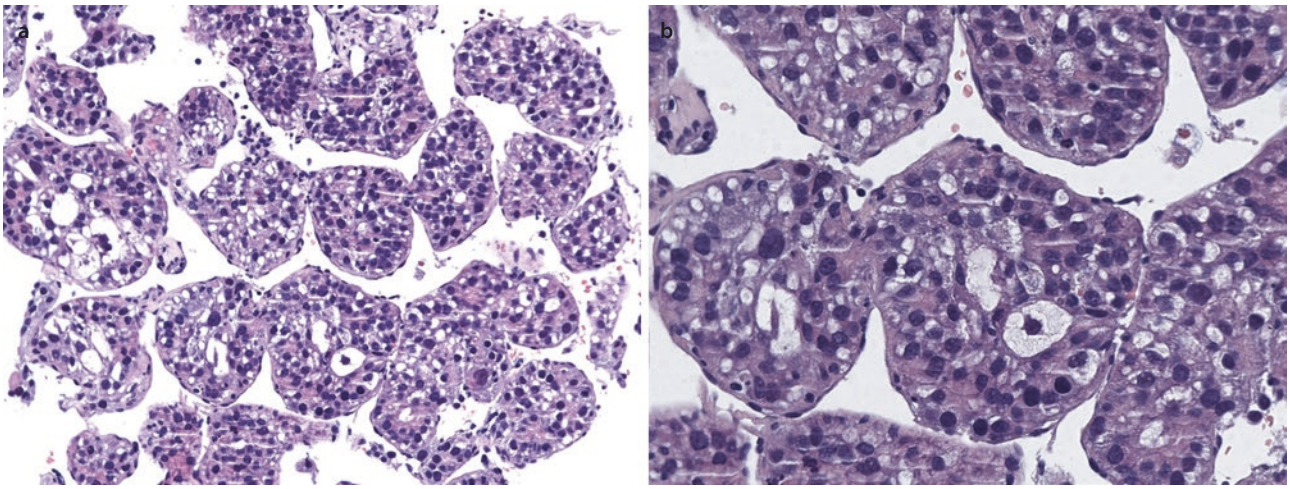


Fig. 42.4 **a** Well-differentiated HCC. Typical roll-off appearance due to the capillaryization of sinusoids. 20× (H/E). **b** Greater magnification (40×). Endothelins continuously delimit the aggregates of atypical hepatocytes (H/E)

tion, and peliosis hepatis-like changes are occasionally observed in advanced HCCs (Fig. 42.5).

Pseudoglandular and acinar variants of HCC frequently show a glandular pattern, usually admixed with the trabecular pattern.

An uncommon HCC subtype is scirrhous. It is characterized by marked fibrosis along the sinusoid-like blood spaces with varying degrees of atrophy of tumor trabeculae. The scirrhous type must not be confused with cholangiocarcinoma or fibrolamellar carcinoma.

The term "sclerosing hepatic carcinoma" has been used to designate a variety of tumors arising in non-cirrhotic livers. This variant is often associated with hypercalcemia, but it doesn't constitute a distinct histopathological entity [23].

Cell Variants

*Pleomorphic HCC*s show marked variation in cellular and nuclear size, shape, and staining. Multinucleated or mononuclear giant cells are often present, appearing as osteoclast-like giant cells. They are frequently observed as common in poorly differentiated tumors. In clear cell HCC, cancer cells present clear cytoplasm due to the presence of abundant glycogen. Those features make the differential diagnosis from metastatic clear cell type renal carcinoma challenging.

Sarcomatoid HCC is a subtype with sarcomatous change which is characterized by the proliferation of spindle cells or bizarre giant cells. It is more frequent in patients who have undergone TACE. Most of them are positive for vimentin or desmin.

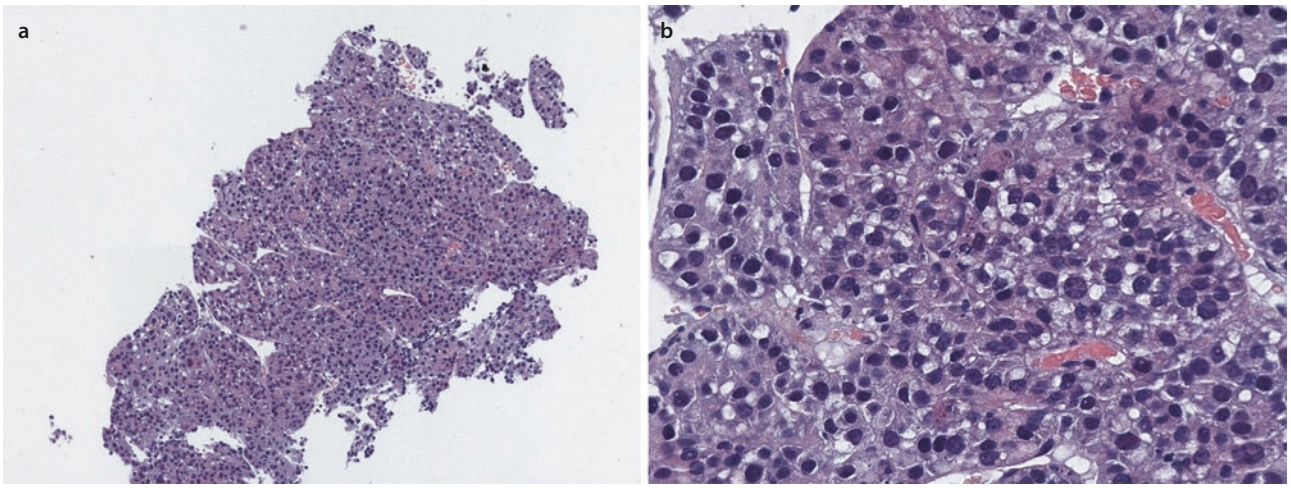


Fig. 42.5 **a** Moderately differentiated trabecular hepatocarcinoma. 20× hematoxylin/eosin. **b** Greater magnification (40×). Evident nuclear dysmetries with hypercromasia (H/E)

Fatty change HCC is most frequent in early-stage tumors with a diameter lower than 2 cm. Its frequency declines as tumor size increases, with rather infrequent fatty changes in advanced tumors. It could be associated with metabolic disorders related to hepatocarcinogenesis and insufficient blood supply in the early neoplastic stages.

Bile production HCC is occasionally observed, usually as plugs in dilated biliar ducts, with a prominent bile production. It is interesting to see that cancer cells turn green after formalin fixation. Mallory hyaline bodies are intracytoplasmic, irregular in shape, eosinophilic, and PAS-negative.

Fibrolamellar HCC is usually observed in noncirrhotic livers with a higher incidence in adolescents or young adults. Cancer cells are grouped in sheets or small trabeculae which are divided by hyalinized collagen bundles with a characteristic lamellar pattern. These cells contain deeply eosinophilic and coarsely granular cytoplasm and distinct nucleoli. Pale bodies are present, and stainable copper, usually in association with bile, can occasionally be shown.

Undifferentiated carcinoma represents about 2% of epithelial liver tumors. Its characteristics resemble those of all the undifferentiated cancers, with poorly differentiated small cells and a high mitotic cell rate. Its prognosis is worst compared to other HCC variants [23].

Grading

According to the histological grade of differentiation, HCC can be divided into well-differentiated, moderately differentiated, and poorly differentiated.

