Chapter 7

Evaluation and Surgical Management of Hepatocellular Carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver, being the sixth most common cancer in the world and the third cause of cancer mortality. Most of the patients with HCC have an established background of cirrhosis and chronic liver disease. Magnetic resonance imaging (MRI) is the best technique for evaluation of the liver nodules in patients with cirrhosis, especially when a HCC is suspected. HCC staging is mandatory to select the appropriate primary and adjuvant therapy and to evaluate the prognosis. Hepatic resection is the treatment of choice in non-cirrhotic patients who have been diagnosed with HCC. In this chapter we underline the main diagnostic methods used for HCC staging, together with the treatment possibilities, highlighting the importance of surgical management, conventional or minimally invasive.

Keywords: hepatocellular carcinoma, hepatic resections, laparoscopy, ablative therapy

1. Introduction: generalities

Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver, which is arising from hepatocytes, the liver's parenchymal cells. Most of the patients with HCC have an established background of cirrhosis and chronic liver disease due to hepatitis B virus or hepatitis C virus. HCC is the sixth most common cancer in the world and the third cause of cancer mortality [1].

2. Diagnosis

Clinical features of HCC may include pain in the upper right quadrant and weight loss. Most of the patients diagnosed with HCC are patients known with liver cirrhosis. Despite this fact, there is a rare complication such as rupture of a liver tumor with intra-abdominal bleeding, which will need immediate surgical care [2]. These patients will present with acute abdominal pain, peritoneal irritation and hypotension. Other patients present with nonspecific signs such as fever, jaundice, ascites, anorexia or encephalopathy [3].

Clinical examination can reveal an abdominal mass in the upper right quadrant or hepatomegaly. Obstructive jaundice can indicate tumor extension into the extrahepatic biliary structures [4].

HCC can metastasize to any organ, the most frequent being metastasis to bone, lung or other abdominal viscera; so, patients can present with various clinical signs and symptoms related to the affected organs. Watery diarrhea is more common in patients with cirrhosis and HCC because of the increased production of intestinal secretory substances such as gastrin and vasoactive intestinal peptide (VIP) [5, 6].

Alpha-1 fetoprotein is the most commonly used marker for HCC. Patients with AFP > 400 ng/ml tend to have a greater size, bilobar involvement, portal vein thrombosis and decreased survival [7]. If the tumor producing AFP is left untreated, the AFP value will increase over the time, so this marker can be used for detecting tumor progression. APF may be increased in a variety of other malignancies and in patients with chronic liver disease without HCC, particularly in hepatitis C [8]. The sensitivity, specificity and positive predictive value of AFP range from 39 to 64%, 76 to 91% and 9 to 32% [8]. Patients with values of AFP greater than 1000 ng/ml have a higher incidence of vascular invasion (61%) compared with patients with values of AFP <1000 ng/ml [9].

Other clinical biomarkers used for the diagnosis of HCC are: microRNAs [10], des-gamma-carboxyprothrombin (DCP) [11], glypican-3 (GPC3) [12], proteomic profiling [13], and alpha-L-fucosidase [14].

Imaging has an important role in the diagnosis of HCC. Even if over the past decades the imaging technology has improved and the hepatic lesions are better characterized, detection of the small tumors continues to be difficult especially in patients with liver cirrhosis whose parenchymal architecture is abnormal. The most common imaging techniques used for evaluation of the liver parenchyma are as follows: ultrasound scanning (US), CT scan, MRI, and angiography.

Ultrasound scanning is the most used technique, and it is performed as a routine test for screening focal hepatic lesions. Ultrasound imaging has now been replaced in diagnosis by CT scan and MRI. Contrast-enhanced ultrasound (CEUS) uses contrast agents such as intra-arterial dioxide carbon and helium. Also, application of color Doppler sonography can be useful in the assessment of intrahepatic vascular flow and the Doppler of the portal vein can differentiate bland thrombus from tumor invasion.

Contrast-enhanced ultrasonography (*CEUS*) can offer information about the nature of the liver tumor which cannot be obtained with conventional ultrasonography. CEUS is safe, and it is

usually performed after detection of a focal lesion on standard US. The characterization of the hepatic lesion depends on all phases of contrast enhancement.

Most of the HCC are characterized by arterial phase enhancement and wash-out of the contrast during the late phase. According to some studies, more the differentiated a lesion is, the more gradually it is to washout [15, 16].

CEUS is an alternative for CT and MRI especially when there are contraindications for these investigations and it offers equivalent accuracy to CT and MRI if there is an experienced and skilled operator [17, 18].

