Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond
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Survival Analysis and Prognostic Nomogram for Patients Undergoing Resection of Extrahepatic Cholangiocarcinoma

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ABSTRACT

Background
Tumor location of extrahepatic cholangiocarcinoma (CCA) might influence survival after resection.

Methods
A consecutive series of 175 patients who had undergone a potentially curative resection of extrahepatic CCA was analyzed. We calculated concordance indices of different constructed prognostic models for survival including TNM (tumor–node–metastasis) staging and developed a nomogram of the most sensitive model.

Results
Overall cancer-specific survival rates were 83%, 58%, and 26% at 1, 2, and 5 years, respectively. Cancer-specific survival according to location was 42% for proximal, 23% for mid, and 19% for distal CCA after 5 years. Tumor location was not an independent significant predictor (P=0.06). A prognostic model using all potential prognostic variables predicted survival better compared with TNM staging (concordance index 0.65 versus 0.63). A reduced model containing only lymph node status, microscopically residual tumor status, and tumor differentiation grade, also outperformed TNM staging (concordance index 0.66).

Conclusions
Tumor location of extrahepatic CCA does not independently predict cancer-specific survival after resection. We developed a nomogram, based on a prognostic model with lymph node status, microscopically residual tumor status of resection margins, and tumor differentiation grade, that predicted survival better than TNM staging.
INTRODUCTION

Extrahepatic cholangiocarcinoma (CCA) is the primary cancer of the main bile ducts and arises from the ductal epithelium.\textsuperscript{1,2} Although it is an uncommon disease with a reported incidence of 1-2 cases per 100,000 per year, its incidence is increasing. Surgical treatment, consisting of hilar resection with extended hepatectomy (PHx), pancreatoduodenectomy (PD) or sometimes local bile duct excision, is the only curative treatment option. Despite comprehensive preoperative staging to select patients for potentially curative resection, many patients present with recurrent disease within 2 years after tumor resection. Overall, 5-year survival rates from 20\% to 40\% have been reported after resection.\textsuperscript{3-9}

Differentiation between proximal, mid and distal extrahepatic CCA is primarily based on surgical approach, rather than differences in tumor biology. CCA in the distal or middle part of the bile duct is usually associated with better prognosis, because these tumors result in complete bile duct obstruction leading to early clinical symptoms, which prompt intervention. Proximal tumors tend to commence with partial biliary obstruction consequently resulting in delayed complaints and jaundice. However, available studies focusing on tumor location and long-term outcome irrespective of type of operation show no differences or conflicting results.\textsuperscript{4,10-14}

The purpose of cancer staging systems is to predict survival. This information is used to tailor (neo)adjuvant therapy and to estimate prognosis after surgery. The most widely used staging system is the TNM (tumor–node–metastasis) system, based on the pathological extent of tumor. However, the adequacy of the current TNM staging system for prognostic stratification has been questioned for CCA, especially for proximal lesions.\textsuperscript{14,15}

The aim of the current study is to evaluate the role of tumor location of extrahepatic CCA on survival after resection, to analyze the predictive value of TNM staging, and to compare different prognostic models.

METHODS

Patients

A consecutive series of 175 patients underwent resection of extrahepatic CCA, from January 1992 to December 2007. The clinicopathological data were prospectively collected in a database. Operations were performed with curative intent, i.e. in the absence of extensive local invasion or distant metastases. The routine diagnostic workup consisted of standard abdominal ultrasonography with subsequent staging by contrast enhanced spiral computed tomography (CT) scan.\textsuperscript{16} For distal lesions, as apparent on CT, diagnostic laparoscopy, diagnostic endoscopic retrograde cholangiopancreatoangiography (ERCP), and endoscopic ultrasonography were used, but not consistently throughout the years because of changing strategies.\textsuperscript{16,17} Diagnostic laparoscopy was routinely carried out for proximal lesions to exclude the presence of
metastatic disease. Diagnostic ERCP with endoscopic biliary drainage or percutaneous transhepatic biliary drainage was carried out when bilirubin levels exceeded 40 μmol/l. Preoperative therapy was confined to routine low-dose radiotherapy in proximal lesions to destroy free floating tumor cells in the bile. Routine adjuvant chemo- or radiation therapy was not administered.

