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# A Comparison of Prognostic Schemes for Perihilar Cholangiocarcinoma

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## Abstract

**Introduction—**Although widely used, the 7th edition American Joint Committee on Cancer (AJCC) staging system for perihilar cholangiocarcinoma (PHC) may be limited. Disease-specific nomograms have been proposed as a better means to predict long-term survival for individual patients. We sought to externally validate a recently proposed nomogram by Memorial Sloan Kettering Cancer Center (MSKCC) for PHC, as well as identify factors to improve the prediction of prognosis for patients with PHC.

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Analysis or interpretation of data: Buettner, van Vugt, Gani, Koerkamp, Margonis, Guglielmi, IJzermans, Pawlik

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All authors agree to the publication of this work and agree to being held accountable to the accuracy and integrity of the work.

**Compliance with Ethical Standards**

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Methods—**Four hundred seven patients who underwent surgery for PHC between 1988 and 2014 were identified using an international, multi-center database. Standard clinicopathologic and outcome data were collected. The predictive power of the AJCC staging system and nomogram were assessed.

**Results—**Median survival was 24.4 months; 3- and 5-year survival was 37.2 and 20.8 %, respectively. The AJCC 7th edition staging system (C-index 0.570) and the recently proposed PHC nomogram (C-index 0.587) both performed poorly. A revised nomogram based on age, lymphovascular invasion, perineural invasion, and lymph node metastases performed better (C-index 0.682). The calibration plot of the revised PHC nomogram demonstrated good calibration.

**Conclusion—**The 7th edition AJCC staging system and the MSKCC nomogram had a poor ability to predict long-term survival for individual patients with PHC. A revised nomogram provided more accurate prediction of survival, but will need to be externally validated.

### Keywords

Nomogram; perihilar cholangiocarcinoma; Risk factors; prognostic tools; Survival

## Introduction

Perihilar cholangiocarcinoma (PHC) is the most commonly diagnosed subtype of cholangiocarcinoma in the USA with an incidence of nearly 2 per 100,000.[1–3] PHC if often characterized by its diffuse, sclerotic nature and tends to invade local structures. As a consequence, many patients are diagnosed at an advanced stage of disease when curative resection is no longer feasible.[4, 5] For example, in one recent report, only 36 % of patients were amenable to surgery at the time of diagnosis due to metastatic/locally advanced disease.[6] For patients who are candidates for curative-intent resection, 5-year survival following surgery has been reported to range from 11 to 42 %.[7–9] Despite the large number of factors associated with prognosis, prediction of long-term survival can be difficult to determine.[10, 11] Several prognostic schemes have attempted to aggregate the most relevant clinicopathological factors to estimate long-term survival.[12–16] Commonly used prognostic tools include the American Joint Committee on Cancer (AJCC) Staging System, as well as the Bismuth-Corlette and Blumgart staging systems.[10, 11, 17–19] These staging schemes have been criticized, however, for being inaccurate, as well as lacking specificity.[20–24]

Nomogram prediction models have been proposed as a better means to predict long-term survival for individual patients with various malignancies.[20–24] Nomograms may provide more accurate prognostic information for individual patients, as well as better stratify patients for randomized, controlled trials and enable adjustment for confounding factors when comparing patient outcomes across centers.[20–24] More accurate prediction of individual patient outcomes may also improve identification of high-risk groups who may benefit from targeted adjuvant therapy.[20] A nomogram model for estimation of long-term prognosis following surgery for PHC has, however, not been generally available.[20] Recently, Groot Koerkamp et al. proposed a nomogram for patients with resected PHC based on data from the Memorial Sloan Kettering Cancer Center (MSKCC) and the Academic Medical Center in Amsterdam (AMC).[20] Utilizing lymph node involvement, resection margin status,

and tumor differentiation, the authors claimed that the proposed nomogram markedly improved the accuracy of predicting disease-specific survival (DSS).[20] When developing a prediction model, there is an inherent risk of overestimating its accuracy and generalizability, given the lack of validation in a wider patient population. While statistical methods such as bootstrapping can be employed, the generalizability of the proposed model can only be assessed through external validation[20–24] As such, the objective of the current study was to validate the PHC nomogram proposed by Groot Koerkamp et al. using a large, multi-center, external, cohort of patients who had undergone curative intent resection of PHC. In addition, we sought to assess the overall performance of the proposed nomogram compared with the AJCC staging system to predict overall survival, as well as identify other possible factors that might improve the ability to predict long-term outcomes.