CT scan is an important investigation for the characterization of the HCC. It includes 4 phases: pre-contrast, hepatic arterial phase, portal venous and delayed phases.

HCC must be differentiated from regeneration nodules, hemangioma, focal fat, dysplastic nodules and peliosis [19].

Factors such as injection of the contrast, tumor size and vascularity can affect the diagnostic accuracy of the HCC. In small tumors (less than 2 cm), the efficacy of CT is diminished due to the hypo-vascularization of small-sized tumors. The sensitivity of four phase CT in detecting HCC was up to 100% for tumors larger than 2 cm, 93% for tumors size between 1 and 2 cm and 60% for tumors less than 1 cm [20–22].

Multidetector helical CT (*MDCT*) is a new technique. which allows collection of early (18–28 s after administration of the contrast agent) and late or early parenchymal (35–45 s) arterial phase images. This new technique has improved the sensitivity and positive predictive values [23, 24]. Vascular tumors appear hypodense compared with liver parenchyma during the equilibrium phase (3–5 min after the administration of the contrast agent) and this technique is compared with MRI for early detection of small HCC (<1 cm) [24, 25].

Magnetic resonance imaging (*MRI*) is the best technique for evaluation of the liver nodules in patients with cirrhosis. HCC aspect varies on MRI because of the following factors: hemorrhage, degree of fibrosis and necrosis and histologic pattern. MRI is more accurate than CT or ultrasonography in detecting and characterization of HCC even for patients with liver cirrhosis. HCC appears hyper-intense on T2-weighted images while in T1-weighted images it may appear hypointense, isointense or hyperintense.

The sensitivity of MRI depends on tumor size, and it is about 95% in tumors larger than 2 cm and reduced to 30% for tumors, which are less than 2 cm in size [26].

Even if the MRI is the best investigation to characterize a liver nodule and to put the diagnosis of HCC, often the nodules might not be distinguished so a histological examination or advance imaging modalities will be necessary.

Angiography can be used to define hepatic anatomy before surgical resection.

Liver biopsy is performed with fine needle aspiration biopsy (FNAB) under ultrasonography or CT guidance and is considered the best method for a sure diagnosis of HCC. The sensitivity and specificity are about 96 and 95%, respectively, superior to any other test [27]. Sometimes, because the HCC lesions cannot be accurately located by radiographic methods, it is necessary

to perform open surgical biopsy. The most important complications are the risk of tumor spreading along the needle tract, estimated at up 3%, important bleeding or infectious complications [7] [28–30]. Contraindications for liver biopsy are platelet count <50,000 per mm^3 or the international normalizing ratio (INR) > 2 [7].

3. Diagnostic guidelines

According to European Association for the Study of the Liver (EASL):

- HCC lesions of greater than 2 cm in diameter can be diagnosed non-invasively in patients with cirrhosis based on radiographic criteria;
- Nodules with arterial hypervascularization in two imaging modalities or in only single imaging modality associated with values of AFP > 400 ng/ml in the cirrhotic liver is considered HCC [31];
- Evaluation of the liver nodules should be performed by US, CT and MRI; liver biopsy is not mandatory [32];
- EASL recommend repeated US every 3 months for lesions which are smaller than 1 cm, until it grows [31];
- Nodules between 1 and 2 cm in size are more likely to be HCC and confirmation by liver biopsy is recommended [33].

According to American Association for the Study of Liver Disease (AASLD):

- AFP > 200 ng/ml should lead to diagnostic suspicion of HCC and requires more investigation;
- Nodules <1 cm should be repeatedly imaged for up to 2 years;
- Nodules between 1 and 2 cm should be investigated with two techniques: CEUS, CT scan, MRI. If there is a hypervascularity with washout in the portal venous phase the lesion can be diagnosed as HCC [34];
- Nodules larger than 2 cm can be diagnosed as HCC with a use of only one imaging modality (arterial hypervascularity with wash-out in the early or delayed venous phase) [35];
- Liver biopsy is recommended if the vascular pattern is not characteristic for HCC on imaging modalities [34].

4. Stadialization

HCC staging is mandatory to select the appropriate primary and adjuvant therapy and to evaluate the prognosis. There are eight different staging systems available for the management of HCC but none of them are universally accepted. The currently available staging systems for

HCC include: pathologic tumor-node-metastasis (pTNM) [36], Okuda [37], Cancer of the Liver Italian Program (CLIP) [38] and Barcelona Clinic Liver Cancer (BCLC) [39].