Surgical Technique and Pathology
Surgical procedures for proximal CCA consisted of hilar resection with or without concomitant partial liver resection (PHx) depending on the extent of the lesion, local bile duct resection for mid CCA, and subtotal pylorus preserving PD for distal CCA. In case of suspicion on tumor ingrowth in the proximal duodenum a classical Whipple’s procedure was carried out including distal gastrectomy. In case limited tumor ingrowth into the portal or superior mesenteric vein was found during the operation, a segmental venous resection or wedge resection was carried out. The surgical procedure for proximal lesions consisted of hilar resection with complete lymphadenectomy of the hepatoduodenal ligament. Up to 1998 the intraoperative finding of frozen-section proven-lymph node metastases was a reason to abandon resection, while afterwards resection was carried out when lymph node metastases were confined to the hepatic pedicle or the hepatoduodenal ligament. As of 1998, we applied the concept of complete excision of segment 1 along with partial hepatectomy and portal vein bifurcation (extended PHx) when involved by tumor. In case of mid CCA, the extrahepatic bile duct was excised with construction of a single or double hepaticojejunostomy.

Pathological findings were described in a standardized format: pTNM-stage, differentiation grade, residual tumor status of resection and dissection planes, total number of resected lymph nodes, and total number of positive lymph nodes including their location were recorded. The pTNM staging system (American Joint Committee on Cancer (AJCC) and Union Internationale Contre le Cancer (UICC)) was used to classify patients according to pathological findings. Tumor-positive paraaortal nodes (group 16), nodes around the celiac trunk or at the mesenteric root, were considered as distant metastasis (M1). Lymph nodes surrounding the anterior and posterior face of the head were considered to be regional lymph nodes. An R0 resection was defined as a microscopically complete removal in a non-contaminated operation with radical margins, an R1 resection as macroscopically complete removal of disease but with microscopic evidence of residual tumor at the resection or dissection margins.

Follow-Up
Patient follow-up took place according to a standardized scheme at regular intervals for up to 5 years after discharge. To obtain definitive follow-up data, general practitioners were contacted in addition to evaluation of the patients’ files. Recurrence of disease was suspected on clinical grounds. When recurrence was suspected, additional (radiological) examinations were carried out and, when indicated, palliative
treatment was offered. Follow-up comprised the period from the date of operation until death, or until the time of the last visit to the outpatient clinic, or the last visit to the general practitioner when still alive. Patients who were identified as having died of recurrent CCA, all had progressive locoregional and/or distant recurrences at the time of death.

**Statistical Analysis**

Time until death due to (recurrent) CCA, i.e. cancer-specific survival (CSS), was the primary outcome parameter. Patients who died due to postoperative complications and unrelated causes were censored at their time of death. Cumulative survival was estimated with the Kaplan–Meier method. We used Cox proportional hazards regression analyses to examine the association between potential prognostic variables and CSS. The following potential prognostic variables were assessed: age, sex, tumor location, T-stage, N-stage, tumor diameter, tumor differentiation grade, presence of microscopic residual disease at resection or dissection plane (R1), predominant papillary component, and perineural invasion. Considering the limited number, missing values for tumor diameter were estimated using the mean of measurements from other patients.28

Continuous variables were examined in relation to the outcome by using restricted (natural) cubic splines (four knots), in case graphical analyses showed that the relation was nonlinear. Three different types of prognostic models were investigated. The first model contained indicators for the different TNM stages (TNM model) without analyzing other variables. The second model contained all potential predictors (full model), irrespective of significance in univariable analysis. The third model (reduced model) was obtained from the full model after backward selection of variables using the criterion of a threshold P-value of <0.05. Discrimination of the different models was compared using the concordance index, which is defined as the proportion of all usable patient pairs in which the predictions and outcomes are concordant.28 Values can range from 0.5 (due to chance; no discrimination) to 1.0 (perfect discrimination). Concordance indices were calculated for the three models in 200 bootstrap samples and compared after bootstrapping to reduce overoptimism of the predictive power of each model. Calibration of the best discriminative model was assessed by comparing for different patient proportions, the predicted with observed survival estimates.

