

One Year Survival of Extrahepatic Cholangiocarcinoma Patients Who Did Not Undergo Curative Resection and Palliative Chemotherapy and Its Associated Factors

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ABSTRACT

Background: Extrahepatic cholangiocarcinoma is rare but fatal. Patients who come are usually already in the advanced stage that can not undergo curative resection and chemotherapy also seems to be very rarely done. The survival rate and its associated factors in Indonesia are unknown. This study aimed to identify 1-year survival of patients with extrahepatic cholangiocarcinoma without curative resection and palliative chemotherapy and its associated factors. **Methods:** This is a cross-sectional study using medical records of extrahepatic cholangiocarcinoma (perihilar and distal) inpatient and outpatient patients at Cipto Mangunkusumo Hospital, Jakarta from January 2015 to March 2020, reviewed retrospectively. The following factors were analyzed in terms of mortality: metastasis, sepsis, hypoalbuminemia, serum bilirubin level, serum CA 19-9 level, biliary drainage, neutrophil lymphocyte ratio (NLR) and comorbid factors. **Results:** 115 out of 144 patients were enrolled in this study with male proportion of 50.4%, and proportion of patients aged 65 years or above was 71.3%. 1 year survival rate was 10 % and median survival was 3 months (CI 95% 2.388-3.612) Multivariate analysis showed that only sepsis, unsuccessful or no prior biliary drainage and total bilirubin >19.8 mg/dl were independent predictors of mortality. **Conclusion:** 1 year survival of extrahepatic cholangiocarcinoma without curative resection and palliative chemotherapy was 10 %. Sepsis, unsuccessful or no prior biliary drainage, and total bilirubin >19.8 mg/dl are factors significantly associated with shortened survival in malignant obstructive jaundice patients.

Keywords: Survival, extrahepatic cholangiocarcinoma, curative resection, palliative chemotherapy, mortality-related factors

INTRODUCTION

Cholangiocarcinomas are malignancies that arise from the biliary tract epithelia. Patients with cholangiocarcinoma usually present at late stages of the disease, and early symptoms might be nonspecific. Therefore, these cancers remain difficult to diagnose and treat and their prognosis is generally poor. Approximately half of untreated patients die within 3–4 months.¹

Until now there is no data on the prevalence of cholangiocarcinoma published in Indonesia, but in daily practice extrahepatic cholangiocarcinoma cases are more common, and patients who come usually undergo biliary drainage therapy. Patients who come are usually already in the advanced stage that could not undergo curative resection. Chemotherapy also seems to be very rarely done, as patients usually come with poor performance status.

Several overseas studies have been conducted to try to identify factors related to the survival of people with cholangiocarcinoma, especially extrahepatic cholangiocarcinoma. Metastasis², sepsis³, comorbid⁴, failure of drainage therapy³, hypoalbuminemia⁵, hyperbilirubinemia⁵, high CA 19-9⁶ and high Neutrophyl Lymphocyte Ratio (NLR).⁷

Until now there has been no comprehensive research on the survival of extrahepatic cholangiocarcinoma patients in Indonesia and the factors that affect it. There has also been no research on the survival of extrahepatic cholangiocarcinoma sufferers who do not undergo resection and palliative chemotherapy. So the purpose of this study is to find out the survival of one year of extrahepatic cholangiocarcinoma sufferers who do not undergo curative resection and palliative chemotherapy and factors that affect the mortality of 1 year.

METHODS

This is a cross-sectional study which was retrieved using total sampling technique by tracing medical records and electronic health record of the extrahepatic biliary cancer (perihilar and distal) patients aged 18 years or older who had been hospitalized in Cipto Mangunkusumo Hospital in Jakarta from January 2015 to March 2020. We include patients without curative

resection and paliative chemotherapy. This study has been approved by The Ethics Committee of the Faculty of Medicine, University of Indonesia, with registry number KET-31/UN2.F1/ETIK/PPM.00.02/2021.

The subjects characteristics are divided into two, clinical characteristics and characteristics by treatment. Clinical characteristics contain age, gender, symptoms, onset of symptoms to diagnosis, tumor location, risk factors for cholangiocarcinoma, bilirubin levels, CA levels 19-9, Albumin levels, NLR values, presence of cholangitis, sepsis, comorbidity, and metastasis.

