

# Management of Hepatocellular Carcinoma: The Role of the Advanced Practitioner in a Multidisciplinary Approach

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## Abstract

The management of cirrhosis in conjunction with hepatocellular carcinoma (HCC) can be an overwhelming, time-consuming task. However, close monitoring and detection for early complications from cirrhosis, with appropriate treatment, can stabilize the cirrhosis enough to allow treatment of the HCC. Having a clinical team with a hepatology background trained in the management of chronic liver diseases and cirrhosis is critical for the HCC patient. This article describes our experiences at the University of Florida, where our group has developed a streamlined evaluation and management strategy for patients facing this complicated disease. This “one-stop shop” strategy takes a multidisciplinary approach, with advanced practitioners—including nurse practitioners and physician assistants—at the forefront in treatment decisions and adjustments as well as the ongoing care of the patient.

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**H**epatocellular carcinoma (HCC) represents a major global health challenge, as an increasing number of cases make it one of the most rapidly rising cancers. It is the fifth most common cancer in the world and the third leading cause of cancer-related death. There are over 600,000 new cases diagnosed yearly around the world and nearly the same number of deaths from the disease (Parkin, Bray, Ferlay, & Pisani, 2005). Most cases of HCC occur in people with underlying chronic liver disease

and cirrhosis. In fact, the leading cause of death among patients with cirrhosis is HCC, which underscores the importance of diagnosing chronic liver disease and screening these high-risk individuals (Parkin et al., 2005).

## Cirrhosis and HCC: Causes and Diagnosis

The main causes of cirrhosis include hepatitis B, hepatitis C (HCV), alcohol abuse, and non-alcoholic fatty liver disease. Less common causes are immune-mediated diseases and genetic disorders like alpha-1 anti-trypsin

deficiency and hereditary hemochromatosis (excess iron) (El-Serag, Tran, & Everhart, 2004). The steep rise in the incidence of HCC over the past 2 decades is mainly due to the epidemic of cirrhosis caused by chronic HCV (Deuffic, Poynard, Buffat, & Valleron, 1998). Patients with cirrhosis, regardless of cause, should be enrolled in a surveillance program that performs serial imaging studies at 6- to 12-month intervals to detect HCC early, when treatment is curative.

The diagnosis of early HCC is a challenge, as the majority of patients are asymptomatic and the cirrhotic liver can be difficult to interpret on imaging (Bruix & Sherman, 2005). The asymptomatic nature of early HCC is mainly due to the liver's large functional reserve (Gines et al., 1987). A diagnosis of HCC should be suspected in a patient with an elevated or rising serum alpha-fetoprotein (AFP) level, although this tumor marker is nonspecific and can be falsely elevated in patients with viral hepatitis without the presence of HCC. The sensitivity of the test ranges from 41% to 65%, while the specificity is between 80% and 94% (Gupta, Bent, & Kohlwes, 2003). Therefore, a strategy that combines the serum AFP and/or a contrast-enhanced CT or MRI scan is useful in making the radiological diagnosis of HCC (Bruix & Sherman, 2010). In the background of cirrhosis, the presence of a nodule detected that is greater than 1 cm and displays arterial enhancement and loss of contrast during the venous or delayed phases of imaging is enough to make the diagnosis of HCC without the need for a biopsy (Bruix & Sherman, 2010).

### Treatment Considerations

Once a patient is diagnosed with HCC, the question then becomes, "What is the best treatment option for this patient?" The answer, as it relates to the most effective therapy, is complicated. Unlike other solid malignancies, with HCC one must carefully consider the degree of liver function impairment as well as the extent of the tumor when deciding on a treatment plan. The severity of underlying cirrhosis has a profound effect on all treatment decisions and can limit treatment modalities.

Prior to discussing any line of treatment, the severity of cirrhosis needs to be evaluated and described with a number of tools: (1) a physical examination to evaluate for complications related

to cirrhosis, including encephalopathy, jaundice, ascites, and lower extremity edema; (2) Child-Pugh classification, based on severity of ascites, encephalopathy, INR, albumin, and bilirubin; (3) the MELD score, based on INR, creatinine, and bilirubin; and (4) an upper endoscopy to screen for esophagogastric varices. Once the cirrhosis component of the disease has been thoroughly classified, then the tumor-related factors such as size or number of tumors, as well as whether there is vascular invasion, can be placed into the context of treatment. The role of the advanced practitioner (AP) with a background in hepatology is a critical one during the initial evaluation and throughout the management of the disease: the AP needs to be able to accurately assess each patient and situation individually, and have an understanding of the underlying disease process so that timely and accurate adjustments to medications can be made.

