Surgery for extrahepatic cholangiocarcinoma: predictors of survival

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Abstract

The incidence of extrahepatic cholangiocarcinoma is increasing worldwide and is often in an advanced stage at diagnosis and difficult to treat. The TNM (tumor node metastasis) cancer staging system predicts survival on the basis of tumor histopathology and the presence of distant metastases. However, numerous prognostic factors have been described that are not included in the TNM system. This review focuses on the prognostic significance of clinical, surgical, and histopathological factors as reported in the literature. Overall, the most important independent prognostic factors for long-term survival are negative surgical margins, lymph node status, and differentiation grade of the tumor. Further improvement of staging systems and identification of prognostic factors are crucial if we are to better select patients for surgical and adjuvant therapy and, hence, increase the rate of curative resections.

Key Words: Cholangiocarcinoma, lymph nodes, prognostic factors, resection margin, survival

Introduction

Cholangiocarcinoma (CCA) can be classified into intrahepatic and extrahepatic CCA, the latter including distal and hilar cholangiocarcinoma (HCCA), depending on its location within the biliary tree [1]. Surgical treatment, consisting of hilar resection with extended hepatectomy, pancreatoduodenectomy (PD), or sometimes local bile duct resection, is the only curative treatment option [2–6]. Despite comprehensive preoperative staging to select patients for potentially curative resection, many patients present with recurrences within 2 years after tumor resection. Overall, 5-year survival rates of 20% to 35% have been reported after resection [6–15].

There is no single staging system for all CCA, reflecting the different patho-biology of intrahepatic and extrahepatic tumors [16]. For staging of intrahepatic CCA, the proposed TNM (tumor node metastasis) system has been shown to correlate with survival after hepatic resection [17]. To stage extrahepatic CCA, accounting for approximately two-thirds of all CCA, a different pTNM system is used [18,19]. Several modifications and alternatives have been implemented with the objective of improving the prognostic and therapeutic predictions for each cancer stage. However, to improve the currently available staging systems, additional clinical and histopathologic factors have been suggested [20].

The current study reviews the major clinical-pathological factors, operative techniques, and adjuvant treatment strategies that influence survival of resectable extrahepatic CCA. Future directions towards improving staging systems are proposed.

Methods

A review of the English-language literature (January 1995 through September 2007) concerning resectable CCA was performed (intrahepatic, gallbladder, and periampullary adenocarcinoma were excluded) focusing on the prognostic power of clinical, surgical, and histopathological factors in relation to resectable extrahepatic CCA.

Results

Clinical prognostic factors (summarized in Table I)

Age and sex. In case of comparable therapy, age was found not to be of any prognostic significance in several studies [8,21,22]. However, two studies...
showed a worse long-term outcome for older patients [9,12]. Three studies reported a survival benefit in multivariate analyses for female compared to male patients with extrahepatic CCA [8,9,23].

**Symptoms at initial presentation.** The majority of patients with extrahepatic CCA present with jaundice. Three studies describe a long-term favorable prognostic effect of low initial plasma bilirubin level in univariate analysis [24,25] as well as in multivariate analysis [2]. Weight loss is usually a reflection of advanced disease. However, none of the studies found this clinical sign to be a prognostic factor.

**Co-morbidity.** It has been suggested that the presence of hepatolithiasis hinders diagnosis of underlying CCA preoperatively and precipitates biliary sepsis, which affects resectability. Hepatolithiasis per se, however, did not influence long-term survival [26].

**Tumor location.** Extrahepatic CCAs are subclassified mostly according to their location within the biliary tree. It has been suggested that CCAs in the distal or middle part have better prognosis because these give rise to total obstruction and therefore are detected earlier, whereas proximal tumors tend to commence with partial biliary obstruction consequently resulting in fewer complaints and late jaundice. However, in one study there was only a survival benefit for patients with distal lesions at univariate analysis [27], and in the other two studies no difference in survival was found in respect of tumor location [11,28].

