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Retrospective Study

Significance of dysplasia in bile duct resection margin of patients with extrahepatic cholangiocarcinoma: A retrospective analysis

Choe JW *et al.* Dysplasia margin in resected cholangiocarcinoma

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Abstract

BACKGROUND

Radical resection is the only indicator associated with survival in extrahepatic cholangiocarcinoma (EHCC). However, limited data are available regarding the implications of dysplasia at the resection margin following surgery.

AIM

To evaluate the prognostic significance of dysplasia-positive margins in patients diagnosed with EHCC.

METHODS

We reviewed the records of patients who had undergone surgery for EHCC with curative intent between January 2013 and July 2017. We retrospectively analyzed the clinicopathological data of 116 patients followed up for longer than three years. The status of resection margin was used to classify patients into negative low-grade dysplasia (LGD) and high-grade dysplasia (HGD)/carcinoma *in situ* (CIS) categories.

RESULTS

Based on postoperative status, 72 patients underwent resection with negative margins, 19 patients had LGD-positive margins, and 25 patients showed HGD/CIS-positive margins. The mean survival rates of all patients with negative margin, LGD margin, and HGD/CIS margin were 49.1 ± 4.5 , 47.3 ± 6.0 , and 20.8 ± 4.4 mo ($P < 0.001$). No difference in survival was found between groups with LGD margin and negative margin (P -value = 0.56). In multivariate analysis, age > 70 years and HGD/CIS-positive margins were significantly independent factors for survival (HR = 1.90 and 2.47).

CONCLUSION

HGD/CIS margin in resected EHCC was associated with poor survival. However, the LGD-positive resection margin was not a significant indicator of survival in patients with EHCC.

Key Words: Dysplasia; Cholangiocarcinoma; Survival; Extrahepatic cholangiocarcinoma; Low-grade dysplasia; High-grade dysplasia

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Core Tip: This study indicated that the status of the bile duct resection margin in operable extrahepatic cholangiocarcinoma (EHCC) is an important indicator of recurrence and survival. High-grade dysplasia/carcinoma in situ margin in resected EHCC was associated with poor survival and high tumor recurrence. However, low-grade dysplasia positive margin was not a significant prognostic factor in patients with EHCC.

INTRODUCTION

The incidence of extrahepatic cholangiocarcinoma (EHCC) is increasing worldwide due to advances in diagnostic modalities and increased life expectancy^[1]. Despite multidisciplinary management, only 20% of these patients are eligible for surgical resection, and the disease is associated with poor prognosis and less than 10% 5-year overall survival^[2]. Even though surgical resection for EHCC has been performed more frequently in recent years, the prognosis is still dismal because of frequent recurrence in R1 (microscopic residual tumor) resection margins^[3,4]. The status of bile duct resection margin is the most important indicator of recurrence and survival, and a carcinoma-negative margin is the only factor associated with survival^[5-7].

However, ensuring an adequate resection margin is still a challenge due to perioperative morbidity associated with extensive surgical procedures. Biliary malignant disease occurs mainly in elderly patients, who represent a unique surgical category because of the higher risk of postoperative complications. Several newly published studies indicate that ² high-grade dysplasia (HGD) and carcinoma *in situ* (CIS) of the biliary duct margin are not independent prognostic factors for disease-specific survival in patients with operable EHCC, unlike invasive carcinoma margin^[8]. Further, additional resection fail to improve the prognosis when the margin was HGD/CIS^[8]. The significance of low-grade dysplasia (LGD) at the resection margin in EHCC is unclear. The clinical relevance of dysplasia in resection margins remains largely unknown.

Therefore, this study was designed to evaluate the prognostic impact of dysplasia-positive margins on EHCC.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of 116 consecutive patients who had undergone curative surgery for EHCC at two tertiary academic centers, Korea University Ansan Hospital and Guro Hospital, from January 2013 to July 2017. The study included the clinicopathological data of patients identified from a database over more than three

years. We defined EHCC as distal common bile duct (CBD) cancer, proximal CBD cancer, or common hepatic duct (CHD) cancer/Klatskin tumor. We excluded patients with intrahepatic cholangiocarcinoma, cancers of gallbladder or ampulla of Vater, patients with a history of chronic biliary diseases, such as primary sclerosing cholangitis and autoimmune-related cholangiopathy, or invasive carcinoma arising from intraductal papillary neoplasm. This study did not include patients diagnosed with invasive carcinoma at the resection margin during the final pathologic review or those who had undergone surgery with palliative intention. Most patients underwent preoperative biliary drainage for obstructive jaundice, and surgical resection was performed to secure a negative proximal margin with curative intent. Not all patients underwent additional resection surgery. Each patient's past medical history was reviewed for previous cancer treatment and comorbidities, such as chronic kidney disease (CKD), diabetes mellitus (DM), liver cirrhosis (LC), chronic obstructive pulmonary disease (COPD), coronary heart disease, or human immunodeficiency virus infection. This study was approved by the Institutional Review Board of Korea University Guro Hospital (2021AS0282).