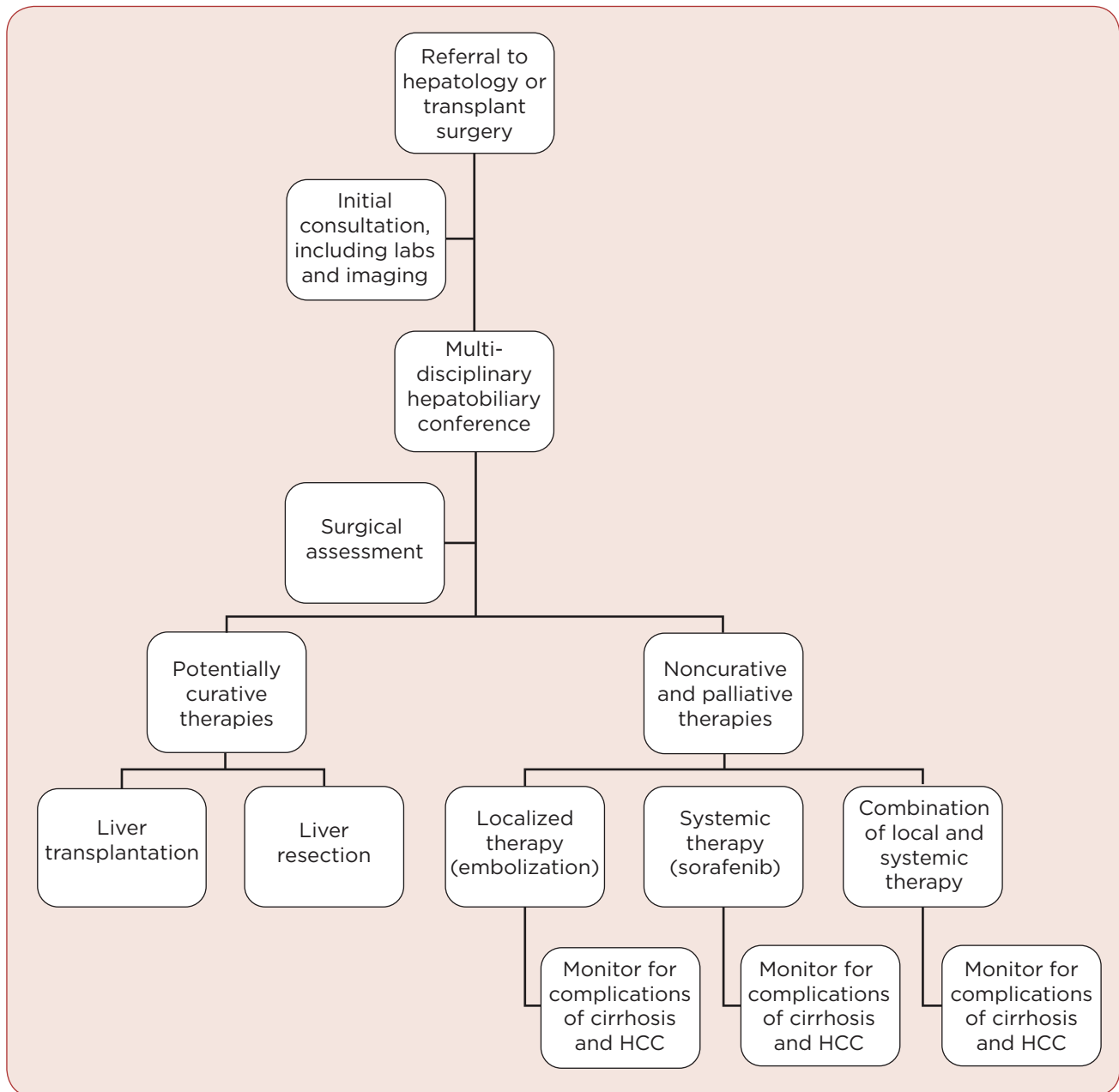
Early referral and evaluation at a center with the potential to offer the various interventions to treat the tumor is extremely important. During this evaluation, a multidisciplinary approach allows all of the liver- and tumor-related factors to be carefully weighed. This approach can positively affect the outcome of the patient, in addition to improving functional status by providing an individualized treatment plan for each patient. Educating the patient on status and expected outcomes is a key aspect of the treatment process. The AP is ideally positioned to help the patient and their family members to understand and assimilate the information they have just received.

