# Comparison of the 7th and 8th editions of the American Joint Committee on Cancer Staging Systems for perihilar cholangiocarcinoma

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A R T I C L E   I N F O

A B S T R A C T

*Background:* The performances of the American Joint Committee on Cancer staging systems of the 7th and 8th edition were compared using a cohort of patients undergoing surgery for perihilar cholangiocarcinoma at 2 tertiary referral Italian hepatobiliary centers.
*Methods:* The American Joint Committee on Cancer 7th and 8th edition staging systems were used to classify 214 patients who underwent surgery for perihilar cholangiocarcinoma. The performances of the 2 staging systems were compared using the concordance index.
*Results:* Using the American Joint Committee on Cancer 7th edition staging system, we found that the 5-year overall survival for stages I, II, and IVa was 71%, 34%, and 34%, while no patients in stages IIIa, IIIb, and IVb survived 5 years. In comparison, when the American Joint Committee on Cancer 8th edition staging system was used, the 5-year overall survival was 71% and 35% in stages I and II, resulting in 23%, 19%, and 22% in stages IIIa, IIIb, and IIIc, respectively. Of note, no patients in stages IVa and IVb survived 5 years. The American Joint Committee on Cancer 8th edition staging system had a slightly better discriminatory ability with a concordance index of 0.624 compared with 0.619 for the American Joint Committee on Cancer 7th edition.
*Conclusion:* The newly released classification American Joint Committee on Cancer 8th edition staging system demonstrated a poor to moderate ability to predict prognosis of patients undergoing liver resection for perihilar cholangiocarcinoma, which was only slightly better than the previous edition. Further refinements are needed to improve the prognostic ability of the American Joint Committee on Cancer staging system for perihilar cholangiocarcinoma.

## Introduction

Perihilar cholangiocarcinoma (PH-CCA) is the second most common primary liver cancer.

Even though resection still represents the only possible curative treatment, the prognosis of patients after surgery remains dismal.[1,2] The American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system is the most common clinical tool to predict the prognosis of PH-CCA patients undergoing curative intent surgery. Recently, the new TNM AJCC 8th edition introduced several changes to better discriminate the prognosis of PH-CCA patients.[3–6] In particular, while patients with a Bismuth-Corlette Type IV PH-CCA (involving the second-order biliary radicals bilaterally) were in stage T4 according to the AJCC 7th edition, the Bismuth-Corlette classification was removed from the new TNM classification; in the 8th edition, stage T4 is now defined as tumor invading the main portal vein or its branches bilaterally, the common hepatic artery, or the unilateral, second-order biliary radicals with contralateral portal vein or hepatic artery involvement.[4] Moreover, the 8th edition introduced substantial changes in the nodal staging of patients with PH-CCA. While the location of metastatic lymph nodes (LN) determined the N stage in the 7th edition (N1, regional LN metastasis; N2, periaortic, pericaval, superior mesenteric artery, and/or celiac artery LN metastasis), the 8th edition defined stage N1 as patients with 1–3 metastatic lymph nodes and stage N2 as patients with >3 lymph nodes.[7] Even though Ebata et al,[8] investigating the long-term outcomes of

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1,352 patients undergoing liver resection for PH-CCA at Japanese HPB centers, reported that the new T4 and N stages were more accurate in predicting patient prognosis, the new AJCC 8th edition staging system for PH-CCA has not yet been tested in patients undergoing surgery in Western centers. For these reasons, the present study sought to evaluate and validate the newly published AJCC 8th edition staging system, using a large series of patients who underwent surgery for PH-CCA at 2 tertiary-referral Western hepatobiliary (HPB) centers.

## Materials and Methods

### Patient demographic and clinical data

Patients undergoing operative intervention for PH-CCA between 2000 and 2015 at 2 major HPB centers in Italy (University of Verona, School of Medicine, Verona, Italy, and Catholic University of Rome, School of Medicine, Rome, Italy) were identified. Only patients with a histologically confirmed PH-CCA were included in the study, while patients who died within 90 days of the operation were excluded from the analyses. PH-CCA were defined as cholangiocarcinoma involving the hilar bile duct (the duct located topologically between the right side of the umbilical portion of the left portal vein and the left side of the origin of the right posterior portal vein).[9] The institutional review board of each institution approved the study.