Characteristics based on therapy are: resectability, drainage type, drainage failure, drainage failure based on drainage method, failed drainage based on tumor location, ERCP stent type, ERCP complications, and PTBD complications

Eight potential prognostic factors were studied: metastasis, comorbidity, sepsis, unsuccessful or no history of biliary drainage, albumin levels, bilirubin levels, CA 19-9 levels and neutrophyl Lymphocyte Ratio. All malignant tumors found in the extrahepatic biliary duct (perihilar and distal) were included in the study after confirmation through Computed Tomography (CT) scan and/or MRI-MRCP (Magnetic Resonance Imaging-Magnetic Resonance Cholangiopancreatography and/or Endoscopic Retrograde Cholangiopancreatography (ERCP) and/or Endoscopic Ultrasound (EUS) with or without biopsy confirmation.

The presence of comorbidities in the subjects was identified based on the total score of Charlson comorbidity index as documented on their medical records. Sepsis was identified according to Sepsis-3 criteria with the quick SOFA score ≥ 2 .

Laboratory parameters include albumin, bilirubin and CA 19-9, and were measured on the first day of admission. Albumin levels below 3.4 g/dl was defined as hypoalbuminemia. High bilirubin was defined if bilirubin ≥ 19.8 mg/dl. High CA 19-9 levels was defined as levels ≥ 300 U/ml.

Biliary drainage had been performed through PTBD (Percutaneous Transhepatic Biliary Drainage) and ERCP. Drainage procedure

was considered success if a minimal 2 mg/dl bilirubin serum decreased after 2 to 5 days post drainage. Patients were divided into two groups: first group with history of successful biliary drainage procedure and the second group with unsuccessful or no history of biliary drainage.

We evaluated outcomes of mortality and the time of death of the observed subjects (time to event), which were determined since the first visit to hospital. Follow up for assessment of survival was done by phone calls. If the patient was unreachable via phone call, we did a home visit to the patients' registered adress.

Data analysis was performed using SPSS version 23.0 for univariate, and multivariate analyses. The level of significance used in our study was $\alpha = 0.05$. Variables were considered significant when the p value < 0.05 . Cumulative one year survival was measured from the date of diagnosis of extrahepatic cholangiocarcinoma to the event and calculated by the methods of Kaplan-Meier, which was followed by Cox proportional hazard regression. The variables were then included into a multivariate model when the p value < 0.25 .

RESULTS

Within the period of the study, we found 154 adult patients aged >18 years with extrahepatic cholangiocarcinoma. As many as 29 subjects were excluded due to data loss in their medical records; 10 were excluded for having curative resection (5 patients) and paliative chemotherpay (5 patients) therefore, we were left with 115 subjects with characteristics as shown in **Table 1**.

Table 1. Clinical characteristics of subjects

Clinical characteristic	Frequency, n (%) N=115
Age	
- ≥ 65	82(71.3)
- < 65	33(28.7)
Sex	
- Male	58(50.4)
- Female	57(49.6)
Risk Factors,	
- Hepatitis B	8(6.9)
- Hepatitis C	1(0.8)
- Cirrhosis	5(4.3)
- Choledochal cyst	1(0.8)

Symptoms	
- Icterus	112 (97.4)
- Abdominal Pain	57 (49.6)
- Weight loss	46 (40.0)
- Itching	12 (10.4)
Onset from symptom to diagnosis (median)	2 months (0-12)
Tumor location	
- Perihilar	92 (80.0)
- Distal	23 (20.0)
Cholangitis	
- Yes	59 (51.3)
- No	56 (48.7)
Sepsis	
- Yes	31 (27.0)
- No	84 (73.0)
Comorbidity (CCI index)	
- ≥ 2	13 (11.3)
- 0-1	102 (88.7)
Metastasis	
- Yes	64 (55.7)
- No	51 (44.3)
Total bilirubin	
- >10 mg/dl	104 (90.4)
- ≤ 10 mg/dl	11 (9.6)
Total bilirubin	
- >19.8 mg/dl	71 (61.7)
- ≤ 19.8 mg/dl	44 (38.3)
CA 19-9	
- >300 IU/ml	60 (52.2)
- ≤ 300 IU/ml	55 (47.8)
Albumin	
- <3.4 g/dl	100 (87.7)
- ≥ 3.4 g/dl	15 (12.3)
Neutrophyl/Lymphocyte Ratio (NLR)	
- >7.45	54 (47.0)
- ≤ 7.45	61 (53.0)
Neutrophyl/Lymphocyte Ratio (NLR)	
- >5.5	47 (40.9)
- ≤ 5.5	68 (59.1)
Pathology Results	
- Adenocarcinoma	23 (20.0)
- Atypical malignancy suspicion	4 (3.4)
- Atypical	22 (19.1)
- Dysplasia	2 (1.7)
- Malignant	3 (2.6)
- No malignant cell	26 (22.6)
- Not examined	35 (30.6)

Table 2. Clinical characteristic by treatment.