## Methods

### Data Sources and Patient Population

Patients undergoing curative intent surgery for PHC between January 1, 1988 and December 31, 2014 at one of twelve academic institutions in the USA and Western Europe were identified (Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University, Stanford, California; University of Wisconsin, Milwaukee, Wisconsin; Ohio State University, Columbus, Ohio; Washington University, St. Louis, Missouri; Vanderbilt University, Nashville, Tennessee; New York University, New York, New York; University of Louisville, Louisville, Kentucky; Wake Forest University, Winston-Salem, North Carolina; Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands; Verona University Medical Center, Verona, Italy). Sociodemographic and clinicopathologic data were collected including age, sex, and race, as well as tumor size, AJCC stage, histologic grade, presence of nodal disease, final resection margin, and the presence of vascular and/or perineural invasion. Histologic grade was defined as well, moderate, or poorly differentiated. Using the final pathologic report, the resection margin was categorized according to the nomogram proposed by Groot Koerkamp et al.: R0: no microscopic disease at resected margin, R1: presence of microscopic disease at the resected surgical margin and R1–>R0: reresection of a positive frozen section margin during surgery to achieve a final microscopically negative margin.[20] Nodal status (absence, N− vs. presence, N+ of metastases), as well as the number of lymph nodes examined (≥4 vs. <4) was also recorded.

Only patients undergoing a curative intent surgery for histologically confirmed PHC were included in the final study population; patients with gross residual disease (R2) were excluded. Since the focus of this study was long-term overall survival (OS), patients who died within 30 days of surgery were excluded from further analysis. Because of the high case mortality related to PHC, and the potential of misclassifying cause of death, only overall survival was assessed. The institutional review board of each participating institution approved the study.

### Model Comparisons

The statistical code used to construct the Groot Koerkamp et al. nomogram was obtained from the authors.[20] The risk factors included in the model were margin status (R0, R1, and R1–>R0), nodal status (N0 with ≥4 lymph nodes harvested, N0 with <4 lymph nodes harvested and N+ disease), and tumor differentiation (well, or moderately/poorly differentiated). Beta coefficients from the original model were applied to data derived from the current cohort and model performance was assessed, as well as compared with the AJCC staging system. In addition, separate analyses were performed to identify other clinical and pathological factors that were independently associated with survival.

### Statistical Analysis

Categorical variables were described as whole numbers and percentages while continuous variables were reported as medians with interquartile (IQR) range. Univariable comparison of categorical variables was performed using the Pearson chi-square test. The primary outcome of the study was 3- and 5-year OS. OS was calculated as the time from the date of surgery to the date of death or date of last available follow-up; OS was estimated using the Kaplan-Meier method. Associations between OS and potential risk factors were evaluated using Cox proportional hazards analyses with a stepwise backwards selection procedure based on the Akaike Information Criterion. Risk factors were reported as hazard ratios (HR) with corresponding 95 % confidence intervals (95 % CI). Multiple imputations were performed using the MICE package for R version 3.03 (http://www.r-project.org) to account for missing data. Multiple imputations result in unbiased estimates, while preserving sample size and statistical power. Model performance was assessed using Harrell's concordance index (c-index) and bootstrap resampling was performed to quantify model overfit. Beta coefficients from the multivariable model were used to construct a nomogram to predict 3- and 5-year survival after curative intent resection of PHC. All analyses were performed using SPSS 22.0 (IBM, New York) and R version 3.03 (http://www.r-project.org). A $p < 0.05$ was used to define statistical significance.