A nomogram, based on the logistic regression formulas, was developed to visualize the prognostic strength of the best predictive model in a single figure. The total number of points derived by specifying values for all predictors was used to calculate the expected survival probabilities from the Cox model. Statistical analysis was carried out with the use of SPSS statistical software version 17.0.1 (SPSS Inc., Chicago, IL) and the R 2.11.0 statistical package Project for Statistical Computing (Harrell’s Design, Hmisc packages).
RESULTS

A consecutive series of 175 patients underwent a macroscopically radical resection for extrahepatic CCA and was included in this analysis. Of these patients, 48 (28%) had a proximal CCA, 37 (21%) mid, and 90 (51%) a distal CCA. Table 1 displays the clinicopathological parameters of all patients. During follow-up, 119 patients died. Median length of follow-up was 19 months [interquartile range (IQR) 10–37] for the deceased patients and 54 months (IQR 34–99) for the 36 patients (21%) alive at last follow-up. Twenty-six patients (14.8%) died from other causes than (recurrent) CCA. These patients were censored at the time of death in the analysis.

Table 1  Clinicopathological characteristics of 175 patients with extrahepatic cholangiocarcinoma who underwent macroscopically radical resection.

<table>
<thead>
<tr>
<th>Clinicopathological characteristics</th>
<th>(N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at operation, mean, year (SD)</td>
<td>62 ±11</td>
</tr>
<tr>
<td>Male gender - n (%)</td>
<td>107 [61]</td>
</tr>
<tr>
<td>Extrahepatic bile duct tumor localization - n (%)</td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>48 (28)</td>
</tr>
<tr>
<td>Mid</td>
<td>37 (21)</td>
</tr>
<tr>
<td>Distal</td>
<td>90 (51)</td>
</tr>
<tr>
<td>pT-stage - n (%)</td>
<td></td>
</tr>
<tr>
<td>pTis</td>
<td>6 (3)</td>
</tr>
<tr>
<td>pT1</td>
<td>21 (12)</td>
</tr>
<tr>
<td>pT2</td>
<td>56 (32)</td>
</tr>
<tr>
<td>pT3</td>
<td>79 (45)</td>
</tr>
<tr>
<td>pT4</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Tumor diameter, median - cm (IQR)</td>
<td>2 [1.5-2.7]</td>
</tr>
<tr>
<td>Presence of lymph node metastasis - n (%)</td>
<td>65 (37)</td>
</tr>
<tr>
<td>Median number of positive nodes (min-max)*</td>
<td>2 [1-13]</td>
</tr>
<tr>
<td>Lymph node ratio, median (min-max)¶</td>
<td>0.4 (0.04-1.0)</td>
</tr>
<tr>
<td>Stage - n (%)</td>
<td></td>
</tr>
<tr>
<td>Stage 0</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Stage 1a</td>
<td>15 (9)</td>
</tr>
<tr>
<td>Stage 1b</td>
<td>42 (24)</td>
</tr>
<tr>
<td>Stage 2a</td>
<td>47 (27)*</td>
</tr>
<tr>
<td>Stage 2b</td>
<td>56 (32)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Differentiation grade - n (%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>49 (28)</td>
</tr>
<tr>
<td>Moderate</td>
<td>40 (23)</td>
</tr>
<tr>
<td>Poor</td>
<td>86 (49)</td>
</tr>
<tr>
<td>Resection plane microscopically irradical (R1) - n (%)</td>
<td>99 (57)</td>
</tr>
<tr>
<td>Tumor predominantly papillary - n (%)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Perineural invasion - n (%)</td>
<td>112 (64)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; SD, standard deviation.
* includes four T4 cases without lymph node Metastasis.
¶ of patients with positive lymph nodes.
Chapter 15  Survival Analysis of Extrahepatic Cholangiocarcinoma

Figure 1  Estimated cancer-specific survival of extrahepatic cholangiocarcinoma after resection, grouped according to tumor location.

Figure 2  Estimated cancer-specific survival according to the American Joint Committee on Cancer and Union Internationale Contre le Cancer stage grouping for carcinomas of the extrahepatic bile ducts.
Table 2  Results of the three prognostic models; the TNM staging system, the full prognostic model, and the reduced model.

