Original Article

External validation study of the 8th edition of the American Joint Committee on Cancer staging system for perihilar cholangiocarcinoma: a single-center experience in China and proposal for simplification

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Background: Several changes have been made to the primary tumor (T) and lymph node (N) categories in the new 8th edition of the American Joint Committee on Cancer (AJCC) staging system for perihilar cholangiocarcinoma (pCCA). This study was conducted to validate the 8th edition of the AJCC staging system for pCCA in China.

Methods: A total of 335 patients who underwent curative-intent resection for pCCA between January 2010 and December 2018 were retrospectively enrolled. The overall survival (OS) of groups of patients was calculated using the Kaplan-Meier method. The log-rank test was used to compare OS between groups. The concordance index (C-index), Akaike information criteria (AIC), and time-dependent area under receiver operating characteristic (ROC) curve (AUC) were computed to evaluate the discriminatory power of the 8th and 7th editions of the AJCC staging system.

Results: The T category changed in 25 (7.5%) patients, the N category changed in 39 (11.6%) patients, and the tumor-node-metastasis (TNM) stage changed in 157 (46.9%) patients when the 8th and 7th editions were compared. No statistically significant difference in survival was observed between T2aN0M0 and T2bN0M0. The C-index of the 8th edition was 0.609 [95% confidence interval (CI): 0.568–0.650], which was slightly higher than that of the 7th edition (C-index, 0.599, 95% CI: 0.558–0.640). The time-dependent AUC value also corroborated that the 8th edition had a better performance than the 7th edition.

Conclusions: The 8th edition of the AJCC staging system for pCCA showed a better ability than the 7th edition to discriminate patient survival. However, further simplification of the 8th edition is still needed.

Keywords: Perihilar cholangiocarcinoma (pCCA); American Joint Committee on Cancer (AJCC); prognosis; overall survival; curative-intent resection

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Introduction

Cholangiocarcinoma (CCA) is a rare biliary tract tumor that often presents as advanced disease and is usually challenging to diagnose and treat (1,2). CCA is divided into intrahepatic and extrahepatic CCA, which includes perihilar CCA (pCCA) and distal CCA (3). PCCA is a tumor that arises from the bifurcation of the hepatic ducts; the lower boundary is the site of cystic duct origin and the upper boundary is the secondary branches of the left and right hepatic ducts (4). Despite improvements in diagnosis and treatment, pCCA is often associated with universally poor outcomes (5,6). Complete resection of tumors with a negative margin is the primary curative option for patients with pCCA (7-9), although the majority of patients are not suitable candidates for curative resection at the time of presentation (1,10). Yet, even though some patients accept radical resection, the prognosis is still poor (8,11). In addition to radical resection, liver transplantation is another curative treatment option for selected patients with pCCA (12,13).

The American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) tumor-nodes-metastasis (TNM) staging system is the most popular and powerful prognostic tool for predicting overall survival (OS) for most malignancies (14-19). It provides clinicians with a knowledge-based and robust tool in the battle against cancer (20). Since the 7th edition of the AJCC staging system was published in 2009, a separate staging system has been established for pCCA (14). Several changes were introduced to enhance the discrimination ability of the 8th edition in predicting the prognosis of patients with pCCA (21). In terms of T category, this new classification excluded Bismuth-Corlette Type IV from the T4 category. In the 7th edition, the N category was classified according to the site of metastatic lymph nodes (LNs), with N1 representing regional LN metastasis and N2 defined as metastatic LNs located near the pericaval, superior mesenteric, periaortic artery, and/or celiac artery (14). Meanwhile, the 8th edition has introduced an entirely new N category for pCCA, defining N1 as 1–3 metastatic regional LNs and N2 as >3 metastatic regional LNs (21).

The new AJCC staging system (8th edition) for pCCA has been tested in a few centers (22-24). However, so far, no research has been conducted in China, where the incidence of pCCA is high. Thus, the objective of this study was to externally validate the new AJCC staging system (8th edition) for pCCA using data from a high-volume center. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-348).

Methods

The current study had a retrospective design and was carried out in accordance with the principles of the Declaration of Helsinki (as revised in 2013). The ethics committee of West China Hospital, Sichuan University, approved this analysis and waived the requirement for informed consent owing to its retrospective nature (No. 2019753).

Patient demographic

Owing to the retrospective nature, the ethics committee waived the requirement for informed consent. All patients who underwent radical resection for pCCA between January 2010 and December 2018 in our institution were identified. Patients with histologically confirmed pCCA were included in the study. The exclusion criteria were as follows: (I) loss to follow-up since discharge; (II) patients who underwent non-curative intent surgery; (III) postoperative mortality within 90 days; (IV) patients with a final pathological diagnosis other than pCCA; and (V) patients with missing data. A routine histopathological workup was carried out by the Department of Pathology for all resected specimens.

Standard patient demographic information was collected. Each patient's admission notes, radiologic reports, operation records and pathologic reports were collected. The following data were collected: age; sex; hepatitis B virus (HBV) infection; maximum tumor diameter; fluke; cholelithiasis; preoperative bile duct drainage; operation details; resection margin status; Bismuth type; postoperative complications; histologic grade; T category; the site and number of LNs dissected; the number and site of metastatic LNs; vascular invasion; the presence or absence of perineural invasion; adjuvant therapy (gemcitabine-based chemotherapy); preoperative indirect bilirubin (IBIL), direct bilirubin (DBIL), total bilirubin (TBIL), gamma-glutamyl transpeptidase (GGT), aspartate amino transferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA); and survival status. All laboratory indicators were examined within the 1 week prior to surgery. OS was defined as the

interval between the date of operation and the last follow-up or date of death.

Medical treatment and follow-up

The operative technique was depicted in our previous study (25). "LNs of the proper hepatoduodenal ligament and the hepatic artery, along with those posteriors to the pancreaticoduodenal artery were routinely resected. Except for Bismuth type I, hemihepatectomy and resection of the caudate lobe was performed routinely. R0 was defined as no residual tumor (neither macroscopically nor microscopically), and R1 was defined as microscopic positivity. The T category of pCCA was mainly determined by surgical and pathologic records. They attended outpatient follow-ups every 2–3 months for the first year postoperatively, and every 3–6 months thereafter. Measurements of tumor markers and liver function, as well as computed tomography (CT) and/or magnetic resonance imaging (MRI) examinations, were performed for assessment at each visit. Patients were followed-up until January 2020.

