Liver Transplantation for Advanced Hepatocellular Carcinoma after Downstaging Without Up-Front Stage Restrictions

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BACKGROUND: The incidence of hepatocellular carcinoma (HCC) continues to increase dramatically worldwide. Liver transplantation (LT) is now the standard and optimal treatment for patients with HCC in the setting of cirrhosis, but only for tumors within Milan criteria. In patients presenting beyond Milan criteria, locoregional therapy (LRT) can downstage to within Milan criteria for consideration for LT. Although controversial, the current study aims to evaluate the outcomes of LT in patients presenting with advanced-stage HCC who underwent downstaging and compare these outcomes with those of patients who met Milan criteria at presentation.

STUDY DESIGN: Our protocol does not set a priori limitations as long as HCC is confined to the liver. In this retrospective study between January 1, 2002 and December 31, 2014, we reviewed outcomes associated with 284 patients who presented within Milan criteria and patients who presented with more-advanced stage tumor who were potential transplantation candidates. The patients with advanced disease were then subdivided into those who were within or beyond University of California San Francisco criteria. Imaging, details of LRT, recurrence, and survival were compared between the groups.

RESULTS: Sixty-three of 210 (30%) eligible patients were downstaged and underwent transplantation; 14 additional downstaged and listed patients were withdrawn for the following reasons: death while waiting (n = 4), disease progression (n = 8), development of other malignancy (n = 1), and declined LT (n = 1). Twelve patients underwent resection after downstaging and did not require LT. Survival for patients who were downstaged was similar to those who were within Milan criteria initially. Recurrence of HCC at 5 years was similar between groups (10.9% vs 10.8%; p = 0.84).

CONCLUSIONS: Patients with beyond–Milan criteria HCC who are otherwise candidates for LT should undergo aggressive attempts at downstaging without a priori exclusion. This highly selective approach allows for excellent long-term results, similar to patients presenting with earlier-stage disease. (J Am Coll Surg 2017;224:610–621. Published by Elsevier Inc. on behalf of the American College of Surgeons.)

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the second leading cause of cancer-related mortality in the world, responsible for about 1 million deaths per year.[1-4] In the US, HCC is predicted to become one of the leading causes of cancer-related mortality by 2030. Noninvasive criteria for HCC diagnosis are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic

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Abbreviations and Acronyms

AFP = α-fetoprotein
ALTSG = American Liver Tumor Study Group
B-UCSF = beyond University of California San Francisco criteria
HCC = hepatocellular carcinoma
LRT = locoregional therapy
LT = liver transplantation
MELD = Model for End-Stage Liver Disease
RFA = radiofrequency ablation
TACE = transarterial chemoembolization
UCSF = University of California San Francisco
W-UCSF = within University of California San Francisco criteria
Y-90 = yttrium-90 radioembolization

contrast-enhanced MRI. This diagnosis is usually based on identification of a hypervascular lesion in the arterial phase with washout in the portal venous or delayed phases.[5,6] Treatment for HCC depends on the number of tumors, tumor size, and overall liver function. Liver function is assessed according to Child-Turcotte-Pugh class and Model for End-Stage Liver Disease (MELD) criteria.[7-10]

Liver transplantation (LT) represents the first-line treatment option for selected patients with HCC in the setting of cirrhosis. In 1996, Mazzaferro and colleagues[11] provided sentinel work showing that patients with early-stage HCC could undergo LT with excellent results. The criteria as defined by the authors—solitary tumor ≤5 cm or ≤3 tumors each <3 cm—are now referred to as the Milan criteria, and have been applied worldwide in the selection of patients with HCC for LT. When these selection criteria are applied, excellent overall 4-year actuarial (75%) and recurrence-free survival rates (83%) can be achieved.[6,12-14] Although the Milan criteria remain the standard for the selection of patients with HCC, in recent years, specialized centers have proposed the expansion of these criteria. A few sites have reported survival rates in appropriately downstaged patients that are similar to patients who present within Milan criteria.[15,16]

Some authors consider the Milan criteria too restrictive and can exclude patients who would benefit from LT. The University of California San Francisco (UCSF) criteria—a single HCC nodule up to 6.5 cm, or up to 3 lesions, the largest of which is ≤4.5 cm and the sum of the diameters (cumulative tumor size) no larger than 8 cm—have shown outcomes comparable with those of patients meeting the Milan criteria.[17] Other centers believe that patients who present with advanced-stage disease might become reasonable candidates for transplantation after downstaging with locoregional therapy (LRT). Locoregional therapy includes transarterial chemoembolization (TACE), selective yttrium-90 radioembolization (Y-90), and/or radiofrequency ablation (RFA). These techniques, when used in the setting of multidisciplinary care and in properly selected patients, can be used to downstage tumor burden to within an acceptable range, that is, within Milan criteria.[18] The consideration of more-advanced stage patients, especially those who are downstaged using LRT, for LT remains controversial and additional validation of good outcomes is necessary, given the limited pool of transplantable organs. In this study, we present 63 patients with HCC beyond Milan criteria who underwent LT after successful downstaging to within Milan criteria. We compared the results with patients, initially within Milan criteria, who received transplants in the same time period.

METHODS

Approval was obtained from the Washington University IRB for this retrospective study. Our prospective liver transplant database was queried to identify HCC patients who received transplants between January 1, 2002 and December 31, 2014. Their original HCC disease extent was analyzed based on Milan criteria and the American Liver Tumor Study Group (ALTSG) staging. Variables potentially impacting survival and disease recurrence after LT were identified and compared.

Throughout the majority of the study timeline, HCC tumors were diagnosed by cross-sectional imaging according to the diagnostic criteria defined in the American Association for the Study of Liver Diseases guidelines, which require a contrast-enhancing mass >1 cm in size in the arterial phase with venous or delayed phase washout in the setting of cirrhosis. After implementation of a new national policy on October 31, 2013, the more stringent Organ Procurement and Transplantation Network criteria for imaging diagnosis were used.[19] Liver biopsies were not performed unless atypical features were present.

Inclusion criteria for the study were age older than 18 years at HCC diagnosis; a single nodule >5 cm, 2 to 3 nodules at least 1 >3 cm, corresponding to stage III of the ALTSG Classification, or ≥4 nodules of any size (stage IVA1 of the ALTSG classification), or HCC with any tumor stage plus intrahepatic portal or hepatic vein involvement (stage IVA2 of the ALTSG classification); possible transplantation candidate; and able to undergo LRT for possible downstaging. α-Fetoprotein (AFP) level was not included as an inclusion or exclusion criteria. Patients with regional lymph nodes or metastatic disease (including extrahepatic main portal or hepatic vein involvement),