Well-differentiated HCC cells present minimal atypia and increased nuclear/cytoplasmic ratio. They are organized in trabecular patterns: pseudoglandular or acinar structures are frequently observed.

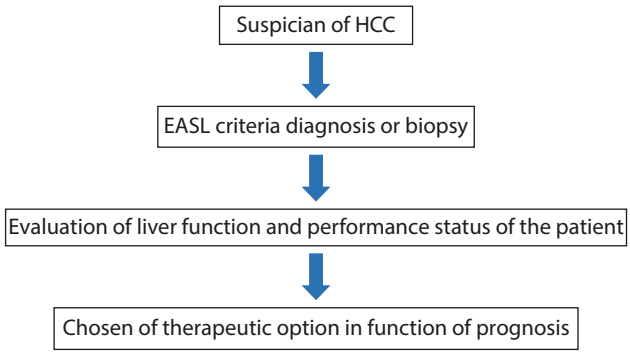
Moderately differentiated HCC is the most common in tumors which are larger than 3 cm in diameter. Cells show abundant eosinophilic cytoplasm and round nuclei. A pseudoglandular pattern is also frequent with bile or proteinaceous fluid. Cancer cells are organized in trabeculae.

In *poorly differentiated HCC*, cancer cells show an increased nuclear/cytoplasmic ratio, frequent pleomorphism, and high proliferation rate. Poorly differentiated HCC is frequent in late stages of the disease [23].

42.5 Staging

One of the most important moments in the onset of an HCC is the possibility to achieve a correct staging of the cancer to choose the best therapeutic option. Currently, the most common staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which determines cancer stage and patient's prognosis based on tumor burden, severity of the diseases, and patient's performance status [24].

We identify very early and early stage (BCLC 0 and BCLC A) in patients with solitary lesion or up to three nodules ≤3 cm (no macrovascular invasion or extrahepatic disease). In this case patients can benefit from potentially curative treatment (resection, transplant, or ablation). In case of intermediate stage HCC (BCLC B), in asymptomatic patients with multifocal HCC, without vascular invasion or extrahepatic disease, patients could be candidate for transarterial chemoembolization (TACE). In case of multifocal HCC with vascular invasion or extrahepatic disease, systemic treatment with tyrosine kinase inhibitor (sorafenib) currently offers the best therapeutic option. Patients with end-stage liver disease (BCLC D) have a very poor prognosis and require supportive care alone.



Ablation	Preserved liver function, 1 nodule <2cm
Resection	Preserved liver function, 1 nodule
TACE	Internmediate liver fuction, multiple nodules
Transplant	Any liver function, 1 nodule <5 cm or 3 nodules >3cm
Systemic therapy	Preserved liver function, and in rarecase intermediate liver function, advanced and metastatic stages
Bestsupportive care	Terminal stages

Fig. 42.6 Therapeutic algorithm

42.6 Treatment

Considering the multifactorial evaluation of cirrhotic patient with HCC, different therapeutical options are available to treat cancer (Fig. 42.6).

42.6.1 Surgery

In order to achieve a correct diagnosis of HCC in cirrhotic patients, the EASL panel of experts and the American Association for the Study of Liver Disease (AASLD) [1] adopted the definition of HCC radiological hallmark, considering radiological criteria for diagnosis, based on typical contrast uptake of the nodule in arterial phase and washout in the late phase. In case of >1 cm nodule, one radiological technique (CT, MRI, US-contrast) could be sufficient for diagnosis. If the diagnosis is uncertain, a second radiological exam could integrate the result. In case of further doubts, a specimen biopsy is necessary. The AFP value might be useful for diagnosis but in practice it will not affect the treatment strategy.

42.6.1.1 Liver Resection

With a 50% 5-year overall survival (OS), liver resection is considered the only therapy which seems to cure the disease while maintaining liver function. Liver resection remains the most accessible treatment for liver malignancies, because a limited availability of graft limits transplantation in selected cases. There has been some progress recently which has aimed at improving the results of liver resection. Better patient selection and preoperative studies, associated with the improvement of surgical tools and techniques including laparoscopic [25] and robotic surgery [26], have enhanced postoperative outcome. Unfortunately, only 20–30% of patients have resectable disease at diagnosis. The ideal resection candidate is a patient with a single nodule, Child-Pugh A, without satellite nodules or vascular invasion, and the possibility to perform an anatomical resection to reduce the risk of untreated satellite nodules. Bilobar pathology is usually a surgery contraindication, and more conservative strategies are preferred in order to control the pathology.

42.6.1.2 Preoperative Assessment of the Patient Plays a Key Role

The main risks related to liver resection are hepatic insufficiency and failure [27]. This risk is heightened in case of an excessively large amount of hepatic parenchyma liver resection [28]. For that reason, the preoperative risk assessment is a fundamental process before liver resection. In case of liver resection, we should consider two fundamental evaluations: a quantitative evaluation based on the percentage of hepatic parenchyma [29] that could be resected and a qualitative evaluation [30] involving functional reserve of the whole liver. For liver resection in cirrhotic patients, a minimal amount of 40% of liver should be preserved to avoid liver failure. For qualitative measurement, the main test is the evaluation of the indocyanine green at 15 min retention rate. Another feature evaluated before liver resection is portal hypertension [31], which should be absent in order to achieve better postoperative course and Child-Pugh classification, which allows the calculation of a score based on biological tests and clinical evidence to estimate the cirrhosis severity [32]. This classification is used to assess the prognosis of chronic liver disease, mainly in cirrhotic patients. It is based on the analysis of five items and divides patients in three classes in function according to the cumulative score. Analyzed items are total bilirubin, serum albumin, prothrombin time or INR, ascites and hepatic encephalopathy. The combination of these factors could minimize the risk of liver failure.

The ECOG (Eastern Cooperative Oncology Group) [33] (Table 42.1) scale of performance status is a scale which helps to understand how the disease can impact the patient's daily life. It measures the patients' level of functioning in terms of their ability to take care of themselves in terms of daily activity and physical ability. Grade 0 and 1 describe patients who are able to perform the same activity before disease or patients, who, although with restrictions in performing physical activ-

Table 42.1 ECOG performance status

ECOG	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but able to move and to carry out tasks of a light or sedentary nature, e.g., light house work, office work
2	Able to move and capable of any personal tasks but unable to carry out any work activities; up and about for more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair for more than 50% of waking hours
4	Completely disabled; unable to carry on any self-care; totally confined to bed or chair
5	Dead

ity, could nonetheless perform simple tasks. These categories are the ideal categories of patients who could undergo treatment, with a low risk of posttreatment complications.

Firstly, a CT scan of abdomen and thorax is mandatory to exclude major parenchymal involvement or distal metastases. The role of the CT can facilitate both the definition of a correct diagnosis and the evaluation of the relationship between nodules and both vascular and biliary structures. In case of major resection, it is mandatory to calculate the amount of theoretical future remnant liver (FRL) through a CT 3D reconstruction [34]. FRL corresponds to the quantity of liver which should be preserved after surgery in order to be sufficient to guarantee a normal liver function. In case of insufficient FRL, portal vein embolization [35] (selective occlusion of monolateral portal flow to obtain contralateral hypertrophy of the liver) could be useful for its increase. In case of major resection, at least 40 % of FRL should be preserved in cirrhotic patients.