**Bismuth–Corlette staging system.** Hilar lesions can be classified according to location and segmental infiltration into the biliary tree, as suggested by the Bismuth–Corlette system [29]. In several studies, this staging system had no predictive value for survival [7,21,22,30–33]. In two studies at univariate analysis [34,35] and in another at multivariate analysis [25] a favorable outcome for stages I and II was observed.

**Chemoradiation therapy.** The main goal of adjuvant chemoradiation therapy is improvement of local control and consequently survival. In a retrospective analysis, improved survival was observed for patients with adjuvant radiation therapy [36]; however, this was not confirmed in other studies [37,38]. In one study, patients referred after neoadjuvant chemotherapy had an unexpected survival benefit [9]. Furthermore, a significant improvement in survival was demonstrated after adjuvant chemotherapy in both univariate analysis [39,40] and multivariate analysis [10,41].

**Surgical prognostic factors (summarized in Table I)**

<table>
<thead>
<tr>
<th>Clinical/surgical factor</th>
<th>Prognostic impact</th>
<th>Favouring survival benefit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Minor</td>
<td>Younger age</td>
<td>[9,12]</td>
</tr>
<tr>
<td>Sex</td>
<td>Considerable</td>
<td>Female</td>
<td>[8,9,23]</td>
</tr>
<tr>
<td>Level of jaundice</td>
<td>Considerable</td>
<td>Low initial plasma bilirubin level</td>
<td>[2,24,25]</td>
</tr>
<tr>
<td>Hepatolithiasis</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td>Dubious</td>
<td>Distal lesion</td>
<td>[27]</td>
</tr>
<tr>
<td>Bismuth–Corlette staging</td>
<td>Dubious</td>
<td>Type I, II lesion</td>
<td>[25,34,35]</td>
</tr>
<tr>
<td>Chemoradiation therapy</td>
<td>Considerable</td>
<td>(Neo)adjuvant therapy</td>
<td>[9,10,39–41]</td>
</tr>
<tr>
<td>Type of operation</td>
<td>Considerable</td>
<td>Concomitant PHx</td>
<td>[3,67]</td>
</tr>
<tr>
<td>Portal vein resection</td>
<td>Considerable</td>
<td>Portal vein resected</td>
<td>[3,7,14,32,45]</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>Considerable</td>
<td>No blood transfusion</td>
<td>[23,33]</td>
</tr>
</tbody>
</table>

Prognostic impact on clinical and surgical factors is scored as none (no evidence), dubious (conflicting evidence), minor (evidence from univariate analysis), considerable (evidence from uni- and multivariate analysis) and strong (evidence from several multivariate analyses). PHx = Partial hepatectomy.
**Portal vein resection.** Portal vein invasion was previously considered a main cause of unresectability of HCCA. However, this view has been abandoned. Two studies found a survival benefit of portal vein resection in univariate analysis [3,32], and one in multivariate analysis [14]. In a multivariate analysis after R0 resection, additional resection of the portal vein was the only variable with a significant influence on patient survival [7,45]. However, microscopic invasion of the resected portal vein was found in only 12% of patients [7]. In another study, the microscopic invasion rate of the resected portal veins was 69% [6]. These authors did not find a survival benefit of portal vein resection.

**Surgical complications.** A prognostic relation between the amount of intraoperative blood loss (and consequently blood transfusions) and overall survival has been hypothesized. In patients resected for HCCA, two studies confirmed this hypothesis in multivariate analysis [23,33]. A study focusing on overall postoperative complications found a negative survival effect resulting from these complications, although this effect was not identified as an independent factor [9].

