

Survival Analysis of Hilar Cholangiocarcinoma Treated by Endoscopic Biliary Drainage at Srinagarind Hospital, Khon Kaen, Thailand

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ABSTRACT

Cholangiocarcinoma (CHCA) is a major common problems in the northeastern region of Thailand. Because the diagnosis is usually made at a late stage, palliative treatment is often the treatment of choice. Internal stent biliary drainage is accepted as a good palliative treatment. The objective of this study was to analyse the survival of hilar CHCA patients treated by internal stent biliary drainage. A retrospective review was made involving CHCA patients at Srinagarind Hospital, Khon Kaen, Thailand. Data were collected from 1st January 2001 to 31st December 2004. The outcomes of patients were assessed up to 30th June 2005, or to the time of death. Survival analysis was performed. Fifty-five patients were enrolled. The overall median survival rate was 64 days (95% CI = 48-91) with the cumulative 30, 90 and, 150 days survival rates of 78%, 40% and, 24% respectively. There were 2 types of CHCA, ERCP1 (or Bismuth I) and ERCP2 (equal or higher than Bismuth II). The median survival rates for ERCP 1 at 30, 60 and, 90 days were not different from those of ERCP2. The overall median survival rates were 82 days (95% CI = 33-101) in ERCP 1 and 57 days (95% CI = 34-83) in ERCP2. The ultimate outcome of patients with CHCA was poor despite of the palliative treatment.

Key words : hilar cholangiocarcinoma, *opisthorchis viverrini*, jaundice, biliary drainage

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INTRODUCTION

Cholangiocarcinoma (CHCA) is a cancer which originates in the biliary tree. It is commonly found in the Northeastern region of Thailand. Male and female are equally affected. The etiology is unknown, but there is a strong association with *Opisthorchis viverrini* in-

festation. In addition, many studies have demonstrated that biliary stone may also play a role in the pathogenesis of the disease. Most CHCA patients present with non-specific symptoms such as dyspepsia, whereas jaundice, generalized pruritis and pale feces usually present at later stages. As a result, the diagnosis of CHCA is usually delayed.

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Treatment of CHCA depends on the disease staging. The curative tumor resection can be performed in the early stage. In contrast, the prognosis of cancer in a late stage is poor because of the anatomic proximity of the tumor to the vital structures in the hepatic hilum. For this reason tumor resection is not possible and palliative treatment is crucial. Currently, internal biliary drainage, external biliary drainage (PTBD) and chemotherapy are the alternative treatments of choice.

The objective of this study is to identify the survival of our CHCA patients, especially the hilar type, who had been palliatively treated by internal biliary drainage with internal stent.

PATIENTS AND METHODS

This retrospective study involved patients who were diagnosed as having hilar CHCA and admitted to Srinagarind Hospital for internal biliary drainage between 1st January 2001 and 31st December 2004. Hilar CHCA was diagnosed with either an ultrasonography, or a CT scan or a MRCP (all confirmed by two radiologists), or with an endoscopy (ERCP). Tumor markers (CA19-9 or CEA) were obtained for confirm action of diagnosis. The patients enrolled were classified into 2 groups- Bismuth I and at least Bismuth II and higher, based upon endoscopic retrograde cholangiopancreatography (ERCP) findings. All were followed-up until death or up to 30th June 2005. Only tumor-related death, such as sepsis from cholangitis, was counted. The cause of death was confirmed by reviewing the death certificate and by interviewing the relatives.

Statistical analysis

All data were presented as percentage of cases and/or mean standard deviation of the mean. Survival analysis was made using the Kaplan-Meier method. P-value <0.05 was considered as statistical significance.

RESULTS

There were 55 CHCA patients enrolled and all were treated by internal biliary drainage during the 4-year period. (Thirty-six were males (65.45%) and 19 were females (34.54%), with a mean age of 57.6 ± 11.02 years.) Jaundice was found in 43 patients (78.18%) with a mean bilirubin level of 14.3 mg/dL (41 cases). Hepatomegaly was found in 49 patients

(89.09%). The mean alkaline phosphatase level was 431 U/L (41 cases). Fever was found in 13 patients (23.63%), and ascites was presented in 6 cases (10.91%). (Table 1)

