

Prognostic Accuracy of the Eighth Edition of TNM Classification Compared with the Seventh and Sixth Edition for Perihilar Cholangiocarcinoma

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Abstract

Background This study was conducted to evaluate and compare the prognostic value and performance of the 6th, 7th, and 8th editions of the American Joint Committee on Cancer (AJCC) staging system when applied to patients undergoing surgery for perihilar cholangiocarcinoma (PHC).

Methods Patients undergoing liver resection with curative intention for PHC between 2002 and 2019 were identified from a prospective database. Histopathological parameters and stage of the PHC were assessed according to the 6th, 7th, and 8th editions of the tumor node metastasis (TNM) classification. The prognostic accuracy between staging systems was compared using the area under the receiver operating characteristic curve (AUC) model.

Results Data for a total of 95 patients undergoing liver resection for PHC were analyzed. The median overall survival time was 21 months (95% CI 8.1–33.9), and the 3- and 5-year survival rates were 46.1% and 36.2%, respectively. Staging according to the 8th edition versus the 7th edition resulted in reclassification of 25 patients (26.3%). The log-rank p-values for the 7th and 8th edition were highly statistically significant ($p \leq 0.01$) compared to the 6th edition ($p = 0.035$). The AJCC 8th edition staging system had a slightly better discrimination ability, with an AUC of 0.69 (95% CI: 0.52–0.84) compared to 0.61 (95% CI: 0.51–0.73) for the 7th edition. Multivariate survival analysis revealed male gender, age > 65 years, positive resection margins, presence of distant metastases, poorly tumor differentiation, lymph node involvement such as no caudate lobe resection as independent predictors of poor survival ($p < 0.05$).

Conclusion The newly released 8th edition of the AJCC staging system demonstrated a poor to moderate ability to predict prognosis of patients undergoing liver resection for perihilar cholangiocarcinoma; the result was only slightly better than the previous 7th edition. Further refinements are needed to improve the prognostic ability of the AJCC staging system for perihilar cholangiocarcinoma and to identify other prognostic factors that can potentially improve individual patient prognostication.

Introduction

Perihilar cholangiocarcinoma (PHC) is a relatively uncommon disease, but the treatment of this cancer remains a medical challenge. Chemotherapy and radiotherapy, either alone or in combination, have failed to provide marked improvements in the long-term patient outcomes, and operative resection still represents the only possible curative treatment for these patients [1, 2]. However, surgery for PHC is complex and continues to be a most difficult task for hepato-pancreatobiliary surgeons. Hepatectomy, with en bloc resection of the caudate lobe and extrahepatic duct and lymph node dissection, together with resection of the portal vein and/or hepatic artery when indicated, is an aggressive approach for PHC that can result in disease-free and overall survival [3–5]. Recent studies have reported 5-year survival rates following curative-intent liver resection varying from 25% to 40% [1, 3, 6–8]. Unfortunately, the

majority of patients at presentation have metastatic or locally advanced disease; consequently, they do not benefit from resection [9–13].

PHC has a large number of factors associated with its prognosis, and yet prediction of long-term survival can be difficult to determine and accurate stratification of patient prognosis remains challenging [11, 14, 15]. Several prognostic schemes have attempted to aggregate the most relevant clinicopathological factors to provide estimates of long-term survival [6, 7, 14, 16–18]. Commonly used prognostic tools include the Bismuth-Corlette classification and the Blumgart T-stage system, which focus on determining resectability using preoperative imaging [7, 19, 20]. However, the American Joint Committee on Cancer (AJCC) staging system is still the most widely used for determining prognosis and appropriate treatment and for comparing outcomes between other centers [21].

In the 6th edition (2003) of the AJCC staging system, all patients with extrahepatic bile duct tumors were covered by a single classification [22]. By contrast, the 7th edition (2010) was the first system to stage perihilar (proximal) and distal cholangiocarcinoma separately [23, 24]. The recently published 8th edition of the AJCC staging manual now has introduced notable changes to the T-, N-, and overall stage category classification schemes [16, 20, 21, 23, 25] (**Table 1**). In particular, the T4 disease category excludes bilateral second-order bile duct extension and is now defined as a 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 [26]. This new definition now means that T4 tumors are downstaged from stage IVA to IIIB and a newly introduced stage IIIC (Any T, N1, M0). The 8th edition has also introduced substantial changes in the nodal staging of patients with PHC. With respect to N-stage, the N1- and N2-stage categories have changes in the counts of lymph nodes (N1: involvement of 1–3 regional lymph nodes; N2: involvement of 4 and more regional lymph nodes).

The current literature contains few studies that have utilized the newly published AJCC 8th edition staging system for patients, and especially those undergoing liver resection for PHC with curative intent at Western high-volume hepato-pancreato-biliary (HPB) centers [25]. Against this background, the aim of the current study was to compare the prognostic accuracy and validation of the newly published tumor node metastasis (TNM) classification of the AJCC 8th edition with the 7th and 6th editions for patients with PHC following liver resection. Specifically, we wanted to evaluate whether the new PHC classification provides better differentiation between tumor stages and more accurate prediction of patient survival. We also wanted to evaluate survival rates with regard to biological tumor markers and pathological characteristics.

Methods

Study Population

This study included patients whose prospective data was contained in a database at the University Hospital of Leipzig. The study was approved by the local Ethics Committee (AZ EK: 243-14-14072014). Only patients with resected and histologically confirmed PHC were included in the study. Patients with final pathology indicative of a diagnosis other than PHC, those who had suffered in-hospital mortality (such as patients who underwent an R2 resection), those who had undergone a palliative operation, and those who had undergone ablation were excluded from this study.

PHC was defined as cancer 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) [27].

Patient management

Preoperatively, a diagnostic workup was performed for a multidisciplinary decision.

Before surgery, every patient was staged by anamnesis, physical examination, and cross-sectional imaging with computed tomography (CT) of the abdomen and chest, as well as magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) of the liver at or before initial referral, ideally prior to biliary drainage. This imaging allowed evaluation of distant metastases, the biliary extent of the tumor, and involvement of the portal vein and hepatic artery.

In recent years, preoperative biliary drainage of the presumed remnant liver was carried out in some cases percutaneously, rather than endoscopically, to minimize bacterial contamination of the biliary tract. However, many of the included patients had undergone endoscopic drainage before referral. A brush was typically used at the time of preoperative biliary drainage, but pathologic confirmation of malignancy was not required to proceed with surgical resection. Diagnostic laparoscopy to rule out distant metastatic disease was frequently performed, but not in all patients, given the decreasing yield as preoperative imaging improved over time.

Patients considered to have an insufficient size and function of the future liver remnant underwent a portal vein embolization (PVE). Neoadjuvant chemotherapy was administered in fewer than 10% of the study patients.

