RESEARCH ARTICLE

Clinical Characteristics and Treatment Outcomes of Patients with Unresectable Cholangiocarcinoma in Thailand: Are there Differences Dependent on Stent Type?

Varayu Prachayakul[1,2]*, Suthasinee Chaisayan[2], Pitulak Aswakul[3], Morakod Deesomsak[3]

Abstract

Cholangiocarcinoma, though very rare in Western countries, is one of the commonest liver malignancies in Southeast Asia, especially in Thailand. More than half of the patients present with advanced stage disease. Given the poor treatment outcomes of adjuvant therapeutic options, many patients undergo only biliary drainage for palliative treatment. Clinical characteristics and treatment outcomes after biliary stenting were here analyzed for a total of 224 uresectable cholangiocarcinoma cases, 58.9% in men. The mean age was 61.5 years. Hilar involvement was the most common location. The patients underwent biliary drainage using plastic and metallic stents equally, early stent occlusion being encountered in 21.4% and 10.7%, respectively. The median survival time was 4.93 months for patients who received plastic and 5.87 months for patients who received metallic stents.

Keywords: Cholangiocarcinoma - unresectable - clinical outcome - prognosis - biliary stent type

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Introduction

Cholangiocarcinoma (CCA) is a fatal malignancy that accounts for 10-25% of primary hepatobiliary cancers (Anderson et al., 2012). Although the incidence was only 0.58-0.88 per 100,000 people in the USA, some particular endemic areas in Southeast Asia, especially northeastern Thailand, reported incidences as high as 39.4 and 94.8 per 100,000 people for females and males, respectively (Ruys et al., 2012; Sangchan et al., 2012). However, the incidence in Western countries had gradually risen in recent decades (Aslanian and Jamidar, 2011). The reasons for this increment are unclear.

The etiology of CCA in Asian countries appears related to infestation by liver fluke, particularly the Opistorchiidae family (Shin et al., 2010), whereas CCA in Western countries is caused by chronic bile duct inflammation, particularly primary sclerosing cholangitis. A meta-analysis revealed that chronic hepatitis B and hepatitis C infection also increase the risk of this malignancy (Zhou et al., 2012). CCA is generally divided to intrahepatic and extrahepatic types. Extrahepatic CCA was also classified as distal or hilar CCA according to the Bismuth-Corlette classification (Klatskin, 1965).

In Western countries, approximately 60-70% of cases of CCA were reported to be hilar CCA, whereas distal and intrahepatic CCA comprised 20-30 and 5-10% of cases, respectively (Nagino et al., 2008; Akamatsu et al., 2011; Sangchan et al., 2012; Anderson et al., 2012). In Khonkaen, the region that reported the highest incidence of CCA, including Opisthorchis viverrini infestation in 15.7% of cases, intrahepatic and extrahepatic CCA comprised 40% and 60% of the cases, respectively. The patients with distal CCA had better clinical outcomes than those with hilar or intrahepatic CCA (Aslanian and Jamidar, 2011; Sangchan et al., 2012; Anderson et al., 2012; Ruys et al., 2012).

Because of the natural history of silent disease, the majority of patients with CCA presented with locally advanced disease; thus, radical surgery was not possible. Although advances in radical surgical treatment in resectable cases of this malignancy improved the clinical outcomes, the 5-year survival rate was only 25-43%. Chemotherapy is not effective for palliative treatment in advanced cases; therefore, the median survival of patients with unresectable CCA was only 3-13 months (Nagino et al., 2008; Akamatsu et al., 2011; Van der Gaag et al., 2012). Regarding the data of poor treatment outcomes for unresectable CCA despite adjuvant chemotherapy or radiation treatment (Shin et al., 2010; Aslanian and Jamidar, 2011; Sangchan et al., 2012; Ruys et al., 2012), many patients preferred only palliative treatment, particularly biliary drainage. However, there are only a few reports of the clinical outcomes of this particular group of

*[1]Siriraj GI Endoscopy Center, Division of Gastroenterology, [2]Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, [3]Liver and Digestive Institute, Samitivej Sukhumvit Hospital, Bangkok, Thailand *For correspondence: kaiyjr@gmail.com*

patients at present. Therefore, we conducted the present retrospective study to highlight the clinical manifestations, diagnosis, and treatment outcomes of patients with unresectable CCA who underwent only biliary drainage without any adjuvant therapy in our tertiary care university hospital located in central Thailand.