**Pathologic prognostic factors (summarized in Table II)**

**Pathologic staging systems.** The 6th edition of the American Joint Committee on Cancer [19] (AJCC) and Union Internationale Contre le Cancer [18] (UICC) for adenocarcinoma of the extrahepatic biliary tract are TNM based. Compared to the 5th edition these systems now also focus on vascular invasion requiring vascular resection and reconstruction, as well as lymph node (LN) metastasis [20]. Obviously, stage groupings should represent strong independent prognostic factors, with a higher stage implying more advanced disease. Surprisingly, only five studies confirmed the TNM staging system as an independent prognostic factor [2,3,5,46–48]. In several studies, the staging system had no predictive value for survival [3,8,21,32,33,49] and, in a few, only in univariate analysis [23,31,50].

**Radicality.** The incidence of a microscopically positive surgical resection margin in patients who have undergone a resection with curative intent can increase to 50%. The most consistent independent determinant for long-term survival after potentially curative resection of a biliary tumor is the surgical margin status of the resected bile duct [3,7–9,14,25,30–32,41,45–49,51–57]. A study focusing particularly on radicality found a survival benefit for patients with residual carcinoma in situ in comparison to invasive carcinoma at the ductal resection margins [52].

**Tumor invasion.** Increased depth of tumor invasion is associated with the presence of lymphatic dissemination [13], vascular/perineural invasion, and is a known independent prognostic parameter [47,58,59].

**Lymph nodes.** The incidence of LN involvement in resected specimens has been reported to range from 30% to more than 50% [7,11,14,30,41,48,60–62]. In one study, already 55% of the T2 tumors had positive LN [62]. The presence of lymphatic dissemination is an important independent prognostic factor, as has been confirmed in many studies [6,8,10,12,14,21,25,30–32,39,48,50,51,53,54,58,63].

**Number of positive nodes (ratio).** The chance of identifying involved LNs increases with the number of resected (pathologically identified) LNs and is influenced by the extent of dissection. A higher number of positive nodes indicates further progression of disease. Only two studies have reported a worse survival in patients with a higher number of positive LN metastases [41,58].

Table II: Pathological prognostic factors in extrahepatic CCA.

<table>
<thead>
<tr>
<th>Pathologic factor</th>
<th>Prognostic impact</th>
<th>Favouring survival benefit</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM staging systems</td>
<td>Considerable</td>
<td>Early stage</td>
<td>[2,35,46–48]</td>
</tr>
<tr>
<td>Radicality</td>
<td>Strong</td>
<td>R0 resection</td>
<td>[3,7–9,14,25,30–32,41,45–49,51–57]</td>
</tr>
<tr>
<td>Tumor invasion</td>
<td>Considerable</td>
<td>Early stage</td>
<td>[47,58,59]</td>
</tr>
<tr>
<td>LN metastases</td>
<td>Strong</td>
<td>Metastases absent (N0)</td>
<td>[6,8,10,12,14,21,25,30–32,39,48,50,51,53,54,58,63]</td>
</tr>
<tr>
<td>No. of positive LN</td>
<td>Minor</td>
<td>Fewer positive nodes</td>
<td>[41,58]</td>
</tr>
<tr>
<td>Location of positive LN</td>
<td>None</td>
<td>Micrometastases absent</td>
<td>[65]</td>
</tr>
<tr>
<td>Micrometastases in LN</td>
<td>Dubious</td>
<td>Micrometastases absent</td>
<td>[65]</td>
</tr>
<tr>
<td>Extracapsular LN involvement</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Differentiation grade</td>
<td>Strong</td>
<td>Good differentiation</td>
<td>[2,3,6–8,25,28,35,45,49,50,52,56]</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>Considerable</td>
<td>No invasion</td>
<td>[12,49]</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>Considerable</td>
<td>No invasion</td>
<td>[7,45,66]</td>
</tr>
</tbody>
</table>

Prognostic impact on clinical and surgical factors is scored as none (no evidence), dubious (conflicting evidence), minor (evidence from univariate analysis), considerable (evidence from uni- and multivariate analysis) and strong (evidence from several multivariate analyses). LN = Lymph node.
Location of positive LN. Although there is an individual preference of lymphatic spread of adenocarcinomas in the proximal, middle, and distal bile ducts [62], a pericholedochal node in the hepatoduodenal ligament is the most common site of metastasis [61]. Regional and para-aortic LNs are frequently involved in advanced CCA and extended lymphadenectomy has been suggested as providing a survival benefit in selected patients [13]. Survival was favorable in the presence of distant LN metastasis in selected patients [13,20,64].