With some exceptions, patients with involvement of the main portal vein, the portal vein bilaterally, the common hepatic artery or the hepatic artery bilaterally were considered unresectable. Patients with involvement of the second-order bile ducts were considered resectable if clear margins were anticipated

at the segmental bile ducts. The presence of extensive bilobular metastases, such as peritoneal dissemination, was also considered to indicate unresectable disease.

The operative technique consisted of extrahepatic bile duct resection, with complete dissection of the hilar structures, as well as the fatty and lymph node tissue surrounding the common hepatic artery, the main portal vein, and the bile duct. Lymph nodes of the hepatoduodenal ligament, the proper hepatic artery, and the posterior surface of the head of the pancreas were dissected routinely and retrieved. Intraaortocaval lymph nodes were retrieved when they appeared macroscopically abnormal.

The type of hepatectomy was determined by the relative location and extent of the tumor, according to the bismuth classification [19, 28]. Resection/reconstruction of the portal vein or hepatic artery was undertaken when macroscopic vascular invasion was encountered during surgery.

Prior to December 2007, caudate lobectomy (TCL) was performed at the discretion of the surgeon. If, during the operation, the surgeon felt the tumor had infiltrated the caudate bile duct, TCL was performed to obtain a radical resection. From January 2008 onward, TCL was customarily performed with prophylactic portal vein resection and extended hepatectomy as a part of no-touch technique [3].

Data Collection

Standard patient demographic and clinicopathological characteristics, including age, sex, American Society of Anesthesiologists (ASA) classification, and presence of cirrhosis, were collected and analyzed. Serum levels of carcinoembryonic antigen (CEA), Cancer Antigen (CA) 19-9, and preoperative bilirubin levels were also analyzed.

We also collected data regarding the treatment characteristics, including administration of neoadjuvant chemotherapy, type of surgery, preoperative drainage/endoscopic stenting, portal venous embolization (PVE), and administration of adjuvant treatments.

Resection margin status was classified as microscopically negative (R0) or microscopically positive (R1). Macroscopically positive tumors (R2 tumors) were not considered for analysis of the TNM classification.

Tumor-specific characteristics, including tumor size and number of tumors, liver capsule involvement, histological grade, morphological type, the number and site of lymph nodes, and the number of collected metastatic lymph nodes, were evaluated. The presence of lymphovascular/perineural/biliary invasion and direct invasion of the portal vein, hepatic artery, and contiguous organs were also recorded.

Staging

Table 1 presents differences in the AJCC staging classifications for the 6th, 7th, and 8th editions. With the help of pathological, surgical, and radiological reports, data on tumor stage were collected and each patient was classified separately according to the 6th, 7th, and 8th edition AJCC staging systems.

Statistical Analysis

Continuous variables were summarized as mean/median values with interquartile range (IQR)/ standard deviation depending on the normality of the distribution. Categorical variables were expressed as whole numbers and percentages.

The outcome for survival analyses was overall survival (OS), defined as the time interval between the surgery and the date of death or last follow up for living patients.

Survival rates were measured using the Kaplan–Meier methodology, and a log-rank test was used to compare survival curves.

Cox proportional hazards models were used to evaluate associations between tumor stage and OS. In the survival analysis, clinicopathological and demographic variables resulting in a statistically significant value ($P < 0.05$) in the univariate analysis were entered into the multivariate analysis to assess their independency.

The coefficients from the Cox models were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs).

The area under the receiver operating characteristic curve (AUC) was calculated to test the discriminative power of each TNM edition for whether a patient would survive or die. Calibration was assessed using the Hosmer–Lemeshow Chi-square test to determine the goodness of fit, and patients with ongoing follow-up were censored at the last time point of examination.

Results

Baseline Characteristics

A total of 189 consecutive patients underwent surgery between 2002 and 2019. In 95 patients, liver resection was performed with curative intention, whereas 94 (49%) patients underwent an explorative laparotomy due to peritoneal carcinosis, reduced liver function, or major tumor extension.

The baseline characteristics of our patients are summarized in **Table 2**. The median age of the study population was 64.9 ± 10.2 years, and 54.7% (n = 52) of the patients were male. The mean preoperative total bilirubin levels before operation were 44.2 ± 11.1 $\mu\text{mol/l}$. Preoperative biliary drainage was performed in 73 patients (77%), with endoscopic biliary drainage as the most common procedure (n = 64; 67%). Preoperative portal vein embolization was performed in 21 patients (n = 22.1%).

Major hepatectomy was performed in 91 patients (96%), with left hepatectomy in 11 (12%), right hepatectomy in 10 (11%), and a left and right trisectionectomy in 16 (17%) and 54 (57%), respectively. Portal vein resection was performed in 64 patients (67.3%), whereas a caudate lobe resection was performed in 67 patients (70.5%).

The most common types of Bismuth-Corlette classification were Type IV (n = 49; 51.6%), but 6 patients (6.3%) had type I, 8 patients (8.4%) had type II, and 23 patients (24.2%) had type III. In total, 9 patients (9.5%) received neoadjuvant chemotherapy and 26 patients (27%) received adjuvant chemotherapy.

Pathologic Findings

All resected specimens were confirmed as adenocarcinomas. Negative resection margins (R0) were achieved in 68 patients (71.6%) (**Table 2**). Microvascular invasion was found in 24 (25.3%) patients and perineural invasion in 59 (62.1%) patients. Invasion of small lymphatic vessels was observed in 68 patients (71.6%).

Pathology revealed poorly differentiated tumors in most patients (n = 48, 50.5%) and either well differentiated (n = 5, 5.3%) or moderate tumors (n = 42, 44.2%) in the remainder. Almost one out of three patients had lymph node metastases (n = 27, 28.4%) and approximately one in ten patients had metastatic disease at diagnosis (n = 8, 8.8%).

The median number of lymph nodes harvested was 4 (IQR 3-8), and the median number of metastatic lymph nodes was 1 (IQR 0-2).

Stage transitions

The 6th edition of the AJCC staging categorized 5 (5.3%) patients as TNM stage Ia, 18 (18.9%) as stage Ib, 38 (40.4%) as stage IIa, 20 (21.1%) as stage IIb, 6 (6.3%) as stage III, and 8 (8.4%) patients as stage IV.

The 7th edition of the AJCC staging categorized 5 (5.3%) patients as TNM stage I, 52 (54.7%) as stage II, 4 (4.2%) as stage IIIa, 18 (18.9%) as stage IIIb, 5 (5.3%) as stage IVa, and 11 (11.5%) patients as stage IVb.