The most important aspect related to liver resection is the identification of appropriate candidates who could stand liver resection. A correct assessment of the patient's general status and liver function must be performed to reduce the risk of an uneventful postoperative course to a minimum. One of the main concepts in liver resection is the necessity to preserve a quantity of functional liver parenchyma after surgery to avoid postoperative liver failure. This quantity of functional liver is called FRL, and it is calculated before surgery with an appropriate software. According to Couinaud's classification and the division of the anatomy of the liver in eight segments [36], minor liver resection is the definition used when ≤3 segments are resected, or there is a major resection involving >3 segments. According to these classifications, patients that can be considered for minor resection should be Child A with bilirubin levels ≤2 mg/dL and an absence of ascites and with more than 100.000/mm^3 platelets. If major resection indicated, criteria for minor resection should be respected with the addition of bilirubin levels ≤1 mg/dL, the absence of portal hypertension, and portal vein embolization for future remnant liver of <40 %.

Surgical Technique

The aim of liver resection is to offer the best treatment with adequate resection margins [37]. A tumor-free margin of at least 1 cm should be guaranteed, with better results when there are more than 2 cm of margins. This is due to the necessity to remove the zone in which satellite nodule could be present and therefore inducing an early pathology recurrence. For the same reason, anatomical resection is preferred to nonanatomical resection [38] due to intrahepatic diffusion following portal vein pedicle, which could be ideal in patients with inadequate liver function, in order to reduce the liver failure risk.

Liver resection needs an initial intraoperative ultrasound, in order to identify liver lesions and anatomical relation among liver lesion and vascular and biliary structure. Once assessed the resection feasibility and identified a surgical plan, liver resection could be performed using different techniques and devices, to reduce blood loss and perform an easier hepatectomy [39]. In the majority of liver resections, a tape is passed around the round ligament in order to clamp the inflow (Pringle maneuver) of the liver and to control a possible intraoperative bleeding, even if the duration of pedicle clamping is limited in time. More measures could be adopted to achieve a better control of bleeding, including vascular exclusion of the liver with pedicle clamping associated to caval and hepatic vein clamping, along with an important hemodynamic impact.

42.6.1.3 Laparoscopic Liver Surgery

In last 20 years, the improved accuracy and diffusion of laparoscopic liver surgery in combination with the development of new surgical tools have made liver resection easier and increasingly less invasive. Apart from the advantage of minimally invasive access on postoperative pain, laparoscopic liver surgery has been demonstrated to reduce intraoperative bleeding, leading to faster recovery and with the same short- and long-term oncological results [40]. It is possible to associate liver resection and radiofrequency ablation. Recently, robotic surgery has increased the number and reproducibility of liver resection. In terms of percentage with robotic surgery a 5-year disease-free survival is almost 45%, compared with a 25% disease-free survival due to the high rate of recurrence and the presence of vascular invasion or microsatellite nodules, most of the time with the presence of liver cirrhosis.

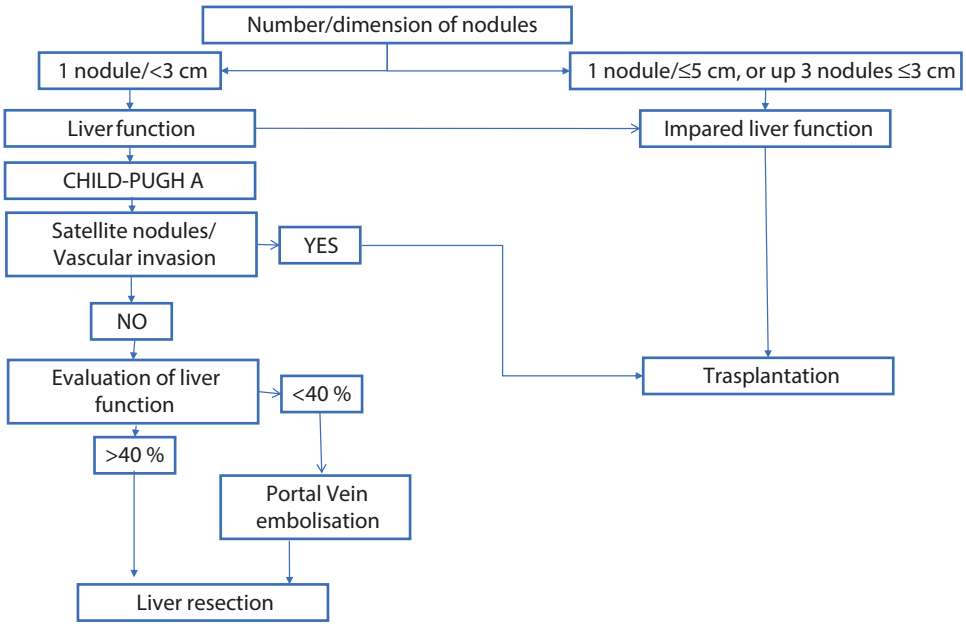


Fig. 42.7 Surgery: flow chart

42.6.1.4 Liver Transplant

Liver transplant offers a better (OS) (70 % at 5 years); it is limited by strict selection criteria and organ shortage. It's indicated especially for HCC patients with impaired liver function.

HCC often onsets on a pathological liver condition. Even if viral hepatitis reduced its frequency after the development of antiviral therapies, other causes including fatty liver disease and alcohol still represent a fertile ground on which HCC can easily develop, compared to a non-pathological liver [41]. Transplant offers the possibility to treat both the cancer and the underlying disease. Unfortunately, not all patients with liver disease and HCC could benefit from liver transplant, due to organ shortage and to limited benefit of treatment for patients with advanced liver disease. For this reason, to optimize transplant benefits, some criteria have been established. The most common criteria are "Milan criteria" [42], which consider the presence of any solitary HCC ≤5 cm, or up to three lesions ≤3 cm each, without vascular invasion or metastasis as the ideal candidate for liver transplant.

In order to treat patients who are beyond transplant criteria, it is possible to treat liver nodules in order to reduce tumor load, for example, with liver resection [43], or locoregional therapies, allowing the patients to fill translatability criteria. This strategy allows the HCC downstaging within Milan criteria in 40 % of patients outside criteria; however, posttransplant HCC recurrence rates are high at 16 % [44].

In order to allow more patients to be transplanted, some strategies have been considered to expand donor pools [45]: partial graft, deriving from living donor, or donor after cardiac death and recently, some tools as perfusion machine are used to improve the quality of grafts and to prolong their viability before being transplanted to recipient patients.

Even if transplant centers are trying to expand the donor pool, one of the main problems of liver transplant remains the dropout [46] of those patients waiting for liver transplant, in whom liver disease progresses.

Nowadays, surgery represents the only change of long-term survival in these patients. Figure 42.7 is a summary of the characteristics of HCC patients able to underwent to surgery (Fig. 42.7).

42.6.2 Locoregional Procedures

42.6.2.1 Ablation

HCC locoregional treatment [47] is gaining increasing treatment interest. Even if surgical resection guarantees the possibility to ablate the tumor and eventually satellite nodules, recent studies demonstrate that locoregional treatment leads to equivalent results. It could also be considered as a palliative treatment for patients who can't undergo other treatments for HCC.

The most common ablation treatments are percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MWA). All these approaches are image-guided procedures, in most cases performed through ultrasound.

