

Diagnostic and Therapeutic Approaches to Hepatocellular Carcinoma: Understanding the Barcelona Clínic Liver Cancer Protocol



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ABSTRACT: Each year, hepatocellular carcinoma is diagnosed in more than half a million people worldwide and it is the fifth most common cancer in men and the seventh most common cancer in women. This article reviews the Barcelona-Clínic Liver Cancer protocol for the diagnosis, staging, and treatment of this disease, and four cases are presented for the discussion of the therapeutic approach. Understanding the diagnostic and therapeutic approaches to this disease is essential, especially if we keep in mind the quintessential basics of prevention and early detection.

KEYWORDS: hepatocellular carcinoma, neoplasm staging, liver cirrhosis

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Introduction

Each year, hepatocellular carcinoma (HCC) is diagnosed in more than half a million people worldwide.¹ It is the fifth most common cancer in men and the seventh most common cancer in women. The greatest burden of this disease is borne by developing countries, such as Southeast Asia and Sub-Saharan Africa, where hepatitis B is endemic.² Its incidence is rising worldwide, and although new therapies have been developed, we still achieve low five-year survival rates. In the United States, it has remained below 12%.³

Due to its high prevalence in patients with cirrhosis or advanced fibrosis, screening with ultrasonography every six months (excluding the nowadays-controversial measurement of serum alpha-fetoprotein levels due to its low sensitivity) has been recommended as the standard of care.⁴ Thus, early diagnosis could mean more effective treatment and an increase of survival. A Chinese study showed that the combination of ultrasonography and measurement of alpha-fetoprotein translates into a 37% reduction in mortality due to HCC.⁵

The objective of this article is to review the guidelines on the diagnostic and therapeutic approach for HCC, while presenting four cases for discussion of this subject.

Finding a Nodule in the Ultrasonogram—How to Proceed

The 2011 update to the Practice Guidelines for the Management of HCC by the American Association for the Study of Liver Diseases (AASLD) intends to clarify the approach to be taken for the diagnosis and therapy of the hepatic nodule in the cirrhotic patient.⁴ Due to the unique radiologic characteristics of nodules, most diagnoses can be made using dynamic studies without the need of a liver biopsy.

Nodules with a size less than 10 mm detected on screening should be rescreened every three months with ultrasonography (if possible, with the same ultrasonographer—because it is examiner dependent). Any change in its characteristics or an increase in size should sound the alarm and trigger a deeper investigation with a dynamic study.

Nodules with a size of 10 mm or greater should be investigated primarily with four-phase multidetector computed tomography (4-p MDCT) or dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). In the cirrhotic or advanced liver fibrosis patient, if arterial hypervascularity and venous- or delayed-phase washout are present in one of these dynamic studies, then HCC diagnosis is recommended. If the first study is negative, it is recommended to move on to