The 8th edition of the AJCC staging categorized 5 (5.3%) patients as stage I, 52 (54.7%) patients as stage II, 4 (4.2%) as stage IIIa, 3 (3.1%) as stage IIIb, 18 (18.9%) as stage IIIc, 5 (5.3%) as stage IVA, and 8 (8.4%) patients as stage IVB.

Table 3 shows a cross-tabulation of stage distributions and transitions for the AJCC stages for the 6th, 7th and 8th editions. Comparing the 6th edition with the 7th edition, stage migration was observed in a total of 45 (47.4%) patients, based on changes in major group definitions (**Table 3**). Comparing the 7th with the 8th edition, 25 patients (26.3%) were reclassified when considering substages (e.g., stage IIIa and IIIb) and 23 patients (25%) when considering only the major stages (i.e., stage I, II, III, or IV).

Staging according to the 8th edition upstaged 18 patients (18.9%) and downstaged 6 patients (6.3%) when compared with the 7th edition. A total of 18 patients (18.9%) with N1 disease (stage IIIb) in the 7th edition were upstaged to IIIc (N = 15 patients; 1–3 positive lymph nodes positive) or IVa (n = 3 patients; >4 or more positive lymph nodes) in the 8th edition. Most patients with T4 disease (n = 5 patients; stage IVa) in the 7th edition were downstaged to IIIb (n = 3 patients) or IIIc (n = 1 patient) in the 8th edition.

Univariate and multivariate analysis of factors associated with OS after curative resection

The median follow-up time of patients after liver resection was 4.3 ± 2.9 years.

The overall median survival time of the entire patient cohort was 21 months (95% CI 8.1–33.9) and the survival rates for 1, 3, and 5 years were 60.4%, 46.1%, and 36.2%, respectively. Tumors recurred in 34 (37.4%) patients after a median disease-free survival time of 35 (95% CI: 25.9–54.4) months.

We tested several clinical and pathological factors on OS. As shown in **Table 4**, OS was significantly longer in female patients ($p = 0.02$), patients with no extrahepatic distant metastases ($p < 0.001$), those with negative resection margins ($p = 0.003$), those aged < 65 years ($p = 0.03$), those with good/moderate tumor differentiation ($p = 0.01$), and patients with no microvascular invasion ($p < 0.01$).

Lymph node status was strongly associated with OS. Patients who were lymph node negative had a 5-year overall survival of 33.3% compared with 24.3% and 0% for patients with 1–3 and >3 metastatic lymph nodes ($p < 0.01$).

Portal vein resection was not associated with significantly better overall survival ($p > 0.05$), but patients who underwent caudate resection had a 5-year OS of 28.7% compared with 17.1% for those who did not undergo caudate lobe resection ($p = 0.004$).

The multivariate analysis (**Table 4**) revealed that gender (male versus female; HR = 2.6, 95% CI: 1.4–4.9; $p < 0.01$), age (> 65 years versus <65 years; HR = 1.9, 95% CI: 1.2–3.2; $p = 0.04$), margin status (R1 versus R0; HR = 2.1, 95% CI: 1.2–3.5; $p = 0.01$), distant metastases (M1 versus M0; HR = 4.2, 95% CI: 1.1–10.8; $p = 0.002$), metastatic lymph nodes (1-3 MLN versus 0MLN, HR = 1.1, 95% CI: 0.5–2.1; $p = 0.04$; > 3MLN versus 0 MLN; HR = 3.5, 95% CI: 1.4–9.1; $p < 0.01$), tumor differentiation (G3 versus G1; HR = 7.9, 95% CI: 1.1–58.1; $p = 0.04$) and caudate lobe resection (no versus yes; HR 2.2, 95% CI: 1.2–4.1; $p < 0.01$) remained associated as independent predictors of OS.

Survival Across Stages

Overall, an unbalanced distribution was observed that favored stage IIa (40%) in the 6th edition and stage II (54.7%) in 7th and 8th editions. **Table 6** present stage-specific median OS values for 1-, 3- and 5-year survival in patients staged according to the 6th, 7th and 8th editions of the AJCC staging system.

The median OS for patients staged according to the 6th, 7th and 8th edition per TNM classification were as follows: stage I (6th, 7th, and 8th edition: 58 months [95% CI: 48.8–67.2] versus 62 months [95% CI: 34.4–89.6] versus 62 months [95% CI: 34.4–89.6]), stage II (6th, 7th and 8th edition: 37 months [95% CI: 21.4–52.6] versus 43 months [95% CI: 19.5–66.5] versus 43 months [95% CI: 19.5–66.5]), stage III (6th, 7th, and 8th edition: 28 month [95% CI: 8.8–47.2] versus 37 [95% CI: 1.6–72.4] versus 38 [95% CI: 24.6–51.4]) and stage IV (6th, 7th and 8th edition: 12 months [95% CI: 0–24.5] versus 22 [95% CI: 7.6–36.4] versus 16 [95% CI: 10.1–21.9]), respectively (p -values between stages in the 6th edition = 0.039 vs. in the 7th = 0.010 versus in the 8th = 0.002).

Figures 1 and 2 show the Kaplan-Meier curves for OS for the main stages and sub-stages of the 6th, 7th, and 8th TNM editions. According to the 6th AJCC edition, we found that patients in stage IA and IB had 5-year OS rates of 80% and 37.5%, respectively, whereas patients in stage IIA and IIB had similar 5-year OS rates of 32.6% and 25%, respectively. Notably, patients in stage III had a 5-year OS rate of 16.7%. None of the patients in stage IV survived 5 years after operation.

Using the AJCC 7th edition, we found that patients in stage I, II, and IVa had a 5-year OS rates of 80%, 33.2%, and 20.0%, respectively. Notably, patients in stage IIIa and IIIb had 5-years OS rates of 50% and 14.3%, respectively (**Table 6**). No patients in stage IVb survived 5 years after operation.

Use of the AJCC 8th edition revealed 5-year OS rates for patients in stages I and II of 80% and 33.2%, respectively, which were similar to the rates for the 7th AJCC edition. Patients in stages IIIa, IIIb, and IIIc had 5-year OS rates of 50%, 33.3%, and 28%, respectively. No patients in stage IVa or IVb survived 5 years after operation

Use of the 6th edition resulted in no differences in risk of death for patients in stages Ib, IIIa, IIb, and III (both $P > .05$) when compared with patients in stage Ia. By contrast, when compared with patients in

stage Ia, patients in stage IV had the greatest risk of death (stage IV versus stage Ia, HR 8.41, 95% CI 1.74–40.57, $p < 0.01$).

Use of the AJCC 7th edition revealed no differences in risk of death between patients in stage I and those in stages II, IIIa, IIIb and IVa ($p > 0.05$; **Table 6**). However, when compared with patients in stage I, those in stages IVb had the greatest risk of death (stage IVb versus stage I, HR 7.05, 95% CI 1.54–32.36, $p = 0.01$).