42.6.2.2 PEI

This procedure [48] needs to monitor the distribution of alcohol in the nodule to achieve the best results. The particularity of this procedure is the low cost of the material. It is feasible and safe, especially for lesions

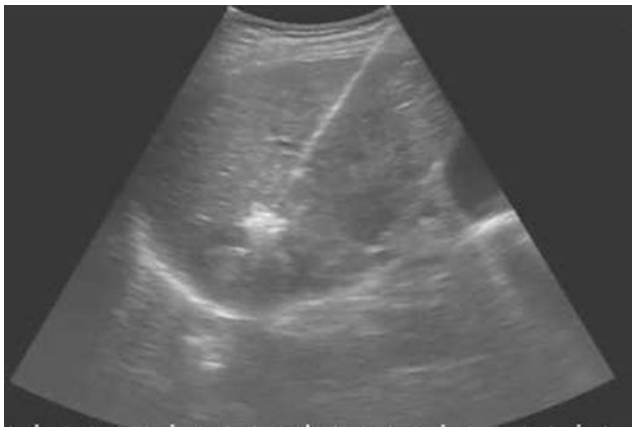


Fig. 42.8 Ultrasound guided ablation of liver lesion

close to the bile duct or to the bowel, due to the non-transmission of energy during the procedure. In fact, alcohol is easily diffused in hyper vascularized HCC. Furthermore, it can be performed in patients with portal thrombosis.

42.6.2.3 RFA and MWA

RF [49, 50, 51] is considered the gold-standard ablation technique. Even if transplantation and liver resection represents the best chance for patients concerning long-term survival, RF represents a valid alternative, and it could be used in association with resection or could be part of a downstaging treatment before liver transplant. Based on constant radiofrequency, energy-generated heat, it transmits the energy to the lesion and to surrounding tissue. It can be performed in sedation or general anesthesia. Under ultrasound control (Fig. 42.8), the needle is placed in the middle of the lesion, to transmit energy uniformly in and around the lesion. In case of more than one lesion, simultaneous treatment could be performed.

In literature, the best results are described for HCC Child A patients with lesions <3 cm, with long-term 5-year OS (50–60 %) comparable to surgical resection and liver transplantation. Small solitary HCC can achieve 5-year OS of 85 %. It is associated with a shorter postoperative stay and lower mortality rate compared to resection [50].

MWA [52, 53] is a recent technique which proposes faster and more extensive ablation areas, allowing the treatment of larger lesions closer to large vessels and biliary structures.

42.6.3 TACE

TACE is a radiological technique which combines inflow occlusion of feeding artery tumor inflow with

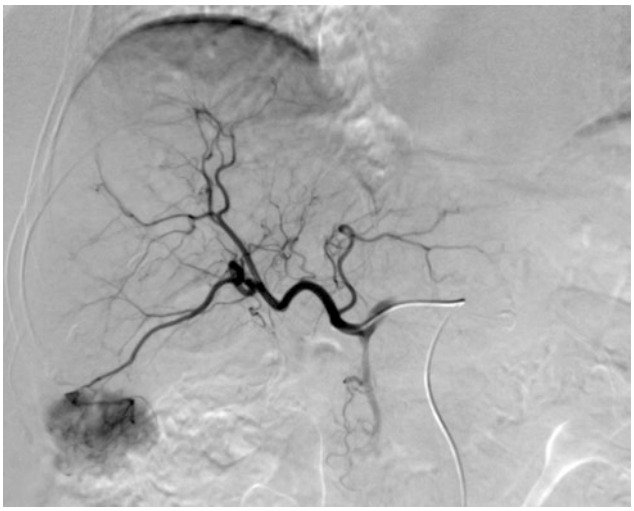


Fig. 42.9 TACE of HCC of right liver

the locoregional therapy directly in the tumor area [35] (Fig. 42.9). This treatment induces the local necrosis of the tumor associated with high intratumor concentration of chemotherapy.

TACE could allow the treatment either of multiple nodules or a selective treatment of a single nodule. Moreover, when during the radiological evaluation of tumor response, the treatment results incomplete, it can be repeated, since it is well tolerated by liver function, due to the low impact on liver function. It is indicated for patients with liver disease associated with impaired liver function.

Herein (Fig. 42.10), it is represented the summary of HCC patients features able to underwent to locoregional approaches.

42.6.4 Systemic Treatments

Even if for the last 10 years, sorafenib was the only therapeutic strategy, nowadays new tyrosine kinase inhibitors [54] and immune checkpoint inhibitors [55] improved the survival of HCC patients.

42.6.4.1 Sorafenib

The efficacy of sorafenib, a small-molecule multitarget kinase inhibitor, in the treatment of advanced HCC has been demonstrated in two randomized phase III trials, the SHARP [56] study and the Asia-Pacific study [57]. Both studies enrolled patients not eligible for locoregional treatment (at diagnosis or after failure of any previous treatment) but with good hepatic function (Child-Pugh A). In both trials, sorafenib treatment (400 mg twice daily up to instrumental and clinical progression or unacceptable toxicity) resulted in a significant prolongation of OS and time to progression (TTP).

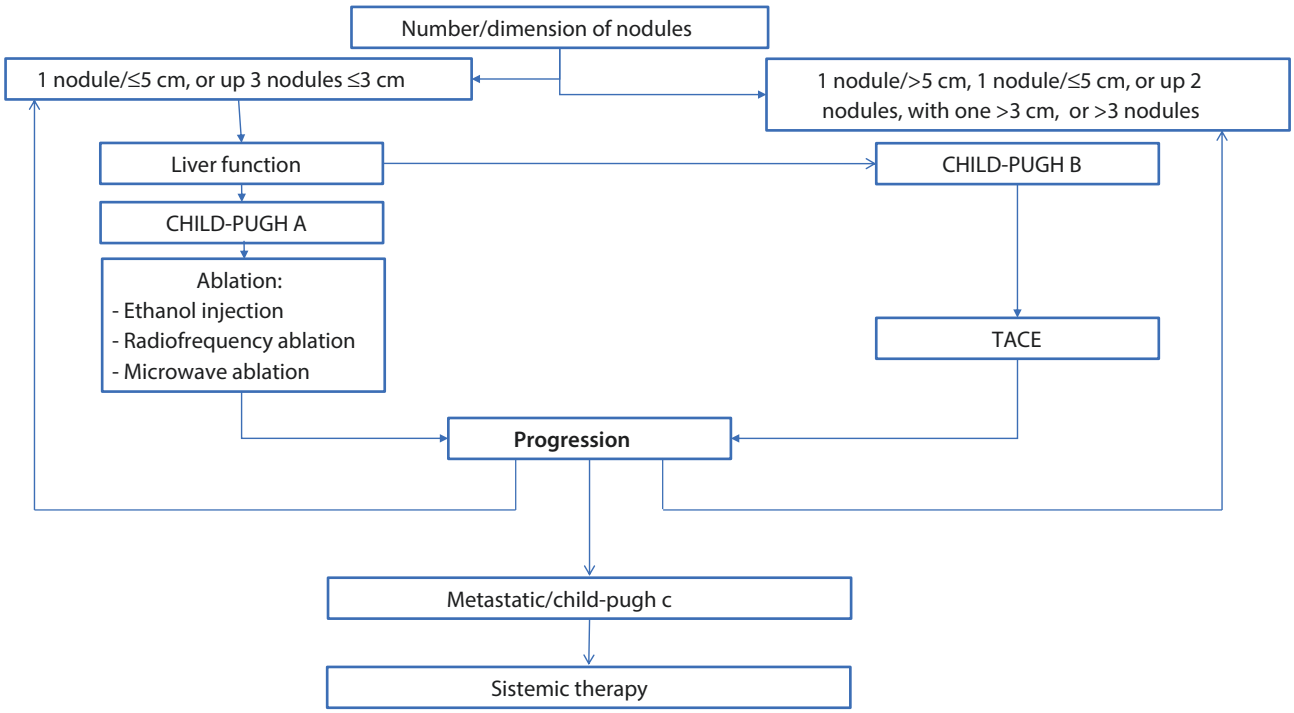


Fig. 42.10 Locoregional procedures: flow chart

In absolute terms, the median survival prolongation was approximately 3 months in the SHARP study and approximately 2 months in the Asian study, but findings are only comparable in relative terms (hazard ratio 0.69 and 0.68, 95 % CI 0.55–0.87, and 0.50–0.93, respectively). On the basis of these results, sorafenib was approved by the EMA for the treatment of HCC in October 2007 (Table 42.2).