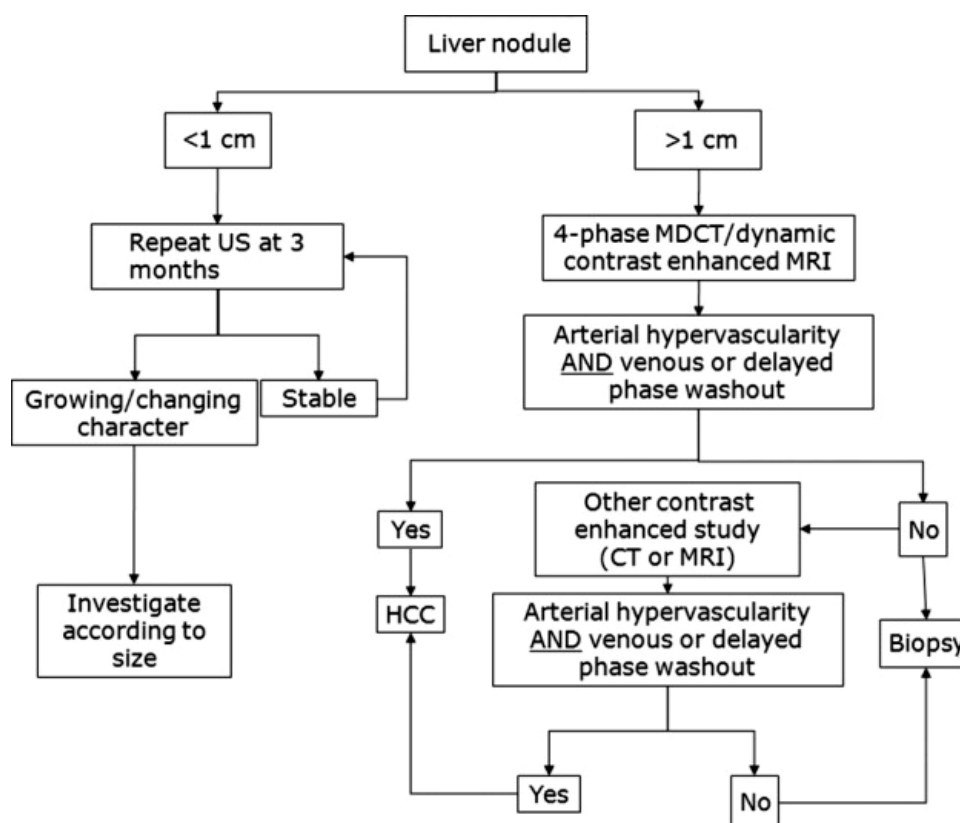


Figure 1. Diagnostic algorithm for suspected HCC.⁴

Note: Reprinted with permission from Bruix J and Sherman M. (2011), Management of hepatocellular carcinoma: An update. *Hepatology*, 53:1020–1022. doi:10.1002/hep.24199.

Abbreviations: CT, computed tomography; HCC, hepatocellular carcinoma; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasonography.

the next (if a 4-p MDCT was performed, then a DCE-MRI, for instance). If the two examinations are not diagnostic, only then it is time to move on to a liver biopsy—that too only in exceptional cases. Sometimes, after analyzing each case—depending on the patient and the nodule, it is even preferable to repeat a dynamic study every three months instead of deciding in favor of a liver biopsy. These recommendations are summarized in Figure 1, which is an excerpt from the AASLD guidelines.

A prospective study of 89 cases of nodules with sizes between 5 mm and 20 mm detected during the screening program showed that noninvasive diagnostic criteria have a specificity of 100%, with a 30% loss in sensitivity (about two-thirds of the nodules required histological confirmation).⁶ Another prospective study suggested that a sequential algorithm has absolute specificity and increases sensitivity, reducing the amount of biopsies in nodules from 10 nm to 20 mm.⁷

Got the Diagnosis—How to Proceed Now

This time, a European protocol is better suited to guide our approach to the diagnosed HCC, and it is called the Barcelona-Clínic Liver Cancer (BCLC) protocol.

1. The first step is staging the patient. This protocol describes five stages for the disease, ranging from zero to D. It describes a specific approach for each stage. Patients with a single HCC nodule up to 20 mm with good performance status, preserved liver function (Child-Pugh score A with normal bilirubin), and absence of portal hypertension—stage 0, should be offered curative therapies: if risk is acceptable, nodule resection; otherwise, radiofrequency ablation (RFA). Because, in 2015, two studies addressing the subject of resection versus RFA have found resection to be superior, it seems adequate to always strive for the first and leave the latter for cases with prohibitive surgical risk.^{8,9} The adjuvant use of sorafenib to prevent recurrence after resection has also been studied, with some promising results.¹⁰ It is not, however, a protocol used in our service.
2. Patients with a single nodule of any size with preserved liver function (Child-Pugh score A with normal bilirubin) and absence of portal hypertension—stage A, should be offered curative therapies: if risk is acceptable, nodule resection; otherwise, RFA. The size and localization of the nodule should be considered to arrive at the decision of which therapy to use.

