Review Article

Progress in surgical and nonsurgical approaches for hepatocellular carcinoma treatment

Ender Gunes Yegin, Erkan Oymaci, Emrah Karatay and Ahmet Coker

Izmir, Turkey

BACKGROUND: Hepatocellular carcinoma (HCC) is a complex and heterogeneous malignancy, frequently occurs in the setting of a chronically diseased organ, with multiple confounding factors making its management challenging. HCC represents one of the leading causes of cancer-related mortality globally with a rising trend of incidence in some of the developed countries, which indicates the need for better surgical and nonsurgical management strategies.

DATA SOURCES: PubMed database was searched for relevant articles in English on the issue of HCC management.

RESULTS: Surgical resection represents a potentially curative option for appropriate candidates with tumors detected at earlier stages and with well-preserved liver function. The long-term outcome of surgery is impaired by a high rate of recurrence. Surgical approaches are being challenged by local ablative therapies such as radiofrequency ablation and microwave ablation in selected patients. Liver transplantation offers potential cure for HCC and also correction of underlying liver disease, and minimizes the risk of recurrence, but is reserved for patients within a set of criteria proposed for a prudent allocation in the shortage of donor organs. Transcatheter locoregional therapies have become the palliative standard allowing local control for intermediate stage patients with noninvasive multinodular or large HCC who are beyond the potentially curative options. The significant survival benefit with the multikinase inhibitor sorafenib for advanced HCC has shifted the direction of research regarding systemic treatment toward molecular therapies targeting the disregulated pathways of hepatocarcinogenesis. Potential benefit is suggested from simultaneous or sequential multimodal therapies, and optimal combinations are being investigated. Despite the striking progress in preclinical studies of HCC immunotherapy and gene therapy, extensive clinical trials are required to achieve successful clinical applications of these innovative approaches.

CONCLUSION: Treatment decisions have become increasingly complex for HCC with the availability of multiple surgical and nonsurgical therapeutic options and require a comprehensive, multidisciplinary approach.

(*Hepatobiliary Pancreat Dis Int 2016;15:234-256*)

KEY WORDS: hepatocellular carcinoma; surgical liver resection; liver transplantation; locoregional therapies; molecular targeted systemic therapies; immunotherapy; gene therapy

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide and major global health problems. Approximately 782 000 new liver cancer cases were estimated to occur worldwide in 2012; it was reported as the fifth most common cancer in men and the ninth in women.[1] Because of its high mortality rate (95%), it is the second most frequent cause of cancer-related death.[1] The highest HCC incidence rates are seen in areas such as Southeast Asia, Middle and Western Africa. Although the incidence rates are much lower in most developed areas of the world, there has been a rise at alarming rates in the North America and in some parts of Europe.[2] The age-adjusted incidence rates of HCC tripled between 1975 and 2005 in the United States (USA),[3] while the prognosis of HCC remained poor with a 5-year survival rate of only 16.6% (liver and intrahepatic bile duct cancers).[4] Patients are still infrequently diagnosed at earlier stages

Author Affiliations: Department of Gastroenterology (Yegin EG) and Department of Gastroenterology Surgery (Oymaci E), Bozyaka Training and Research Hospital, Izmir; Department of Radiology, Bulanık State Hospital, Mus (Karatay E); Department of General Surgery, Ege University Faculty of Medicine, Izmir (Coker A), Turkey

Corresponding Author: Ender Gunes Yegin, MD, Department of Gastroenterology, Bozyaka Training and Research Hospital, Bahar Mh., Saim Cikrikci Cad. No: 59, Izmir 35170, Turkey (Tel: +90-232-250-5050; Email: drendergunes@hotmail.com)

doi: 10.1016/S1499-3872(16)60097-8
Published online May 17, 2016.

of HCC, which is in part related to the low utilization rates of surveillance in clinical practice.[5] Treatment decisions have become increasingly complex for HCC with the availability of multiple therapeutic options, which require a comprehensive, multidisciplinary approach. This review provides comprehensive data on the current status of surgical or nonsurgical treatment of HCC.

Treatment strategies

The therapeutic approach to HCC is dictated by the stage of disease, patient's performance status and comorbidities, available expertise, and lastly, the hepatic functional reserve and extent of portal hypertension (PHT), since many forms of therapies are related to the risk of worsening functional impairment of the liver. The therapeutic options include surgical therapies (liver resection [LR], liver transplantation [LT]), nonsurgical invasive therapies (e.g., radiofrequency ablation [RFA], percutaneous ethanol injection [PEI], transarterial chemoembolization [TACE]), and systemic medical therapies (e.g., sorafenib). Promising advanced radiotherapy (RT) technologies, immune-based and gene therapies are currently in development for HCC.