The main adverse events of sorafenib are hand-foot skin reaction, hypertension, and diarrhea. Numerous studies have focused on the role of factors and biomarkers predictive and/or prognostic to response to sorafenib, but currently no marker is used in current clinical trials. The most interesting factors studied are the correlation between toxicity and response [58, 59], immune inflammation indicators, and level of lactate dehydrogenase [60, 61, 62].

42.6.4.2 Lenvatinib

Recently, the results from a multicenter randomized non-inferiority phase 3 study comparing lenvatinib and sorafenib were published [63]. Patients with advanced HCC or HCC not recommendable for locoregional treatment and who had never received systemic treatment were recruited and randomized to receive lenvatinib (12 mg/day (body weight ≥ 60 kg) or 8 mg/day (body weight < 60 kg) or sorafenib (400 mg twice daily for 28-day cycles). The primary endpoint was OS,

Table 42.2 Main TKI in use for HCC, lines of indication, survival, side effects

Drug	Lines of indication	Overall survival in phase 3 trial [Months (95 % CI)]	Adverse events
Sorafenib	First	10.7 (9.4–13.3)	Hand-foot skin reaction, hypertension, and diarrhea
Lenvatinib	First	13.6 (12.1–14.9)	Hypertension, fatigue, diarrhea, joint and muscle pain
Regorafenib	Second	10.6 (9.1–12.1)	Breathlessness and looking pale, bruising, bleeding gums or nosebleeds, fatigue, hand-foot skin reaction
Cabozantinib	Second	10.2 (9.1–12.0)	Severe bleeding (hemorrhage), emesis, blood red or black tarry stool

measured from the date of randomization to the date of death from any cause. Median survival time for lenvatinib was 13.6 months (95 % CI 12.1–14.9), therefore not lower than sorafenib (12.3 months, 10.4–13.9; HR 092, 95 % CI 0.79–1.06). Among secondary endpoints (progression-free survival [PFS] and TTP), although lenvatinib was superior to sorafenib, in the study design, the evaluation of the radiological response according to mRECIST was not centralized. Among adverse events of any grade, hypertension occurred more frequently in lenvatinib-arm patients (42 % vs. 30 %), while palmar-plantar erythrodysesthesia syndrome was more frequent in those treated with sorafenib, as expected. In conclusion, lenvatinib did not result inferior to sorafenib in terms of OS in untreated advanced HCC. The safety and tolerability profiles of lenvatinib were consistent with those previously observed (Table 42.2).

42.6.4.3 Atezolizumab Plus Bevacizumab

IMbrave150 trial [64], a randomized double-blind phase III trial, evaluated the efficacy of atezolizumab plus bevacizumab versus sorafenib in first-line chemotherapy. Study meets the co-primary endpoint for OS and PFS. Atezolizumab plus bevacizumab improved OS (hazard ratio [HR] 0.58; 95 % CI 0.42–0.79, $p = 0.0006$) and PFS (hazard ratio [HR] 0.59; 95 % CI 0.47–0.76, $p < 0.0001$) with respect to sorafenib. mOS was not reach in atezolizumab plus bevacizumab arm compared to 13.2 months for sorafenib arm; PFS was 6.8 months in atezolizumab plus bevacizumab arm compared to 4.3 months for sorafenib arm.

42.6.4.4 Regorafenib

In the RESORCE study [65], a randomized double-blind phase III study, Child-Pugh A patients with advanced or intermediate HCC (the latter was not eligible for locoregional treatment) who had tolerated first-line sorafenib at a dose of at least 400 mg/day for at least 20 of the 28 days prior to discontinuation but had progressed during treatment were randomized to receive the best supportive therapy (BSC) in combination with oral regorafenib (160 mg once a day for 21 days of each 4-week cycle) vs. BSC and placebo. The primary endpoint was OS (defined as the time from randomization to death from any cause). Regorafenib improved OS (HR 0.63; 95 % CI 0.50–0.79, $p < 0.0001$). Median OS was 10.6 months (95 % CI 9.1–12.1) for regorafenib compared to 7.8 months (6.3–8.8) for placebo. Adverse events (AEs) were reported in all patients treated with regorafenib. In particular, the AEs with the highest grade (3 or 4) were hypertension (15 % in the regorafenib group vs. 5 % in the placebo group), hemorrhagic fever with renal syndrome (HFRS) (13 % vs.1 %), fatigue (9 % vs. 5 %), and diarrhea (3 % vs. no patient in the placebo group). In all additional efficacy endpoints (PFS, TTP, response rate [RR] and disease control rate [DCR]), regorafenib was statistically superior to placebo (Table 42.2).

42.6.4.5 Cabozantinib

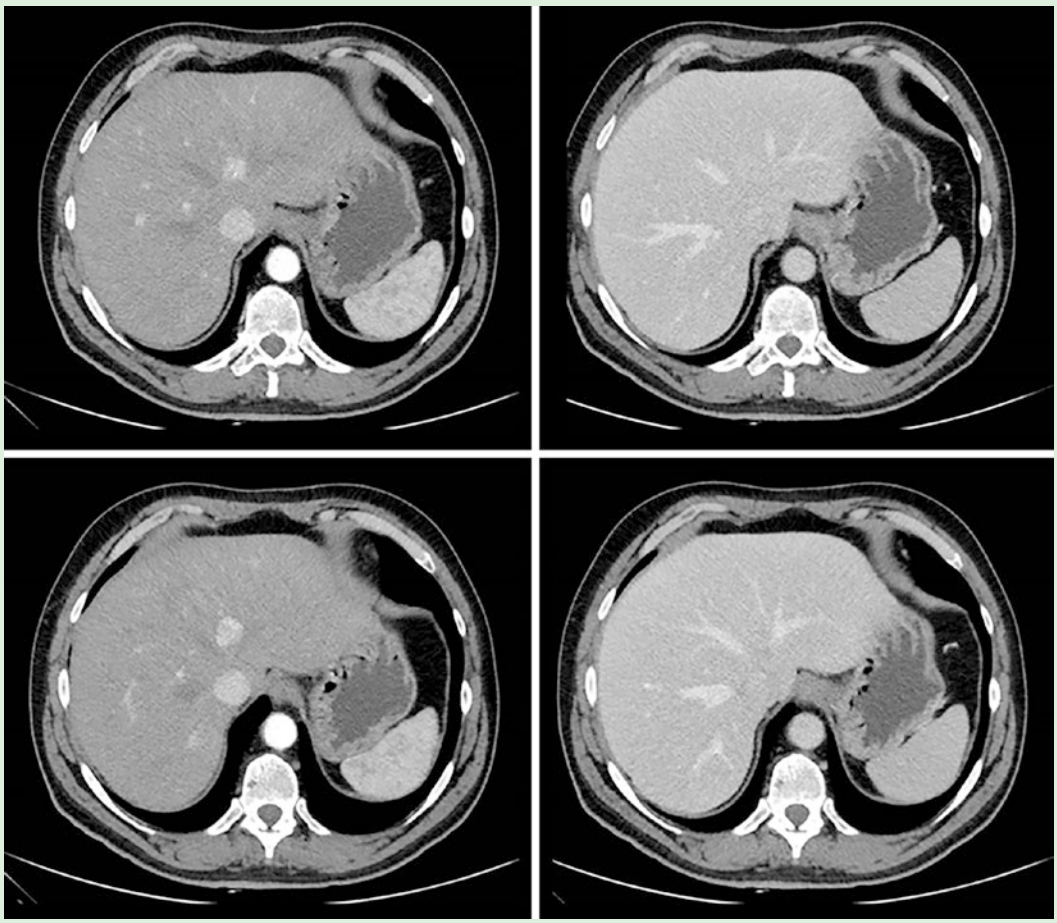
The CELESTIAL study [66], a randomized double-blind phase III trial, evaluated the efficacy of cabozantinib in patients progressing on sorafenib. Cabozantinib improved OS (hazard ratio [HR] 0.76; 95 % CI 0.63–0.92, $p = 0.0049$). mOS was 10.2 months (95 % CI 9.1–12.0) for cabozantinib compared to 8 months (95 % CI 6.8–9.4) for placebo. In addition to being statistically superior to placebo in terms of PFS, TTP, RR, and DCR, cabozantinib was also superior in terms of PFS and ORR (Table 42.2).