Statistical analysis

Categorical variables were expressed as whole counts and percentages. Continuous variables were expressed as medians with interquartile ranges (IQR). The cutoff values of preoperative TBIL (142.4 μmol/L), DBIL (128.9 μmol/L), IBIL (16.4 μmol/L), ALT (98 IU/L), AST (80 IU/L), ALP (328 IU/L), GGT (337 IU/L), CEA (3.03 ng/mL), and CA19-9 (215.3 U/mL) were defined as their respective medians. Patient survival was analyzed using the Kaplan-Meier method. Comparisons of OS were performed using the log-rank test. Additionally, the 1-, 3-, and 5-year survival rates (YSRs) were calculated. Univariate and multivariate Cox proportional hazard regression analyses were employed to determine the prognostic predictors of OS. Variables that were found to be significant in the univariate analysis (P<0.05) were included in multivariate analysis. Variables were expressed as hazard ratios (HR) with 95% confidence intervals (95% CI). Akaike information criteria (AIC) and Harrell's concordance index (C-index) were calculated to assess the prognostic discrimination ability of the 8th and 7th editions of the AJCC staging systems. Generally, lower AIC of a predictive model reflected a better model fit and a higher C-index represented better discriminatory ability (26). Finally, the time-dependent area under receiver operating characteristic (ROC) curve (AUC) was used to verify the accuracy of the models. Statistical analyses were performed using MedCalc (version 15.2.2, http://www.medcalc.org), R software (Version: 3.5.3, https: www.r-project.org) and SPSS (version 22, IBM, Armonk, NY, USA). The level of statistical significance was two-sided and a P value <0.05 was considered to indicate a statistically significant difference.

Results

Patient demographic and clinicopathological characteristics

A total of 377 consecutive patients with pCCA who underwent radical surgery were identified. Seventeen (4.5%) patients who had died in hospital or within 90 days after surgery were excluded. A further 20 patients who were lost to follow-up since discharge were censored, and 5 patients with missing data were also excluded. Finally, 335 patients were included in the present research. The baseline characteristics of the patients are displayed in *Table 1*. Among the included patients, there were slightly more males (n=183, 54.6%) than females, and the overall median age was 61 years (IQR, 52–65). The median postoperative hospital stay was 17 days (IQR, 14–24). Preoperative percutaneous transhepatic cholangiography drainage (PTCD) was conducted in 63 patients (18.8%). The types of surgery are illustrated in *Table 1*. Most patients (n=278, 83.0%) underwent a caudate lobe resection. The remaining 57 (17.0%) patients underwent out-hepatic bile duct resection without hepatectomy. Vascular resections were accepted by 142 (42.4%) patients. Sixty-eight (20.3%) patients underwent hepatic artery resection, 101 (30.1%) patients had portal vein resection, and 27 (8.1%) patients received both portal vein and hepatic artery resection. Besides liver resection, 18 (5.4%) patients had partial pancreatectomy. Of the resected specimens, 289 (86.3%) patients had negative (R0) operative margins, while 46 (13.7%) patients had R1 margins. On the basis of the Bismuth-Corlette classification, 47 (14.0%) patients had type I pCCA, and 108 (32.2%) patients had type II pCCA. Types IIIa, IIIb, and IV accounted for 59 (17.6%), 84 (25.1%), and 37 (11%) patients, respectively. LNs were negative in 234 (69.9%) patients, and 101 (30.1%) patients had metastatic LNs. The median number of harvested and metastatic LNs was 4

Table 1 Demographic and clinicopathological information of patients with pCCA (n=335)

Variables	Values (IQR or %)
Sex	
Female	152 (45.4%)
Male	183 (54.6%)
Age (years)	61 (52–65)
Type of resection	
Left hepatectomy	135 (40.3%)
Right hepatectomy	70 (20.9%)
Left trisectionectomy	16 (4.8%)
Right trisectionectomy	17 (5.1%)
Mesohepatectomy	27 (8.1%)
Bile duct resection with caudate lobe resection	11 (3.3%)
Bile duct resection only	57 (17.0%)
Liver transplantation	2 (0.6%)
Caudate lobe resection	278 (83.0%)
Blood loss (mL)	400 (300–800)
Resection margins	
R0	289 (86.3%)
R1	46 (13.7%)
Bismuth-Corlette classification	
Type I	47 (14.0%)
Type II	108 (32.2%)
Type IIIa	59 (17.6%)
Type IIIb	84 (25.1%)
Type IV	37 (11%)
Postoperative complications	
No	278 (83.0%)
Yes	57 (17.0%)
Adjuvant chemotherapy	
No	310 (92.5%)
Yes	25 (7.5%)

IQR, interquartile range.

(IQR, 2–7) and 2 (IQR, 1–3), respectively. Postoperative complications included infection (n=37), postoperative bleeding (n=12), biliary fistula (n=11), stress ulcer (n=6), hypohepatia (n=4), deep venous thrombosis (n=2), and hepatic encephalopathy (n=1). The median blood loss during resection was 400 mL (IQR, 300–800). As for the final pathology, tumors were classified as well- (n=34, 10.1%), moderately (n=236, 70.4%), and poorly (n=65, 19.4 %) differentiated. Twenty-five (7.5%) patients underwent gemcitabine-based adjuvant chemotherapy postoperatively. The median follow-up period was 54 months, and 219 (65.4%) patients died during the follow-up period. For the whole cohort, the 1-, 3-, and 5-year survival rates were 85.2%, 43.2%, and 21.3%, respectively.