Use of the AJCC 8th edition revealed no differences in risk of death for patients in stages II, IIIa, IIIb, and IIIc ($p > 0.05$) when compared with patients in stage I. However, when compared with patients in stage I, the risk of death was greater for patients in stage IVa and IVb (stage IVa versus stage I, HR 6.36, 95% CI 1.22–33.24, $P = 0.028$; stage IVb versus stage I, HR 8.66, 95% CI 1.79–41.83, $p < 0.01$).

Prognostic accuracy

Table 7 presents the ROC analysis and Hoshmer- Lemeshow test (HLT) for discrimination and calibration of all the evaluated staging systems. The prognostic accuracy was remarkably similar across the three analyzed AJCC staging systems. The prognostic accuracy of the main stages was higher for the 8th edition than for the 7th edition (AUC: 8th edition versus 7th edition: 0.66 versus 0.61) but the difference did not reach statistical significance. Expanding the 7th edition to include substages slightly diminished its prognostic accuracy (AUC: from 0.61 to 0.58), whereas, expansion of the 8th edition with substages increased the prognostic accuracy (AUC main stages versus substages: 0.66 to 0.69) and a statistical trend was observed ($p = 0.09$). With regard to calibration of the evaluated stagings systems, the HLT shows acceptable calibration and fitness of the analyzed 7th and 8th staging systems (**Table 8**).

Discussion

PHC is a challenging disease to manage, and only selected patients are candidates for curative-intent surgery [29, 30]. Therefore, accurate staging with a standardized staging system is essential not only for planning the frequency of post-operative surveillance, making therapeutic decisions, and/or selecting patients for adjuvant treatment, but also for informing both patients and physicians about long-term clinical outcomes and for allowing for a standardized exchange of information about the extent of the disease [1, 2]. While the optimal method for risk stratification of patients with PHC remains unclear, the TNM system provided by the AJCC and the International Union Against Cancer (UICC) is the most commonly used method for stratifying outcomes among cancer patients [15, 20, 24, 31].

In this context, the newly released 8th edition of the AJCC staging system has introduced four major modifications (Table 1) and has especially included the recommendations by Ebata et al. [15], who

modified the T-categories of the previous 7th TNM edition in a large survival analysis of 1399 patients undergoing liver resection for PHC at 8 Japanese liver centers [15]. These authors reported that survival was slightly better for patients with advanced disease (T4 tumors, stage IVa) than for patients with regional lymph-node positive disease (stage IIIb), a finding confirmed in our study. However, as already recognized, and as previous data have shown, marked differences exist in peri-and operative strategies and outcomes between Eastern and Western centers; therefore, external validation of the prognostic accuracy of staging systems in Western patients is essential [32, 33].

A recently published study from two Western hepatobiliary centers evaluated the prognostic accuracy of the 8th TNM classification of the AJCC staging system in a cohort of 214 patients undergoing liver resection for PHC. In that study population, about 40% of the patients changed their stages from the 7th to the 8th AJCC edition. The authors determined that the new 8th TNM edition was only slightly better than the previous 7th edition [25].

Our analysis confirmed findings that could validate the new 8th TNM classification. For example, we observed a reclassification in a total of 25 patients (26.3%) when considering substages (e.g., stage IIIa and IIIb) and in 23 patients (25%) when considering only the major stages (i.e., stage I, II, III, or IV). However, these modifications and consecutive reclassifications failed to provide any significant improvement in prognostic accuracy. Consequently, comparison of the prognostic accuracy of 7th and 8th editions of the AJCC staging system using our results paralleled the findings of the study by Ruzzente et al., wherein the 8th edition had only a slightly better discriminatory ability and power, with an AUC of 0.69 compared to 0.58 for the 7th edition. Nevertheless, the performance and ability to stratify patient prognosis of the newly released 8th edition was still unsatisfactory (AUC < 0.7).

The extent of intrahepatic biliary invasion is a critical factor that determines surgical indications and the type of hepatectomy that should be performed in patients with PHC. To ensure a curative liver resection (R0 margins) in patients with Bismuth type II and III PHC, the resection should include a hemihepatectomy combined with en bloc resection of the first segment (caudate lobe), as well as an extrahepatic bile duct resection to ensure negative resection margins [25, 28]. However, in patients with Bismuth type IV disease (characterized by having bilateral involvement of the second-order intrahepatic bile ducts), the standard operative approach remains unclear, and many centers still consider Bismuth type IV tumors unresectable [2, 34–37]. Conversely, as surgical techniques and perioperative management have improved, some surgeons have suggested that a type IV tumor does not always imply unresectability [6, 15, 34, 38]. In this context, these surgeons have proposed a more aggressive operative approach for patients with a Bismuth type IV PH-CCA, including an extended hepatectomy combined with caudate lobectomy, extended lymph node dissection, and vascular resection with portal vein and/or hepatic artery reconstruction, to achieve negative resection margins [3, 8, 15, 34, 39, 40]. The results of previous studies indicate that this aggressive strategy could further improve long-term outcomes and prolong patient survival; therefore, this procedure could be established as a state-of-the-art operation for patients with locally advanced PHC, and especially for Bismuth-Corlette types III-IV hilar cholangiocarcinomas [3, 34, 41, 42].

The Japanese group associated with Ebata et al. [35] was the first to report that patients with P0M0N0 disease who underwent an R0 liver resection showed no significant differences in survival when compared with patients with Bismuth type I/II, III and IV tumors, as the 5-year OSs were 63.1%, 65.6%, and 59.2%, respectively [35]. Similar findings were obtained in a recently published study by Ruzzenenete et al. [25], as well as in the present study, as the 5-year survival rate was 50.1% in our 30 patients with pM0N0 who underwent R0 resection for a Bismuth Type IV PHC. Although these patients represent a highly selected subset of patients undergoing aggressive surgery, these findings nevertheless suggest that an aggressive operative approach with or without vascular resection could offer a curative option even for patients with Bismuth type IV PH-CCA [25, 35]. Furthermore, the T staging should separate the longitudinal extension of the disease from its vascular invasion.

Collectively, these data suggest that while PHC generally has a poor prognosis, large differences in survival can be observed among patients based on a subset of clinical and pathological factors. In our cohort of patients, several factors, including gender, age, surgical radicality, extent of liver resection (\pm caudate lobe resection), tumor differentiation and distant metastases (e.g., lymph node status), were independent prognostic factors for long-term survival, in agreement with previous observations [12, 41, 42].

