Clinicopathological analysis and prognosis of extrahepatic bile duct cancer with a microscopic positive ductal margin

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Abstract

Background: The fate of a microscopic positive ductal margin (MPDM) of extrahepatic bile duct (EHBD) cancer is unclear. The purpose of this study was to analyse the clinicopathological features of EHBD cancer with MPDM and to identify the prognostic factors associated with survival.

Methods: Between 1995 and 2007, a retrospective analysis of 464 patients who had undergone surgical resection for EHBD cancer was conducted. Clinicopathological factors likely to influence survival were assessed using univariate and multivariate analysis.

Results: One hundred twenty-four patients had MPDM which included invasive carcinoma (IC) (n = 85) and carcinoma in situ (CIS)/ high-grade dysplasia (HGD) (n = 39). The median survival (MS) of R0, R1 as CIS/ HGD, and R1 as IC were 41 months, 29 months, and 18 months, respectively. Adverse prognostic factors were ‘IC’ on the resection margin [HR = 1.66, 95% confidence intervals (CIs) 1.06–2.59, P = 0.026], and no use of adjuvant chemoradiotherapy (HR = 1.57, 95% CIs 1.04–2.39, P = 0.033). Adjuvant chemoradiotherapy was beneficial in patients with MPDM as IC (5-year survival rate 19.7 compared with 2.8%, P = 0.011).

Conclusions: The presence of MPDM is an important prognostic factor in EHBD cancer. When a ductal resection margin is positive, discrimination between ‘IC’ and ‘CIS/ HGD’ is important.

Introduction

A surgical resection has been the mainstay of curative treatment for extrahepatic bile duct (EHBD) cancer. Overall, 5-year survival rates (5YSR) of 20–35% have been reported after resection of EHBD cancer. In addition, most patients who undergo a resection die of local tumour recurrence. This is because a complete surgical resection with tumour-free histological margins is difficult to obtain.

Anatomically, EHBD cancers are classified as perihilar and distal bile duct cancers. However, tumours are rarely confined to the short segment as bile duct cancer tends to longitudinally spread along the bile duct wall. Recent advances in imaging modalities and surgical strategies have improved the outcome of the surgical treatment for EHBD cancer. A surgical resection for EHBD cancer is determined by the location and extent of the tumour.

Although a pre-operative diagnosis for the extension of EHBD cancer has improved in recent years, it is difficult to decide the surgical resection margin pre-operatively. In some patients, a margin positive resection was inevitable considering the operative risk. A positive resection margin has been considered an adverse prognostic factor; however, the reported incidence of a positive surgical resection margin in patients who have undergone a resection with curative intent has varied from 9% to as high as 74%. This could be explained by a variation...
between institutions or investigators on the principle of the operation or the definition of a positive resection margin. However, there are few reports on the long-term outcome and factor analysis associated with survival in patients with a positive resection margin.

The purpose of this retrospective study was to analyse the clinicopathological features of EHBD cancer with a microscopic positive ductal margin (MPDM) after a surgical resection, and to explore the prognostic factors in patients with EHBD cancer with MPDM. The clarification of whether residual carcinoma in situ (CIS)/high-grade dysplasia (HGD) at ductal resection margins differs prognostically from residual invasive ductal disease in patients with EHBD cancer was also assessed.

**Patients and methods**

**Patients and surgical procedures**

With the approval from the institutional review board, all patients with EHBD cancer who underwent a resection at Seoul National University Hospital (SNUH) were entered into a prospectively maintained database between 1995 and 2007.

Pre-operatively, the predominant location of the tumour and the extent of the tumour along the biliary tract were evaluated using imaging studies, including an enhanced computed tomography (CT) scan, ultrasonography, magnetic resonance imaging (MRI), cholangiography and sometimes choledochoscopy. Surgical procedures were decided by each attending surgeon with consideration of the balance between the tumour extent and the safety of each procedure. Distant metastasis, extensive lymph node metastasis such as para-aortic lymph node involvement, bilateral extensive intrahepatic duct infiltration, involvement of major vessels except focal portal vein invasion and other systemic poor operative risk factors were contraindications of a curative resection.