Comparison of T category of pCCA between the 7th and 8th AJCC editions

Compared to the 7th edition, 25 (7.5%) patients had a different T category in the 8th edition. According to the 7th edition, 14 cases were categorized as T1 (4.2%), 74 as T2a (22.1%), 87 as T2b (26.0%), 67 as T3 (20.0%), and 93 as T4 (27.7%) tumors. Patients with T1, T2a, T2b, T3, and T4 tumors based on the 7th edition had a median survival time (MST) of 58, 36, 30, 24, and 29 months, respectively. In terms of the 7th edition AJCC T category, patients with T3 and T4 tumors had an elevated risk of death compared to patients with T1 disease (T2a *vs.* T1, HR 1.756, 95% CI: 0.747–4.129, P= 0.196; T2b *vs.* T1, HR 2.141, 95% CI: 0.920–4.982, P=0.077; T3 *vs.* T1, HR 2.916, 95% CI: 1.245–6.827, P=0.014; T4 *vs.* T1, HR 2.571, 95% CI: 1.111–5.952, P=0.027; Table S1). Based on the T category of the 7th edition, there was an overall significant difference in OS among patients (*Figure 1A*, P=0.018); however, there was no notable difference between adjacent subcategories (*Figure 1A*).

Using the 8th edition, 14 cases were categorized as T1 (4.2%), 80 as T2a (23.9%), 98 as T2b (29.3%), 75 as T3 (22.4%), and 68 as T4 (20.3%). The MST of patients with T1, T2a, T2b, T3, and T4 tumors was 58, 36, 31, 23, and 32 months, respectively. Similar to the 7th edition, using the 8th edition, patients with T3 and T4 tumors had an elevated risk of death compared to patients with T1 disease (T2a *vs.* T1, HR 1.770, 95% CI: 0.754–4.152, P=0.189; T2b *vs.* T1, HR 2.109, 95% CI: 0.911–4.882, P=0.082; T3 *vs.* T1, HR 3.141, 95% CI: 1.351–7.304, P=0.008; T4 *vs.* T1, HR 2.495, 95% CI: 1.063–5.859, P=0.036; Table S1). Overall, a significant difference was observed in the OS of patients with pCCA based on the T category of the 8th edition (*Figure 1B*,

P=0.004). Marked differences also existed between T3 and T2b (P=0.021), but there was no notable difference between adjacent subcategories (*Figure 1B*). Both the 7th and 8th editions failed to discriminate T2a and T2b disease (P=0.341 for the 7th edition and P=0.354 for the 8th edition).

Comparison of N category of pCCA between the 7th and 8th AJCC editions

Survival curves based on the N categories are elucidated in *Figure 1C,D*. According to the 7th edition (*Figure 1C*), 234 (69.9%), 62 (18.5%), and 39 (11.6%) patients were classified as N0, N1, and N2, respectively. The MST of patients with N0, N1, and N2 was 35, 27, and 22 months, respectively. Patients with N1 and N2 had an elevated risk of death compared to patients with N0 (N1 *vs.* N0, HR 1.442, 95% CI: 1.032–2.014, P=0.032; N2 *vs.* N0, HR 1.887, 95% CI: 1.295–2.750, P=0.001; Table S1). Based on the N category (7th edition), patients with pCCA overall showed a considerable difference in survival (*Figure 1C*, P=0.001). A significant difference also existed between N0 and N1 (P=0.028); however, no notable difference was observed between N1 and N2 (P=0.267).

Compared to the 7th edition, 39 (11.6%) patients had a different N category in the 8th edition. In the 8th edition, extra-regional lymph node metastasis belongs to the M1 phase; therefore, we analyzed M1 simultaneously with the N category. Twenty-four patients with metastatic LNs distributed posterior to the pancreaticoduodenal were reclassified (18 patients as N1 and 6 patients as N2). Using the 8th edition (*Figure 1D*), we found that 13 (3.9%), 73 (21.8%), and 234 (69.9%) patients were classified as N2, N1, and N0, respectively. Meanwhile, 15 patients (4.5%) had extra-regional metastatic LNs as M1. The MST of patients with N0, N1, N2, and M1 was 35, 24, 21, and 24 months, respectively. Patients with N1 or N2 tumors had an elevated risk of death compared to patients with N0 tumors; however, this difference was absent in regard to patients with M1 tumors (N1 *vs.* N0, HR 1.494, 95% CI: 1.097–2.035, P=0.011; N2 *vs.* N0, HR 2.147, 95% CI: 1.189–3.877, P=0.011; M1 *vs.* N0, HR 1.777, 95% CI: 0.960–3.287, P=0.067; Table S1). Based on the N category of the 8th edition, a significant difference was found in OS (*Figure 1D*, P=0.003). Similarly to the 7th edition, a marked difference existed between patients with N0 and N1 tumors (P=0.010), but no notable differences were observed between N1 and N2 (P=0.256) or between N2 and M1 disease (P=0.515).

Subgroup comparison of the OS of patients with pT2a and pT2b in the N0 category based on the 8th edition

In the 7th and 8th editions of the AJCC staging system, both T2aN0M0 and T2bN0M0 are classified as TNM stage II. We compared the OS between pT2a and pT2b patients in the N0 category based on the 8th edition. To avoid the influence of surgical technique on prognosis, patients with R1 margins (n=28) were excluded from the analysis. Finally, 52 and 54 patients were included in the T2aN0M0 and T2bN0M0 groups, respectively. Patients with T2a tumors had a 1-, 3-, and 5-year survival rate (YSR) of 92.2%, 58.2%, and 22.8%, respectively, compared with 90.6%, 50.3%, and 31.1% for patients with T2b tumors, respectively. No statistically significant difference in survival was observed (P=0.745). Next, we merged T2a and T2b into a T2 category for further investigation. After modification, based on the 7th edition (*Figure 1E*), differences between T2 and the adjacent subcategories, which were previously absent, became apparent. We found that the differences between T2 and the adjacent subcategories were more obvious when the 8th edition was used (*Figure 1F*).