In this context, the prognostic impact of the lymph node (LN) status is considered as one of the most important factors for long-term survival following liver resection for PHC [5, 18, 43–45]. A certain benchmark number of retrieved lymph nodes is necessary to secure a representative and adequate staging. However, the extent of the lymphadenectomy during the resection of PHC, such as the minimum number of lymph nodes to be retrieved, remains under controversial debate, and marked differences in the operative approach between Western and Eastern centers have been reported [43, 44, 46, 47]. Recent SEER register analyses showed that the retrieved LN counts are independent prognostic survival factors for node-negative and node-positive PHC patients [48, 49]. Therefore, an insufficient LN count may result in understaging of the extent of disease, and a subsequent poor recovery of LNs may increase the rate of incorrectly classified N0 patients and overestimate the survival expectancy.

The required extent of lymphadenectomies for patients with PHC remains controversial, especially with respect to the minimum number of LNs should be examined. The latest TNM classification recommended a lymph node count greater than or equal to 15 LNs as a requirement for adequate LN staging. Since then, a wave of criticisms emerged among experts, and some retrospective and prospective studies examined several different LN staging systems in an attempt to obtain a better prediction of the survival of patients with gastrointestinal tumors [43, 44, 47, 50, 51]. The authors of a previously published systemic review of 20 studies suggested that a LN count greater than or equal to 7 is adequate for prognostic staging, while a LN count greater than or equal to 15 does not improve detection of patients with positive LNs [43]. By contrast, a recently published international, multi-center study that included 437 patients with PHC who underwent liver resection reported a required median number of retrieved LNs of 3 (IQR 1–7), and the incidence of LN metastasis was 36%, similar to other published values from Western centers [46].

We found similar results in our study, where lymphadenectomy was performed in almost all patients (n = 97 patients, 94%) undergoing a curative-intent hepatectomy. In up to 48% of patients, more than 5 LNs were retrieved. The number of lymph nodes harvested did not have an impact on patient survival, but multivariate survival analysis confirmed that the number of metastatic lymph nodes (MLNs) was strongly associated with prognosis (1–3 MLN versus 0 MLN, HR = 1.7, 95% CI: 1.1–2.8; p = 0.04; > 3MLN versus 0 MLN; HR = 3.2, 95% CI: 1.2–8.3; p = 0.01). Notably, no patients with more than 3 metastatic lymph nodes (N2, according to the AJCC 8th edition N staging) survived 5 years after operation, compared with a 5-year OS of 24.1% for patients with 1–3 metastatic lymph nodes (N1, according to the 8th edition; data not shown).

The results of the current study should be interpreted while considering several limitations. One limitation is that, although our study is surely one of the larger Western series of patients with resected PHC to be reported in the literature, our sample size is nevertheless still insufficient to allow drawing of definitive conclusions about small modifications in this staging system. The retrospective nature of our study and the long study time (over 17 years) presents a risk of selection and confounding biases regarding the diagnosis and treatment options of the patients. Therefore, larger cohorts of patients are needed to test the TNM classification, although this is challenging given the rare incidence of PHC.

A second limitation is our inclusion only of patients who underwent a liver resection. The TNM classification offers a precise tumor-staging algorithm aside from the treatment set and is widely used in cancer staging. However, only surgery and pathological examination are able to provide an accurate confirmation of the TNM stages. The advantage of our study is that pathological confirmation of the TNM stage was available for all patients. The disadvantage is that the observed results cannot be extrapolated to patients who did not undergo resection because of extrahepatic metastasis or locally advanced tumor disease. However, we included only resected patients because the assessment of both T-stage and N-stage is inaccurate without microscopic evaluation of a resected specimen. In this context, the accuracy of estimation of the nodal status based on an evaluation of the size criteria on cross-sectional imaging is very limited. For example, Ruys et al. [54] showed sensitivity and specificity estimates of 61% and 88% for lymph node involvement based on CT staging of patients with PHC. Furthermore, only 37% of the lymph nodes > 30 mm in diameter were confirmed as positive after analyzing slides of 147 patients undergoing liver resection for PHC. These findings indicate a very low diagnostic accuracy of cross-sectional imaging for staging of perihilar cholangiocarcinoma, and especially for nodal involvement [52].

A third limitation is that our study included patients undergoing nonradical (R1) and suboptimal tumor resections (distal bile duct resections, no caudate lobe resections) and/or patients with involvement of main portal vein or common hepatic artery. The improvements in standard operative and perioperative approaches, in combination with new neoadjuvant or adjuvant chemotherapeutic agents, necessitates inclusion of sensitivity analyses of those patients who underwent R0 extended hepatectomy with caudate lobe resections to compare them with the whole cohort of patients.

Conclusions

An optimal staging system should provide information about the prognosis, guide the therapy, and allow comparison with different staging systems. However, none of the currently existing PHC staging systems fulfills these criteria. Historically, the AJCC staging is based mainly on the anatomic extent of the tumor. Although non-anatomic factors have been introduced into the staging of some cancers (e.g., mitotic rate in melanoma), with reference to PHC, the 6th, 7th, and 8th editions of the AJCC staging system have all adhered to the anatomic extent of the tumor, as in all other hepatobiliary and pancreatic cancers [11, 23]. Despite recently encouraging results reported by Ebata et al. at a large Eastern hepatobiliary center, who attempted to improve the staging and prognosis of PHC patients, the results of our retrospective study of 95 resected PHC patients indicates that the newly released 8th edition of the AJCC staging system does not provide a better ability to stratify the prognosis and predict clinical outcomes of patients with PHC when compared with the previous 6th and 7th editions.

New advances in genomic and transcriptomic profiling have contributed to a better understanding of the genetic landscape of molecular alterations in PHC and offer hope for the development of novel targeted therapies [53–55]. Future randomized clinical controlled trials are needed to focus on targeting of deregulated signaling pathways, with the goal of personalizing treatment for patients with PHC and for prospective assignment of patients based on their transcriptomic and genetic profiles. In this context, this new information, in combination with other clinico-pathologic features (i.e., extended negative margins, lymph node status, use of neoadjuvant and adjuvant chemotherapy), might improve our ability to predict the prognosis of patients with PHC. Nevertheless, for outcome comparisons, future refinements are needed to improve the staging of patients with PHC. Future research should therefore investigate whether a combination of AJCC staging and non-anatomic independent prognostic factors can further improve individual patient prognosis.

