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# Validation of the American Joint Committee on Cancer eighth edition staging system in patients undergoing hepatectomy for hepatocellular carcinoma: a US population-based study



Guoqing Zhang, MD, Renfeng Li, MD, Xiaoyang Zhao, MD,  
Songfeng Meng, MD, Jianwen Ye, MD, and Longshuan Zhao, MD\*

Department of Hepatobiliary and pancreatic surgery, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China

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## ABSTRACT

**Background:** The American Joint Committee on Cancer (AJCC) eighth edition staging system for hepatocellular carcinoma (HCC) has incorporated several significant changes. This study aims to evaluate the newly proposed staging system and assess its strengths and weaknesses. **Materials and methods:** Using the Surveillance, Epidemiology, and End Results database, we identified patients with pathologically confirmed stage I-III HCC diagnosed between 2004 and 2014.

**Results:** After all exclusion criteria were applied, AJCC seventh and eighth edition staging was possible in 4931 patients. According to the AJCC eighth edition staging system, stages IB and II did not differ significantly in terms of overall survival (OS) and cause-specific survival (CSS) ( $P = 0.928$  and  $0.872$ , respectively). On the basis of the above results, we reclassified T1a, T1b, and T2 into several subgroups. According to the modified AJCC eighth edition staging system, OS and CSS among the five groups of patients differed significantly. For OS predication, the Akaike information criterion values for the AJCC seventh, eighth, and modified eighth edition staging systems were 29,288.24, 29,282.85, and 27,182.21, respectively, and the c-indices for the AJCC seventh, eighth, and modified eighth edition staging systems were 0.5716, 0.5805, and 0.6082, respectively. Regarding CSS, the Akaike information criterion values for the AJCC seventh, eighth, and modified eighth edition staging systems were 21,701.11, 21,682.12, and 20,313.26, respectively, and the c-indices for the AJCC seventh, eighth, and modified eighth edition staging systems were 0.5983, 0.6117, and 0.6436, respectively.

**Conclusions:** This is the first large-scale validation of the AJCC eighth edition staging system for patients undergoing hepatectomy. Our study revealed that there was a lack of discrepancy in the outcomes for stage IB and II tumors for AJCC eighth edition staging system of HCC. Our modified AJCC eighth edition staging system allows for finer stratification of patients undergoing hepatectomy according to more detailed tumor size and vascular invasion classifications.

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\* Corresponding author. Department of Hepatobiliary and pancreatic surgery, First Affiliated Hospital of Zhengzhou University, No. 1 Jian She Road, Zhengzhou, Henan Province 450000, China. Tel.: +86 371-66913114; fax: +86 371-66916261.

E-mail address: [15036107143@163.com](mailto:15036107143@163.com) (L. Zhao).  
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## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second most common cause of cancer death worldwide.<sup>1</sup> As reported, the annual incidence of HCC reached approximately 8.6 per 100,000 men and women, with approximately 6.3 deaths per 100,000 men and women annually in the United States.<sup>2</sup> Therefore, HCC has become a major public health issue worldwide. In the past decades, hepatectomy, liver transplantation, and several local therapies, such as radiofrequency and microwave ablation, percutaneous ethanol injection, and transcatheter arterial embolization or chemoembolization, have been developed. In recent years, early detection, improvement in surgical skills, and emergence of new treatment modalities have also made great contributions toward the prognosis of patients with HCC.<sup>3</sup> However, there is still a lack of consensus on optimizing the therapeutic strategy for patients with HCC because the optimal staging system for evaluating HCC prognosis remains a controversial topic.<sup>4–6</sup>