Comparison of the TNM staging system for pCCA between the 7th and 8th AJCC editions

Compared to the 7th edition, 157 of 335 patients (46.9%) had a different overall stage in the 8th edition (*Figure 2*). Twelve patients belonged to stage I in both the 8th and 7th editions. According to the 7th edition classification, 111 (33.1%), 52 (15.5%), and 44 (13.1%) patients belonged to stages II, IIIA, and IIIB, respectively. However, according to the 8th edition, 120 (35.8%), 56 (16.7%), and 46 (13.7%) patients belonged to stages II, IIIA, and IIIB, respectively. A new stage, IIIC, which was developed for the 8th edition, included 73 (21.8%) patients. According to the 7th edition, stage IVA involved 77 (23.0%) patients, but only 13 (3.9%) patients were included in this stage in the 8th edition. Furthermore, 39 patients belonged to stage IVB in the 7th edition, but only 15 patients were included in this stage in the 8th edition. Using the 8th edition, more than 50% of the patients (55.9%) with stage I tumors were alive at last follow-up. However, patients with stage II tumors had a 1-, 3-, and 5-YSR of 91.4%, 51%, and 26.2%, respectively, while patients with stage IIIA tumors had a 1-, 3-, and 5-YSR of 78.6%, 32.9%, and 23.1%, respectively. Surprisingly, patients with stage IIIB tumors had a 1-, 3- and 5-YSR of 93.6%, 45.6%, and 20.8%, respectively, while

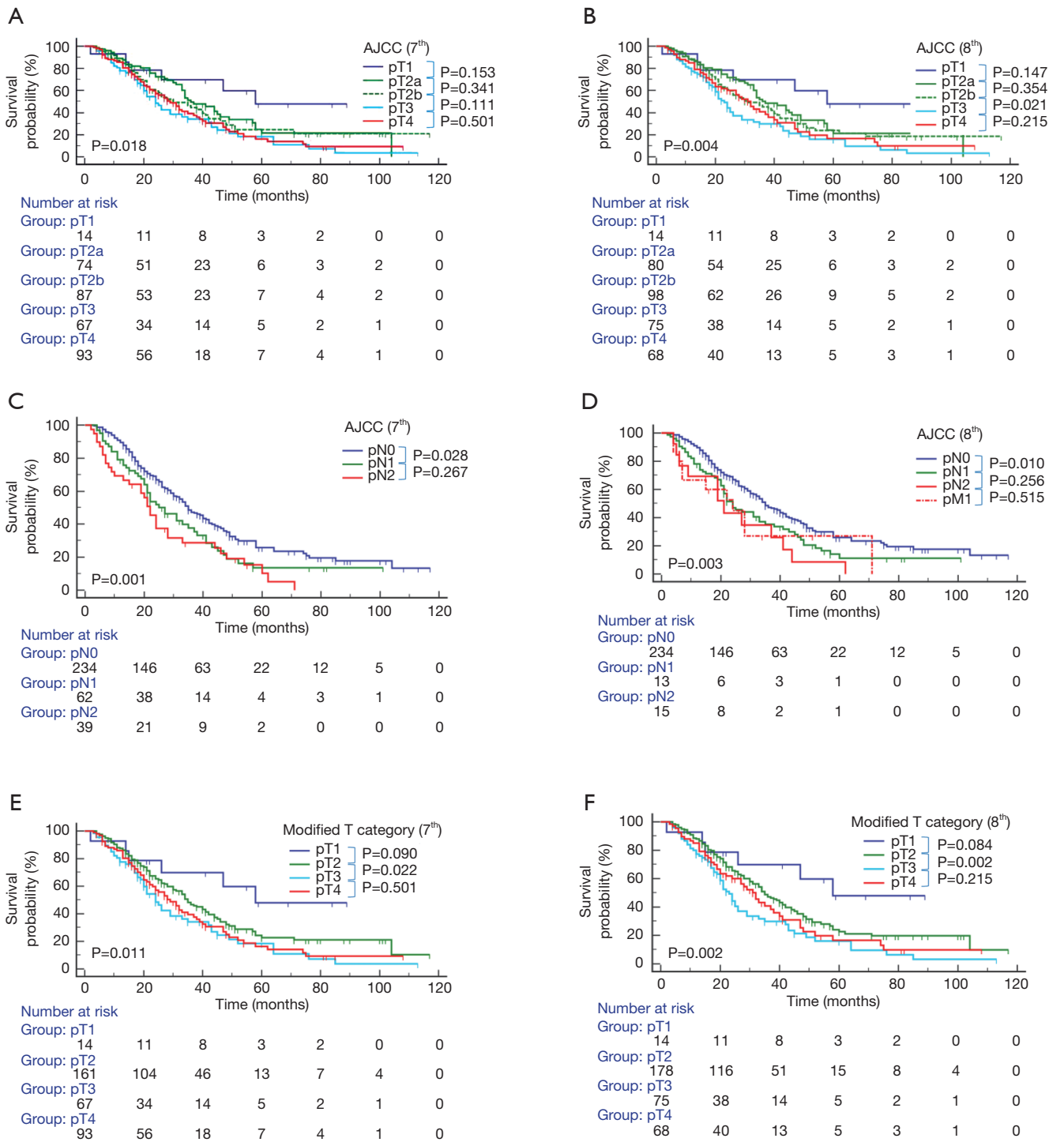

Figure 1 The 10-year OS rate of patients who underwent curative resection for pCCA. (A) Patients stratified by the T categories (7th edition of the AJCC). (B) Patients stratified by the T categories (8th edition of the AJCC). (C) Patients stratified by the N categories (7th edition of the AJCC). (D) Patients stratified by the N categories (8th edition of the AJCC). (E) Patients stratified by the simplified T categories based on 7th edition. (F) Patients stratified by the simplified T categories based on 8th edition. The pairwise and overall log-rank test results between neighboring subgroups' survival were expressed as P values in the upper-right and bottom-left corners, respectively. OS, overall survival; pCCA, perihilar cholangiocarcinoma; AJCC, American Joint Committee on Cancer.

