Consensus and Controversy in the Management of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) continues to grow as a disease of the Western hemisphere because of its association with hepatitis C virus (HCV). For these reasons, HCC is a global health care concern. Various nonsurgical treatments exist for HCC, but none are currently considered standard, in part because of the lack of efficacy. In general, these nonsurgical approaches are used in HCC as palliation or as an adjunct to a surgical attempt at cure.

Although palliative treatment algorithms vary among centers, transplantation, resection, or both offer the only chance for cure. Because of the many treatment options and overall low rate of cure, there is continued disagreement among centers that manage HCC. In this article, current standards and controversies in the management of HCC will be critically assessed.

Pathogenesis of hepatocellular carcinoma

Hepatocellular carcinoma in the cirrhotic liver

Because more than 80% of cases develop in the setting of cirrhosis,[1] treatment of HCC presents added challenges to the clinician. Although not fully characterized, the pathogenesis of HCC in cirrhosis is thought to be multifactorial, with important implications on its natural history and on strategies to treat it.[2,3]

Hepatocellular carcinoma in the noncirrhotic liver

Twenty percent of patients with HCC do not have underlying cirrhosis. European series analyzing noncirrhotic patients found that the causes of HCC were HCV in 3% to 54%, hepatitis B virus (HBV) in 4% to 29%, and heavy alcohol use in 0% to 28%.[4-8] These noncirrhotic patients have similarities in the histopathology of their nontumoral liver: periportal and lobular necrosis, portal inflammation, steatosis, and iron overload were found, respectively, in 15%, 57%, 52%, and 54% of patients in one series.[7] These data suggest that even in noncirrhotic patients, most in whom HCC develops have some degree of liver abnormality marked by fibrosis and inflammation. The propensity of noncirrhotic patients to experience HCC is explained by mechanisms of viral genetic replication (HCV), necroinflammation, and chromosomal alterations within affected hepatocytes.

Another mechanism for HCC in noncirrhotic patients is aflatoxin, a food contaminant found in humid regions, that causes a mutation at codon 249 p53. Particularly in the HBV-infected liver, this mutation causes a threefold increase in HCC.[9] In addition, there is a minority of patients with HCC who have otherwise histopathologically normal livers and no known risk factors. These patients remain largely an enigma.

In summary, most cases of HCC arise in the setting of predisposing liver disease, whether or not there is underlying cirrhosis. But all patients need thorough evaluation for their cancer and their underlying liver disease so that appropriate treatments can be used.

Staging, natural history, and prognosis

Because patient survival and choice of treatment depend on both HCC stage and the severity of liver disease, an effective staging classification would incorporate both of these factors. Because the combined impact of liver disease and tumor burden is not yet fully understood, and may vary geographically, no one staging classifications has emerged as a standard. For example, both the Cancer of the Liver Italian Program (CLIP) and the Okuda system take into account liver function indicators (bilirubin, albumin, and ascites), but only broadly assess the tumor characteristics, precluding any risk stratification based on the latter.[10] In contrast, the American Joint Committee on Cancer TNM system examines the tumor characteristics but does not address liver func-

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Abbreviations and Acronyms

HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
IFN-α = interferon-α
PEI = percutaneous ethanol injection
RFA = radiofrequency ablation
TACE = transarterial chemoembolization
TAE = transarterial embolization

tion.[11] Perhaps the most comprehensive system is the Barcelona-Clinic Liver Cancer (BCLC) staging system, which assesses tumor characteristics and liver function to generate a treatment algorithm.[12] The variability among these systems is demonstrated by the disparate survival rates of 15% to 80% for the best stages.

HCC patient survival is confounded by the significant effects of underlying cirrhosis. To better predict survival by taking into account both of these factors, some groups have broadly categorized these patients as having early, intermediate, and advanced disease.[12]

Early HCC is defined as a single, well-differentiated lesion that is < 2 cm in diameter. These patients are often Child-Pugh class A and early class B, so they are candidates for curative resection or transplantation. Because they are treatable, there are few data on their natural history. But one study of Child-Pugh class A patients with a single lesion showed a 65% 3-year survival without treatment.[1]

Intermediate-advanced HCC is a large heterogenous group with lesions > 2 cm, or tumors that are multifocal. Typically these lesions are moderately to poorly differentiated. Advanced lesions behave more aggressively with vascular invasion, locally advanced stage, or regional lymph node metastases. Based on one review of 25 randomized control trials of untreated patients with advanced disease, the 1- and 2-year survival rates were 10% to 72% and 8% to 50%, respectively.[12] The presence of cancer-related symptoms and aggressive disease demonstrated by macrovascular invasion or distant metastases are associated with poorer survival.[13] These patients are most often candidates for liver transplantation when their tumor(s) fall within criteria listed in the proceding text.

End-stage HCC is associated with poor liver function and physiologic status, and has a median survival of 5 to 6 months.[10] These patients are usually not candidates for treatment. In one prospective trial in which 102 non-

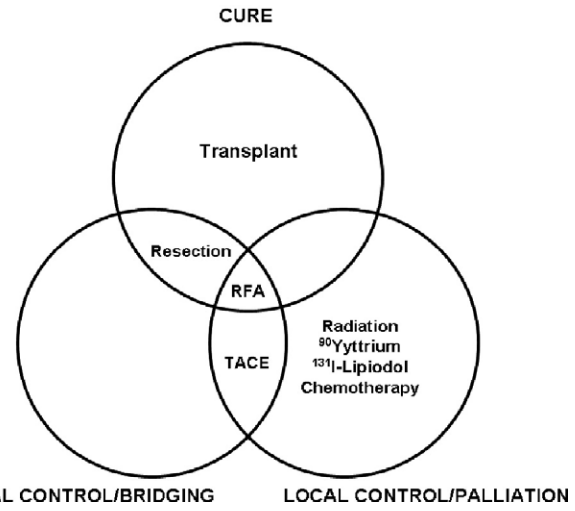

Figure 1. Current treatment modalities can be broadly categorized as curative, palliative, or bridging. Some modalities may serve more than one purpose. RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

treatable patients were randomized to receive only symptomatic treatment, the overall actuarial survival rates at 1, 2, and 3 years were 54%, 40%, and 28%, respectively. The main causes of death for this group were HCC progression and liver failure (and related complications) in 78% and 18%, respectively. These data demonstrate the deleterious effects of underlying liver disease on the natural history of HCC patient survival.[13]

Curative treatment

Each treatment modality for HCC can be considered to have one of three goals: cure, local control and bridge to transplantation, and local control and palliation (Fig. 1). An effective staging classification for HCC should incorporate tumor characteristics and underlying liver disease as both of these factors impact patient survival and the choice of treatment. The following discussions on curative treatments for HCC relate to patients with varying degrees of cirrhosis.

In general, patients who undergo treatment for cure have early HCC and Childs A cirrhosis, and overall survival rates range from 50% to 70% after transplantation, resection, or ablation.[1] The choice of treatment modality depends on many factors including stage of HCC, underlying liver disease, and overall surgical risk.

Although there has been no randomized control trial comparing resection and liver transplantation for Child-Pugh class A patients with a small HCC lesion, retrospective data suggest that the two modalities are compa-