BCLC staging system seems to be the best for selection of early-stage HCC that should benefit from orthotopic liver transplantation, hepatic resection or local ablation while the CLIP score may be more useful at stratifying patients who are not candidates for resection or transplantation.

5. Treatment

Nowadays, many of the patients with HCC are diagnosed at an early stage when there are no signs of an advanced cancer. In the past, most of the patients were diagnosed only when they became symptomatic and no treatment had a chance of being effective or to improve the survival rates. There are a number of treatments available which seems to improve the survival rates, but to achieve the best results a careful selection of the patients is needed. Liver transplantation is the best option treatment for the patients with solitary HCC in the setting of decompensated cirrhosis and for those with early multifocal disease (up to 3 lesions, none larger than 3 cm) [40, 41], while for the patients with solitary tumors in well-compensated cirrhosis the best treatment strategy is under debate [42]. Treatments which offer the best survival rate are surgical resection, liver transplantation, percutaneous ablation and transarterial chemoembolization [40, 43]. Systemic chemotherapy has been demonstrated that has no benefits on survival rates [44, 45], while agents like tamoxifen [43], anti-androgens [46] or octreotide [47] are completely ineffective.

Hepatic resection is the treatment of choice in non-cirrhotic patients who have been diagnosed with HCC (**Figure 1a** and **b**). Patients with cirrhosis have to be very well selected for surgical resection due to the high risk of postoperative liver failure which can lead to death after the surgery. Cirrhotic patients have a higher rate of decompensation if they are operated with right hepatectomy than if a left hepatectomy is performed; however, the 5-year survival rate after resection can exceed 50% [42, 48, 49]. Before the surgery there are some specific factors which need to be considered:

- Stage of the tumor;
- Size of the tumor;
- Presence/absence of a chronic liver disease and portal hypertension assessed clinically or by hepatic vein catheterization. If the upper endoscopy shows varices or diuretic treatment is necessary, the portal hypertension is severe and there is no need for catheterization of the hepatic veins;
- Quality and volume of the future functional liver remnant.

The most important causes of death after liver resections are postoperative hemorrhages, liver failure and sepsis, but all these complications have a lower incidence due to the improvements of the surgical techniques (Pringles maneuver), the development of ultrasonic dissectors and vascular staplers.

To perform a *right hepatic resection*, you have to mobilize completely the right lobe of the liver to have control on the right hepatic vein before the parenchymal transection. Sometimes the

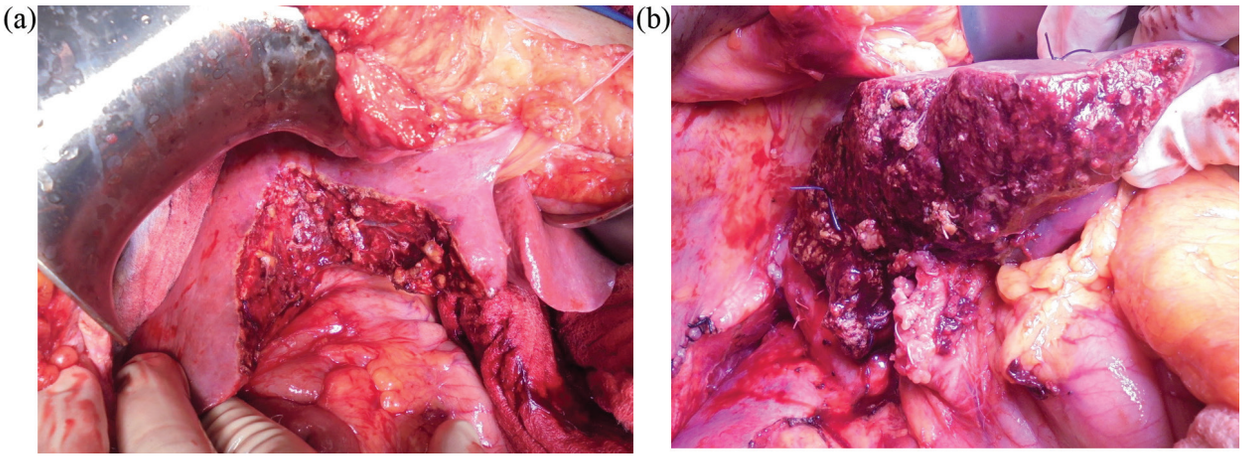

Figure 1. (a) Segment V resection. Intraoperative aspect after removal of the specimen (from the personal archive of the authors). (b) Right hepatectomy. Intraoperative aspect after removal of the specimen (from the personal archive of the authors).