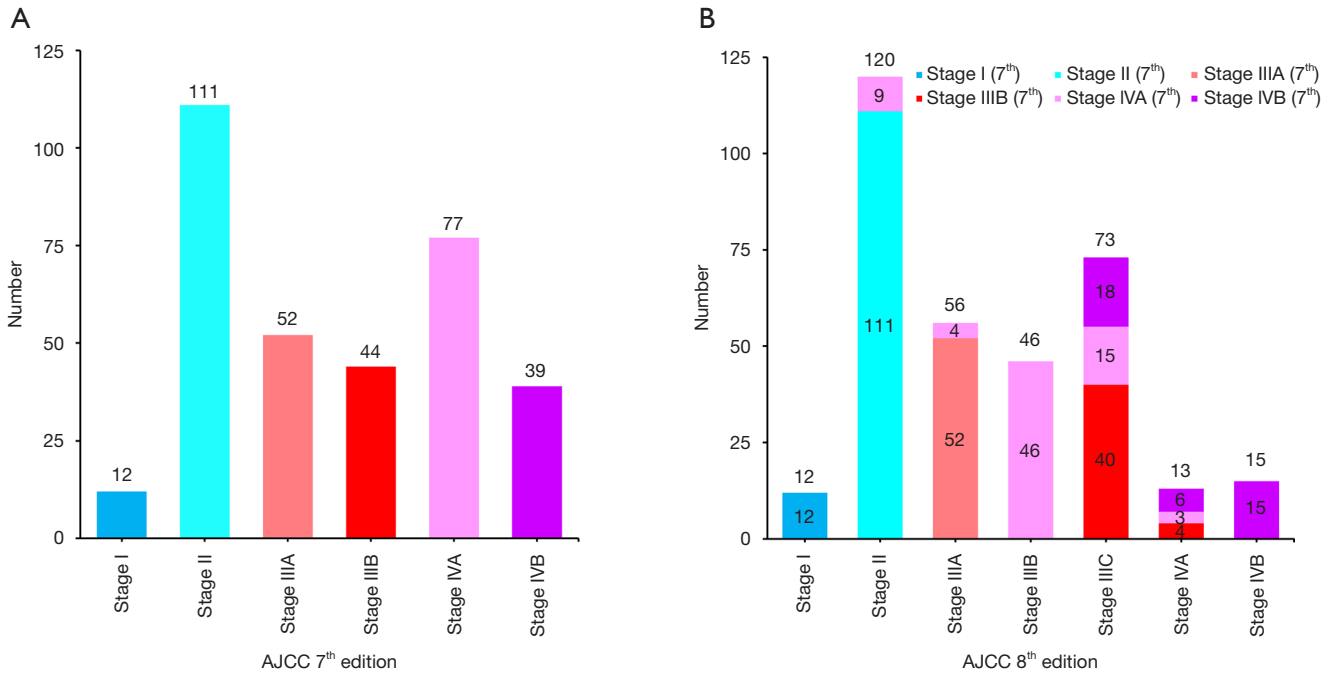

Figure 2 Comparison of TNM stages of patients who underwent curative resection for pCCA. (A) Patients stratified by the AJCC TNM staging system (7th edition). (B) Patients stratified by the AJCC TNM staging system (8th edition). pCCA, perihilar cholangiocarcinoma; AJCC, American Joint Committee on Cancer.

patients with stage IIIC tumors had a 1-, 3- and 5-YSR of 78.9%, 34.8%, and 9.4%, respectively. Interestingly, none of the patients with stage IVA and IVB tumors survived to 5 years postoperatively. The 1- and 3-YSRs of patients with stage IVA tumors were 66.7% and 27.0%, respectively, and were 69.2% and 34.6% for stage IVB, respectively. Patients with stages II, IIIA, IIIB, IIIC, and IVA had an MST of 37, 23, 33, 24, and 21 months, respectively. Using the AJCC 7th edition, a significant overall difference existed between the groups (*Figure 3A*, P=0.0005). No notable differences were observed between IIIA and IIIB (P=0.895), or between IIIB and IVA (P=0.667). In the 8th edition, significant differences were observed overall (*Figure 3B*, P=0.0001), as well as between II and IIIA (P=0.004). After simplifying the staging scheme, the 7th edition failed to distinguish stages III and IV (*Figure 3C*, P=0.894). However, using the 8th edition, these stages could be distinguished, although statistical significance was not reached (*Figure 3D*, P=0.117).

Concordance validation analysis was also carried out, to compare the discrimination ability of the 8th and 7th editions of the AJCC TNM staging system. The C-index of the 8th edition of the AJCC staging system was 0.609 (95% CI: 0.568–0.650), whereas the C-index of the 7th edition was 0.599 (95% CI: 0.558–0.640). Furthermore, the 8th edition had a smaller AIC value than the 7th edition (2,187.753 *vs.* 2,189.547). Time-dependent ROC curves also confirmed the superiority of the 8th edition of the AJCC compared to the 7th edition (*Figure 4*).

Univariate and multivariate survival analyses

Univariate analysis (Table S1) showed no significant differences in survival based on the following factors: age, sex, maximum diameter of the tumor, Bismuth type, hepatitis, DBIL, IBIL, ALT, AST, ALP, GGT, cholelithiasis, performance of PTCD, postoperative complications, hospitalization time, fluke, and adjuvant therapy. However, the following factors were shown to be associated with survival: preoperative TBIL (P=0.027), preoperative CA19-9 (P=0.009), preoperative CEA (P=0.008), positive margin status (P<0.001), perineural invasion (P<0.001), pathological differentiation (P<0.001), vascular invasion (P<0.001), T category (7th, P=0.026), N category (7th, P=0.001), AJCC TNM stage (7th, P=0.001), T category (8th, P=0.009), N