<table>
<thead>
<tr>
<th>Factor</th>
<th>TNM staging HR (95% CI)</th>
<th>Full model HR (95% CI)</th>
<th>Reduced model HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, one year increment</td>
<td>NA</td>
<td>1.00 (0.99–1.03)</td>
<td>NA</td>
</tr>
<tr>
<td>Male gender</td>
<td>NA</td>
<td>1.27 (0.84–1.93)</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor localization</td>
<td></td>
<td>1.29 (0.70–2.40)</td>
<td>NA</td>
</tr>
<tr>
<td>Mid</td>
<td>NA</td>
<td>1.21 (0.65–2.24)</td>
<td>NA</td>
</tr>
<tr>
<td>Distal</td>
<td>NA</td>
<td>2.28 (1.46–3.57)</td>
<td>2.34 (1.52–3.57)</td>
</tr>
<tr>
<td>pT-stage (compared with pTis, pT1)</td>
<td></td>
<td>0.42 (0.08–2.22)</td>
<td>NA</td>
</tr>
<tr>
<td>pT2</td>
<td>NA</td>
<td>0.57 (0.12–2.83)</td>
<td>NA</td>
</tr>
<tr>
<td>pT3</td>
<td>NA</td>
<td>0.82 (0.15–4.58)</td>
<td>NA</td>
</tr>
<tr>
<td>pT4</td>
<td>NA</td>
<td>0.93 (0.78–1.10)</td>
<td>NA</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td>NA</td>
<td>2.38 (1.64–3.45)</td>
<td>2.43 (1.59–3.69)</td>
</tr>
<tr>
<td>Presence of lymph node metastasis (pN1)</td>
<td>NA</td>
<td>1.73 (0.88–3.40)</td>
<td>1.79 (0.98–3.27)</td>
</tr>
<tr>
<td>Differentiation grade (compared to good)</td>
<td>NA</td>
<td>2.28 (1.46–3.57)</td>
<td>2.34 (1.52–3.57)</td>
</tr>
<tr>
<td>Moderate</td>
<td>NA</td>
<td>1.73 (0.88–3.40)</td>
<td>1.79 (0.98–3.27)</td>
</tr>
<tr>
<td>Poor</td>
<td>NA</td>
<td>1.78 (1.02–3.12)</td>
<td>2.03 (1.23–3.36)</td>
</tr>
<tr>
<td>Resection plane microscopically irradical (R1)</td>
<td>NA</td>
<td>1.56 (1.00–2.42)</td>
<td>1.60 (1.08–2.36)</td>
</tr>
<tr>
<td>Tumor predominantly papillary</td>
<td>NA</td>
<td>0.51 (0.22–1.21)</td>
<td>NA</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>NA</td>
<td>1.16 (0.75–1.80)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage (compared to stage 0, 1a)*</td>
<td></td>
<td>1.20 (0.57–2.54)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 1b</td>
<td></td>
<td>1.42 (0.66–2.99)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 2a</td>
<td></td>
<td>3.16 (1.19–8.29)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 2b</td>
<td></td>
<td>5.17 (1.97–13.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Stage 3</td>
<td></td>
<td>5.17 (1.97–13.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Concordance index</td>
<td></td>
<td>0.64</td>
<td>0.71</td>
</tr>
<tr>
<td>Uncorrected</td>
<td></td>
<td>0.64</td>
<td>0.71</td>
</tr>
<tr>
<td>After bootstrap validation</td>
<td></td>
<td>0.63</td>
<td>0.65</td>
</tr>
</tbody>
</table>

* TNM stage according to UICC and AJCC, sixth edition. AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; NA, not applicable; R1, microscopically tumor left at the resection margin; TNM, tumor–node–metastasis; UICC, Union Internationale Contre le Cancer.

CSS for the entire group was 85%, 58%, and 26% at 1, 2, and 5 years, respectively. The breakdown of 5-year CSS, according to location, was 42% for proximal, 25% for mid, and 19% for distal CCA (log-rank test, P=0.055) (Figure 1). Figure 2 shows the survival curves according to the TNM classification for extrahepatic CCA. Stage 0 (Tis) and Ia were grouped due to small numbers. From a hierarchical point of view, only patients with stage IIb and stage III had a significantly worse survival, compared with the reference stage (0, 1a) with hazard ratios (HRs) of 3.15 (95% confidence interval (CI) 1.59–6.26) and 5.17 (95% CI 2.02–13.2).