### The University of Florida Approach: An Integrated Evaluation and Management Strategy

Our group at the University of Florida has developed a streamlined evaluation and management strategy for patients facing this complicated disease. This strategy, illustrated in Figure 1, is based on a "one-stop shop" that takes a multidisciplinary approach with advanced practitioners—including nurse practitioners and physician assistants—at the forefront in treatment decisions and adjustments as well as the ongoing care of the patient.

#### TEAM MEMBERS AND TREATMENT OPTIONS

This integrated approach involves face-to-face discussion between the members of our



**Figure 1.** Management of hepatocellular carcinoma (HCC).

multidisciplinary team—including hepatobiliary/transplantation surgeons, hepatologists, radiologists, pathologists, and oncologists—and ensures the development of an individualized care plan that best fits each patient and expedites treatment. In our model, hepatology directs the management of patients due to the unique nature of the disease and the importance of monitoring the cirrhosis during the interventions. However, the participation of representatives from all of these disciplines is a critical element, since the

treatment plan involves a multimodal approach that can combine surgical resection, liver transplantation, local-regional therapies (such as radiofrequency ablation, cryoablation, chemoembolization, and radioembolization), and molecular targeted therapy such as sorafenib (Nexavar) (Bruix & Llovet, 2002).

Radiofrequency ablation causes thermal necrosis to tumors by delivering electromagnetic energy through single or multiple needle electrodes, inducing a wide region of tumor necrosis.

Cryoablation is the use of alternating freeze and thaw cycles through the use of a probe inserted directly into the tumor. Both chemo- and radio-embolization involve selectively accessing the blood vessels that supply the tumor and injecting the tumor with chemotherapy-laden beads or radioactive isotopes, respectively. The second part of this process involves causing the occlusion of those blood vessels to essentially starve the tumor of blood (Cabrera & Nelson, 2009). The use of sorafenib, a multitargeted tyrosine kinase inhibitor, is relatively new; FDA approval was granted in 2008. Currently, it is only approved in more advanced stages of HCC, but there are clinical trials underway to evaluate its efficacy when combined with local-regional therapies and other multikinase inhibitors (Abou-Alfa et al., 2008).

At the University of Florida, the APs are directly involved in both the discussion of each patient's treatment plan and ongoing management throughout the treatment course. The role of the AP includes ongoing review of laboratory data and clinical status to ensure the selected treatment remains appropriate. In this capacity, the AP also serves as the primary medical contact person for patient questions about treatment decisions and medication adjustments for side-effect management.

### **CIRRHOSIS: PATIENT EDUCATION AND CLOSE OBSERVATION**

The unique aspect of our HCC management clinic is that our patients are not only managed for their cancer, but they are also monitored for their underlying liver disease (cirrhosis), which can worsen during the treatments. The AP with a background in cirrhosis management is perfectly suited for front-line management of these complex issues. In our clinic, APs serving in this role have vast knowledge and experience with complications of both HCC and cirrhosis.

It is not uncommon for a patient to receive diagnoses of both HCC and cirrhosis at the same time upon initial evaluation (Cabrera & Nelson, 2009). This dual diagnosis, which brings tremendous complexity to the management of this patient population, is particularly daunting for patients and their families. At the University of Florida, following the multidisciplinary review of each patient, the dual diagnosis (HCC and cirrhosis) is discussed in detail with the patient and

family, along with the individualized treatment plan. A detailed discussion of both processes—cirrhosis and HCC—as well as the potential complications facilitates the difficulties in treatment decisions. It is important for patients and their families to understand that while they are connected, each of these conditions is also a separate problem with its own list of potential complications. At any point in time one aspect may be under control, while the other may not. Common cirrhosis-related complications that may occur any time during treatment are explained. These include ascites, spontaneous bacterial peritonitis, gastroesophageal varices with potential for bleeding, renal insufficiency, hepatic encephalopathy, and lower extremity edema.