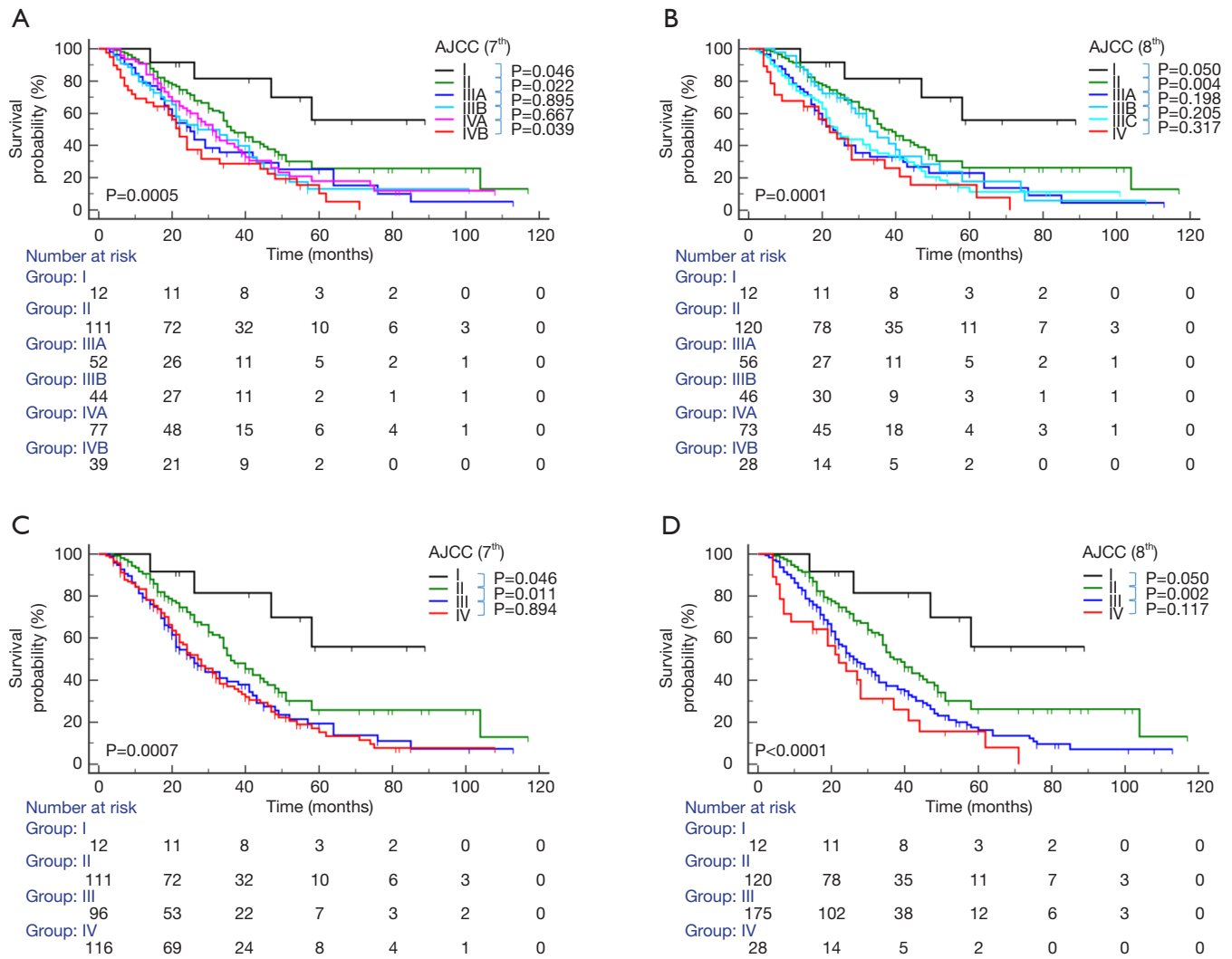

Figure 3 The 10-year OS rate of patients who underwent curative resection for pCCA. (A) Patients stratified by the AJCC TNM staging system (7th edition). (B) Patients stratified by the AJCC TNM staging system (8th edition). (C) Patients stratified by the simplified AJCC TNM staging system (7th edition). (D) Patients stratified by the simplified AJCC TNM staging system (8th edition). The pairwise and overall log-rank test results between neighboring subgroups' survival were expressed as P values in the upper-right and bottom-left corners, respectively. OS, overall survival; pCCA, perihilar cholangiocarcinoma; AJCC, American Joint Committee on Cancer.

category (8th, P=0.005), and the AJCC TNM stage (8th, P=0.001). To avoid collinearity of variables, T category (7th), N category (7th), AJCC TNM stage (7th), T category (8th), and N category (8th) were not included in multivariate analysis. The multivariate analysis (*Table 2*) revealed that pathological differentiation (P=0.020), vascular invasion (P=0.020), and perineural invasion (P=0.038) were the only independent prognostic predictors of poor OS in patients with pCCA after surgery.

Discussion

After surgery, accurate assessment of tumor stage is essential for predicting prognosis and guiding clinical decision-making. The AJCC staging system is the accepted benchmark for classifying patients with various cancers (20). Since the AJCC 7th edition was published in 2009, a separate system for pCCA has been released (14). Recently, the AJCC 8th edition was published (21). So far, only a few studies have been carried out to validate the AJCC manual

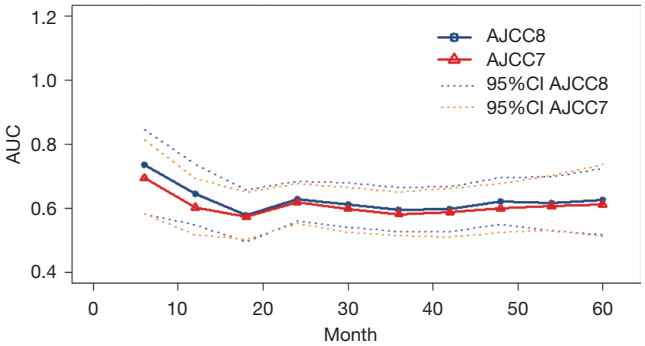

Figure 4 Time-dependent curves of 7th and 8th editions of the AJCC TNM staging system. ROC, receiver operating characteristic.

(8th edition) for pCCA, none of which were conducted in China. A study from The Netherlands evaluated the performance of the AJCC staging system (7th edition), and reported a C-index of 0.59 (27), which is consistent with the result observed in the present study. We also observed that the overall predictive performance of the 8th edition was slightly higher than that of the 7th edition of the AJCC staging system in predicting survival of pCCA (C-index, 0.609 *vs.* 0.599). Similarly, Ruzzenente *et al.* (22) demonstrated that the C-index of the 8th edition was higher than that of the 7th edition (0.624 *vs.* 0.619), and this result was confirmed by a South Korean study (C-index, 0.621 *vs.* 0.582) (23). Furthermore, another study from The Netherlands also demonstrated that the prognostic accuracy of the 8th edition was higher than that of the 7th edition (C-index, 0.67 *vs.* 0.65) in patients who underwent curative-intent resection (24). Thus, the new classification of the AJCC TNM staging system is more reasonable than the 7th edition, despite its poor ability to predict prognosis (C-index <0.7). At the same time, in this study, the 8th edition of the AJCC staging system was found to have a lower AIC, which reflects a better model fit. The time-dependent AUC value also supported the conclusion that the 8th edition is more reasonable than the 7th edition.