Definitions

During the pathological analysis, the status of the resection margin was classified into negative (negative for carcinoma or dysplasia), LGD-positive, and HGD/CIS types. We excluded margins with invasive carcinoma. Since it was extremely difficult to distinguish between HGD and CIS, we combined them into the HGD/CIS group in this study.^[9] In most cases, histological examination of resection margin was performed by a gastrointestinal pathologist. In case of ambiguous histological findings, the final results were reported after discussion with other pathologists.

We divided patients into two groups based on age: > 70 years and ≤ 70 years. Given the peak incidence of ECC between 50 and 70 years of age, this study defined elderly patients as those above 70 years of age^[10]. The overall survival (OS) was calculated from the date of the hospital visit to the last follow-up date or the date of death. Operation-related mortality was defined as death on the day of surgery in the hospital.

Endpoints

The primary endpoint of the study was overall survival according to the status of the resection margin in patients who underwent surgery with curative intent. The secondary endpoints were tumor recurrence rate depending on the resection margin and risk factors for overall survival.

Statistical analysis

Fisher's exact test or chi-squared test was used to compare categorical variables. Quantitative variables and treatment endpoints were analyzed using the one-way analysis of variance or Kruskal-Wallis test. Kaplan-Meier curves were used for survival analysis, and the differences were assessed using log-rank test. Univariate and multivariate Cox proportional-hazards regression analyses were used to evaluate the prognostic factors for survival. All results were considered significant at a *P* value < 0.05. All statistical analyses were performed using IBM SPSS software (Version 20.0; SPSS, Inc., Chicago, IL, United States).

RESULTS

Patients and surgical outcomes

We enrolled a total of 116 patients who had been followed for more than three years after curative surgery. The patient characteristics are summarized in Table 1. The mean patient age was 69.7 ± 8.8 years (50-91 years), and 50.9% (59/116) were elderly patients > 70 years of age. Forty-one patients (35%) manifested chronic comorbidities, such as CKD, DM, LC and COPD. Surgery with curative intent was performed in 51 patients with distal CBD cancer, 43 with proximal CBD cancer and 22 patients with Klatskin tumor. Preoperative bile drainage was performed in 95.7% of enrolled patients. Endoscopic bile drainage was used in 78% of cases and percutaneous transhepatic biliary drainage was used in 22%. Seventy-two patients underwent curative resection with R0 margins, while 44 patients had R1 (microscopic residual tumor)-positive resection margins. Of the 44 patients with

positive margins, 19 patients carried LGD-positive margins, and 25 patients showed HGD/CIS-positive margins. In the elderly patients, 33 patients had R0 resection margin, whereas 9 patients had LGD margin, and 17 patients showed HGD/CIS margin. The operations most commonly performed were pylorus-preserving pancreaticoduodenectomy (PPPD) or Whipple operation involving 70 patients. Perineural and lymphatic invasion was detected in 41 and 81 cases, respectively. Moderate differentiation was most commonly identified. Postoperative mortality occurred in 10 patients including eight elderly cases, due to surgical complications. Adjuvant chemotherapy with or without radiation therapy was administered to 46 patients, depending upon clinician's discretion considering lymph node status and resection margin.

Survival

The mean OS in all patients was 44.2 ± 3.4 months (95% confidence interval [CI]: 37.5–55.9) (Fig 1a). The mean survival of patients in the > 70-year-old group was 34.7 ± 4.4 months, which was significantly poorer than in patients belonging to the ≤ 70 -year-old group (53.3 ± 4.9 mo; $P = 0.006$) (Figure 1).

The mean survival rates of patients with negative resection margin, LGD margin, and HGD/CIS margin were 49.1 ± 4.5 , 47.3 ± 6.0 , and 20.8 ± 4.4 mo, respectively. Also, the median survival was 36.0 (15.6–56.4), 40.0 (30.7–49.3), and 29.0 (10.2–36.8) months, respectively ($P < 0.001$) (Figure 2A). The survival of patients in the HGD/CIS-positive margin group was significantly less than in those with negative margin and LGD margin. Patients with LGD margins showed OS similar to those in the negative margin group ($P = 0.56$).