Of the patients with a distal tumor, 45 of 90 (50%) had positive lymph nodes compared with 8 of 48 (17%) patients with a proximal tumor (P<0.001). A microscopically tumor-positive resection margin was present in 39 of 90 (43%) patients with a distal tumor versus 32 of 48 (67%) patients with a proximal tumor (P=0.009). The
presence of a poorly differentiated tumor was not different between patients with a distal or a proximal tumor, 43 of 90 (48%) versus 23 of 48 (48%), respectively. Table 2 shows the HRs with 95% CI of all available potential predictors of the three multivariable models (TNM, full, and reduced model). With backward selection, the best fitting reduced model was constructed and contained the variables lymph node status, microscopically residual tumor status at resection/dissection plane, and tumor differentiation grade. In the multivariable analysis, location of the tumor was not an independent prognostic factor (reduced model).

Discrimination of both the full and reduced model was better compared with that for TNM staging, with concordance indices after bootstrap validation of 0.65 and 0.66 versus 0.63, respectively. A nomogram on basis of the reduced model was constructed and is shown in Figure 3. The nomogram predicts the 12- and 24-month CSS probabilities. Figure 4 shows the calibration of the reduced model as demonstrated by the predicted probability of 3-year CSS plotted against the observed probability (solid line). All CIs lie over the 45° dotted line of perfect calibration, and the closeness of the lines indicates absence of systematic bias.

Figure 3  Nomogram for prediction of cancer-specific survival based on the reduced model. Cancer-specific survival probabilities at 12 and 24 months after resection are presented. N0: negative lymph node metastasis; N1: positive lymph node metastasis; R0: tumor margin-free resection; R1: microscopically tumor margin-positive resection. Instruction: Locate for nodal metastasis the number of points (upper line) the patient receives depending whether lymph node metastasis (N1) has occurred or not (N0). Repeat this for each variable. Sum the points for each of the three predictors and locate the sum on the total points axis. Draw a line straight down to find the patient’s probability of surviving 12 or 24 months following resection of an extrahepatic cholangiocarcinoma, assuming that he/she does not die of another cause.
DISCUSSION

Even after potentially curative surgery for extrahepatic CCA, more than half of the patients die ultimately of their disease during the follow-up period. Analysis of the present series shows an overall 5-year survival rate of 26%, with the best CSS of 42% at 5-year follow-up in the group of patients with proximal tumors. However, location was not an independent prognosticator. Both a full model containing multiple potential clinicopathological factors and a reduced model with only lymph node status, microscopically residual tumor status at resection margins, and tumor differentiation grade predicted survival better than the TNM staging system.

According to the current literature, the prognostic significance of the location of an extraprostatic CCA is uncertain. The largest single-institution study comparing intrahepatic and proximal bile duct with distal extrahepatic bile duct cancer found a 5-year overall survival rate of 10% for proximal tumors and 23% for distal lesions. Similarly, in a report from the Memorial Sloan-Kettering Cancer Center including 206 patients, the 5-year estimated CSS was 29% and 43% for proximal and
The conclusion from both studies was, however, that tumor location appeared of low prognostic significance and that a tumor margin-free resection remains the best prognosticator for long-term survival, followed by negative lymph node status.

Significant factors identified for decreased survival in this series included disease spread to regional lymph nodes, microscopically residual tumor status at resection margins, and poor tumor differentiation. The prognostic significance of location was only present at the level of univariable analyses, and in contrast to the above-mentioned studies, there was a trend for a survival benefit in the proximal group. Notwithstanding the observation that these tumors most often showed positive surgical margins, the good mid-term survival is rather considered good palliation. Still, the hypothesis, as proposed by others, that location of the tumor within the duct has prognostic significance because of the readiness to resect the lesion and to obtain a negative margin cannot be confirmed in this series. Nevertheless, to obtain a microscopically tumor-free resection margin is the main goal, since from multivariable analyses this remained an independent prognosticator for the entire group of CCA. Specifically, patients with a mid CCA who would undergo a local resection could benefit from a more extensive surgical approach. Other recent studies all advocate an extensive surgical approach to achieve favorable long-term results.