Standard patient demographic and clinicopathologic data were collected, including age, sex, American Society of Anesthesiologists (ASA) classification, and presence of cirrhosis. Serum levels of carcinoembryonic antigen (CEA) and Cancer Antigen 19-9 (CA 19-9) were also collected. We also collected data regarding treatment characteristics, including receipt of neoadjuvant chemotherapy, type of operation, and receipt of adjuvant treatments. The status of the resection margin was classified as microscopically negative (R0), microscopically positive (R1), and macroscopically positive (R2). Tumor-specific characteristics, including tumor size, number of tumors, involvement of the liver parenchyma, histologic grade, number and site (according to the Japanese classification) of lymph nodes achieved, and number of metastatic lymph nodes were collected. Lymph nodes of the hepatoduodenal ligament, the proper hepatic artery, and of the posterior surface of the head of the pancreas were dissected routinely and retrieved; interaortocaval lymph nodes were retrieved when macroscopically abnormal. The operative technique included complete dissection of the hilar structures, as well as all the fatty and lymph nodal tissue surrounding the common hepatic artery, the main portal vein, and the bile duct. Presence of lymphovascular/perineural/biliary invasion and direct invasion of the portal vein and the hepatic artery were also recorded. Data on tumor stage were collected according to both the 7th and the 8th editions of AJCC staging systems. Perioperative complications and mortality were considered within 90 days from the date of operation.

### Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQR), while categorical variables were reported as whole numbers and percentages. The outcome for survival analyses was overall survival (OS), defined as the time interval between the date of surgery and the date of death. Time was censored at the date of last follow-up for living patients. Estimates of OS were calculated using the Kaplan-Meier method. Cox proportional hazards models were used to evaluate associations between tumor stage and OS. In the survival analysis, the clinicopathologic variables resulting in a statistically significant value ($P < .05$) in the univariate analysis were tested using a Cox multivariable model to

**Table 1**

Baseline characteristics ($n = 214$).

| Variables | n (%) |
|---|---|
| **Sex** | |
| Female | 96 (44.8) |
| Male | 118 (55.2) |
| Age, median (IQR) | 65.7 years (57.7–71.5) |
| **Type of resection** | |
| Bile duct resection | 30 (14.0) |
| Left hepatectomy | 70 (32.7) |
| Right hepatectomy | 88 (41.1) |
| Left trisectionectomy | 19 (8.9) |
| Right trisectionectomy | 7 (3.3) |
| **Hepatic artery resection** | |
| Not performed | 210 (98.1) |
| Performed | 4 |
| **Portal vein resection** | |
| Not performed | 186 (86.9) |
| Performed | 28 (13.1) |
| **Vascular resection** | |
| Not performed | 184 (85.9) |
| Performed | 30 (14.0) |
| **Caudate lobe resection** | |
| Not performed | 65 (30.4) |
| Performed | 149 (69.6) |
| **Margins** | |
| R0 | 131 (61.2) |
| R1 | 61 (28.5) |
| R2 | 22 (10.3) |
| **Bismuth-Corlette classification** | |
| Type I | 10 (4.7) |
| Type II | 28 (13.3) |
| Type IIIa | 50 (23.7) |
| Type IIIb | 71 (33.7) |
| Type IV | 52 (24.6) |
| NA | 3 |
| **Lymphadenectomy** | |
| No | 17 (7.9) |
| Yes | 197 (92.1) |
| **Lymph node status** | |
| Negative | 125 (63.5) |
| Metastatic | 72 (36.5) |
| NA | 17 |
| Harvested lymph node, median (IQR) | 5 (3–10) |
| Metastatic lymph node, median (IQR) | 2 (1–3) |
| **Complication** | |
| No | 211 (51.9) |
| Yes | 103 (48.1) |
| **Neoadjuvant chemotherapy** | |
| No | 205 (94.8%) |
| Yes | 9 (4.2%) |
| **Adjuvant chemotherapy** | |
| No | 141 (65.9%) |
| Yes | 73 (34.1%) |

*NA*, not available.

assess their independency. The coefficients from the Cox models were reported as hazard ratio (HR) with corresponding 95% confidence intervals (CIs). To assess the performance of the 7th and the 8th editions of the AJCC staging systems, the concordance index (C-index) was used.[10] Standard errors, CIs, and *P* values for the C-index were computed by assuming asymptotic normality

## Results

### Clinicopathologic characteristics of the study group

A total of 214 patients underwent operative intervention for PH-CCA and were included in the study (Table 1). The majority were male ($n = 118$, 55.2%) and the overall median age was 65.7 years (IQR, 57.7–71.5; Table 1). A major hepatectomy was performed on 184 (86.0%) patients: left hepatectomy in 70 (32.7%), right hepatectomy in 88 (41.1%), and a left and right trisectionectomy in 19 (8.9%) and 7 (3.3%), respectively; the remaining