Although there is not one universal staging system for HCC, the Barcelona Clinic Liver Cancer (BCLC) system is a well-accepted algorithm for treatment allocation in the USA and Europe. It stratifies HCC disease into five stages (BCLC 0: very early; BCLC A: early; BCLC B: intermediate; BCLC C: advanced, and BCLC D: terminal stages) providing an integrated assessment of tumor extension (size, number, vascular invasion, and extrahepatic spread), liver function status by Child-Pugh system and patient's performance status by ECOG (Eastern Cooperative Oncology Group), and links each prognostic stage with an evidence-based treatment strategy (Fig.). The BCLC staging system has gained wide acceptance because of its design conceptualizing various therapeutic options and providing prognostic prediction, and it has been endorsed by liver associations of the USA (American Association for the Study of Liver Diseases [AASLD])[6] and Europe (European Association for the Study of the Liver-the European Organization for Research and Treatment of Cancer [EASL-EORTC]).[7] The algorithm suggests no alternatives when patient is not a suitable candidate for the treatment offered in the defined stage; but a shift to the most suitable treatment in the next BCLC stage (stage migration concept) has been advised in those cases.[7] There are some limitations of approaches like the BCLC system concerning the rigidity of the algorithm, absence of rapid evolving new therapeutic approaches and second-line or combined/sequential therapies, and the availability of options upon the resource

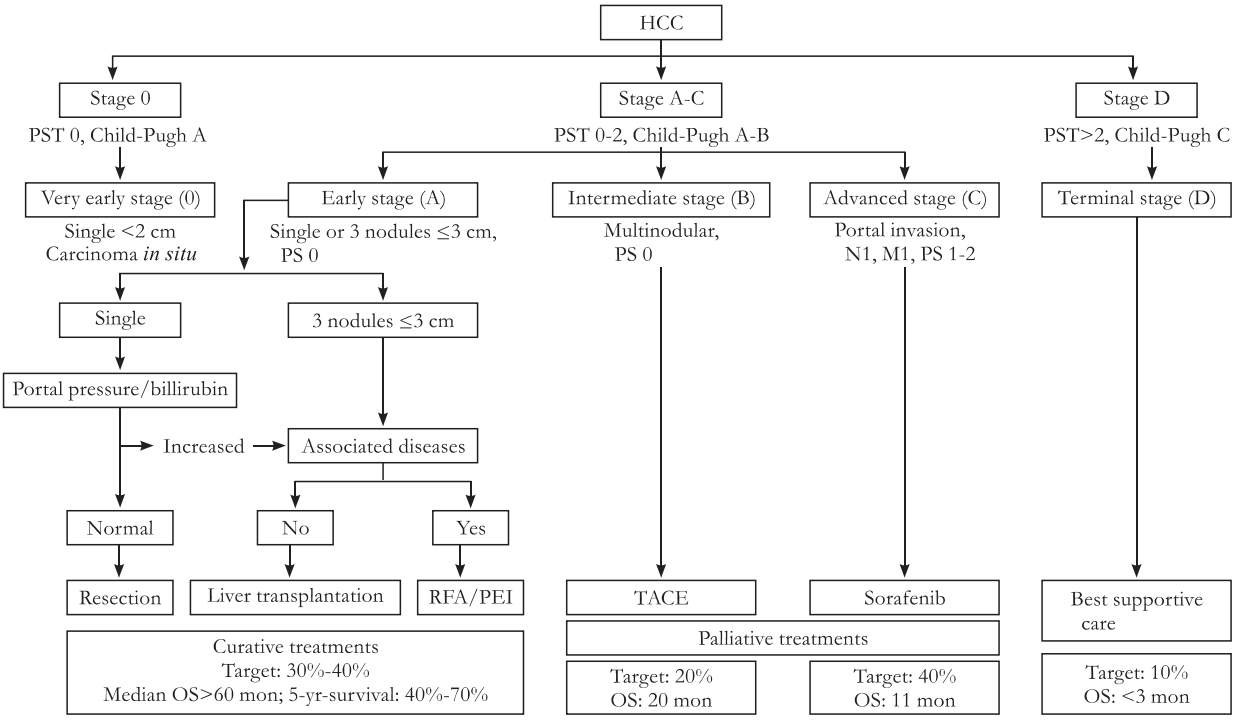

Fig. Barcelona Clinic Liver Cancer staging system and treatment algorithm. HCC: hepatocellular carcinoma; PST: performance status; OS: overall survival; PEI: percutaneous ethanol injection; RFA: radiofrequency ablation; TACE: transarterial chemoembolization (Reprinted from European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer.[7] Copyright 2015, with permission from Elsevier).