size of the tumors does not permit to mobilize the right lobe of the liver and to expose the anterior surface of the inferior vena cava, so the surgeon has to perform an anterior approach. The anterior approach implies initial completion of parenchymal transection before mobilizing the right lobe of the liver and after hilar dissection is performed to control the right hepatic artery and portal vein. Intraoperative ultrasound is useful to mark on the Glisson capsule the plane of parenchymal transection. Transection is performed from the anterior surface of the liver down to right side of the liver hilum and down to the anterior surface of the inferior vena cava; then the right hepatic vein is isolated, clamped, divided and sutured. Only after the specimen is removed from the inferior vena cava, the right hepatic lobe is mobilized from the abdominal cavity by dividing the triangular ligament and other posterior attachments [50, 51].

Even if the anterior approach can be potentially dangerous because of the massive bleeding which can occur when deeper plane of the parenchyma is transected, it is an effective alternative when difficulty is encountered during liver mobilization using the conventional technique [52].

One of the most important factors which can lead to recurrence are microportal invasion and intrahepatic metastasis, these being associated with a poor prognosis. Anatomic resection implies the systematic removal of a hepatic segment or segments bearing the tumors (**Figure 2**). This technique has been shown to be effective in eradicating intrahepatic metastasis of HCC and it is associated with a prolonged survival. From the oncological perspective, anatomical resections which include satellite lesions are more efficient than limited resections without a surrounding margin [53].

Laparoscopic liver resection was initially used for non-anatomic liver resection for peripheral benign tumors (**Figure 3**), but nowadays, with the development of instrumentation and techniques, it has become a safe and feasible option for both benign and malignant liver lesions [54]. Regarding the advantages of laparoscopic liver resection, there are some advantages comparing with conventional liver resection such as reduced postoperative pain, less blood loss, less operative morbidity and a shorter length of hospitalization, while the long-term outcomes are similar especially for cirrhotic patients [55, 56].

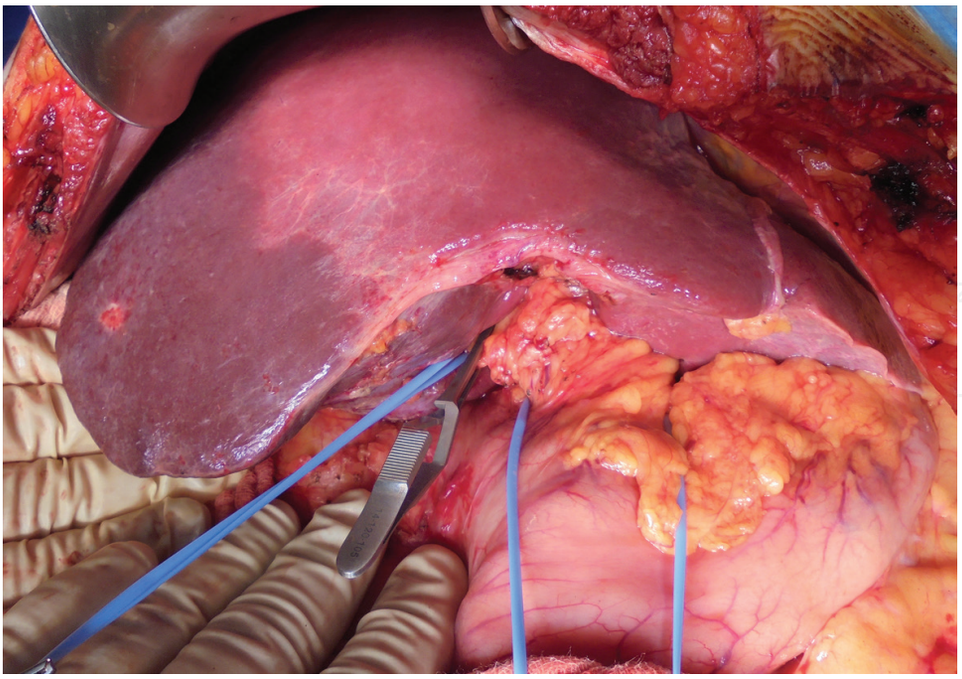

Figure 2. Anatomical resection of the VI–VII segments. Delimitation of the transection line after clamping the VI–VII pedicle (from the personal archive of the authors).