After a laparotomy and the exclusion of distant metastasis, all of the following surgical procedures including a regional lymphadenectomy at the right side of the celiac artery, and all tissues in the hepatoduodenal ligament except the portal vein and the hepatic artery, were removed (skeletonization of the hepatoduodenal ligament). The type of resection was determined in patients with diffuse bile duct cancer. When the tumour was mainly located in the perihilar bile duct or involved in the liver parenchyma, unilateral hepatic artery, or portal vein, an extended hemihepatectomy including caudate lobectomy combined with bile duct resection (HBR) was performed. When the tumour was chiefly located in the distal bile duct, a pancreatoduodenectomy (PD) was usually performed. Since 1991, pylorus preservation has been attempted in all patients undergoing PD, except when duodenal ischaemia, duodenal ulcer or duodenal tumor infiltration was present. A hepatopancreatoduodenectomy (HPD) was indicated in patients with diffuse bile duct cancer.

**Diagnosis and definition of surgical margins**

A R0 resection was defined as no residual ductal disease. Intraoperative evaluation of the proximal (hepatic)-side and/or distal (duodenal)-side ductal margins was performed using frozen sections among all patients. Operative specimens were submitted for permanent histopathology. On the basis of the type of resection procedure performed, the appropriate proximal and distal bile duct margins were identified, and a cross-section of each was submitted for histology. When the distal-side ductal margin was positive, additional resection of the intra-pancreatic bile duct or PD was performed, as far as possible in principle. When the proximal-side ductal margin was positive, additional resection of the hepatic duct or an additional hepatectomy was performed where possible. Positive surgical margins were classified into two categories: ‘invasive carcinoma (IC)’ and ‘CIS/HGD’. In the present study, HGD was included in the category of CIS owing to the extreme difficulty if distinguishing between the two epithelial lesions. Radial margins were defined as surgical margins other than the ductal margins of the resected specimen, but there were no isolated positive radial margins without MPDM. Microscopic positive ductal margins were confirmed by permanent pathological examination of a resected margin.

**Comparison of clinicopathological variables in patients with MPDM and patients follow-up**

Resected specimens were submitted to the Department of Pathology in SNUH for histological evaluation, in which experienced hepatobiliary pathologists examined all the specimens without knowledge of any previous diagnoses and clinical details. Clinicopathological variables including age, gender, location of a positive margin, histological grade and type of patient with MPDM were evaluated. Histological findings were described in accordance with the 7th edition TNM staging of the American Joint Committee on Cancer (AJCC). Patients were followed regularly in outpatient clinics every 3–6 months, and the information during follow-up for all patients was obtained. The sites of initial disease recurrence were determined from cross-sectional imaging studies, such as computed tomography or magnetic resonance imaging. They were classified as local disease recurrence (resection margin, bilioenteric anastomosis, or porta hepatis), regional disease recurrence (retroperitoneal lymph nodes) and distant disease recurrence (intrahepatic, peritoneum, or extra-abdominal sites). The overall survival was analysed from the date of surgical resection to the date of death from all causes. The causes of death were determined from the medical records. The follow-up period was defined as the intervals between the date of surgical resection and that of the last follow-up.

**Adjuvant treatment**

Other than for poor performance status or refusal to the chemoradiation, adjuvant treatment was performed after the patients were informed of the prognosis and of the effects of each treatment modality. Decisions were made after thorough discussions with patients, physicians and each attending surgeon.
Fluorouracil (5-FU)-based concomitant chemo-radiotherapy (CCRT) consisted of up to 40 Gy at 2 Gy/fraction with a 2-week planned rest, and an intravenous bolus of 5-FU (500 mg/m²/day) given on day 1 to 3 of each split course.27 Some patients received 5-FU monthly for 1 year after radiotherapy.28 In patients treated with chemotherapy alone, various fluoropyrimidines including 5-FU, S-1, capecitabine or uracil-tegafur were used.28

### Statistical analysis

The data was analysed using SPSS® version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous and normally distributed variables are presented as the medians and range. Continuous parameters in each group were compared using the independent t-test or the Mann–Whitney U-test, and categorical parameters using the χ² test or Fisher’s exact test. Medical records and survival data were obtained for all patients. Survival curves were constructed using the Kaplan–Meier method and differences in survival were evaluated using the log-rank test. Multivariate analysis for prognostic factors used Cox’s proportional hazards model. Probability (P)-values of 0.05 or less were considered statistically significant.

### Results

#### Clinicopathological analysis of EHBD cancer with curative-intended resection

The clinicopathological findings in patients with EHBD cancer with a curative-intended resection are listed in Table 1.

### Clinicopathological analysis of EHBD cancer with MPDM

A total of 124 patients were identified for MPDM after reviewing the pathological diagnosis of resected margin, the results of which are shown in Table 2.