Based upon ERCP findings, 10 patients (18.18%) were categorized as ERCP 1 (Bismuth I) and 45 patients (81.81%) were categorized as ERCP 2 (at least Bismuth II). Nine patients in ERCP 2 group (16.36%) developed ascending cholangitis after the procedure. (Table 2)

The overall median survival rate was 64 days (95% CI = 48-91), with the cumulative 30, 90 and 150 day survival rates of 78%, 40% and, 24% respectively. (Figure 1)

The median survival rates of patients in ERCP 1 and ERCP 2 were 82 days (95% CI = 33-101) and 57 days (95% CI = 34-83) respectively. The cumulative 30, 60 and 90 day survival rates of ERCP 1 were 100%, 50% and 20% respectively. In the ERCP 2 group, the cumulative 30, 60, and 90 day survival rates were 73%, 38%, and 24% respectively. There was no statistical difference between the two groups (p-value >0.05). (Figure 2)

The median survival rates between jaundice and

Table 1 General Characteristic of patients

Number of patients	55
Male	36
Female	19
Age (range)	39-80 years
Mean age	57.6 ± 11.02 years
Jaundice	43 (78.18 %)
Hepatomegaly	49 (89.09 %)
Fever	13 (23.63%)
Ascites	6 (10.91%)
ERCP - Bismuth I (ERCP1)	10 (18.18%)
- Bismuth II, III, IV (ERCP2)	45 (81.81%)

Table 2 Result of treatment of hilar CHCA with internal stent drainage

Number of patients	55
Hospital death	-
Post operative ascending cholangitis	9 (16.36%)
Lost to follow up	-
Available to follow up	55 (100%)

(All died within 6 months post operation)

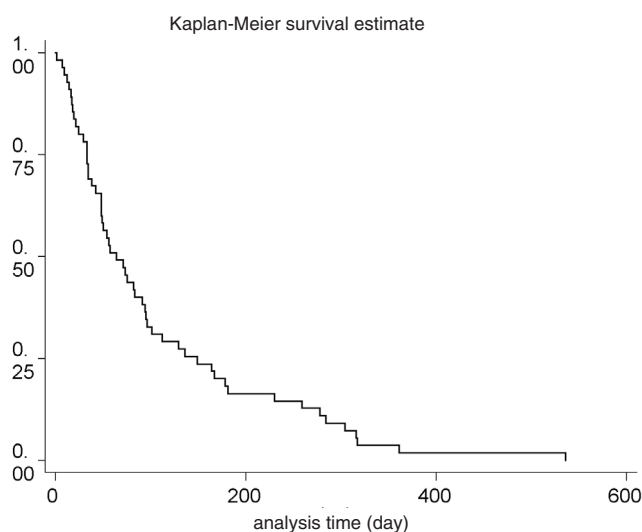


Figure 1 Survival analysis of patients with hilar CHCA treated by internal stent biliary drainage at Srinagarind Hospital, Khon Kaen. The median survival rate was 64 days (95% CI = 48-91)

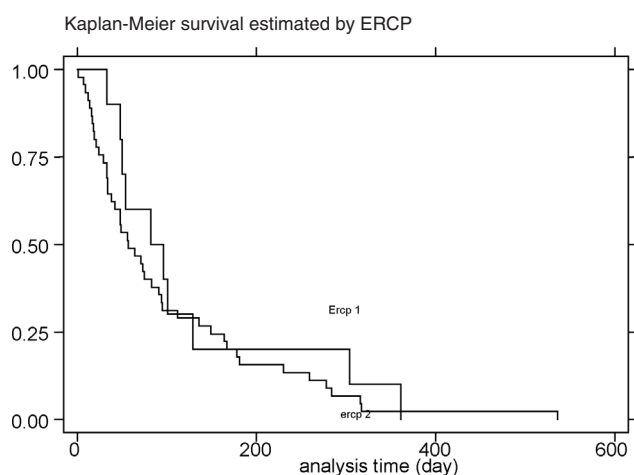


Figure 2 Survival analysis of patients with hilar CHCA treated by internal stent drainage at Srinagarind Hospital, Khon Kaen, Catagorized by ERCP into ERCP1 and ERCP 2 (n = 55), (p-value = 0.43), (the Log rank = 0.63)

non-jaundice patients were not statistically different. (Figure 3)

DISCUSSION

Cholangiocarcinoma (CHCA) is a common tumor that causes considerable public health's problem in Thailand. The number of cases increases every year, especially in the Northeastern region of Thailand.