## Results

### Demographic and Clinicopathologic Characteristics

A total of 407 patients were identified who met inclusion criteria (Table 1). At the time of surgery, most patients underwent a major hepatectomy (≥3 Couinaud segments; $n = 301$, 74.0 %), while a smaller number of patients ($n = 106$, 26.0 %) had a minor (<3 Couinaud segments) resection. On final pathology, tumor grade was classified as well- ($n = 63$, 17.5 %), moderate($n = 220$, 60.6 %) or poorly- ($n = 75$, 20.4 %) differentiated. Lymphovascular and perineural invasion were present in 78 (36.8 %) and 169 (74.8 %) patients, respectively. While most patients had a R0 surgical margin ($n = 220$, 54.1 %), 128 (31.4 %) had an R1 margin; data on surgical margin was missing in 59 (14.5 %) patients. Lymph node metastases were present in 138 (38.7 %) patients, while 219 (53.8 %) had no lymph node metastasis identified in the surgical specimen. Of note, among the 219 patients who did not have lymph node metastasis, 84 (38.4 %) had ≥4 lymph nodes examined, while 135 (61.6 %) had <4 lymph nodes assessed. Data on lymph node status was missing for 50 (12.3 %) patients. Among the 310 (76.2 %) patients on whom complete staging information

was available, 34 (11.0 %) patients were categorized as AJCC stage I, while 119 (38.4 %) were stage II, 129 (41.6 %) stage III, and 28 (9.0 %) stage IV.

## Comparison of Prognostic Schemes

Overall median survival was 24.4 months; 3- and 5-year survival was 37.2 and 20.8 %, respectively. On multivariable analysis, age (HR 1.02, 95 % CI 1.01–1.03), lymphovascular invasion (HR 1.35, 95 % CI 1.00–1.81), perineural invasion (HR 3.52, 95 % CI 2.44–5.06), and lymph node metastases (HR 1.82, 95 % CI 1.29–2.58) were independently associated with overall survival (all $p < 0.05$) (Table 2).

The performance of the 7th edition AJCC staging system to predict long-term outcome was poor (C-index 0.570). In addition, while the performance of the Groot Koerkamp et al. nomogram was slightly better, the overall accuracy in predicting overall survival was also poor (C-index 0.587). Given the poor performance of both the AJCC and Groot Koerkamp et al. staging schemes, factors from the current analysis were utilized to develop a novel nomogram (Fig. 1). Specifically, the regression coefficients from the factors that were independently associated with overall survival on multivariable analysis were used to develop a weighted points score. The nomogram to predict overall survival was created based on four independent prognostic factors: age (continuous), lymphovascular invasion (present, absent), perineural invasion (present, absent), and lymph node status (N0 <4 lymph nodes examined, N0 ≥4 lymph nodes examined, N1). A higher total points based on the sum of the assigned number of points for each factor in the nomogram was associated with a worse prognosis. For example, a 70-year-old patient who underwent resection of a tumor characterized by lymphovascular and perineural invasion but N0 disease with ≥4 lymph nodes examined (age = 69.23 points, lymphovascular invasion = 17.84 points, perineural invasion = 91.55 points, N0 with ≥4 lymph nodes examined = 0 points) would have a predicted 3- and 5-year overall survival of 29.3 and 12.6 %, respectively. In contrast, the predicted 3-and 5-year survival for a 55-year-old patient following resection of a tumor that had no lymphovascular and no perineural invasion, but N1 disease (age = 46.15 points, no lymphovascular invasion = 0.0 points, no perineural invasion = 0.0 points, N1 = 44.10 points) would be 70.1 and 54.4 %, respectively.

To further assess the discriminative ability of the model, the predicted probability of overall survival was then plotted as Kaplan-Meier curves stratified by tertile of predicted probability calculated from the nomogram. Patients in the tertile with the highest nomogram score (tertile 3) did substantially worse (5-year mortality 94.5 %) compared with patients in tertiles 1 and 2 (5-year mortality 84.2 and 49.6 %, respectively) ($p < 0.001$) (Fig. 2). Discrimination ability of the final model for overall survival was also assessed using the C-statistic (C-index 0.682) and was noted to be better than both the AJCC staging and the Groot Koerkamp et al. nomogram in stratifying patient survival (Fig. 3). Finally, overfitting of the new nomogram was assessed by a bootstrapped calibration plot. The calibration plot of the proposed PHC nomogram demonstrated good calibration in the validation cohort. This means that compared with actual survival based on Kaplan-Meier tables, 5-year overall survival predicted by the nomogram provided good estimations (Fig. 4).