#### Survival analysis of EHBD cancer with MPDM

The median survival (MS) and 5-year survival rate (5YSR) of R0, R1 as CIS/ HGD, and R1 as IC were 41 months and 44.5%, 29 months and 20.7%, and 18 months and 12.0%, respectively (Fig. 1).

In the univariate analysis, the outcome after a surgical resection was better in patients with a ‘CIS/HGD’ ductal margin than in those with a ‘IC’ ductal margin (Table 3 and Fig. 1). Age 60 years or older, lymph node metastasis (N stage) and no use of adjuvant treatment including CCRT had a marginally significant adverse effect on survival (Table 3).

After multivariate analysis, there were two independent adverse prognostic factors: invasive carcinoma on the resection margin [hazard ratio (HR) = 1.66, 95% confidence intervals 1.06–2.59, P = 0.026] and no use of adjuvant CCRT (HR = 1.57, 95% confidence intervals 1.04–2.39, P = 0.033).

#### Ductal margin status and recurrence

Fifty-three with IC and 25 out of 124 patients with CIS/ HGD had disease recurrence during follow-up. There were no significant differences in local disease recurrence (25 of 85 patients, versus 14 of 39 patients, P = 0.820), regional disease recurrence (9 of 85 patients versus 6 of 39 patients, P = 0.629), distant disease recurrence (31 of 85 patients versus 15 of 39 patients, P = 0.616) between IC and CIS/ HGD.

#### Natural course of MPDM

Figure 2 shows the clinical course of patients with MPDM. As previously noted, the 5YSR of CIS/HGD was higher than that of IC (Table 3 and Fig. 1). In addition, the disease-free (DF) (5YSR) of the CIS/HGD group was higher than that of the IC group with a statistically marginal significance. When subdividing the IC...
group as treated adjuvant treatment including or excluding CCRT, the 5YSR and DF-5YSR of the patients with adjuvant treatment were higher than that without adjuvant treatment (5YSR 19.7 versus 2.8%, \( P = 0.011 \); DF-5YSR 16.6 versus 0%, \( P = 0.012 \)) (Fig. 2).

**Discussion**

The most consistent independent determinant for long-term survival after a potentially curative resection of EHBD cancer is the surgical margin status of the resected bile duct. In consideration of a few studies insisting that the presence of MPDM may not have an effect on the overall mean survival,\(^2\) numerous studies have reported an association of MPDM with a major decrease in survival rates and an increase in recurrence rates.\(^6,15,18–21,24\) This present study added MPDM as an adverse prognostic factor (Fig. 1).

There are several reports showing some patients undergoing a resection with microscopic tumour involvement at the bile duct margin survive longer than expected.\(^6,11,20,30,31\) Among these, several studies reported CIS/HGD at the bile duct margin was prognostically better than residual IC in patients undergoing surgical resection for EHBD cancer.\(^12,20,30,32,33\) However, there are few studies on the long-term fate and on detailed analysis for factor associated survival in patients with a positive resection margin. In the present study, in spite of concerns about a significant correlation of tumour extension, IC on the resection margin was revealed as one of the independent prognostic factors after multivariate analysis. This can be explained by the biological nature of the main tumours displaying extensive superficial spread, which is likely to be responsible for the remnant CIS/HGD at the bile duct stump, tends to be less malignant compared with that of a conventional IC.\(^3\)

**Table 2** Patients characteristics of a microscopic positive ductal margin among a curative intended resection

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tumour location</th>
<th>Total (( n = 124 ))</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Perihilar (( n = 90 ))</td>
<td>62.3 ± 10.5</td>
<td>Diffuse (( n = 4 ))</td>
</tr>
<tr>
<td>Gender (M : F)</td>
<td>64:26</td>
<td>19:11</td>
<td>1:3</td>
</tr>
<tr>
<td>Location of margin (+) PRM/ DRM/ Both/ RM</td>
<td>57/5/28/5</td>
<td>30/0/0/0</td>
<td>3/0/1/0</td>
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<tr>
<td>Histological Grade PP + WD/ MD + PLD</td>
<td>24:60</td>
<td>6:21</td>
<td>1:2</td>
</tr>
<tr>
<td>Op type (n, %)</td>
<td>39 (43.3)</td>
<td>6 (6.7)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>HBR</td>
<td>39 (43.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BDR</td>
<td>41 (45.6)</td>
<td>2 (6.7)</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (6.7)</td>
<td>28 (93.3)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>HPD</td>
<td>4 (4.4)</td>
<td>0</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>21 (1.0–163.0)</td>
<td>18 (0–172.6)</td>
<td>9 (4.0–36.0)</td>
</tr>
</tbody>
</table>

*Five of PRM (+) among patients with perihilar bile duct cancer were revealed as combined radial margin positivity. PRM, proximal resection margin; DRM, distal resection margin; RM, radial resection margin; PP, papillary carcinoma; WD, well-differentiated; MD, moderate-differentiated; PLD, poorly-differentiated carcinoma; HBR, extended hemihepatectomy combined with bile duct resection; BDR, EHBH resection with lymphadenectomy; PD, pancreatoduodenectomy; HPD, hepatopancreatoduodenectomy.