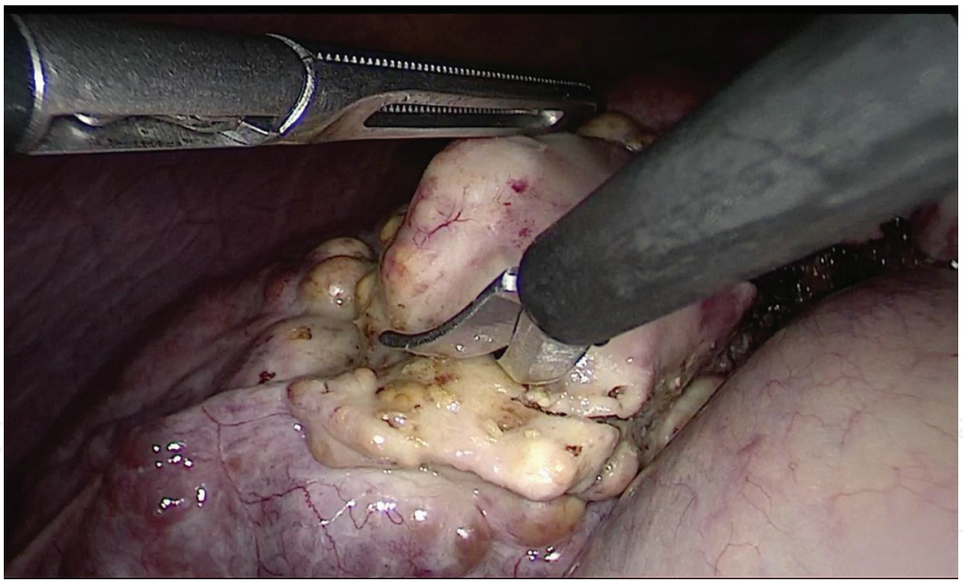

Figure 3. Laparoscopic liver resection of a HCC nodule (sg V) (from the personal archive of the authors).

Most of the patients with HCC are not suitable for the surgery due to the extent of the disease and because there is a high risk of liver failure. However, the patients with HCC who undergo surgery have a high risk of recurrence. The 5-year recurrence rate is about 77–100% and the median survival after the recurrence is between 7 and 28 months [57].

Predictors factors for the poor outcomes in HCC are the same for all therapeutic methods and they are: more than three tumors, tumor larger than 5 cm, portal vein invasion, intrahepatic metastases, absence of a tumor capsule, advanced TNM stage (III or IV), hepatitis C viral infection, and Child-Pugh class C [58, 59].

Liver resection may be used before the liver transplantation in three situations:

- Resection is used as primary treatment and liver transplantation will be an option for patients who develop liver failure or recurrence of the tumor;
- Resection is used as an initial treatment for patients who may undergo for liver transplantation according to detailed examination of the history pathological examination;
- Resection is used as pre-treatment for the patients which are already enlisted for liver transplantation.

Liver transplantation is the best treatment option for patients diagnosed with HCC and cirrhosis Child-Pugh B and C. The Milan criteria [60] are a generally accepted set of criteria used to assess suitability in patients for liver transplantation with cirrhosis and HCC. These criteria are:

- single tumor with diameter ≤ 5 cm, or up to 3 tumors each with diameter ≤ 3 cm;
- no extra-hepatic involvement;
- no major vessel involvement.

Living-donor liver transplantation is a liver transplantation option which has developed over the last years due to the limited availability of deceased-donor organs and can be offered for patients with HCC if the waiting time is long enough to allow tumor progression leading to exclusion from the waiting list [61]. This technique uses the right or left hemiliver from a healthy donor and should be performed by expert surgeons to ensure the lowest morbidity and best outcome. Complications may appear in 20–40% of the donors, while the mortality risk for the donor is still 0.3–0.5% [62].

One of the main problems after the liver transplantation for HCC is the risk for recurrence of the tumor which occurs in 8–20% of the patients. Usually, the recurrence appears in the first 2 years after liver transplantation and is associated with a median survival less 1 year [63].

For better results of the liver transplantation, there are some treatment options which can be performed before liver transplantation, such as liver resections or alcohol injection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and transarterial radioembolization/selective internal radiotherapy (TARE/SIRT). The main purpose of this treatment strategy is to reduce the size and number of the tumors in patients who do not have the accepted criteria for liver transplantation [64]. Most of the above techniques have been used as locoregional therapy for HCC recurrence in patients with limited disease.