## Discussion

PHC is a challenging disease to manage. Many patients present with unresectable disease and only select patients are candidates for curative intent surgery[7–9] Even after curative intent resection, the prognosis of patients with PHC can be guarded. In an attempt to better estimate the prognosis of patients following surgery, several different prognostic schemes have been proposed.[10, 11, 17, 18] The most widely used tools to estimate prognosis include the AJCC staging system, as well as the as the Bismuth-Corlette and Blumgart staging systems.[18, 19] These prognostic schemes have been criticized, however, for being based on aggregate data, rather than individual patient specific factors.[20–24] As such, while these prognostic tools may stratify groups of patients, their ability to predict the survival of individual patients is limited. Rather, prognostic nomograms have become an increasingly popular tool to estimate more accurately patient-specific survival.[20–24] While nomograms have been available for a number of various cancers,[8, 9, 20, 21] only recently has a nomogram for PHC been proposed by Groot Koerkamp and colleagues, which had not been previously validated.[20] The current study is important because we assessed the performance of this nomogram using a large, international, multi-center cohort of patients and noted that the nomogram performed poorly with a C-index of only 0.587. In fact, the overall performance of the Groot Koerkamp nomogram was only slightly better than the 7th edition AJCC staging for PHC (C-index 0.570). The reason for the poor performance of the nomogram probably relates to the lack of association of margin status and tumor grade with overall survival on multivariable analysis. Rather, in our cohort of patients, factors independently predictive of survival included age, perineural invasion, lymphovascular invasion, and lymph node status.

The poor predictive ability of Groot Koerkamp nomogram was likely due to overfitting in its derivation cohorts, as most of the individual risk factors in the nomogram were not significant on Cox proportional hazards analysis in the current study. In the original study by Groot Koerkamp and colleagues, the nomogram was validated but only in a single-center cohort.[20] In contrast, in our large, multi-center cohort, the nomogram by Groot Koerkamp had a poor performance and a low c-index. Similarly, the AJCC also performed poorly, which may have been expected based on data from previous studies.[10, 20] In the current analysis of 407 patients, factors associated with outcome on univariable analysis included patient age, margin status, presence of nodal disease, lymphovascular invasion, and perineural disease. Furthermore, on multivariable analysis age, the presence of nodal metastases, lymphovascular, and perineural disease remained significant. Using these factors, we constructed a revised nomogram. Our proposed nomogram had a c-index of 0.682 and the calibration plot showed no signs of overfitting (Fig. 4). Overall median survival, 3- and 5-year survival were 24.4 months, 37.2 and 20.8 %, respectively.[7–9] Of note, patients could be stratified using data from the revised nomogram. Specifically, patients in the tertile with the highest nomogram score (tertile 3) did substantially worse (5-year mortality 94.5 %) compared with patients in tertiles 1 and 2 (5-year mortality 84.2 and 49.6 %, respectively) (Fig. 2). 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. Information from the nomogram can help provide

estimates to quantitate information regarding the probability of survival among patients with PHC. Accurate data on the prognosis of patients with PHC may be relevant to treating physicians for several reasons. For example, the role of adjuvant chemotherapy or radiation therapy in PHC treatment has been controversial because of the lack of data, even though a recent meta-analysis reported that the use of adjuvant therapy may provide oncological benefit for high-risk subgroups such as those patients with node positive and margin positive disease.[25] While in the present study, only about 1 in 3 patients received adjuvant radiotherapy and less than half (44.4 %) received adjuvant chemotherapy, individualized risk prediction models may have a role in selecting and guiding postoperative treatment in the future.

Results of the current study should be interpreted with several limitations. First, inherent to all retrospective analyses, there may have been a selection bias regarding the diagnosis and treatment of patients. While the multi-institutional nature of the study allowed for a large cohort of patients, the inclusion of multiple centers did not allow for the standardization of operative and perioperative approach. In addition, the validation and results in our multi-institutional cohort are more generalizable, inherently taking into account small differences between hospital practices. Because the majority of patients undergo a resection for PHC, rather than liver transplantation, our cohort focused solely on these patients. Future studies will need to assess the applicability and accuracy of these nomograms to patients undergoing liver transplantation. Finally, while the revised nomogram was internally validated, it similarly needs to be externally validated before widespread use of the revised nomogram can be advocated.