42.6.4.6 Ramucirumab

REACH-2 trial [67], a randomized double-blind phase III trial, evaluated the efficacy of ramucirumab versus placebo sorafenib in patients progressing on sorafenib with α-fetoprotein concentrations of 400 ng/mL or higher. Study meets the primary endpoint for OS. Ramucirumab improved OS (hazard ratio [HR] 0.71; 95% CI 0.53–0.95, $p = 0.0199$). mOS was 8.5 months (95% CI 7.0–10.6) for ramucirumab compared to 7.3 months (95% CI 5.4–9.1) for placebo. In addition, to confirm the better results compared to placebo in terms of PFS, no difference was found in terms of DCR.

Case Study

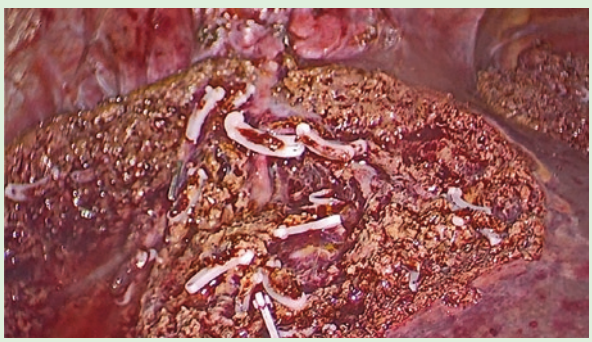
Man: 55 years old
- Family history: negative for malignancies
- APR: treated HCV infection, cirrhosis
- Blood test: normal liver function test, Child A, Meld 8, Afp 200 ng/mL
- TC abdomen and MRI: lesion of 24 × 20 × 22 mm in segment 4, confirmed for HCC



Question

What action should be taken?

1. Surgery
2. RFA
3. Others



Answer

A. Liver resection, if possible laparoscopy

Question

Which is the best follow-up?

1. CT scan every 3 months
2. Nexavar
3. Others

Answer

1. CT scan

Question

Which is the best treatment in case of recurrence?

1. Liver resection
2. Liver transplant
3. Others

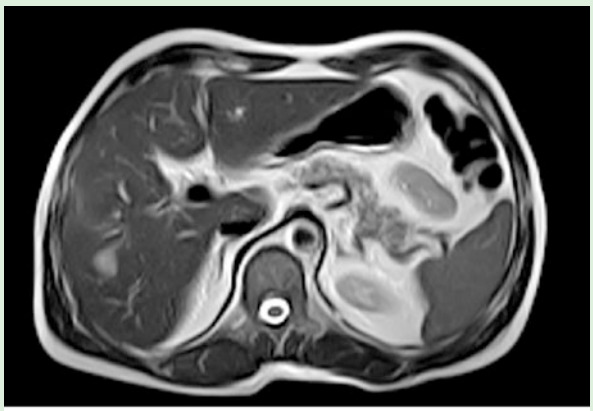
Answer

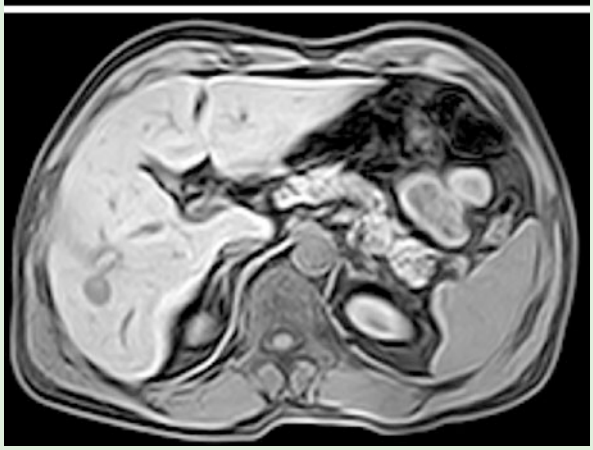
2. In case of recurrence, treatment of choice should be liver transplant, which guarantees best overall and disease-free survival.

Case Study

Man: 75 years old

- Family history: negative for malignancies
- APR: treated HCV infection, cirrhosis, PS 2
- Blood test: normal liver function test, Child A, Meld 8, Afp 500 ng/mL
- TC abdomen and MRI: lesion of 15 × 10 × 12 mm in segment 6, confirmed for HCC





Question

Which is the best treatment of choice?

1. Resection
2. RFA
3. Others

Answer

1. RFA in consideration of performance status of patient and small size of the lesion. Results are comparable to liver resection, with better postoperative outcome in such a fragile patient.

Question

Which is the best treatment in case of recurrence?