In the elderly patients, the mean survival rates of those with a negative margin, LGD margin, and HGD/CIS margin groups were 39.0 ± 6.3 , 46.5 ± 8.5 , and 14.3 ± 2.6 months, respectively ($P = 0.004$) (Figure 2B). Patients with LGD margins showed a better cumulative survival without statistical significance than those with a negative margin ($P = 0.280$).

Tumor recurrence rate

Based on the analysis of patients' resection margin, the rates of tumor recurrence associated with negative margin, LGD margin, and HGD/CIS margin were 47.2% (34/72), 52.6% (10/19), and 76.0% (19/25), respectively. Based on the resection margin of all patients, the actual probability of negative-from-tumor recurrence differed significantly between patients with HGD/CIS margins and the others ($P < 0.001$) (Figure 3A). Patients with negative resection margin showed a tendency towards lower rates of tumor recurrence compared with those carrying LGD dysplasia margins. However, no statistical difference was observed ($P = 0.07$).

This trend was also seen in elderly patients. The rates of tumor recurrence in patients with negative margin, LGD margin, and HGD/CIS margin were 39.4% (13/33), 44.4% (4/9), and 70.6% (12/17), respectively. The actual probability of negative-from-tumor recurrence in elderly patients also differed significantly according to resection margin status ($P = 0.002$) (Figure 3B). However, there was no statistically significant difference between patients with negative resection margins and those with LGD dysplasia margins ($P = 0.32$).

Risk factors associated with survival

The univariate analysis of risk factors for survival revealed that age above 70 years, CHD or Klatskin tumor, extensive operation (combined with bile duct resection and PPPD/Whipple operation and hepatectomy), and HGD/CIS-positive margins were significantly independent risk factors. Adjuvant therapy was the only significant factor, which independently improved survival in univariate, but not in multivariate analysis (Table 2). In multivariate analysis, old age and HGD/CIS-positive margins were significant factors associated with OS (HR = 1.9 and 2.47, respectively). Comorbidity was not a significant factor for survival. N stage, lymphatic invasion, and differentiation were also not significant factors.

DISCUSSION

In this study, we evaluated the prognostic value of margin in resected EHCC. We further investigated the clinical importance of the resection margin for EHCC in elderly patients via subgroup analysis because of relative variation in major comorbidities and higher perioperative morbidities associated with old age. The prognostic factors for resected EHCC were also analyzed.

Currently, the therapeutic gold standard for EHCC is complete surgical tumor resection or curative resection, defined as histologically cancer-free resection margin.^[11] Positive resection margins are considered as the most powerful risk factor for tumor recurrence and survival. However, the use of an aggressive approach to obtain negative resection margins might be controversial and depends on patient's status including potential morbidity and oncologic outcomes following resection. It is hard to decide whether or not aggressive and extensive resection is warranted in elderly patients, because of the higher risk of postoperative complications. Until recently, most studies divided positive margin status into two histological subtypes: invasive carcinoma and HGD/CIS. Several reports of invasive carcinoma-positive margins suggest a strong adverse effect on patient survival and tumor recurrence^[3,12,13]. Few studies involve HGD/CIS, but reported varying results^[13,14]. Further, few studies have explored the significance of LGD in surgical EHCC margin until now. However, LGD and HGD/CIS are frequently found in postoperative bile duct margins, but the clinical significance remains unclear.

In the present study, patients with resection margins containing HGD/CIS had significantly worse survival outcomes than did those with negative or LGD resection margins. However, patients with LGD-positive margins showed mean survivals similar to those with negative resection margins. Regarding HGD/CIS margins, the results are consistent with several other studies showing poor prognosis as well as high tumor recurrence rate in the HGD/CIS group when compared with the negative resection margin group^[15,16]. Even after adjusting for age that strongly influenced the prognosis, HGD/CIS-positive resection margin was a significant prognostic factor in this study.

However, a recently published meta-analysis comparing HGD/CIS margin group and negative margin group reported that ² HGD/CIS of the biliary duct margin did not affect the prognosis of patients with operable EHCC^[14]. Some studies reported that additional resection to achieve negative margins did not improve the prognosis when the margin revealed HGD/CIS^[17,18]. However, the effect of HGD/CIS margins on survival in patients with early stages of EHCC (defined as patient with pathologic N0M0 or T1/T2 or negative lymph node) was different from those with an advanced stage of EHCC^[8,14,16]. HGD/CIS margins in early-stage EHCC patients had a significantly increased incidence of local recurrence, as well as shorter survival, when compared with those carrying negative margins, suggesting that HGD/CIS should be avoided as often as possible during surgery for early-stage EHCC. In our study, a worse prognosis in the HGD/CIS group than in the negative margin group could be explained by the early stages in most patients: T stage 1 or 2 (78.4%, 91/116) and without lymph node (70.7%, 82/116).