At present, several staging systems, such as the Okuda,<sup>7</sup> Barcelona Clinic Liver Cancer,<sup>8</sup> Japan Integrated Staging,<sup>9</sup> Cancer of the Liver Italian Program,<sup>10</sup> Chinese University Prognostic Index,<sup>11</sup> and Tumor-Node-Metastasis (TNM),<sup>12</sup> are used by different academic organizations. Among these staging systems, the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) TNM system has been widely used for patients with HCC undergoing hepatectomy. The TNM staging system for HCC is focused on the primary tumor, regional lymph nodes, and distant metastases. As a modified version of the AJCC seventh edition staging system, the new eighth edition was published in 2016. As shown in [Table 1/Appendix Table 2](#), several major modifications were made from the previous edition, resulting in new definitions for the T-stage. The purpose of this study was to evaluate the discriminative ability of the new AJCC eighth edition staging system with respect to the seventh edition in a series of 4931 patients with HCC who underwent hepatectomy (including total hepatectomy and transplant, similarly hereinafter).

## Material and methods

### Data source and case selection

We first identified patients from the newest available Surveillance, Epidemiology, and End Results (SEER) registry (1973–2014) for this population-based study. The database collects and publishes cancer incidence and survival data from 18 population-based cancer registries, representing 28% of the US population. We extracted the data of 61,039 patients who were diagnosed with HCC, which was identified using the International Classification of Diseases for Oncology, Third Edition; histology codes 8170 to 8175 and site code C22.0 from 2004–2014 before other selection criteria were applied. Patients with other primary malignancies, without microscopic diagnostic confirmation, or without hepatectomy were excluded ( $n = 54,041$ ). The follow-up was limited only to active

follow-up, and patients who died within a month of diagnosis were excluded ( $n = 244$ ). Finally, patients with stage 0 and stage IV disease ( $n = 744$ ) or without sufficient data to stage ( $n = 1079$ ) were excluded. The remaining 4931 patients were included in the final analysis ([Fig. 1](#)).

Demographic variables (gender, age, race, and marital status at diagnosis) and diagnostic information (year of diagnosis, tumor number, tumor location, tumor size, T-stage [seventh], vascular invasion [VI], SEER historic stage, and grade) were assessed. We derived the AJCC seventh and eighth edition staging using data on primary tumor size, lymph node involvement, and distant metastasis, all of which are provided by the SEER database. The primary end point of the study was overall survival (OS), and the secondary end point of the study was cause-specific survival (CSS). OS was defined as the interval from diagnosis until death or the last follow-up (data were censored on December 31, 2014, after the date of HCC diagnosis). CSS was defined as the interval from diagnosis until death due to HCC. Discriminatory ability of the AJCC staging system was measured by survival differences among subgroups.<sup>13</sup>

### Statistical analyses

All of the statistical analyses were performed using SPSS, version 22, for Windows (SPSS Inc, Chicago, IL). Categorical variables are expressed as frequencies ( $n$ ) and proportions (%), and continuous variables are presented as the mean  $\pm$  standard error. Univariate survival analysis was performed using the Kaplan-Meier method, while the log-rank test was performed to identify and compare the outcomes of significant covariates in univariate survival analysis. These significant covariates were considered for inclusion in the final Cox proportional hazards multivariable regression models. The Akaike information criterion (AIC) was used to evaluate the goodness of fit for each Cox proportional hazards multivariable regression models. A smaller AIC or a larger c-index value indicated a more desirable model for predicting prognosis. A statistically significant difference was determined using a 2-tailed test and a  $P$  value less than 0.05.

## Results

We analyzed data of 4931 patients who underwent hepatectomy for HCC between 2004 and 2014. The median follow-up period was 33 mo. The demographic and clinicopathologic characteristics for the entire cohort are presented in [Table 2](#).

### Univariate and multivariable analyses for OS and CSS

The prognostic impact of demographic and clinicopathologic characteristics associated with OS and CSS is shown in [Table 3](#). Among the factors evaluated, race, marital status, year of diagnosis, T-stage (seventh edition), and SEER historic stage were found to be related either to worse OS or to worse CSS. All the significant covariates in the univariate analysis were included in a multivariable analysis. Being widowed, early diagnosis, and advanced T-stage were confirmed as

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