**Figure 1** Overall survival in patients with extrahepatic bile duct cancer with curative intended resection. IC, invasive carcinoma; CIS, carcinoma in situ; HGD, high-grade dysplasia
In spite of the slower growth, remnant CIS/HGD has the potential to develop into lethal IC. In this study, regardless of the prolonged survival compared to MPDM as IC, survival of MPDM as CIS/HGD had a worse prognosis than that of the R0 resection (Fig. 1). Thus, CIS/HGD should be completely resected to achieve long-term survival if possible. However, when CIS/HGD spreads too widely, extended surgery such as HPD may be required. For patients in a poor general condition or with high operative risk, limited resection of the main invasive cancer with CIS/HGD remaining at the ductal stumps, as an alternative procedure, might bring considerable survival benefits.

In this study, many other clinicopathological factors were reported to have a positive or negative impact on survival, including lymph node metastasis, AJCC pT, histopathological grading and gender. In this study, there were no significant differences with respect to survival based on the loca-
tion of the tumour or resection type, suggesting that once the microscopic remnant tumour has occurred, the prognoses of different locational types are similar (Table 3). These results were similar to Jang et al. where they reported on the actual long-term outcome of EHBD cancer after a surgical resection.

There has been controversy whether remnant CIS/HGD at the bile duct stump develops into IC. Jang et al. previously reported that, in attempted curative surgery, microscopic tumor involvement in the resection margin did not always mean early recurrence. However, there are several reports that show a significant relationship between local recurrence and ductal margin status.

Furthermore, some studies suggested residual CIS may cause late local disease recurrences, whereas residual invasive ductal lesions cause early local recurrences. In this study, 14 out of 39 patients with CIS/HGD showed local recurrence at the bile duct stump, such as, bilioenteric anastomosis, or porta hepatitis. However, this result did not have any statistical difference in the local recurrence rate in patients with IC (25 out of 85 patients, \( P = 0.820 \)). As a result, it could be possible that CIS/HGD has the potential to progress to IC.

Even although there is a possibility for CIS/HGD to develop into IC, there are differences in their biological behaviours. Remnant CIS/HGD is likely to develop into IC in the late phase after surgery. In this study, the DF-5YSR of the CIS/HGD group was significantly higher than that of the IC group (Fig. 2), suggesting that CIS/HGD had less malignancy and showed slower growth than IC. In spite of the similar incidence of recurrence, it is noteworthy that a ductal margin with CIS/HGD resulted in a prolonged disease-free survival than that of a ductal margin with IC. Therefore, as mentioned above, for patients in a poor general condition or with high operative risk, limited resection of the main invasive cancer with CIS/HGD remaining at the ductal stumps, as an alternative procedure, may bring considerable survival benefits.

Gawk et al. suggested that adjuvant radiotherapy might be useful in patients with EHBD cancer, especially for those patients with microscopic residual tumours and positive lymph nodes after resection for increasing local control. In this study, there was no survival benefit with adjuvant chemotherapy alone but an increase in survival in patients with MPDM who received CCRT with marginal significance (Table 3), especially the patients with an IC resection margin (Fig. 2). In spite of this study has the limitation that the post-operative adjuvant treatment was given to selected patients and the treatment regimens differed significantly among the individuals, some subsets of patients with a positive margin could have a better prognosis if chemoradiotherapy is combined with a surgical resection.

In conclusion, among patients undergoing a surgical resection for EHBD cancer, IC at the ductal resection margins appears to have a more adverse effect on survival, whereas residual CIS or HGD does not. It is therefore clear that when the ductal resection margin status is positive upon pathological examination, discrimination between CIS/HGD and IC is clinically important, and a resection should be considered and efforts should be made to obtain an IC-free margin. For MPDM, especially IC, adjuvant chemoradiation can be beneficial.

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Conflicts of interest
The authors have no conflicts to disclose.

References