Abbreviations

AJCC	American Joint Committee on Cancer (AJCC)
PHC	perihilar cholangiocarcinoma
TNM	tumor node metastasis
AUC	area under the receiver operating characteristic curve
HPB	hepato-pancreato-biliary
CT	computed tomography

MRI	magnetic resonance imaging
MRCP	magnetic resonance cholangiopancreatography
PVE	portal vein embolization
TCL	caudate lobectomy
ASA	American Society of Anesthesiologists
CEA	carcinoembryonic antigen
CA	Cancer Antigen
IQR	interquartal range
OS	overall survival
HR	hazard ratio
CI	confidence interval
UICC	International Union Against Cancer

Declarations

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Availability of data and materials

Our database contains highly sensible data which may provide insight in clinical and personnel information about our patients and lead to identification of these patients. Therefore, according to organizational restrictions and regulations these data cannot be made publically available. However, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

HMH, FM and RS were responsible for the study conception and design; HMH, FM, SR, RS and DS were responsible for data acquisition; HMH, FM, SR and DS analyzed and interpreted the data; HMH, FM and RS drafted the manuscript; and HMH, FM, SR, RS and DS critically revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the local ethical commission board from the University of Leipzig (AZ- EK: 243-14-14072014).

Due to the retrospective design of the study and accordingly national guidelines, the local ethic committee confirmed, that informed consent was not necessary from participants.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests

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Tables

Table 1a: American Joint Committee on Cancer (AJCC) staging system by tumor-node-metastasis (TNM) stage of the 6th, 7th and 8th edition

	6th Edition	7th Edition	8th Edition
T0	No evidence of primary tumor	No evidence of primary tumor	No evidence of primary tumor
Tis	Carcinoma in situ	Carcinoma in situ	Carcinoma in situ
T1	Tumor confined to the bile duct	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct		
T2a		Tumor invades beyond the wall of the bile duct to surrounding adipose tissue	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b		Tumor invades adjacent hepatic parenchyma	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades the liver, gall bladder, pancreas, and or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)	Tumor invades unilateral branches of the portal vein or hepatic artery	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, e.g., colon, stomach, duodenum, abdominal wall	Tumor invades the main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement	Tumor invades the main portal vein or its branches bilaterally; or the common hepatic artery; or unilateral second order biliary radicals with contralateral portal vein or hepatic artery involvement
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis are the cystic duct, pericholedochal, hilar, peripancreatic (head only), periduodenal, periportal, celiac, and superior mesenteric nodes	Regional lymph node metastasis including nodes along the cystic duct, common bile duct, common hepatic artery, and portal vein	Metastasis to 1-3 regional lymph nodes
N2			Metastasis to 4 or more regional nodes
MX	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed	
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis

Table 1b: American Joint Committee on Cancer (AJCC) staging system

	AJCC, 6th Edition		AJCC, 7th Edition		AJCC, 8th Edition
Stage 0	Tis N0 M0	Stage 0	Tis N0 M0	Stage 0	Tis N0 M0
		Stage I	T1 N0 M0	Stage I	T1 N0 M0
Stage IA	T1 N0 M0				
Stage IB	T2 N0 N0				
		Stage II	T2a,b N0 M0	Stage II	T2a,b N0 M0
Stage IIA	T3 N0 M0				
Stage IIB	T1-3 N1 M0				
Stage III	T4 AnyN M0				
		Stage IIIA	T3 N0 M0	Stage IIIA	T3 N0 M0
		Stage IIIB	T1-3 N1 M0	Stage IIIB	T4 N0 M0
				Stage IIIC	T1-4 N1 M0
Stage IV	T1-4 AnyN M1				
		Stage IVA	T4 AnyN M0	Stage IVA	T1-4 N2 M0
		Stage IVB	T1-4 AnyN M1	Stage IVB	T1-4 AnyN M1

Table 2: Demographic and clinicopathologic characteristics of 95 patients with resected perihilar cholangiocarcinoma

Variables	Patients (%)
Age (years), median (SD)	64.9 +/- 10.2
Bismuth classification	
I	6 (6.3)
II	8 (8.4)
IIIa	11 (11.6)
IIIb	12 (12.6)
IV	49 (51.6)
N/A	9 (9.5)
Gender	
Male	52 (54.7)
Female	43 (45.3)
Type of hepatectomy	
Right hepatectomy	10 (10.5)
Left Hepatectomy	11 (11.6)
Extended right hepatectomy	54 (56.8)
Extended left hepatectomy	16 (16.8)
Other	4 (4.4)
Margin status	
R0	68 (71.6)
R1	27 (28.4)
Tumour differentiation	
Well (G1)	5 (5.3)
Moderately (G2)	42 (44.2)
Poor (G3)	48 (50.5)
Lymph node status	
Negative	60 (63.2)
Metastasic	27 (28.4)
N/A	8 (8.4)
Distant metastasis	
No	86 (90.5)
Yes	9 (9.5)
Vascular invasion	
No	63 (66.3)
Yes	24 (25.3)
N/A	8 (8.4)
Perineural invasion	
No	17 (17.9)
Yes	59 (62.1)
N/A	19 (20.0)
Invasion of small lymphatic vessels	
No	20 (21.0)
Yes	68 (71.6)
N/A	7 (7.4)
Adjuvant chemotherapy	
No	69 (72.7)
Yes	26 (27.3)

Portal vein invasion	
No	87 (91.6)
Yes	8 (8.4)
Portal vein embolization	
No	74 (77.9)
Yes	21 (22.1)
Preoperative bilirubin (mmol/l), mean (SD)	44.2 (11.1)
Preoperative drainage	
No	17 (17.9)
PTCD	9 (9.5)
ERCP	61 (64.2)
both	3 (3.2)
N/A	5 (5.3)
Harvested lymph node, median (IQR)	4 (3-8)
Metastatic lymph node, median (IQR)	1 (0-2)
Portal vein resection	
Yes	64 (67.3)
No	21 (32.7)
Caudate resection	
Yes	67 (70.5)
No	28 (29.5)

Table 3: Univariate Kaplan- Meier survival analysis of the study population (n = 95 patients)