Micrometastases in LN. In one study, LN micrometastases were detected in 24% of patients with pN0 disease, but this did not show any impact on survival [49]. In another study, LN micrometastasis in CCA had a negative effect on survival in univariate analysis [65].

Extracapsular LN involvement. So far, no reports have described the significance of extracapsular LN involvement in extrahepatic CCA.

Differentiation grade. Microscopically, adenocarcinomas are graded as well differentiated, moderately differentiated, or poorly differentiated. Lack of differentiation increases the risk of lymphatic dissemination and therefore has a negative effect on survival. The grade of differentiation has been identified as an independent prognosticator in several studies [2,3,6–8,25,28,35,45,49,50,52,56].

Vascular invasion. The impact of blood vessel invasion (microscopic venous invasion) has mainly been shown in univariate analysis [6,46,51,58,59]. Two studies reported vascular invasion as independent factor for worse survival [12,49].

Perineural invasion. Perineural invasion refers to growth of tumor along the nerve branches present within the biliary tract tissue. This mechanism of spread has shown prognostic significance in a few studies in univariate analysis [6,21] as well as in multivariate analysis [7,45,66].

Discussion

Overall, the most important independent prognostic factors for long-term survival are negative surgical margins, LN status, and differentiation grade of the tumor. Therefore, all patients with a suspicious biliary obstruction should be considered for laparotomy and potential resection, as this provides the only chance for cure. Despite an aggressive surgical approach and advances in surgical techniques, the overall prognosis of patients undergoing potentially curative resection for extrahepatic CCA is still poor, with high local failure rates and associated postoperative mortality.

The adequacy of the current pTNM staging system has been questioned repeatedly, with several authors proposing a revision of the system [3,6,16,20,58]. Firstly of note, the current systems (the Bismuth–Corlette and the AJCC/UICC) are not satisfactory, because they fail to consider all of the relevant local, tumor-related variables that determine respectability, and they correlate poorly with survival. The Memorial Sloan–Kettering Cancer Center (MSKCC) devised a staging system for HCCA that encompasses a full radiological diagnosis and shows a correlation with increasing T stage and survival [3,67]. Secondly, in the current TNM staging system used for extrahepatic CCA, only a N0 and a N1 classification exist. Several studies propose including the number of positive LNs [41,58]. Thirdly, one study focusing on the differences between the 5th and 6th TNM staging systems concluded that cancer invasion of the portal bifurcation and regional LN metastasis should be weighed equally.

The World Health Organization classification of extrahepatic CCA does not distinguish between distal and HCCA. According to the current literature, the prognostic significance of the location of an extrahepatic CCA is uncertain. Important independent factors predicting survival were the same for distal and proximal tumors. Therefore, there is a rationale for classifying all patients with extrahepatic tumors in one TNM staging system. However, the surgical procedure to obtain the most consistent independent prognosticator, i.e. a negative resection margin, is completely different between distal and HCCA. Several surgical prognostic factors were found to have an impact on patient survival specifically in patients with HCCA. One study showed a biological difference between distal and hilar tumors [28]. These findings favor a distinct staging system for distal and proximal CCA.

Conclusions

The simplicity of the TNM system, covering all extrahepatic CCA, is one of the reasons why it has continued to be applied. However, because biological diversity is high in patients with distal CCA or HCCA, many authors feel that additional factors can improve clinical staging. A challenge for the future is therefore to develop a new, dynamic staging system that includes the diverse variables which have been shown to impact on prognosis. Further improvement of staging systems and identification of prognostic factors is therefore crucial as means towards better selection of patients for appropriate surgical and adjuvant therapy and, hence, towards increasing the rate of curative resections.
References