In conclusion, using a large, multi-institutional cohort of patients with PHC, the current study demonstrated that the overall survival following curative intent surgery varied greatly among individual patients. The previously proposed nomogram by Groot Koerkamp et al., as well as the 7th AJCC staging system for PHC, performed poorly. In contrast, a revised nomogram based on four independent prognostic factors: age, lymphovascular invasion, perineural invasion, and lymph node status was better able to stratify patients with regard to overall survival. While the revised nomogram needs to be externally validated, such data may help in the prognostic stratification of patients with PHC.

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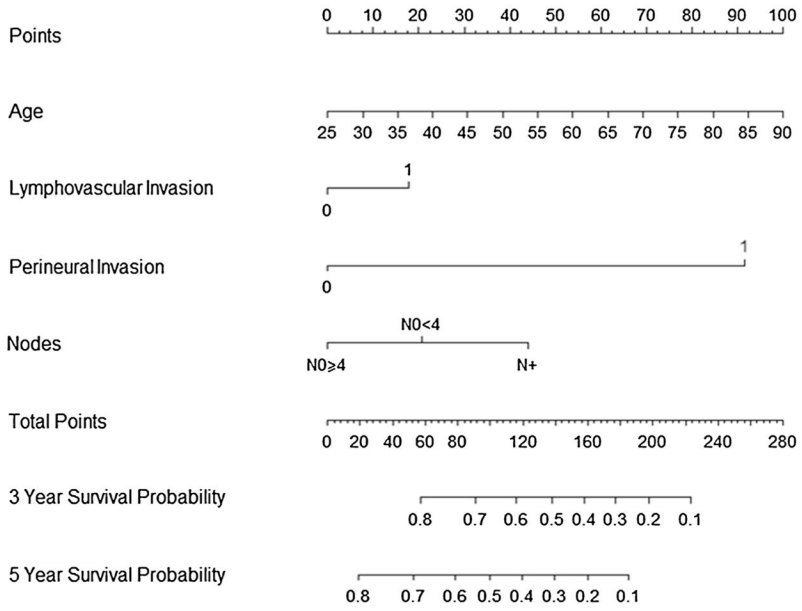


**Fig. 1.**

Nomogram to calculate the 3- and 5-year survival of patients undergoing resection for perhilar cholangiocarcinoma

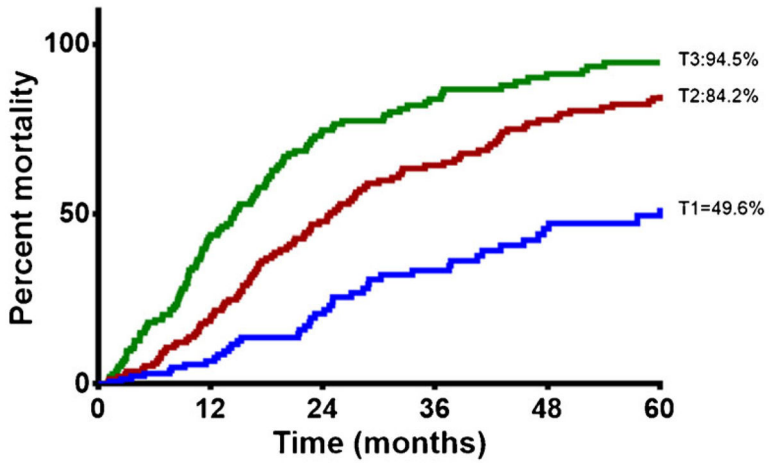


**Fig. 2.**

5-year postoperative mortality stratified by tertiles predicted by our proposed nomogram

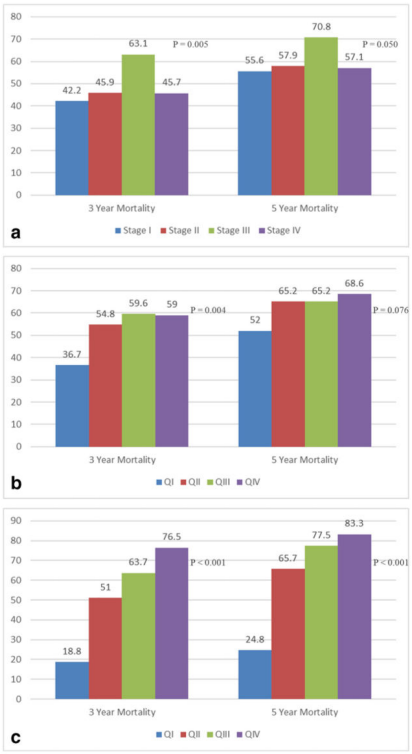


**Fig. 3.**

3- and 5-year mortality after curative resection for perihilar cholangiocarcinoma stratified by quartiles of **a** AJCC stage, **b** MSKCC nomogram, and **c** our proposed nomogram