In the 8th edition, several changes were made to the T- and N-categories, which resulted in the reclassification of the distribution of T- and N-categories of pCCA. Invasion of the bilateral second order biliary radicals was excluded from the T4 category in the 8th edition. Although after changing of T categories, compared to patients in stage T1, patients with stages T3 and T4, but not T2a and T2b, tumors had an elevated risk of death in both the 7th and 8th editions. This result differed from that of the study conducted by Kwon *et al.* (28), who reported that when Bismuth-Corlette type IV was excluded from the T4 category, the discrimination of stages was greatly improved. This difference between the studies may have been caused by the small number of Bismuth-Corlette Type IV cases in our study. In another study, patients with stages T3 and T2b had an elevated risk of death compared to patients with stage T1; however, those with stages T2a and T4 did not (22), which may be due to the small cohort of patients with T2a and T4 cancer in this study. In current clinical practice, except for Bismuth type I, hemihepatectomy with an extrahepatic bile duct resection as well as resection of the caudate lobe is obligatory in most surgical plans (29). However, in the 7th and 8th editions of the AJCC staging system, both T2aN0M0 and T2bN0M0 were classified as TNM stage II. We did not find significant differences in OS between T2aN0M0 and T2bN0M0, which was consistent with the results of Ito *et al.* (30). However, the survival curves of T2a and T2b showed a significant difference in another study (28). The reason for this difference may be attributable to the confounding effect of lymph node metastasis and surgical technique on survival, which were excluded in our study. Based on the similarity in the survival of T2aN0M0 and T2bN0M0 in the current study, we merged T2a and T2b into T2, and found this to be helpful in distinguishing T2 from other adjacent subcategories. This is our proposal for simplification in the future.

After resection of pCCA, lymph node status is considered to be one of the most important prognostic predictors (31,32). In this study, we only demonstrated that the existence of metastatic LNs had a negative effect on survival, but could not distinguish the prognosis of N1 and N2 in neither the 7th nor the 8th edition. This result contrasted with that of the study by Lee *et al.* (23), who found that the difference between N1 and N2 was not significant in the 7th edition, but was statistically significant in the 8th edition. Another study found that patients with >3 positive LNs had significantly worse outcomes than those with ≤3 (33). However, we could not acquire this result in our study. Further demonstration of the effect of the new N category on survival in more centers is necessary in future studies.

In the present study, 46.9% of all patients changed overall stages based on the 8th AJCC TNM staging system, which is consistent with the findings of previous studies (22,23). The prognosis of patients with new stage IIIC was

Table 2 Multivariate Cox regression analysis of prognostic factors for patients with pCCA

Variable	β	SE	Wald	HR	HR (95% CI)		P value
					Lower	Upper	
TBIL (≥142.4 μmol/L)	0.052	0.162	0.101	1.053	0.766	1.447	0.750
CA19-9 (≥215.3 U/mL)	0.196	0.146	1.795	1.216	0.913	1.619	0.180
CEA (≥3.0 ng/mL)	0.158	0.153	1.065	1.171	0.867	1.582	0.302
Perineural invasion	0.624	0.301	4.307	1.867	1.035	3.367	0.038*
Positive resection margin status	0.331	0.199	2.756	1.392	0.942	2.056	0.097
Vascular invasion	0.602	0.258	5.421	1.825	1.100	3.029	0.020*
Pathological differentiation			7.789				0.020*
Well	Ref.	–	–	–	–	–	–
Moderate	0.460	0.304	2.285	1.584	0.872	2.876	0.131
Poor	0.852	0.336	6.439	2.344	1.214	4.527	0.011*
AJCC TNM stage (8^{th})			9.172				0.102
I	Ref.	–	–	–	–	–	–
II	0.034	0.731	0.002	1.034	0.247	4.335	0.963
IIIA	1.030	0.711	2.096	2.800	0.695	11.285	0.148
IIIB	-0.431	0.514	0.701	0.650	0.237	1.782	0.402
IIIC	-0.254	0.411	0.382	0.776	0.347	1.736	0.537
IV	0.182	0.445	0.167	1.200	0.502	2.870	0.682

Significant variables with P<0.05 in the univariate analysis were included in the multivariate Cox proportional hazard model regression analyses. *, P<0.05. TBIL, total bilirubin; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen.

slightly better than that of stage IV patients but worse than that of stage IIIB patients. Therefore, the newly-established stage IIIC (8^{th}) could reflect the poor prognosis of patients with metastatic LNs. In the 8^{th} edition, differences between each stage became more obvious compared to the 7^{th} edition, which could also reflect the rationality of this amendment. In addition to analyzing the changes between the 7^{th} and 8^{th} editions, we also investigated the prognostic factors associated with survival. In the multivariate survival analyses, pathological differentiation, vascular invasion, and perineural invasion were identified as independent predictors of poor survival after surgery in patients with pCCA. Vern-Gross *et al.* (34) demonstrated that lower tumor differentiation had a negative effect on survival. Our result was consistent with the findings of a meta-analysis (35) in which microvascular invasion, perineural invasion, and tumor differentiation were found to be significant prognostic factors.

The current study has several limitations that should be noted. Firstly, owing to the retrospective nature, our study might have a selection bias in terms of the patients' diagnosis and treatment. Secondly, the effect of adjuvant therapy on OS is unclear. However, an association between adjuvant therapy and improved survival has been observed, with the effect limited to those with lymph node-positive disease (36). Due to the small population of patients that received adjuvant chemotherapy in this cohort, solid conclusions could not be drawn to depict the effect of adjuvant chemotherapy on survival. Thirdly, vascular resection was not lucubrated, and some researchers have noticed the effect of hepatic artery and portal vein resection on survival (37-39). However, this study was designed to explore AJCC categories. Furthermore, the present study was performed in a single institute and included 335 cases. Although this is one of the largest cohorts of patients with pCCA outside of the Surveillance, Epidemiology, and End Results (SEER) database, further multi-national and multi-institutional studies are required to derive more

solid conclusions. Lastly, the cohort of this study involved patients who had undergone curative-intent resection, whereas most patients with pCCA had no opportunity to accept radical surgery at initial presentation. Further study is needed to include patients with both conservative treatment and surgical resection.