Ablative techniques are useful for patients, which are not suitable for resection or liver transplantation. Ablation can be done percutaneous, in open surgery or by laparoscopic approach and its purpose is to destruct the tumor cells by modifying the local temperature. The efficacy

of the percutaneous ablation is evaluated after 1 month with a CT scan (absence of the contrast uptake within the tumor reflecting tumor necrosis, while the persistence of contrast uptake indicates treatment failure) [31]. Recurrence rate is higher after ablation and the recurrence will occur nearby of the treated nodule due to the presence of microscopic satellites. Ablation must be performed under ultrasound guidance (**Figure 4**). Ablation techniques use chemical substances (ethanol, acetic acid, boiling saline) or surgical devices which modify the temperature of the tissue (radiofrequency, microwave, laser and cryotherapy).

Ethanol injection is highly effective for small HCC and has a low rate of complications, while the necrosis rate is about 90–100% of the HCC smaller than 2 cm. If the tumor size is between 2 and 3 cm, the necrosis rate is reduced to 70 and 50%, respectively, for the tumor size between 3 and 5 cm [65, 66]. Patients with Child-Pugh A class and HCC with successful tumor necrosis can achieve a 50% survival at 5 years [67, 68].

Radiofrequency ablation (RFA) is an option of treatment which has better result than ethanol injection and requires fewer treatment sessions [69, 70]. This type of treatment requires an insertion of single or multiple cooled tip electrodes or single electrodes with j-hooked needles that deliver heat around a wide region inducing necrosis of the tumor. This treatment is more efficient than ethanol injection but has a higher cost and a higher rate of complications such as

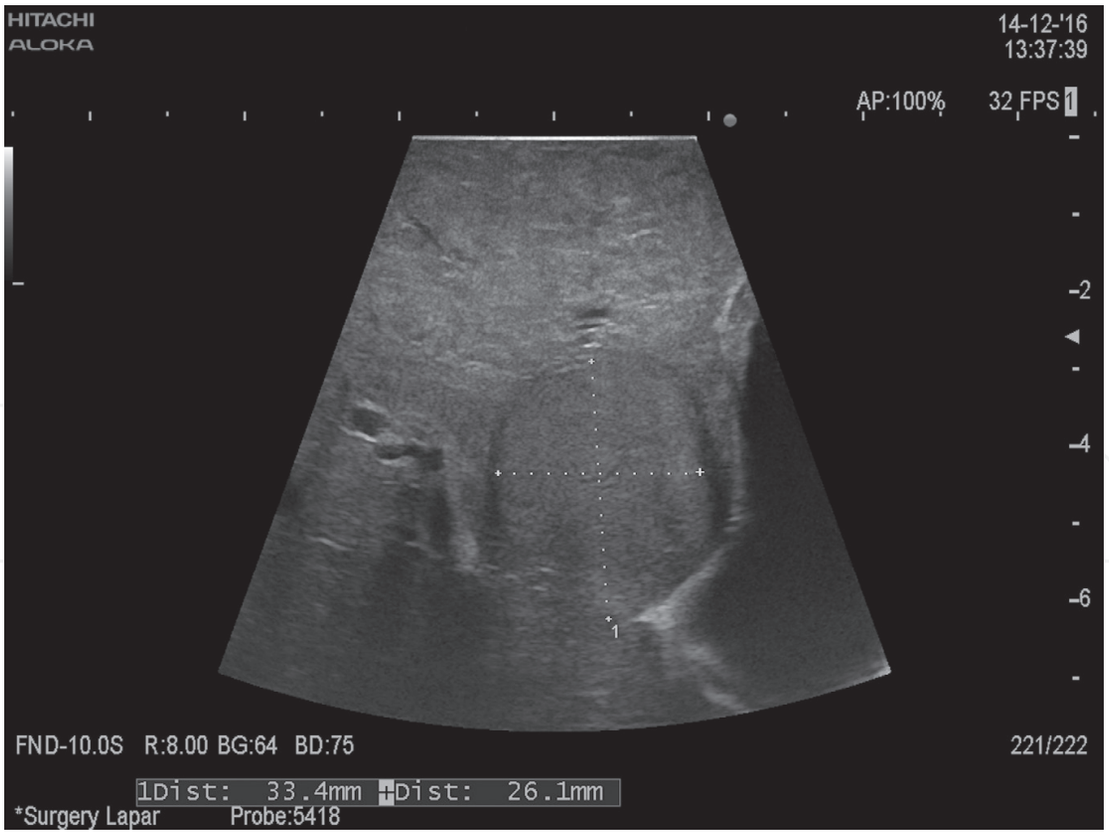

Figure 4. Intraoperative laparoscopic ultrasound of the liver showing a HCC nodule in segment V, next to the gallbladder (from the personal archive of the authors).