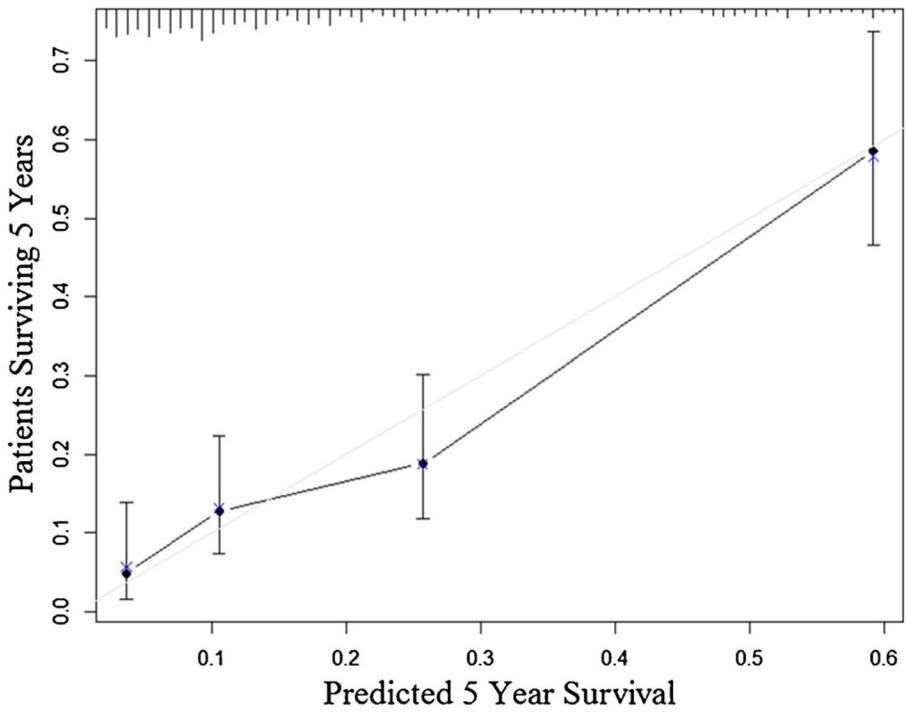


**Fig. 4.**
Calibration plot for the calculated nomogram

## Table 1

Clinicopathologic and operative characteristics

| Variable | *n* = 407, (%)/median (IQR) |
|---|---|
| Male gender | 250 (61.6) |
| Age (years, IQR) | 66.0 (58.0–72.8) |
| Preoperative bilirubin (mg/dL, IQR) | 4.6 (1.8–10.6) |
| Drainage preoperative | |
| None | 83 (24.6) |
| Percutaneous | 125 (37.0) |
| Endoscopic | 85 (25.1) |
| Both | 45 (13.3) |
| Type of resection | |
| Bile duct resection only | 96 (23.8) |
| Segment 4b/5 resection | 5 (1.2) |
| Right hepatectomy | 38 (9.4) |
| Left hepatectomy | 46 (11.4) |
| Extended right hepatectomy | 76 (18.8) |
| Extended left hepatectomy | 83 (20.5) |
| Right trisectorectomy | 32 (7.9) |
| Left trisectorectomy | 22 (5.4) |
| Classic whipple and hepatectomy | 6 (1.4) |
| Caudate resection | 171 (42.1) |
| Margin status | |
| R1 | 128 (36.8) |
| R1–>R0 | 41 (11.8) |
| R0 | 179 (51.4) |
| Tumor diameter (mm, IQR) | 25.0 (15.5–40.0) |
| Lymph node involvement | |
| Yes | 138 (38.7) |
| <4 nodes examined | 135 (37.8) |
| At least 4 nodes examined | 84 (23.5) |
| Differentiation | |
| Well differentiated | 63 (17.5) |
| Moderately/poorly differentiated | 298 (82.5) |
| Lymphovascular invasion | 78 (36.8) |
| Perineural invasion | 169 (74.8) |
| Bismuth classification | |
| I | 56 (15.5) |
| II | 58 (16.0) |
| IIIA | 84 (23.2) |
| IIIB | 95 (26.2) |
| IV | 69 (19.1) |