Treatment characteristic	Frequency, n(%) N = 115
Resectability	
- Unresectable	75(65.2)
- Resectable (not resected)	40(34.8)
Biliary drainage	
- Success	81(70.4)
- Not success/no drainage	34(29.6)

Drainage type	
- ERCP	92 (80.0)
- PTBD	16 (13.9)
- No drainage	7 (6.1)
Failed drainage by drainage type	
- ERCP(n=92)	23/92 (25.0)
- PTBD(n=16)	6/16 (37.5)
Failed drainage by tumor location	
- Perihilar (n=92)	21/92 (22.8)
- Distal (n=23)	8/23 (34.7)
ERCP stent type (n=92)	
- Plastic	64/92(69.6)
- Metal	26/92(28.3)
- NBD (<i>nasobiliary drainage</i>)	2/92(2.1)
ERCP complications, (n=92)	
- Pancreatitis	12/92 (13.0)
- Post sphincterotomy bleeding	2/92 (2.0)
- Perforation (Non fatal)	1/92 (1.0)
- Cholangitis (Fatal)	1/92 (1.0)
PTBD complication, (n=16)	
- Perforation (fatal)	1/16(6.2)
- Leakage	1/16(6.2)

The proportion of survival in patients with extrahepatic cholangiocarcinoma based on observation of month 3, 6, 9, and 12 was 35%, 23%, 10%, and 10%, respectively as can be seen in **Table 2**; therefore, we found that the proportion of 1 year mortality in patients with extrahepatic cholangiocarcinoma who did not undergo curative resection and paliative chemotherapy was 90%. By the Kaplan-Meier curve in **Figure 1**, showed that median survival time (which was the time when 50% of study subjects survived) was 3 months (CI 95% 2.388-3.612).

Bivariate analysis, which is presented in **Table 3**, was performed to evaluate factors that affect the survival of subjects with extrahepatic cholangiocarcinoma. The analysis was done

Table 3. Proportion of survival in patients with extrahepatic cholangiocarcinoma who did not undergo curative resection and paliative chemotherapy.

Survival at month	Cumulative survival
0	0.50
3	0.35
6	0.23
9	0.10
12	0.10

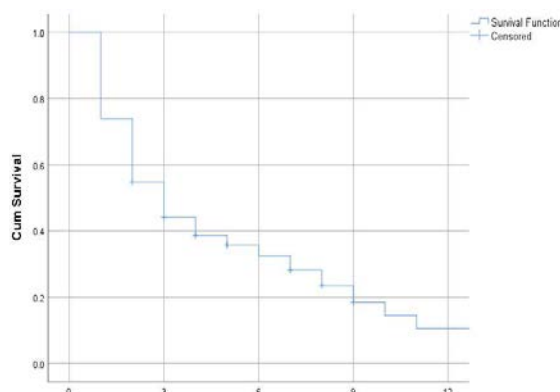


Figure 1. The Kaplan-Meier curve on 1-year survival of patients with extrahepatic cholangiocarcinoma who did not undergo curative resection and paliative chemotherapy.

using Cox regression analysis. The degree of association was presented in the form of hazard ratio (HR). Seven variables, which were included as candidates in the multivariate analysis using Cox Proportional Hazard Model were variables with p value < 0.25 in the bivariate analysis. Those factors were metastasis, unsuccessful biliary drainage or no drainage, comorbidity, sepsis, high bilirubin, low albumin and high NLR.

Table 4. Univariate analysis on factors affecting 1-year survival in patients with extrahepatic cholangiocarcinoma who did not undergo curative resection and paliative chemotherapy.