To date, no study has evaluated the resection margins with LGD in EHCC. In this study, the survival and recurrence rate were comparable between patients with LGD margin and negative margin. Further, the LGD group in the subgroup analysis of elderly patients showed a better survival time and cumulative survival rate than those with negative margin due to the following reasons: (1) The extent of surgery was greater in the negative margin group of elderly patients than in the LGD group of elderly patients. The ratio of patients undergoing hepatectomy compared with those without hepatectomy was lower in the elderly LGD group (0/9) than in the negative margin group (6/33); (2) Operation-related death occurred in five cases of the negative resection margin group. Otherwise, there was no perioperative mortality event in the LGD margin group, which suggests a longer mean survival time in the LGD group; and (3) Despite limited evidence of benefits associated with adjuvant therapy in patients with resected EHCC with a dysplasia margin, adjuvant therapy was performed more frequently in the LGD group. Considering that old age and HGD/CIS were independent factors associated with poor survival in patients with EHCC, LGD-positive resection margin in elderly patients is a reasonable parameter for determining the negative resection margin. In contrast, the

HGD/CIS margin group clearly showed higher recurrence and poorer survival rates compared with other LGD margin and negative margin groups. The prognosis in patients with HGD/CIS margin can be improved, but it is difficult to establish a consensus regarding the benefits of adjuvant chemotherapy or radiation treatment for the HGD/CIS patient group because postoperative adjuvant therapy was performed according to the clinician's decision and the patient's condition. Furthermore, the duration of chemotherapy in the patient, the dose of chemotherapy, and the chemotherapy regimen were varied without specific criteria. Therefore, a comparative study involving a large number of patients with HGD/CIS is needed to establish the benefits of adjuvant therapy in the future.

The study has several limitations. First, it is a retrospective study involving a limited number of patients, especially patients with LGD resection margin. Second, the follow-up period was not adequate to determine delayed recurrence and survival time. Third, missing confounding factors, such as surgical technique and patient's financial condition also play a role. Therefore, further studies involving a large number of patients are needed to develop a guideline for dysplasia-positive-margins in patients with EHCC.

CONCLUSION

In conclusion, the HGD/CIS margin in resected EHCC was associated with poor survival and high tumor recurrence. However, the LGD-positive margin was not a significantly poor prognostic factor in patients with EHCC.

ARTICLE HIGHLIGHTS

Research background

The status of the bile duct resection margin in extrahepatic cholangiocarcinoma (EHCC) is the most important indicator of recurrence and survival.

Research motivation

There is a lack of information regarding the meaning of dysplasia at the resection margin in EHCC. The clinical relevance of dysplasia in resection margins remains largely unknown, and no consensus has been reached.

Research objectives

This study aims to evaluate the impact of dysplasia-positive margins as a prognostic indicator in patients with EHCC.

Research methods

A total of 116 patients who had undergone surgery for EHCC with curative intent were enrolled in this study. Curative resections with free margins were found in 72 patients, while 44 patients had microscopic residual tumor at resection margins. Of the 44 patients, 19 patients carried low-grade dysplasia (LGD)-positive margins, and 25 patients showed high-grade dysplasia (HGD)/ carcinoma *in situ* (CIS)-positive margins.

Research results

The mean survival rates of all patients with negative margin, LGD margin, and HGD/CIS margin were 49.1 ± 4.5 , 47.3 ± 6.0 , and 20.8 ± 4.4 mo ($P < 0.001$). There was no difference in survival between groups with LGD margin and negative margin (P value = 0.56).

Research conclusions

HGD/CIS margin in resected EHCC was associated with poor survival and high tumor recurrence. However, LGD-positive margin was not a significantly poor prognostic factor in patients with EHCC.

Research perspectives

This study provides meaningful information to establish a guideline for dysplasia-positive margins in patients with EHCC.

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SIMILARITY INDEX

PRIMARY SOURCES

1	Tae Yoo, Sang-Jae Park, Sung-Sik Han, Seong Hoon Kim et al. "Proximal Resection Margins: More Prognostic than Distal Resection Margins in Patients Undergoing Hilar Cholangiocarcinoma Resection", Cancer Research and Treatment, 2018	46 words — 1%
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