

posed by the BCLC and by Marrero et al.,<sup>1</sup> also precludes identification of factors predictive of survival or selection factors for optimal treatment if that therapy is not undertaken.

In 2002, the AJCC/UICC adopted a simplified staging for HCC.<sup>4</sup> This staging was based on a detailed evaluation of tumor and liver factors associated with HCC. The study included patients from hepatobiliary centers in Japan, France, and the United States.<sup>5</sup> More recently, this staging was independently validated in eastern and western patients undergoing resection for HCC.<sup>6-8</sup> We agree with Marrero et al. that the lack of a consensus on HCC staging hinders progress in critical areas of HCC research. However, given the heterogeneity of patients with HCC, a need remains for alternate stagings and treatment algorithms.

TIMOTHY M. PAWLIK<sup>1</sup>

EDDIE K. ABDALLA<sup>1</sup>

MELANIE THOMAS<sup>2</sup>

MARK S. ROH<sup>3</sup>

GREGORY Y. LAUWERS<sup>4</sup>

DARIO RIBERO<sup>1</sup>

RONNIE T. POON<sup>5</sup>

JACQUES BELGHITI<sup>6</sup>

DAVID M. NAGORNEY<sup>7</sup>

JEAN-NICOLAS VAUTHEY<sup>1</sup>

<sup>1</sup>Department of Surgical Oncology  
The University of Texas M. D. Anderson Cancer Center  
Houston, TX

<sup>2</sup>Department of Gastrointestinal Medical Oncology  
The University of Texas M. D. Anderson Cancer Center  
Houston, TX

<sup>3</sup>Department of Surgical Oncology  
Allegheny General Hospital  
Pittsburgh, PA

<sup>4</sup>Department of Gastrointestinal Pathology  
Massachusetts General Hospital  
Boston, MA

<sup>5</sup>Department of Surgery, Queen Mary Hospital  
Hong Kong, China

<sup>6</sup>Department of Surgery, Hospital Beaujon  
Paris, France

<sup>7</sup>Department of General Surgery  
Mayo Clinic  
Rochester, MN

## References

- Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *HEPATOLOGY* 2005;41:707-716.
- Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol* 2005;12:364-373.
- Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005;140:450-458.
- Liver (including intrahepatic bile ducts). In: Greene FL, Page DL, Fleming ID, et al., editors. *American Joint Committee on Cancer Staging Manual*. New York, NY: Springer-Verlag, 2002:131-144.
- Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002;20:1527-1536.
- Poon RT, Fan ST. Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. *Surg Oncol Clin N Am* 2003;12:35-50, viii.
- Wu CC, Cheng SB, Ho WM, Chen JT, Liu TJ, P'eng FK. Liver resection for hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 2005;92:348-355.
- Ramacciato G, Mercantini P, Cautero N, Corigliano N, Di Benedetto F, Quintini C, et al. Prognostic evaluation of the new American Joint Committee on Cancer/International Union Against Cancer staging system for hepatocellular carcinoma: analysis of 112 cirrhotic patients resected for hepatocellular carcinoma. *Ann Surg Oncol* 2005;12:289-297.

Copyright © 2005 by the American Association for the Study of Liver Diseases.  
Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20849

Potential conflict of interest: Nothing to report.

## Reply:

We thank Dr. Pawlik and colleagues for their interest in our paper,<sup>1</sup> but we respectfully disagree with their comments. First, our intention was not to propose a new treatment algorithm for hepatocellular carcinoma (HCC), but rather validate existing prognostic classifications in our patients with HCC.

Second, Fig. 2B was misinterpreted. The best overall survival was in patients who underwent surgical therapy followed by ablation as primary treatment, then systemic treatments and no treatment. In addition, 91% of those undergoing transplantation and 100% of those undergoing resection were Barcelona Clinic Liver Cancer (BCLC) Stage A; ablation as primary treatment was performed in 60% BCLC stage A, 36% stage B and 4% stage C. While some of the patients who underwent ablation or chemoembolization as primary treatment may have had tumor burdens in which resection may have been feasible, hepatic dysfunction or poor performance status hindered the ability to perform resection.