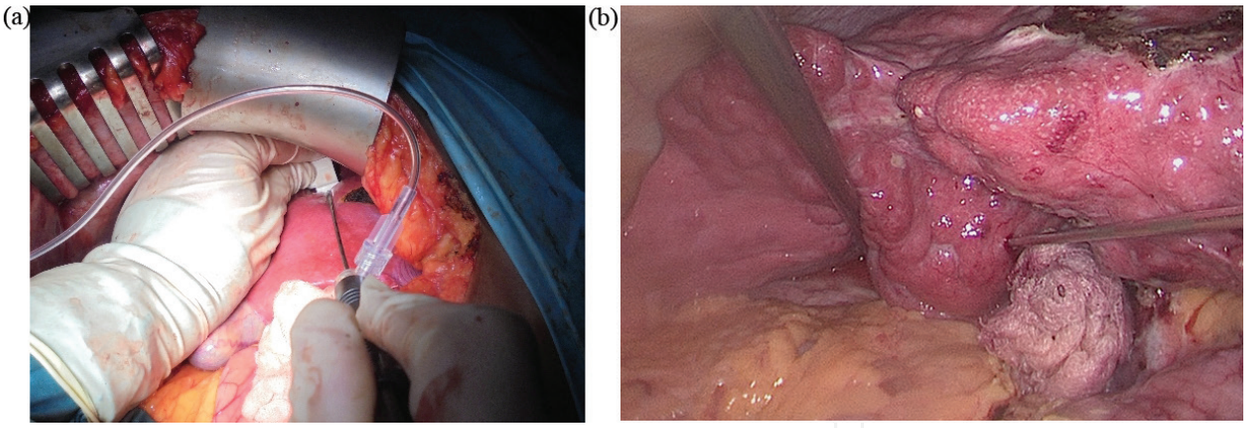

Figure 5. (a) US-guided intraoperative RFA of a liver tumor (from the personal archive of the authors). (b) Laparoscopic RFA of a HCC nodule. Intraoperative aspect (from the personal archive of the authors).

peritoneal bleeding or pleural effusion [69–72]. RFA can be performed by percutaneous under ultrasound guidance, open surgical approach or laparoscopic approach (**Figure 5a** and **b**). Some of the HCC cannot undergo for RFA due to their localization.

Transarterial embolization and chemoembolization are types of treatment which have developed over the last years because HCC exhibits intense neo-angiogenic activity and should be considered for patients who are not suitable for surgical resection or percutaneous ablation [61]. In patients with early-stage HCC, the blood supply comes from the portal vein and only when the tumor is larger it has an arterial blood supply from hepatic artery. This treatment purpose is to obstruct the hepatic artery to induce ischemia to the tumor. Hepatic artery obstruction is performed during an angiographic procedure and is known as transarterial embolization (TAE). If the transarterial embolization (TAE) is associated with the injection of chemotherapeutic agents in the hepatic artery, the procedure is known as transarterial chemoembolization (TACE). The procedure needs advanced catheterization of the hepatic artery and the specific lobar and segmental branches to be as selective as possible and to reduce the damages of the nontumoral liver parenchyma. Chemotherapic agents such as adriamycin or cisplatin must be injected prior to arterial obstruction [73]. Contraindication for TAE/TACE is the lack of portal blood flow due to portal vein thrombosis, portosystemic anastomoses or hepatofugal flow [61]. Also, patients which advanced staged disease (Child-Pugh B and C) should not be considered for this treatment due to the high risk of hepatic failure. Side effects of intraarterial injection of the chemotherapeutic agents are nausea, vomiting, alopecia and sometimes, renal failure. After the transarterial embolization, the so-called post-embolization syndrome can appear, which consists of fever, abdominal pain and ileus. Post-embolization syndrome is usually self-limited in less than 48 hours, but sometimes patients can develop hepatic abscess or cholecystitis. Regarding the response to this treatment there are no significant differences between TAE and TACE, the reported rate of objective response ranging from 16 to 60%, with a significant improvement in survival [43, 73].