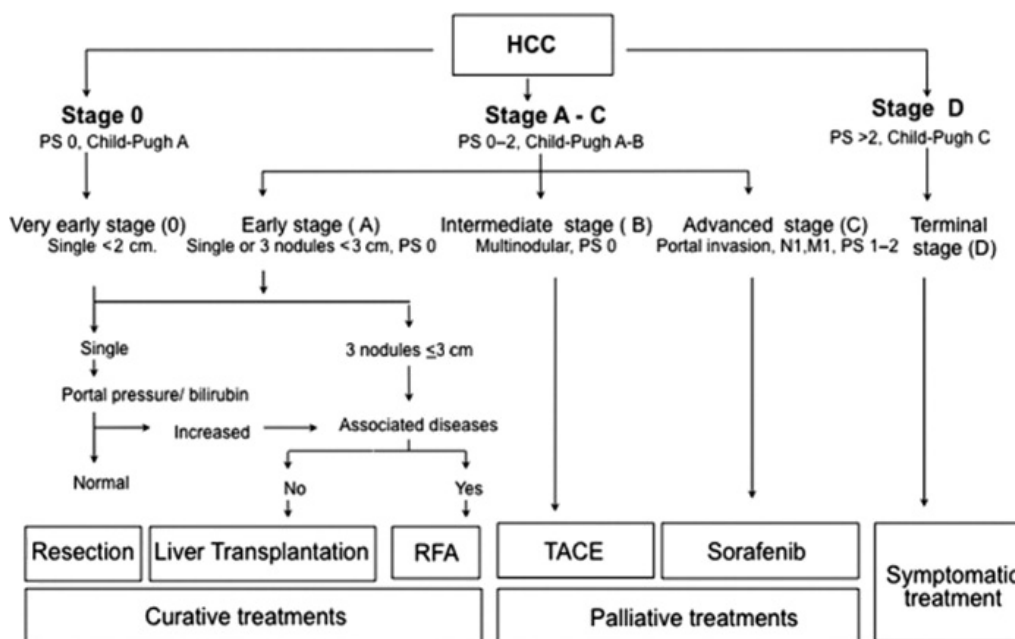


Figure 2. The BCLC staging system for HCC.⁴

Note: Reprinted with permission from Bruix J and Sherman M. (2011), Management of hepatocellular carcinoma: An update. *Hepatology*, 53:1020–1022. doi:10.1002/hep.24199.

Abbreviations: BCLC, Barcelona-Clinic Liver Cancer protocol; HCC, hepatocellular carcinoma; M, metastasis classification; N, node classification; PS, performance status; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

- Patients with a single nodule up to 50 mm or up to three nodules, the largest being up to 30 mm (if your referral liver transplant center uses Milan Criteria), or the sum of the size of the largest nodule plus the total number of nodules resulting in a number up to seven (if your referral liver transplant center uses Up-To-Seven criteria) and bad liver function (Child-Pugh score A or B), or the presence of portal hypertension—stage A, should be offered curative therapies: if risk is acceptable, liver transplantation; otherwise, RFA. Dynamic imaging tests must be performed each three months for follow-up while the patient waits for an organ. If the waitlist for liver transplantation exceeds six months, the so-called bridging therapy is recommended to avoid patient dropout, which can be performed with RFA, alcohol injection, or transarterial chemoembolization (TACE)—the size and localization of the nodule should be considered for the decision on the therapy to be used.^{11,12}
 - Patients with a disease that exceeds the Milan Criteria or the Up-To-Seven criteria, with preserved liver function and good performance status, but in the absence of metastasis or vascular invasion—stage B, should be offered palliative therapies, such as TACE. Although there is no consensus yet, patients with a not-so-advanced disease could be treated with TACE or RFA with an objective of downstaging to the Milan Criteria, and some studies suggest that after a period of observation of the evolution of the disease, they could be offered liver transplantation, with no loss in survival.^{12–14}
 - Patients with nodules of any size and number, with vascular tumor invasion, lymph node or long-distance metastasis, with good-to-moderate performance status—stage C, should be offered palliative therapy with sorafenib, which is an oral chemotherapeutic agent that has been shown to increase survival in these patients by an average of 2.8 months.¹⁵
 - Patients with nodules of any size and number with severely affected liver function (Child-Pugh score C) and poor performance status—stage D, should be offered palliative support care. The patients and their families should be promptly oriented regarding the poor prognosis and lack of effectiveness of the available therapies in this context.
- These recommendations for the diagnostic and therapeutic approaches are summarized in Figure 2.