| Variable | *n* = 407, (%)/median (IQR) |
|---|---|
| Blumgart classification | |
| T1 | 114 (51.4) |
| T2 | 40 (18.0) |
| T3 | 68 (30.6) |
| AJCC stage | |
| Stage I | 34 (11.0) |
| Stage II | 119 (38.4) |
| Stage III | 129 (41.6) |
| Stage IV | 28 (9.0) |
| Preoperative chemotherapy | 10 (3.7) |
| Preoperative radiotherapy | 6 (2.3) |
| Postoperative chemotherapy | 151 (44.4) |
| Postoperative radiotherapy | 108 (32.0) |

**Table 2**

Univariable and multivariable proportional hazards regression models

| Variable name | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| Age | 1.01 | 1.00–1.02 | 0.020 | 1.02 | 1.01–1.03 | <0.001 |
| Male gender | 1.09 | 0.86–1.39 | 0.490 | | | |
| BMI | 0.99 | 0.96–1.03 | 0.665 | | | |
| Drainage preoperative | | | | | | |
| None | Ref. | – | – | | | |
| Percutaneous | 1.05 | 0.74–1.48 | 0.797 | | | |
| Endoscopic | 1.38 | 0.96–1.98 | 0.081 | | | |
| Both | 1.22 | 0.79–1.91 | 0.372 | | | |
| Major resection (≥3 segments) | 0.86 | 0.67–1.12 | 0.271 | | | |
| Caudate resection | 0.82 | 0.65–1.05 | 0.115 | | | |
| Margin status | | | | | | |
| R0 | Ref. | – | – | Ref. | – | – |
| R1–>R0 | 1.31 | 0.88–1.95 | 0.181 | 0.80 | 0.55–1.16 | 0.238 |
| R1 | 1.51 | 1.14–1.99 | 0.004 | 1.14 | 0.86–1.52 | 0.356 |
| Tumor size (mm) | 1 | 1.00–1.01 | 0.245 | | | |
| Grade | | | | | | |
| Well differentiated | Ref. | – | – | | | |
| Moderately/poorly differentiated | 1.15 | 0.83–1.59 | 0.406 | | | |
| Bismuth classification | | | | | | |
| I | Ref. | – | – | | | |
| II | 0.98 | 0.64–1.50 | 0.923 | | | |
| IIIA | 0.95 | 0.64–1.41 | 0.794 | | | |
| IIIB | 0.72 | 0.49–1.07 | 0.100 | | | |
| IV | 1.11 | 0.73–1.67 | 0.629 | | | |
| Blumgart classification | | | | | | |
| T1 | Ref. | – | – | | | |
| T2 | 0.83 | 0.53–1.29 | 0.402 | | | |

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| Variable name | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | *P* value | HR | 95 % CI | *P* value |
| T3 | 1.19 | 0.84–1.70 | 0.333 | | | |
| Portal vein involvement | 1.25 | 0.84–1.86 | 0.282 | | | |
| Lymphovascular invasion | 1.42 | 1.01–1.99 | 0.045 | 1.35 | 1.00–1.81 | 0.047 |
| Perineural invasion | 1.69 | 1.16–2.46 | 0.006 | 3.52 | 2.44–5.06 | <0.001 |
| Lymph node metastases | | | | | | |
| No metastases, ≥4 nodes | Ref. | – | – | Ref. | – | – |
| No metastases, <4 nodes | 1.36 | 0.97–1.92 | 0.078 | 1.38 | 0.99–1.93 | 0.060 |
| Lymph node metastases | 2.04 | 1.44–2.89 | <0.001 | 1.82 | 1.29–2.58 | 0.001 |
| Preoperative chemotherapy | 1.67 | 0.78–3.57 | 0.186 | | | |
| Preoperative radiotherapy | 1.70 | 0.70–4.14 | 0.244 | | | |
| Postoperative chemotherapy | 1.09 | 0.84–1.42 | 0.503 | | | |
| Postoperative radiotherapy | 0.95 | 0.73–1.25 | 0.728 | | | |