Treatment algorithm is described in the next figure based on the Barcelona Clinic Liver Cancer (BCLC) staging classification [74]:

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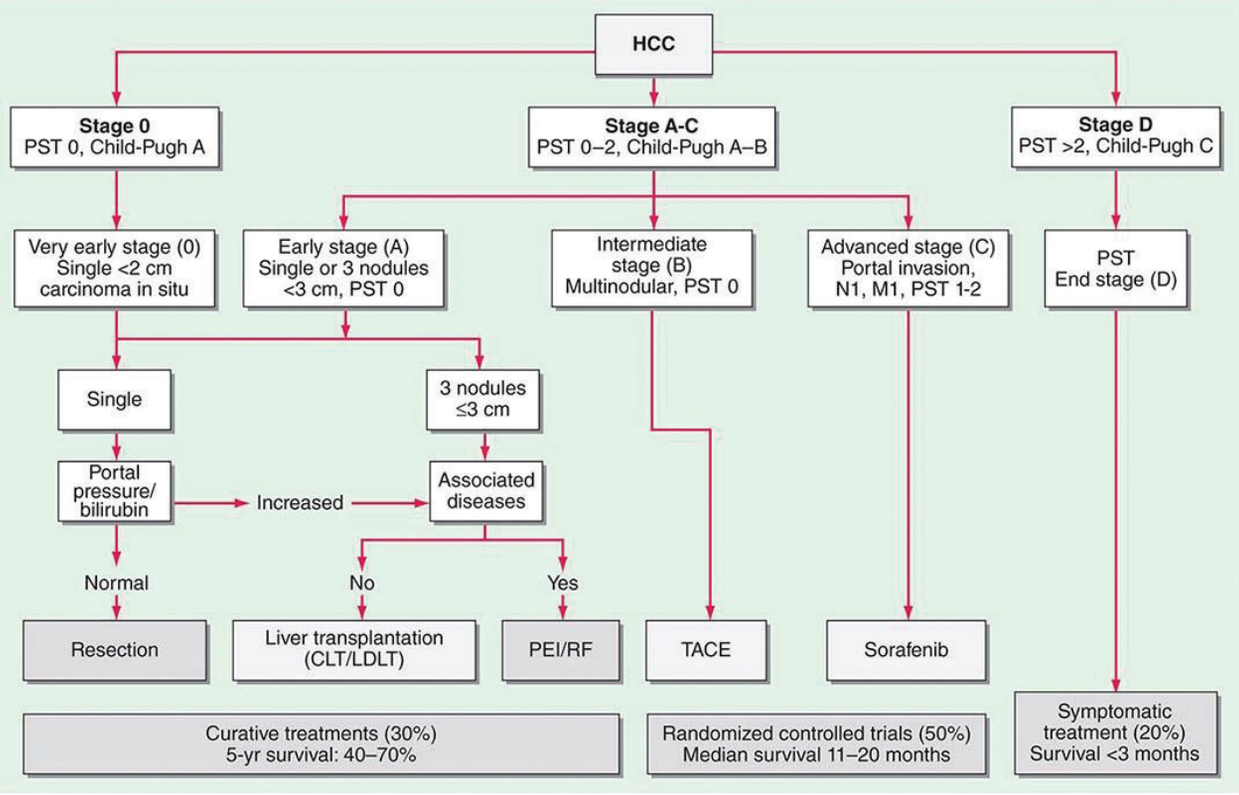

6. Perspectives

There are several areas where active research is needed, starting from molecular pathogenesis, to detection, diagnosis and treatment. Despite recent progress in the management of HCC, treatment of patients with portal vein thrombosis remains still a challenging area. Current clinical guidelines recommend Sorafenib only. However, besides Sorafenib, various therapies including surgery, TACE, external radiation therapy, hepatic artery infusion chemotherapy (HAIC) and radio-embolization may be considered in selected patients; the usefulness of combined treatment needs to be verified. Newer therapeutic options such as immunotherapeutic agent and oncolytic virus are under investigation [75].

7. Conclusions

Management of HCC continues to be improved due to development of newer therapies which are combined with liver resection and liver transplantation. These therapies become better tolerated and more precise even in patients with advanced liver disease. Better surveillance of cirrhotic patients allowed an early detection of HCC and permitted treatments to have a higher rate of cure. For the patients who present with HCC and moderate to severe liver insufficiency, liver transplant remains a critical method to eliminate the cancer and cure the underlying liver disease with a lower risk of recurrence than resection or ablation. The best results for liver resection are obtained in patients with small solitary tumors, but there is a high rate of disease

recurrence due to cell dissemination prior to treatment. Improved survival for patients treated with Sorafenib for advanced disease increases enthusiasm for additional therapies for HCC.

Nowadays, the improvement of the surveillance will allow detection of the early stage of HCC when the loco-regional treatment is effective and transplantation is reserved only for selected cases. Alfa-fetoprotein and ultrasound scan should be used every 6 months for surveillance in high-risk individuals.

Acknowledgements

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