Understanding the Approach—Four Cases

Case 1. This case is a male patient in his 60s. A nodule was detected during screening (Fig. 3). The patient is subjected to a DCE-MRI study.

Nodules: One.

Size: Six cm.

Child-Pugh score: A. Normal bilirubin.

Performance status: Good (independent).

Portal hypertension: Yes—presence of esophageal varices.

Metastasis or vascular invasion: No.

Staging: A.

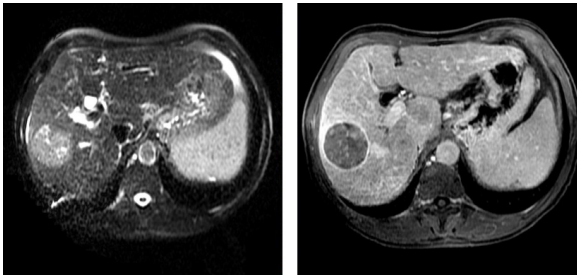


Figure 3. DCE-MRI of case 1.

Abbreviation: DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging.

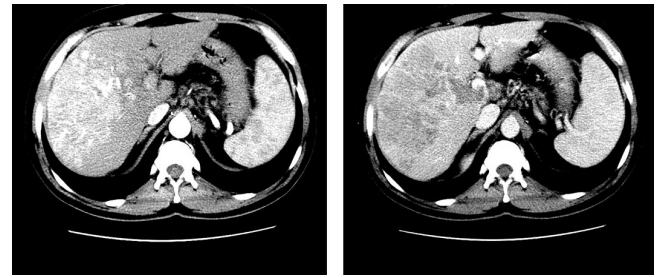


Figure 5. Control 4-p MDCT.

Abbreviations: 4-p, four-phase; CT, computed tomography; MDCT, multidetector CT.

Therapeutic approach: Due to a waitlist period for liver transplantation greater than six months in our country, the patient was offered TACE. Follow-up dynamic studies were performed, with shrinking of the tumor. Liver transplantation was performed, with no major complications.

Case 2. This case involved a male patient in his 50s. A nodule was detected in a screening ultrasonogram. A 4-p MDCT was performed (Fig. 4).

Nodules: Many.

Child-Pugh score: A. Normal bilirubin.

Performance status: Good (independent).

Portal hypertension: Yes—presence of esophageal varices.

Metastasis or vascular invasion: Yes.

Staging: C.

Therapeutic approach: Chemotherapy with sorafenib was initiated. The medication was well tolerated, with no major adverse reactions, and he is alive till date (more than a year and a half of follow-up). No combined therapy was used for this patient, because yttrium-90 radioembolization is not available at our center.¹⁶ A control dynamic study is shown in Figure 5.

Case 3. This case is a male patient in his 50s. A liver nodule was detected in a screening ultrasonogram; a dynamic study was performed, and a small nodule was detected (staging 0). Patient was offered resection and was lost to follow-up afterward. He was admitted to the emergency department a few

years later with upper abdominal pain, encephalopathy, and jaundice. A 4-p MDCT was performed (Fig. 6).

Nodules: One.

Child-Pugh score: C.

Performance status: Poor.

Portal hypertension: Yes—presence of esophageal varices.

Metastasis or vascular invasion: Yes—invasion of the abdominal wall.

Staging: D.

Therapeutic approach: The family of the patient was informed of the severity and irreversibility of the case. Palliative support therapy was initiated. Soon afterward, the patient died.

Case 4. This case involved a female patient in her 40s. A liver nodule was detected in a screening ultrasonogram. A 4-p MDCT was performed, with inconclusive results. A DCE-MRI was performed (Fig. 7).

Nodules: One.

Size: 16 mm.

Child-Pugh score: A.

Performance status: Good (independent).

Portal hypertension: Yes—presence of thick-caliber esophageal varices.

Metastasis or vascular invasion: No.

Staging: A.