1. Liver resection
2. RFA
3. Others

Answer

2. In case of recurrence, treatment of choice should be radiofrequency ablation or TACE in case of multinodular lesions

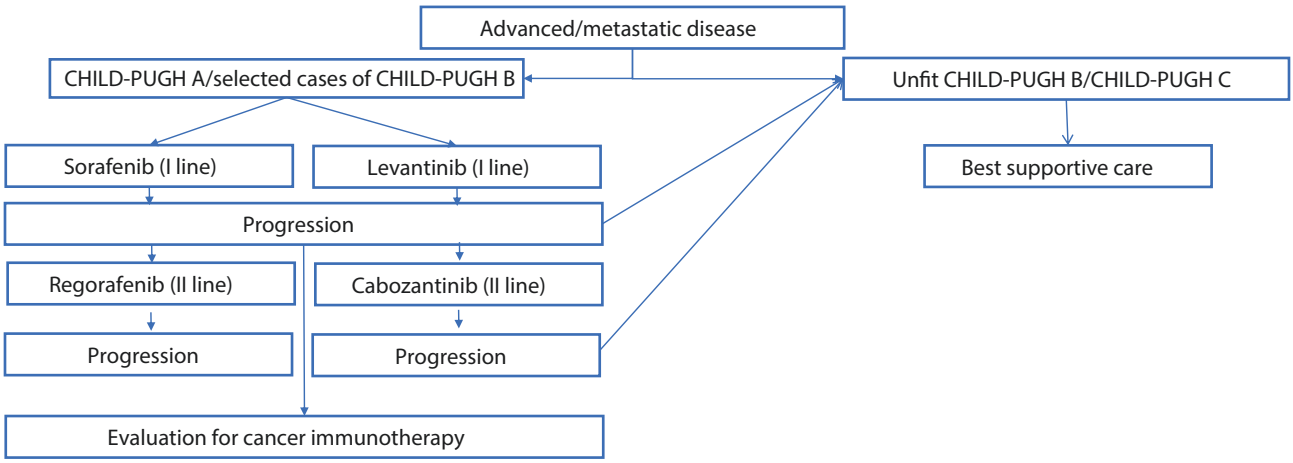


Fig. 42.11 Systemic therapy: flow chart

42.7 Future Perspectives

Even if new molecular approaches have been experimented, only slightly significant improvements have been achieved in survival. Therefore, clinicians need to both identify new therapeutic approaches and select patients suitable for these treatments.

Moreover, it must be pointed out that cancer immunotherapy is the new open option for solid treatments. Different clinical trials evaluating the role of immunotherapy in treating HCC have been conducted. Initial promising results have been obtained among cytokine-induced killer cells and immune checkpoint inhibitors in the adjuvant setting and advanced stages, respectively. Anyway, there are several ongoing trials, the results of which appear intriguing. Conclusively, since the liver immune system the plays an important role in immune tolerance, the possibility of unmasking these mechanisms can be a winning weapon in HCC, so immunotherapy [68] will represent the future therapy in this cancer (Fig. 42.11).

42.8 Highlights

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in adults.

It occurs in the setting of chronic liver inflammation, mostly linked to chronic viral hepatitis B or C.

Hepatic carcinogenesis occurs in stages in 90% of cases: the lesion progresses from regenerative micronodule to regenerative macronodule.

Suspicious nodules should be evaluated with contrast-enhanced MRI and/or CT scan to identify a diagnostic pattern typical of HCC

One of the most important moments in the onset of an HCC is the possibility to achieve a correct staging of the cancer to choose the best therapeutic option. Currently, the most common staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which determines cancer stage and patient's prognosis based on tumor burden, severity of the diseases, and patient's performance status

Very early and early stage (BCLC 0 and BCLC A) in patients with solitary lesion or up to three nodules ≤3 cm (no macrovascular invasion or extrahepatic disease). In this case patients can benefit from potentially curative treatment (resection, transplant, or ablation).

In case of intermediate stage HCC (BCLC B), in asymptomatic patients with multifocal HCC, without vascular invasion or extrahepatic disease, patients could be candidate for transarterial chemoembolization (TACE).

In case of multifocal HCC with vascular invasion or extrahepatic disease, systemic treatment with tyrosine kinase inhibitor (sorafenib/lenvatinib) or in the next future with atezolizumab plus bevacizumab it could be suggested.

Different clinical trials evaluating the role of immunotherapy, antiangiogenic, and TKI or their combinations in treating HCC have been conducted.

Expert Opinion

Vito Di Marco

1. Hepatocellular carcinoma is one of the leading causes of cancer on cirrhotic patients.
2. Many different approaches are available, depending on tumor diffusion and status of the patient.
3. To date, sorafenib and regorafenib are the approved therapies in advanced HCC. Levantinib and cabozantinib could represent other therapies that have shown efficacy in advanced HCC. Even if new molecular approaches have been experimented, only slightly significant improvements have been achieved in survival. Therefore, clinicians need to both identify new therapeutic approaches and select patients suitable for these treatments.
4. Moreover, it must be pointed out that cancer immunotherapy is the new open option for solid treatments. Different clinical trials evaluating the role of immunotherapy in treating HCC have been conducted. Initial promising results have been obtained among cytokine-induced killer cells and immune checkpoint inhibitors in the adjuvant setting and advanced stages, respectively. However, there are several ongoing trials, the results of which appear intriguing. Conclusively, since the liver immune system plays an important role in immune tolerance, the possibility of unmasking these mechanisms can be a winning weapon in HCC, so immunotherapy will represent the future therapy in this cancer.

Recommendations

- ESMO
  ► https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Hepatocellular-Carcinoma

References

1. Llovet JM, Ducreux M, Lencioni R, et al. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Eur J Cancer. 2012;48:599–641.
2. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379:1245–55.
3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365:1118–27.
4. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol. 2013;47:S2–6.
5. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340:745–50.
6. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
7. Kumar V, Abbas AK, Fausto N, et al. Robbins and cotran pathologic basis of disease. 7th ed. Philadelphia: Elsevier Saunders; 2004.
8. Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. Hepatology. 2012;56:769–75.
9. Nomura A, Stemmermann GN, Wasnich RD. Presence of hepatitis B surface antigen before primary hepatocellular carcinoma. JAMA. 1982;247:2247–9.
10. Tsukuma H, Hiyama T, Oshima A, et al. A case-control study of hepatocellular carcinoma in Osaka. Japan. Int J Cancer. 1990;45:231–6.
11. Beasley RP, Hwang LY, Lin CC, et al. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. Lancet. 1981;2:1129–33.
12. Trichopoulos D. Hepatitis B virus and hepatocellular carcinoma. Lancet. 1979;8127:1192.
13. Tabor E. Hepatitis C virus and hepatocellular carcinoma. AIDS Res Hum Retrovir. 1992;5:793–6.
14. Tabor E, Kobayashi K. Hepatitis C virus, a causative infectious agent of non-A, non-B hepatitis: prevalence and structure--summary of a conference on hepatitis C virus as a cause of hepatocellular carcinoma. J Natl Cancer Inst. 1992;84:86–90.
15. Zavitsanos X, Hatzakis A, Kaklamani E, et al. Association between hepatitis C virus and hepatocellular carcinoma using assays based on structural and nonstructural hepatitis C virus peptides. Cancer Res. 1992;52:5364–7.
16. Peers FG, Linsell CA. Dietary aflatoxins and human primary liver cancer. Ann Nutr Aliment. 1977;31:1005–17.
17. Franco D, Capussotti L, Smadja C, et al. Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. Gastroenterology. 1990;98:733–8.
18. Anthony PP. Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. J Pathol. 1973;110:37–48.
19. Bolondi L, Sofia S, Siringo S, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of HCC: a cost effectiveness analysis. Gut. 2001;48:251–9.
20. Sangiovanni A, Del Ninno E, Fasani P, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology. 2004;126:1005–14.
21. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391:1301–14.
22. Tanaka M, Nakashima O, Wada Y, Kage M, Kojiro M. Pathomorphological study of Kupffer cells in hepatocellular carcinoma and hyperplastic nodular lesions in the liver. Hepatology. 1996;24:807–12.
23. Hamilton SR, Aaltonen LA. Pathology and genetics of tumours of the digestive system. Lyon: IARC Press; 2000.
24. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;150:836–53.
25. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg. 2015;261:619–29.