Conclusions

In summary, the modified T and N categories in the newly released 8th edition of the AJCC staging system for pCCA enhance the ability of this staging system to discriminate patient survival. Nevertheless, further simplification is still needed.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethics committee of West China Hospital, Sichuan University, approved this analysis and waived the requirement for informed consent owing to its retrospective nature (No. 2019753).

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Supplementary

Table S1 Univariate analysis of factors associated with long-term survival after resection of pCCA

Variable	N	Survival (median, months)	Univariable analysis	
			HR (95% CI)	P value
Sex				
Female *vs.* male	152/183	34/28	0.796 (0.609–1.041)	0.095
Age				
≥60 *vs.* <60 years	183/152	31/33	1.141 (0.873–1.492)	0.334
Maximum diameter				
≥3 *vs.* <3 cm	129/206	31/34	1.163 (0.887–1.524)	0.275
Bismuth type				
III/IV *vs.* I/II	180/155	34/30	0.962 (0.738–1.255)	0.775
Hepatitis				
With *vs.* without	250/85	32/33	1.060 (0.783–1.435)	0.708
TBIL				
≥142.4 *vs.* <142.4 μmol/L	168/167	28/34	1.355 (1.035–1.772)	0.027*
DBIL				
≥128.9 *vs.* <128.9 μmol/L	168/167	29/33	1.288 (0.985–1.685)	0.064
IBIL				
≥16.4 *vs.* <16.4 μmol/L	168/167	32/33	1.248 (0.955–1.630)	0.104
ALT				
≥98.0 *vs.* <98.0 IU/L	168/167	28/34	1.147 (0.879–1.496)	0.311
AST				
≥80.0 *vs.* <80.0 IU/L	168/167	28/35	1.238 (0.949–1.614)	0.115
ALP				
≥328.0 *vs.* <328.0 IU/L	168/167	30/34	1.099 (0.842–1.434)	0.488
GGT				
≥337.0 *vs.* <337.0 IU/L	168/167	29/33	1.058 (.811–1.380)	0.679
CA19-9				
≥215.3 *vs.* <215.3 U/mL	168/167	29/35	1.428 (1.093–1.865)	0.009*
CEA				
≥3.0 *vs.* <3.0 ng/mL	168/167	27/35	1.439 (1.102–1.880)	0.008*
Cholelithiasis				
With *vs.* without	80/255	36/30	0.849 (0.616–1.170)	0.318
Preoperative bile duct drainage				
With *vs.* without	63/272	28/33	1.143 (0.808–1.617)	0.451
Postoperative complication				
With *vs.* without	57/278	26/33	1.312 (0.930–1.849)	0.122
Hospitalization time				
≥17.0 *vs.* <17.0 days	192/143	30/33	1.059 (0.807–1.389)	0.679
Fluke				
With *vs.* without	11/324	33/26	0.917 (0.432–1.948)	0.822
Perineural invasion				
With *vs.* without	294/41	28/58	3.046 (1.850–5.015)	<0.001*
Positive margin status				
With *vs.* without	46/289	20/34	1.942 (1.367–2.759)	<0.001*
Vascular invasion				
With *vs.* without	142/193	25/37	1.643 (1.259–2.144)	<0.001*
Adjuvant therapy				
With *vs.* without	25/310	37/30	0.695 (0.396–1.218)	0.204
Pathological differentiation				<0.001*
Well	34	58	Ref.	–
Moderately	236	33	2.445 (1.435–4.165)	0.001
Poorly	65	21	4.197 (2.327–7.570)	<0.001
T category (7^{th})				0.026*
T1	14	58	Ref.	–
T2a	74	36	1.756 (0.747–4.129)	0.196
T2b	87	30	2.141 (0.920–4.982)	0.077
T3	67	24	2.916 (1.245–6.827)	0.014
T4	93	29	2.571 (1.111–5.952)	0.027
N category (7^{th})				0.001*
N0	234	35	Ref.	–
N1	62	27	1.442 (1.032–2.014)	0.032
N2	39	22	1.887 (1.295–2.750)	0.001
AJCC TNM stage (7^{th})				0.001*
I	12	NA	Ref.	–
II	111	36	2.616 (0.951–7.202)	0.063
IIIA	52	25	4.143 (1.474–11.648)	0.007
IIIB	44	27	4.000 (1.409–11.357)	0.009
IVA	77	31	3.576 (1.289–9.916)	0.014
IVB	39	22	5.503 (1.948–15.539)	0.001
T category (8^{th})				0.009*
T1	14	58	Ref.	–
T2a	80	36	1.770 (0.754–4.152)	0.189
T2b	98	31	2.109 (0.911–4.882)	0.082
T3	75	23	3.141 (1.351–7.304)	0.008
T4	68	32	2.495 (1.063–5.859)	0.036
N category (8^{th})				0.005*
N0	234	35	Ref.	–
N1	73	24	1.494 (1.097–2.035)	0.011
N2	13	21	2.147 (1.189–3.877)	0.011
M1	15	24	1.777 (0.960–3.287)	0.067
AJCC TNM stage (8^{th})				0.001*
I	12	NA	Ref.	–
II	120	37	2.562 (0.932–7.038)	0.068
IIIA	56	23	4.470 (1.598–12.508)	0.004
IIIB	46	33	3.227 (1.129–9.225)	0.029
IIIC	73	24	4.365 (1.581–12.051)	0.004
IVA	13	21	6.286 (2.021–19.549)	0.001
IVB	15	24	5.205 (1.653–16.390)	0.005

*, P<0.05. TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; ALT, alanine aminotransferase; AST, aspartate amino transferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NA, not available.

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