Therapeutic approach: As bridging therapy, alcohol injection sessions were performed, and subsequent control

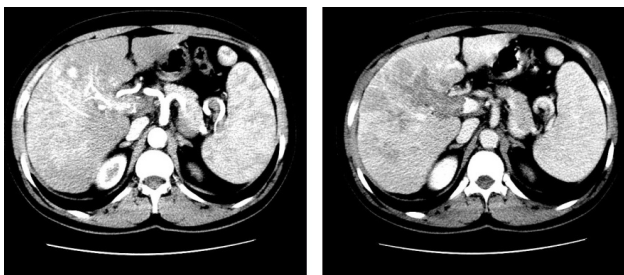


Figure 4. 4-p MDCT of case 2.

Abbreviations: 4-p, four-phase; CT, computed tomography; MDCT, multidetector CT.

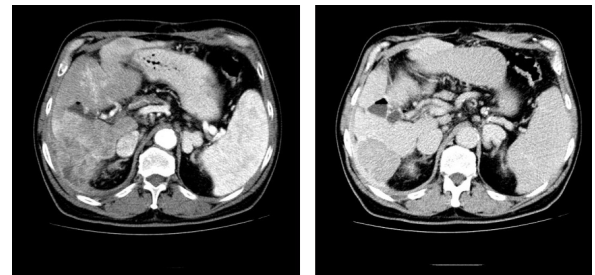


Figure 6. 4-p MDCT of case 3.

Abbreviations: 4-p, four-phase; CT, computed tomography; MDCT, multidetector CT.

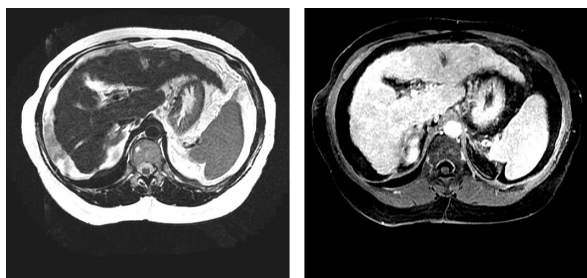


Figure 7. DCE-MRI of case 4.

Abbreviation: DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging.

dynamic studies showed absence of arterial hypervascularization (Fig. 8). She is currently listed as waiting for liver transplantation.

Conclusion

Although the incidence of HCC is rapidly increasing, the available therapeutic arsenal is also growing. The latest addition to it is chemotherapy, with an actually effective agent—sorafenib.¹⁵ This is a milestone not just because of its effectiveness but also because of the perspective it gives us—a new class of agents that could control the disease in the long term, with several drugs and protocols under study.^{17–20}

Nevertheless, our focus must always be on early detection and prevention. Early diagnosis of hepatic diseases and early treatment are essential prevention strategies, including approaches such as screening of asymptomatic risk population for hepatitis B virus (HBV) and hepatitis C virus (HCV). Worldwide HBV vaccination is yet another main prevention strategy. And, of course, for those with cirrhosis or advanced liver fibrosis, the availability of ultrasonography screening (with an experienced ultrasonographer) is necessary for early detection strategies, and it reduces HCC-related mortality.

Therefore, understanding the diagnostic and therapeutic approaches to this disease is essential, especially if we keep in mind the quintessential basics of prevention and early detection.

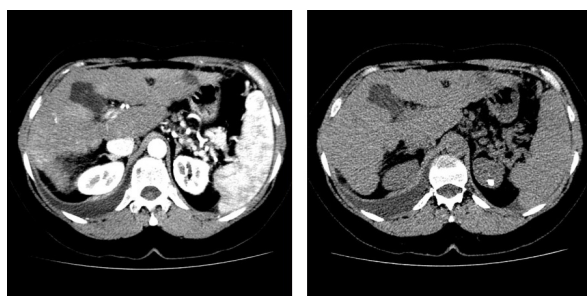


Figure 8. Control 4-p MDCT.

Abbreviations: 4-p, four-phase; CT, computed tomography; MDCT, multidetector CT.

Author Contributions

Wrote the first draft of the manuscript: JS, RAB. Contributed to the writing of the manuscript: JS, SSB, RAB, AGC. Agree with manuscript results and conclusions: JS, SSB, RAB, AGC. Jointly developed the structure and arguments for the paper: JS, RAB. Made critical revisions and approved final version: JS, SSB, RAB, AGC. All authors reviewed and approved of the final manuscript.

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