Variables	Patients (%)	Median Survival (months, 95%CI)	Log-Rank test (p-value)
Age			
≤ 65	47 (49.5%)	43 (1.9-40.1)	0.03
> 65	48 (50.5%)	21 (17.4-68.5)	
Bismuth-Classification			
I/II	14 (14.7)	56 (20.9-91.1)	0.772
III/IV	72 (75.8)	33 (15.2-50.7)	
N/A	9 (9.5)		
Gender			
Male	52 (54.7%)	19 (11.3-26.8)	0.02
Female	43 (45.3%)	56 (37.1-74.9)	
Residual tumour			
R0	68 (71.6)	45 (24.7-65.2)	0.003
R1	27 (28.4)	13 (5.1-23.1)	
Tumour differentiation			
Well/moderately (G1/G2)	47 (49.5)	47 (27.3-66.8)	0.01
Poor (G3)	48 (50.5)	15 (3.8 -26.1)	
Lymph node status			
Negative	60 (63.2)	50 (28.5-71.5)	0.004
Metastatic	27 (28.4)	11 (4.9-17.1)	
N/A	8 (8.4)		
Harvested Lymph node			
<5	50 (51.6)	43 (25.7-60.6)	0.656
>5	45 (48.4)	29 (8.4-41.3)	
Distant metastasis			
No	86 (90.5)	41 (26.1-59.8)	<0.001
Yes	9 (9.5)	8 (7.1-8.9)	
Vascular invasion			
No	63 (66.3)	37 (21.5-52.5)	0.006
Yes	24 (25.3)	12 (5.3-18.7)	
N/A	8 (8.4)		
Perineural invasion			
No	17 (17.9)	57 (8.3-105.6)	0.678
Yes	59 (62.1)	21 (7.4-34.5)	
N/A	19 (20.0)		
Invasion of small lymphatic vessels			
No	20 (21.1)	56 (8.7-103.3)	0.139
Yes	68 (71.6)	20 (6.6-33.3)	
N/A	7 (7.4)		
Adjuvant chemotherapy			
No	77 (81.1)	27 (1.4-52.8)	0.780
Yes	18 (18.9)	38 (28.4-47.6)	
Portal vein invasion			
No	87 (91.6)	27 (21.9-52.1)	0.899
Yes	8 (8.4)	20 (0.1-44.9)	
Portal vein embolization			
No	74 (77.9)	38 (22.1-53.9)	0.849

	Yes	21 (22.1)	21 (1.4-43.9)	
Preoperative drainage				
	No	17 (17.9)	19 (0.1-46.7)	0.194
	Yes	73 (76.8)	37 (16.8-57.2)	
	N/A	5 (5.3)		
Caudate resection				
	Yes	67 (70.5%)	47 (26.8-67.2)	0.004
	No	28 (29.5%)	11 (4.5-17.5)	
Portal Vein Resection				
	Yes	64 (67.3%)	45 (6.5-23.4)	0.069
	No	21 (32.7%)	15 (18.9-71.1)	

Table 4: Multivariate survival Analysis- Cox modell- overall Survival (n = 95 patients)

Variables	Hazard Ratio (95% CI)	p-value
Age (years)		
≤ 65		
> 65	1.9 (1.2-3.2)	0.040
Residual tumour		
R0		
R1	2.1 (1.2-3.5)	0.01
Tumour differentiation		
G1		-
G2	5.7 (0.8-42.3)	0.08
G3	7.9 (1.1-58.1)	0.04
Metastatic Lymph Node		
0		-
1-3	1.1 (0.5-2.1)	0.04
>3	3.5 (1.4-9.1)	0.009
Distant metastasis		
Yes	4.2 (1.7-10.8)	0.002
No		
Vascular invasion		
Yes	1.68 (0.9-3.1)	0.10
No		
Caudate Resection		
Yes	2.2 (1.2-4.1)	0.007
No		
Gender		
Male	2.63 (1.4-4.9)	0.003
Female		

Table 5: Cross-tabulation of the 6th, 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging system

		Stadium 7						
Stadium 6		I	II	IIIa	IIIb	IVa	IVb	Gesamt
	Ia	5						5
	Ib		18					18
	IIa		34	4				38
	IIb				18		2	20
	III					5	1	6
	IV						8	8
		5	52	4	18	5	11	95

		Stadium 8							
Stadium 6		I	II	IIIa	IIIb	IIIc	IVa	IVb	Gesamt
	Ia	5							5
	Ib		18						18
	IIa		34	4					38
	IIb					16	4		20
	III				3	2	1		6
	IV							8	8
		5	52	4	3	18	5	8	95

		Stadium 8							
Stadium 7		I	II	Ia	IIIb	IIIc	IVa	IVb	Gesamt
	I	5							5
	II		52						52
	IIIa			4					4
	IIIb					15	3		18
	IVa				3	1	1		5
	IVb					2	1	8	11
		5	52	4	3	18	5	8	95

Table 6a: Subgroup Stage-specific patient survival according to the 6th, 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging system of our study population (n = 95 patients)

	Anzahl Patienten, % (n)	1-Year-survival, %	3-Year-survival, %	5-Year-survival, %	Median survival, months (95% CI)	Hazard-Ratio (95% CI)	Cox regression (p-value)	Log-rank (p-value)
Overall	100 (95)							
6th Edition								0.035
I	24.2 (23)							
a	5.3 (5)	100.0	100.0	80.0	62 (34.4-89.6)		0.040	
b	18.9 (18)	72.2	55.6	37.5	55 (8.0-102.0)	2.66 (0.60-11.72)	0.196	
II	61.1 (58)							
a	40.0 (38)	73.2	56.3	32.6	45 (25.6-64.4)	2.42 (0.57-10.26)	0.229	
b	21.2 (20)	67.6	37.5	25.0	21 (11.6-30.4)	3.67 (0.83-16.20)	0.086	
III	4.3 (6)	100.0	50.0	16.7	28 (8.8-47.2)	3.30 (0.64-17.08)	0.155	
IV	8.4 (8)	50.0	-	-	12 (0.0-24.5)	8.41 (1.74-40.57)	0.008	
7th Edition								0.012
I	5.3 (5)	100.0	100.0	80.0	62 (34.4-89.6)		0.037	
II	54.7 (52)	70.6	52.5	33.2	43 (19.5-66.5)	2.67 (0.64-11.09)	0.177	
III	23.2 (22)							
a	4.2 (4)	100.0	100.0	50.0	58 (51.8-87.5)	1.19 (0.17-8.47)	0.860	
b	18.9 (18)	69.9	42.9	14.3	21 (12.2-29.7)	3.42 (0.76-15.34)	0.108	
IV	16.8 (16)							
a	5.3 (5)	100.0	40.0	20.0	28 (15.1-40.9)	3.29 (0.60-18.07)	0.170	
b	11.6 (11)	54.5	9.1	-	17 (0.0-35.3)	7.05 (1.54-32.36)	0.012	
8th Edition								0.009
I	5.3 (5)	100.0	100.0	80.0	62 (34.4-89.6)		0.023	
II	54.7 (52)	70.6	52.5	33.2	43 (19.5-66.5)	2.68 (0.64-11.14)	0.175	
III	26.3 (25)							
a	4.2 (4)	100.0	100.0	50.0	58 (51.8-87.5)	1.19 (0.17-8.46)	0.861	
b	3.2 (3)	100.0	66.7	33.3	38 (0.0-76.4)	2.32 (0.33-16.52)	0.400	
c	18.9 (18)	69.9	42.2	28.0	28 (6.4-49.6)	3.30 (0.74-14.80)	0.119	
IV	13.7 (13)							
a	5.3 (5)	80.0	20.0	-	16 (13.9-18.1)	6.36 (1.22-33.24)	0.028	
b	8.4 (8)	50.0	-	-	12 (0.0-24.5)	8.66 (1.79-41.83)	0.007	