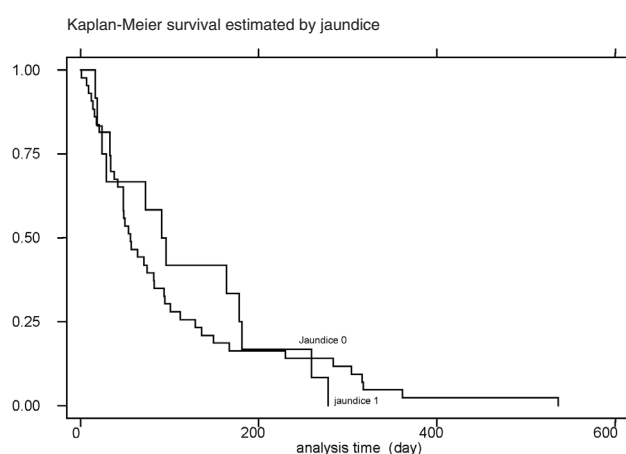


Figure 3 Survival analysis by jaundice states in patients with hilar CHCA treated by internal stent drainage. (n = 55), (p-value = 0.83), (the Log rank = 0.04)

CHCA is common in both males and females. The observed incidence rate is about 71.4-173.3 per 100,000 of population per year and mean age is 65 year.

Many factors are of etiologic relevance, including *Opisthorchis viverrini* infestation being of the strongest association. Liver fluke in the biliary tree results in chronic biliary infection that may eventually lead to malignant transformation of the biliary tract's lining surfaces.

Symptoms of CHCA vary with the clinical staging. In the early stage CHCA, most patients have no symptoms. The most frequent symptoms are jaundice, pruritus, pale stool and deep yellow urine. These symptoms are caused by biliary obstruction. Other less frequent symptoms are high grade fever, chills, and right upper quadrant pain, which suggestive of ascending cholangitis. In the late stage CHCA, the common signs and symptoms are anorexia, weight loss, icteric sclera or generalized jaundice, lymphadenopathy, hepatomegaly, ascites, and edematous legs.

Diagnosis of CHCA depends on the type of tumor. This can be grouped into 2 classes. In the first group with intrahepatic CHCA, patients often present with symptoms resulting from an abdominal mass. In the second group with extrahepatic CHCA, patients present with symptoms of bile duct occlusion, i.e. jaundice. The definitive diagnosis of intrahepatic CHCA requires tissue pathologic examination demonstrating "adenocarcinoma" with absence of cancer in other visceral organs. In case of extrahepatic CHCA, the diag-

nosis necessitates either MRCP or ERCP with tissue brushing or needle aspiration. Overall, the 3 procedures are comparable, in terms of diagnostics yield which is around 50-70%. However, tumor markers (CA 19-9, CEA) analysis combined with ERCP or MRCP may be necessary to increase the sensitivity for the diagnosis.

The choice of either a curative or a palliative treatment for CHCA depends on the clinical severity. As most patients first present at an advanced stage, effective tumor resection is usually not possible. A more appropriate treatment is often focused on a palliative method. The main purpose of each palliative procedure, such as an internal drainage with a plastic stent or a metallic stent, an external drainage or percutaneous transhepatic biliary drainage (PTBD), radiation, or chemotherapy, is to minimize complications of biliary obstruction. Unfortunately, the prognosis is still poor in most patients despite the availability of various methods. De Palma GD, *et al.* reported that in 583 patients with hepatic hilum stenosis treated by internal drainage with stent, the overall median survival was only 190 days.

In this present study of 55 patients, the median survival rate was 64 days, while the cumulative 30, 90 and 150-day survival rates were of 78%, 40%, and 24% respectively. All patients died within 6 months. The survival rate for Bismuth I and that for Bismuth II and higher were not statistically different. The outcomes for jaundiced and non-jaundiced patients were similar. The main complication after ERCP was ascending cholangitis, which occurred in 9 patients (16.36%) in the ERCP 2 group. This could be related to biliary contamination following stent implantation.

In conclusion, patients with an advanced hilar cholangiocarcinoma had a poor prognosis regardless of the palliative intervention. To achieve a better outcome, attention should be focused on a screening and aggressive surveillance program to select the high-risk patients for special treatment.

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