Variables	Mortality		Person Time	Incidence Rate (10 ⁻³)	HR (IK95%)	P
	No	Yes				
Failed biliary drainage, n (%)						
- Yes	1 (2.9)	33 (97.1)	86	38.37		
- No	20 (24.7)	61 (75.3)	411	14.84	2.377 (1.535-3.680)	<0.001
Sepsis, n (%)						
- Yes	2 (6.5)	29 (93.5)	69	42.03		
- No	19 (22.6)	65 (77.4)	428	15.18	2.497 (1.585-3.932)	<0.001
Comorbidity (CCI index) , n (%)						
- 0≥2	0 (0.0)	13 (100.0)	37	35.14		
- 0-1	21 (20.6)	81 (79.4)	460	17.61	1.859 (1.027-3.365)	0.040

Metastasis						
- Yes	7 (10.9)	57 (89.1)	231	24.67		
- No	14 (27.5)	37 (72.5)	266	13.91	1.653 (1.085-2.517)	0.019
Total bilirubin, n (%)						
- >19,8 mg/dl	13 (12.5)	91 (87.5)	99	27.73		
- ≤ 19,8 mg/dl	8 (72.7)	3(27.3)	398	10.81	2.369 (1.505-3.729)	<0.001
CA 19-9 , n (%)						
- >300 IU/ml	12 (20.0)	48 (80.0)	232	20.68		
- ≤300 IU/ml	9 (16.4)	46 (83.6)	265	17.35	1.113 (0.742-1.671)	0.605
Albumin, n(%)						
- <3,4 g/dl	16(16.0)	84(84.0)	108	21.82		
- ≥3,4 g/dl	5(35.7)	9(64.3)	385	8.33	2.428(1.201-4.907)	0.014
Neutrophyl/Lymphocyte Ratio (NLR) , n (%)						
- >5,5	6 (8.8)	62 (91.2)	246	25.20		
- ≤5,5	15 (31.9)	32 (68.1)	251	12.75	1.844(1.19-2.848)	0.006

Tabel 5. Multivariate analysis on factors affecting 1-year survival in patients with extrahepatic cholangiocarcinoma who did not undergo curative resection and paliative chemotherapy.

Variables	HR (CI 95%)	P
Sepsis	1.879 (1.171-3.014)	0.009
Total Bilirubin >19.8 mg/dl	1.972 (1.248-3.117)	0.004
Unsuccessful Biliary Drainage/no drainage	1.807 (1.150-2.842)	0.010

Meaningful variables in multivariate analysis are sepsis, bilirubin levels > 19.8 mg/dl and failed or unattributed biliary drainage. Shown in **Table 4** are the hazard ratio (HR) with a confidence interval (IK) of 95% of each meaningful prognosis factor.

DISCUSSION

In this study there were 58 patients (50.4%) that were male. The most common age group was ≥ 65 years old with as many as 82 people (71.3%), and the median age of the subjects being 58 years (29-86) years. It is similar with a study by Ruiz et al in Spain, where the population of extrahepatic cholangiocarcinoma consists of 34 (50%) males. However, the average age in their study was higher at 73.4±11.5 years.⁴In a study in Korea by Park et al, the proportion of male extrahepatic cholangiocarcinoma patients was 67%, with mean age of 62±10.1.² In research in China by Wang et al in patients with extrahepatic cholangiocarcinoma, proportion of men were 65%, with a higher mean age of 68.9±11.158.⁸

In this study, the proportion of perihilar cholangiocarcinoma (Klatskin tumor) was greater, which is 92 (80%) compared to distal 23 (20%). This is approximately the same as the proportion of incidence of cholangiocarcinoma in general where perihilar cholangiocarcinoma is the most common type of tumor that is 60% cases, 30% cases of distal cholangiocarcinoma and 6-10% cases of intrahepatic cholangiocarcinoma.⁹

In this study, strong risk factors were hepatitis B 8 (6.9%), hepatitis C 1 (0.8%), cirrhosis 5 (4.3%), and choledochal cyst 2 (1.7%). Some other risk factors were diabetes 12 (10.4%) and alcohol 1 (0.8%). This is more or less similar to the population of cholangiocarcinoma sufferers in study by Yusoff in Malaysia.¹⁰

In this study, based on the criteria of resectability via imaging, it was found that as many as 40 (34.8%) were suitable for resection.¹¹ This is similar to the study that approximately one-third of patients can be resected during diagnosis.⁹ But only 5 patients did undergo resection for curative purpose. The reason for this were many, such as refusing surgery, not coming for further evaluation, poor performance status, and preoperative restaging.