Table 6b: Main-group Stage-specific patient survival according to the 6th, 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging system of our study population (n = 95 patients)

Table 7: Discrimination power and calibration of the 6th, 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging system

	Anzahl Patienten	1-Year-survival, % (n)	3-Year-survival, % (n)	5-Year-survival, % (n)	Median survival, months (95% CI)	Hazard-Ratio (95% CI)	Cox regression (p-value)	Log-rank (p-value)
Overall	95	60.4	46.1	36.2	21 (8.1-33.9)			
6th Edition								0.039
I	24.2 (23)	78.3	65.2	46.0	58 (48.8-67.2)		0.027	
II	61.1 (58)	71.4	50.2	30.1	37 (21.4-52.6)	1.25 (0.70-2.25)	0.450	
III	4.3 (6)	100.0	50.0	16.7	28 (8.8-47.2)	1.49 (0.54-4.09)	0.438	
IV	8.4 (8)	50.0	-	-	12 (0.0-24.5)	3.76 (1.55-9.13)	0.003	
7th Edition								0.01
I	5.3 (5)	100.0	100.0	80.0	62 (34.4-89.6)		0.016	
II	54.7 (52)	70.6	52.5	33.2	43 (19.5-66.5)	2.65 (0.64-11.03)	0.180	
III	23.2 (22)	75.8	54.7	32.8	37 (1.6-72.4)	2.68 (0.61-11.83)	0.192	
IV	16.8 (16)	68.8	18.8	6.3	22 (7.6-36.4)	5.27 (1.20-23.36)	0.018	
8th Edition								0.002
I	5.3 (5)	100.0	100.0	80.0	62 (34.4-89.6)		0.005	
II	54.7 (52)	70.6	52.5	33.2	43 (19.5-66.5)	2.67 (0.64-11.09)	0.177	
III	26.3 (25)	78.9	55.9	32.6	38 (24.6-51.4)	2.58 (0.59-11.23)	0.207	
IV	13.7 (13)	61.5	7.7	-	16 (10.1-21.9)	7.47 (1.65-33.74)	0.009	

Edition	AUC (95% CI)	p-value	Calibration χ^2	p-value
AJCC 6th edition- main stages	0.54 (0.43-0.67)	0.42	5.1	0.05
AJCC 6th edition- substages	0.56 (0.42-0.69)	0.32	9.2	0.11
AJCC 7th edition- main stages	0.61 (0.51-0.73)	0.17	1.1	0.27
AJCC 7th edition- substages	0.58 (0.46-0.71)	0.19	2.8	0.21
AJCC 8th edition- main stages	0.66 (0.45-0.79)	0.14	2.1	0.31
AJCC 8th edition- substages	0.69 (0.52-0.84)	0.09	1.6	0.39

Figures

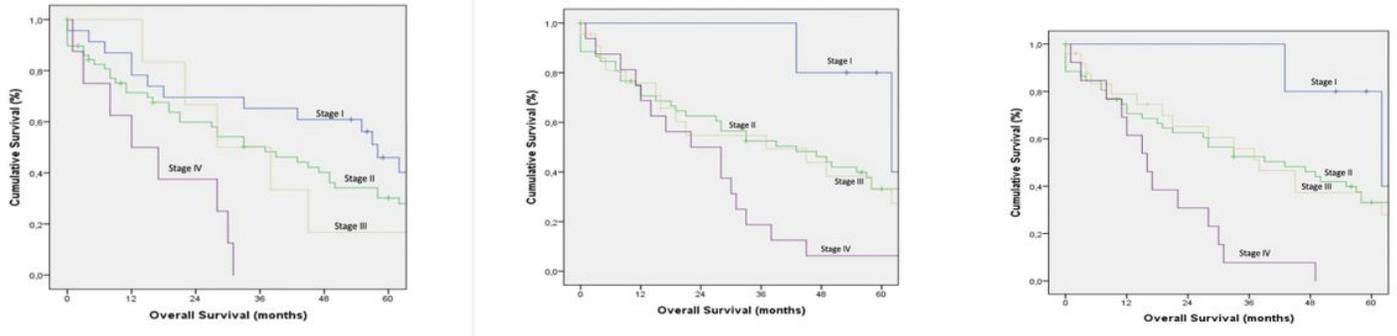


Figure 2

Figure 1a: Overall survival by main- stages according to the 6th edition of the American Joint Committee on Cancer staging system
 Figure 1b: Overall survival by main- stages according to the 7th edition of the American Joint Committee on Cancer staging system
 Figure 1c: Overall survival by main- stages according to the 8th edition of the American Joint Committee on Cancer staging system

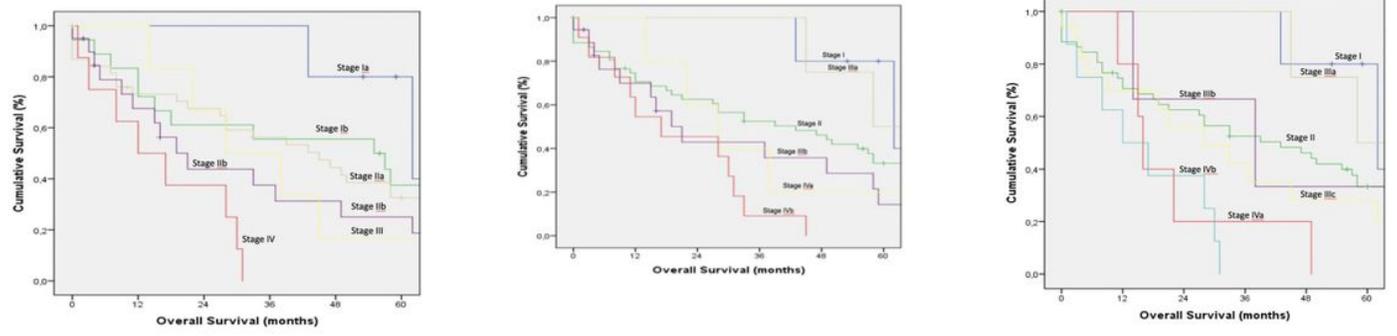


Figure 4

Figure 2a: Overall survival by sub- stages according to the 6th edition of the American Joint Committee on Cancer staging system
 Figure 2b: Overall survival by sub- stages according to the 7th edition of the American Joint Committee on Cancer staging system
 Figure 2c: Overall survival by sub-stages according to the 8th edition of the American Joint Committee on Cancer staging system