The UICC TNM guidelines generally recommend a minimum of 10 lymph nodes for adequate pathological assessment of nodal status. Anatomical differences between patients but also the diligence of the pathologist in recovering lymph nodes from the resection specimen are recognized factors in determining the number of lymph nodes. A detailed knowledge of the anatomical distribution of lymph nodes, e.g. according to the Japanese Pancreatic Society classification for PD specimens, significantly improves lymph node yield and possibly enhances pathologic assessment for staging. A drawback of the present study is that such a classification has not been implemented in the pathological dissection protocol in our institute. Another factor that determines the number of lymph nodes in a resection specimen is the type of surgical resection. Consistent with other studies, we found that distal tumors were more frequently associated with a higher number of recovered lymph nodes and identified tumor positive nodes compared with proximal tumors. A possible explanation could be the anatomic limitation of portal node dissection for proximal tumors that restricts the number of recovered nodes to the hepatoduodenal ligament. Also, lymph node involvement outside the hepatic hilar region, as intraoperatively determined with frozen section, led to cancellation of resection in later years. Probably, this led to a decreased proportion of patients with proximal CCA and lymph node metastases in the resected specimen. Nevertheless, this unequal distribution of positive nodes within groups did not result in a significant survival difference and moreover, the presence of identified tumor-positive nodes remained an independent prognosticator.

From the data of the reduced model, we have developed a nomogram with three variables (lymph node status, tumor differentiation grade, residual tumor margin...
status). In contrast to other gastrointestinal tumors such as esophageal carcinoma, validation of a staging system with these alternative factors as opposed to the TNM staging system has to our knowledge not yet been carried out for CCA. Applying the nomogram requires summarizing points belonging to these three variables and drawing lines. This simplicity allows easy day-to-day clinical use. The nomogram provides survival probabilities to survive 1 or 2 years following surgery, which is valuable and easy to interpret information for the individual patient. The nomogram we have presented estimates prognosis postoperatively in patients who underwent potentially curative surgery for extrahepatic CCA. Its use is limited to the postoperative situation. Although conclusive evidence regarding benefit of adjuvant chemotherapy, the type of regime, and which specific patients might benefit has not been established for CCA, the nomogram could aid in future selection for this kind of treatment.

As shown in previous studies, TNM-staging alone had moderate prognostic qualities. Stage 0 and IA were associated with the most favorable survival, whereas stage III was evidently associated with the worst prognosis. However, for the stages in between, no clear differences were observed, stages IB and IIA even overlapped. This inconsistency of the TNM staging system and the need for revision to achieve more accurate survival estimates have been observed previously. By adding other clinicopathological prognostic factors to the model, more accurate estimates of survival for patients with distal or proximal CCA are possible. The prognostic model in the present study, using variables from the Cox regression analyses, led to an improvement in the prediction of CSS after resection compared with TNM-staging alone. However, there are some limitations with respect to our findings. Precise survival prediction for the individual patient is still not possible; the full and reduced models only predict the likelihood that a population of similar patients will survive a defined period of time. Although internally valid, the nomogram should further be externally validated in another large series of resected CCA for reliability and consistency. Furthermore, prediction models as constructed in the present study should be considered dynamic. The knowledge over different molecular (gene- and protein expression) markers in gastrointestinal tumors is rapidly increasing. Incorporation of such markers into the model could further increase its accuracy.

In conclusion, patients with distal CCA were associated with a less favorable CSS after resection compared with mid or proximal lesions; however, location was not an independent prognostic factor. A microscopically margin-negative resection was the only prognostic factor determined by the surgical procedure. Specifically, for mid CCA, this implicates that, in order to improve survival, the surgical procedure should be extended either with partial liver resection or with PD, depending on the location of the lesion closer to liver or pancreas. A prognostic model using lymph node status, microscopically residual tumor status, and tumor differentiation grade was better compared with TNM staging. This reduced model provides more reliable prognostic information and might be helpful to offer tailored adjuvant therapy.
REFERENCE LIST


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Part IV Diagnosis and Prognosis of Hepatopancreaticobiliary Diseases

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