26. Giulianotti PC, Bianco FM, Daskalaki D, et al. Robotic liver surgery: technical aspects and review of the literature. Hepatobiliary Surg Nutr. 2016;5:311–21.
27. Rahnemai-Azar AA, Cloyd JM, Weber SM, et al. Update on liver failure following hepatic resection: strategies for prediction and avoidance of post-operative liver insufficiency. J Clin Transl Hepatol. 2018;6:1–8.
28. Chan J, Perini M, Fink M, et al. The outcomes of central hepatectomy versus extended hepatectomy: a systematic review and meta-analysis. HPB. 2018;20:487–96.
29. Cieslak KP, Huisman F, Bais T, et al. Future remnant liver function as predictive factor for the hypertrophy response after portal vein embolization. Surgery. 2017;162:37–47.
30. de Baere T, Teriitehau C, Deschamps F, et al. Predictive factors for hypertrophy of the future remnant liver after selective portal vein embolization. Ann Surg Oncol. 2010;17:2081–9.
31. Rhaiem R, Piardi T, Chetboun M, et al. Portal inflow modulation by somatostatin after major liver resection. Ann Surg. 2017;276:e101–3.
32. Okajima C, Arii S, Tanaka S, et al. Prognostic role of Child-Pugh score 5 and 6 in hepatocellular carcinoma patients who underwent curative hepatic resection. Am J Surg. 2015;209:199–205.
33. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
34. Cieslak KP, Runge JH, Heger M, et al. New perspectives in the assessment of future remnant liver. Dig Surg. 2014;31:255–68.
35. Memeo R, De Blasi V, Adam R, et al. Parenchymal-sparing hepatectomies (PSH) for bilobar colorectal liver metastases are associated with a lower morbidity and similar oncological results: a propensity score matching analysis. HPB. 2016;18:781–90.
36. Pauli EM, Staveley-O'Carroll KF, Brock MV, et al. A handy tool to teach segmental liver anatomy to surgical trainees. Arch Surg. 2012;147:692–3.
37. Memeo R, De'Angelis N, Compagnon P, et al. Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case-control study. World J Surg. 2014;38:11.
38. Huang X, Lu S. A meta-analysis comparing the effect of anatomical resection vs. non-anatomical resection on the long-term outcomes for patients undergoing hepatic resection for hepatocellular carcinoma. HPB. 2017;19:843–9.
39. Appéré F, Piardi T, Memeo R, et al. Comparative study with propensity score matching analysis of two different methods of transection during hemi-right hepatectomy: Ultracision Harmonic Scalpel versus Cavitron Ultrasonic Surgical Aspirator. Surg Innov. 2017;24:5.
40. Sotiropoulos GC, Prodromidou A, Kostakis ID, et al. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. Updat Surg. 2017;69:291–311.
41. Byam J, Renz J, Millis JM. Liver transplantation for hepatocellular carcinoma. Hepatobiliary Surg Nutr. 2013;2:22–30.
42. Silva MF, Sherman M. Criteria for liver transplantation for HCC: what should the limits be? J Hepatol. 2011;55:1137–47.
43. Cherqui D, Laurent A, Mocellin N, et al. Liver resection for transplantable hepatocellular carcinoma: long-term survival and role of secondary liver transplantation. Ann Surg. 2009;250:5.
44. Parikh ND, Waljee AK, Singal AG, et al. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transpl. 2015;21:1142–52.
45. deLemos AS, Vagefi PA. Expanding the donor pool in liver transplantation: extended criteria donors. Clin Liver Dis. 2013;2:156–9.
46. Salvalaggio PR, Felga GE, Guardia BD, et al. Time of dropout from the liver transplant list in patients with hepatocellular carcinoma: clinical behavior according to tumor characteristics and severity of liver disease. Transplant Proc. 2016;48:2319–22.
47. Facciorusso A, Serviddio G, Muscatiello N. Local ablative treatments for hepatocellular carcinoma: an updated review. World J Gastrointest Pharmacol Ther. 2016;7:477.
48. Luo W, Zhang Y, He G, et al. Effects of radiofrequency ablation versus other ablating techniques on hepatocellular carcinomas: a systematic review and meta-analysis. World J Surg Oncol. 2017;15:126.
49. Rhim H, Lim HK. Radiofrequency ablation of hepatocellular carcinoma: pros and cons. Gut Liver. 2010;1(Suppl 1):S113–8.
50. Yang W, Yan K, Goldberg SN, et al. Ten-year survival of hepatocellular carcinoma patients undergoing radiofrequency ablation as a first-line treatment. World J Gastroenterol. 2016;22:2993–3005.
51. Lee S, Kang TW, Cha DI, et al. Radiofrequency ablation vs. surgery for perivascular hepatocellular carcinoma: propensity score analyses of long-term outcomes. J Hepatol. 2018;69:70–8.
52. Dou J-P, Yu J, Yang X-H, et al. Outcomes of microwave ablation for hepatocellular carcinoma adjacent to large vessels: a propensity score analysis. Oncotarget. 2017;8:28758–68.
53. Vietti Violi N, Duran R, Guiu B, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2018;3:317–25.
54. Gnoni A, Santini D, Scartozzi M, et al. Hepatocellular carcinoma treatment over sorafenib: epigenetics, microRNAs and microenvironment. Is there a light at the end of the tunnel? Expert Opin Ther Targets. 2015;19:1623–35.
55. Longo V, Brunetti O, Gnoni A, et al. Angiogenesis in pancreatic ductal adenocarcinoma: a controversial issue. Oncotarget. 2016;7:58649–58.
56. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378–90.
57. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25–34.
58. Casadei Gardini A, Scarpi E, Marisi G, et al. Early onset of hypertension and serum electrolyte changes as potential predictive factors of activity in advanced HCC patients treated with sorafenib: results from a retrospective analysis of the HCC-AVR group. Oncotarget. 2016a;12:15243–51.
59. Di Costanzo GG, Casadei Gardini A, Marisi G, et al. Validation of a simple scoring system to predict sorafenib effectiveness in patients with hepatocellular carcinoma. Target Oncol. 2017;6:795–803.
60. Brunetti O, Gnoni A, Licchetta A, et al. Predictive and prognostic factors in HCC patients treated with sorafenib. Medicina (Kaunas). 2019;55:pii: E707.
61. Casadei Gardini A, Scarpi E, Faloppi L, et al. Immune inflammation indicators and implication for immune modulation strategies in advanced hepatocellular carcinoma patients receiving sorafenib. Oncotarget. 2016b;41:67142–9.
62. Faloppi L, Bianconi M, Memeo R, et al. Lactate dehydrogenase in hepatocellular carcinoma: something old, something new. Biomed Res Int. 2016;2016:7196280.
63. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163–73.

64. Cheng A-L, Qin S, Ikeda M, et al. IMbrave150: efficacy and safety results from a Ph 3 study evaluating ATEZOLIZUMAB (atezo) + bevacizumab (bev) vs sorafenib (sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Ann Oncol. 2019;30(9):ix186–7.
65. Bruix J, Qin S, Merle P, Granito A, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56–66.
66. Abou-Alfa GK, Cheng A-L, et al. Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426). J Clin Oncol. 2014;32(5s (suppl)):abstr TPS4150.
67. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20:282–96.
68. Longo V, Gnoni A, Casadei Gardini A, et al. Immunotherapeutic approaches for hepatocellular carcinoma. Oncotarget. 2017;8:33897–910.