While the multidisciplinary team determines the choice and combination of interventions, close patient follow-up to monitor the cirrhosis and detect complications and side effects is just as important to the success of the treatment plan. For example, cirrhosis can limit some of the treatment options, including resection, because the liver must be able to tolerate volume loss and be able to regenerate. With respect to systemic therapy and local-regional therapies, cirrhosis can worsen as these interventions and therapies are started, with signs of confusion/encephalopathy, jaundice, ascites, GI bleeding, peripheral edema, and renal dysfunction. The potential complications from the progression of the cirrhosis and from the side effects of the therapies demonstrate how important it is for the AP trained in hepatology to provide ongoing clinical follow-up for the patients. Not all options may be available to every patient, as underlying liver disease and the extent of the tumor may influence the treatment algorithm selection. Thus, open communication from all specialties is crucial. Advanced practitioners are positioned in critical areas in many of these specialties, with those in hepatology playing a key role.

By monitoring for these potential complications, interventions can be quickly initiated to ensure that patients remain on their individualized courses of therapy and hence maximize treatment responses. A well-integrated and well-coordinated effort between all the disciplines involved is critical to this process. A major goal of the HCC clinic is to streamline the evaluation and management of the patients.

## EXECUTING THE TREATMENT PLAN

Once the patient has agreed to the aspects of his or her individual treatment plan, it is set into action. Often, the patients we follow are not candidates for liver transplantation or resection given the extent of their tumor; therefore, the treatment options are limited to non-curative and palliative interventions that slow tumor progression and improve survival. These treatments may include various interventions that are combined to give the patient the best chance of success. Most often, our patients undergo local-regional therapies provided by interventional radiology such as radiofrequency ablation, transarterial chemoembolization, and selective internal radioembolization (El-Serag et al., 2004). In addition to various local-regional therapies, combinations of these treatments with each other and with targeted molecular therapy, such as oral medications like sorafenib, are possible within an institutional protocol (Cabrera et al., 2011).

During the treatment plan, we work closely with the APs in interventional radiology to coordinate the close follow-up of patients, including laboratory work and dynamic imaging, to evaluate treatment response. Typically, patients require serial local-regional treatments that are given on a demand basis when new tumors are found and/or there is progression of the tumors actively being treated. To ensure that the patient transitions through the process smoothly, we communicate via telephone and email to accommodate any concerns. This telemedicine approach allows the patient to have multiple contacts who are familiar with their care plan and who can help answer questions or adjust medications. The success of management is firmly rooted in the seamless communication between the patient and the medical team, in which the APs play a prominent role.

## Conclusions

The management of cirrhosis in conjunction with HCC can be an overwhelming, time-consuming task. Due to the advanced nature of the conditions in many of these patients, complete resolution of decompensated liver disease is unlikely (Gines et al., 1987). However, close monitoring and detection for early complications from cirrhosis, with appropriate treatment, can

stabilize the cirrhosis enough to allow treatment of the HCC. Therefore, the presence of cirrhosis requires constant monitoring and adjustment of medications.

Having a clinical team with a hepatology background trained in the management of chronic liver diseases and cirrhosis is critical for the HCC patient. The diagnosis of cirrhosis can be a traumatizing and overwhelming experience. Add to this the diagnosis of cancer, and the patient has even more difficulty trying to process the situation. In today's health-care world, it is commonplace for a patient to see multiple specialists over several months. Multiple-day visits that typically involve seeing more than one specialist at various sites create the real likelihood for poor communication, resulting in poor patient care.

The complexity of the diagnosis of HCC and cirrhosis demands that a patient have an evaluation by a multidisciplinary team that includes hepatologists, interventional radiologists, gastroenterologists, oncologists, and hepatobiliary/transplantation surgeons. Having a "one-stop shop" clinic visit with a well-integrated multidisciplinary team streamlines the evaluation process of these medically complex patients and facilitates their management, which undoubtedly leads to better outcomes. The goal at the University of Florida has always been to provide the best patient care; our HCC clinic delivers by streamlining the evaluation and management of patients with HCC and cirrhosis.

## DISCLOSURES

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