Third, the authors showed 2 studies as evidence for performing palliation with surgical resection for HCC >5 cm.<sup>2,3</sup> The study by Ng et al.<sup>2</sup> found that small tumors had better survival than large tumors (>5 cm), but on multivariate analysis cirrhosis and multinodular tumors were among the factors that predicted poor prognosis. The study by Pawlik et al.<sup>3</sup> showed a 3-year survival of 22% in patients with cirrhosis. Two randomized controlled trials showed that chemoembolization in patients with cirrhosis and HCC >5 cm had better 3-year survivals.<sup>4</sup>

Fourth, our algorithm and the BCLC classification do not limit resection according to tumor size. However, the best results of resection are in those with tumors <5 cm and normal hepatic function; and when limited to single compared to multinodular tumors as shown in the largest series to date of resection for HCC.<sup>5</sup>

Finally, the new American Joint Committee on Cancer (AJCC) is not considered the gold standard for staging or prognosis of HCC, and its usefulness has been challenged by others.<sup>6,7</sup> In fact, the panel of experts at the recent European Association Study Liver-American Association Study of Liver Disease-Japanese Society of Hepatology Monothematic HCC meeting endorsed the BCLC classification. The external validation of the AJCC classification excluded postoperative deaths,<sup>8</sup> when an intent-to-treat analysis was performed, the AJCC classification was not an important prognostic variable,<sup>9</sup> and other prognostic classifications were not compared to AJCC. However, the most important limitation of the new AJCC classification is that it is based on postoperative assessment and not at the time of HCC diagnosis when prognosis is of utmost importance. In addition, the new AJCC classification ignores important prognostic factors such as performance status, age, hepatic function and the presence of portal hypertension at the time of HCC diagnosis. Also, pathological information required to define microvascular invasion is available in less than one third of cases, and the new AJCC does not differentiate micro/macrovascular invasion (except for the main trunk), when both entities have different prognostic value as recognized by Poon et al.<sup>10</sup>

JORGE A. MARRERO, M.D., M.S.  
 ROBERT J. FONTANA, M.D.  
 GRACE L. SU, M.D.  
 HARI S. CONJEEVARAM, M.D.  
 ANNA S. LOK, M.D.  
*Division of Gastroenterology, University of Michigan  
 Ann Arbor, MI*

## References:

- Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *HEPATOLOGY* 2005;41:707-716.
- Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol* 2005;12:364-373.
- Pawlik TM, Poon RT, Abdalla EK, Zorzi D, Ikai I, Curley SA, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005;140:450-458.
- Bruix J, Sala M, Llover JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004;127(Suppl 1):S179-S188.
- Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, et al. Reevaluation of prognostic factors after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. *Cancer* 2004;101:796-802.
- Izumi R, Shimizu K, Ii T, Yagi M, Matsui O, Nonomura A, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Gastroenterology* 1994;106:720-727.
- Llover JM, Bruix J, Fuster J, Castells A, Garcia-Valdecasas JC, Grande L, et al. Liver transplantation for treatment of small hepatocellular carcinoma: the TNM classification does not have prognostic power. *HEPATOLOGY* 1998;27:1572-1577.
- Wu CC, Cheng SB, Ho WM, Chen JT, Liu TJ, P'eng FK. Liver resection for hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 2005;92:348-355.
- Ramacciato G, Mercantini P, Cautero N, Corigliano N, Di Benedetto F, Quintini C, et al. Prognostic evaluation of the new American Joint Committee on Cancer/International Union Against Cancer staging system for hepatocellular carcinoma: analysis of 112 cirrhotic patients resected for hepatocellular carcinoma. *Ann Surg Oncol* 2005;12:289-297.
- Poon RT, Fan ST. Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. *Surg Oncol Clin N Am* 2003;12:35-50.

*Copyright © 2005 by the American Association for the Study of Liver Diseases.  
 Published online in Wiley InterScience (www.interscience.wiley.com).  
 DOI 10.1002/hep.20863*

*Potential conflict of interest: Nothing to report*