In multivariate analysis bilirubin levels ≥ 19.8 mg / dl, failed / not performed biliary drainage and sepsis was found as an independent prognostic factor.

In our study, the proportion of patients with high bilirubin levels (>10 mg /dl) was 104 out of 115 patients (90.4%). Median value of bilirubin

was 22 mg / dl (ranging from 5,3 mg / dl to 53.40 mg / dl) which was higher than other studies.^{8, 12}

High bilirubin levels caused by biliary obstruction will cause impaired liver function, disrupt endotoxin cleansing, cause coagulation system disorders, immune system and gastrointestinal intestinal barrier. Endotoxins in normal liver conditions are produced in small amounts and then through the portal vein it enters the liver and are inactivated by the liver reticuloendothelial system. Increased levels of endotoxins in biliary obstruction conditions plus impaired liver function will cause a condition named Systemic Inflammatory Response Syndrome (SIRS) which will cause sepsis and then multiple organ failure. So if these high bilirubin levels were not treated with good drainage, it tends to cause infection, sepsis and death.¹³⁻¹⁵

Under normal conditions the bile fluid is in a sterile state. However, tumor obstruction can lead to bacterial growth and colonization in approximately 25% of patients.¹⁶ Li, et al¹⁷ in China found the proportion of patients with bile duct obstruction due to solid tumors experiencing biliary tract infection was 21 % while in study by Gaspersz et al¹⁸ in Netherland, there are 45% patients with perihilar cholangiocarcinoma experiencing biliary tract infection before the procedure of biliary drainage could be carried out. In our study, 59 patients (51.3%) had acute cholangitis at admission and 31 (27%) had sepsis. While sepsis was one of independent predictive factor in our study. The tendency to develop biliary tract infection in our population may be due to several reasons, namely delays in diagnosis (median from onset to diagnosis was 2 month), and higher bilirubin levels in our study indicating that there has been a long obstruction.

From the results obtained above, the role of biliary drainage becomes very important to improve survival that can be caused by hyperbilirubinemia and sepsis. From our study unsuccessful biliary drainage became one of independent predictive factor for mortality. Biliary drainage in cases of biliary obstruction due to malignancy is considered an important palliative therapy because it can reduce symptoms caused by hyperbilirubinemia, thus allowing

patients to undergo surgery, chemotherapy, radiotherapy and local therapy against tumors so as to increase survival in patients with malignant etiology.¹⁹ Research by Kurniawan et al., with the same drainage success criteria, obtained biliary drainage that failed or not performed will increase the risk of death. Other studies by Brountzos et al²⁰, Zhang, et al¹⁹, with different drainage success criteria also found similar results.

In this study, the 1-year survival rate of extrahepatic cholangiocarcinoma patients who did not undergo curative resection and palliative chemotherapy was 10%, with a median survival of 3 months It is more or less similar to research in Malaysia by Yusoff et al.¹⁰

In this study there were only 5 patients who performed resection with curative purposes and 5 patients who received palliative chemotherapy during this study, which were excluded in this study. In study by Yusoff et al in Malaysia, there were more patient to be resected and these might be due to the median duration from symptom to diagnosis being more early compared to our study which was 30 days, making curative resection more likely to be achieved.¹⁰

This study, is the first study in Indonesia that examines the survival of extrahepatic cholangiocarcinoma patients (perihilar and distal) and is also the first research in to study the population of extrahepatic cholangiocarcinoma undergoing supportive therapy only, giving us data on extrahepatic cholangiocarcinoma prognosis if no procedures that can improve survival (curative resection and palliative chemotherapy) were done and the positive benefit of biliary drainage in this setting.

Limitations of this study include the possibility of information bias due to retrospective design. There were very little histopathological data, so the accuracy of diagnosis in extrahepatic cholangiocarcinoma in this study became less accurate, for in our study the positive result of malignancy from pathology were only 20%. However, this was due to the diagnostic procedure of cholangiocarcinoma extrahepatic examination that is commonly done such as bile duct brushing through ERCP and cytology examination of bile fluid aspiration through

PTBD has a low sensitivity although the specificity is very high.⁹

CONCLUSION

One year survival of patients with extrahepatic cholangiocarcinoma in our study was 10 % and sepsis, unsuccessful or no biliary drainage and total bilirubin >19.8 mg/dl were the three independent prognostic factors for mortality.

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