Materials and Methods

We conducted a retrospective study of consecutive patients diagnosed with CCA including investigations of the clinical manifestations, imaging studies such as computed tomography or magnetic resonance imaging, evaluations of clinical outcomes after a long-term follow-up period, and histopathological studies. The inclusion criteria for patients were as follows: age of more than 18 years; visit to our hospital between January 2007 and December 2010; diagnosis of CCA based on the criteria of Jarnagin et al.; and performance of endoscopic retrograde cholangiopancreatography (ERCP) with biliary drainage. CCA was anatomically classified as intrahepatic, distal, and hilar CCA. Hilar CCA was also classified on the basis of Bismuth and Corlette's classification, although the present study included only hilar CCA types II-IV. Informed consent was given by all patients who underwent ERCP with biliary drainage. The type and length of the stent inserted for biliary drainage were decided by the endoscopists who performed the procedures with consideration of the socioeconomic and clinical status of the patients. All procedures were conducted or supervised by 6 dedicated endoscopists who annually perform more than 250 ERCPs. Most of the patients were observed for at least 24 h after the procedures, and the adverse clinical outcomes were reported by the nurses during hospitalization and during the follow-up period. The clinical details in terms of the demographic data, clinical manifestations, ERCP procedure details, clinical outcomes of the treatment such as complications, stent occlusion rate, clinical presentations during follow-up, and survival time were analyzed. The data were analyzed using SPSS version 13.0 software (SPSS, Inc., Chicago, IL, USA). The overall survival time was defined as the time from presentation to our hospital until the time of death. The results were summarized using standard methods. The descriptive data were reported as the mean±SD or percentage. Student's t-test and the x^2 test were used to assess the intergroup differences according to the clinical data. A P value of <0.05 was considered statistically significant.

Results

A total of 224 patients were enrolled in this study, 132 of whom (58.9%) were men. Thirty percent of the patients had comorbid diseases such as diabetes mellitus, hypertension, and hyperlipidemia. Cirrhosis was found in only a few patients. More than half of the patients lived in central Thailand, whereas another one-fourth lived in northeastern Thailand, which reported the highest incidence of CCA in the world. The mean patient age was 61.5 years (range: 34-91 years). The mean duration of symptoms before the diagnosis was 2.3 months (range: 2 weeks-1 year). The most common clinical manifestations were obstructive jaundice (99.12%), abdominal pain (68.3%), and weight loss (87.5%). Only 8.9% of the CCA patients presented with ascending cholangitis as the first manifestation. The definite diagnosis was based on either the histopathology results or clinical courses (including clinical manifestations indicating malignancy, imaging studies, and clinical outcomes after long-term follow-up). A definite diagnosis based on the histopathology data, particularly in patients with inoperable CCA, was possible in 42.6% of patients. The majority of patients were diagnosed using the combination of clinical manifestations, high CA19-9 levels, cross-sectional imaging revealing a liver mass suggestive of CCA, and cytology data revealing or suggesting malignancy. Forty-two percent of the patients in the present study had positive cytology results, and 37.6% had high CA19-9 levels, with the average CA19-9 level being 17,011.55±115,402.54 U/mL. The rest of the patients had suspicious imaging findings and clinical manifestations, and most patients died during the follow-up period. All patients enrolled in this series underwent ERCP for palliative biliary stenting. Hilar CCA was the most common CCA type, accounting for 76.8% of the study population, followed by intrahepatic and distal CCA, which accounted for 13.8 and 8.9% of the study population, respectively. In patients with obstructive jaundice who underwent ERCP, plastic stent insertion was performed nearly as often as self-expandable metal stent (SEMS) insertion. Thirty-six patients (16.1%) had post-ERCP complications including post-ERCP cholangitis (11.2%), pancreatitis (4.0%), and perforation (0.9%). In total, 22.3%, 5.2%, and 0.9% of patients required second, third, and fourth ERCP procedures, respectively. Thirty-two patients, including 21.4% of patients who received plastic stents and 10.7% of patients who received SEMSs, had early stent occlusion (defined as occurring in less than 4 weeks for plastic stents and less than 12 weeks for SEMSs). Nineteen patients required percutaneous transhepatic biliary drainage (PTBD) instead of ERCP with biliary drainage. The patients were followed-up, and their overall clinical status was classified as improving, stable, and worsening in every follow-up visit. The clinical status of the patients during the follow-up period is shown in Figure 1.

All but 5 patients died during the follow-up period. The median survival time, as calculated by survival analysis

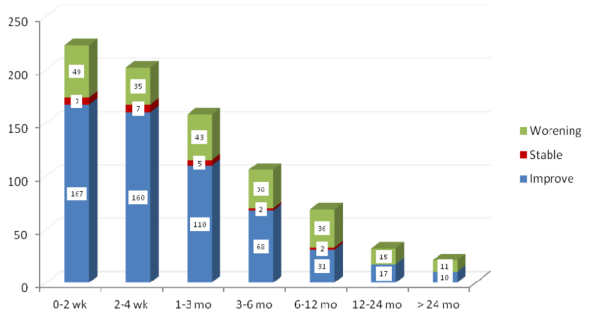

Figure 1. Overall Clinical Status of Patients According to the Follow-up Period

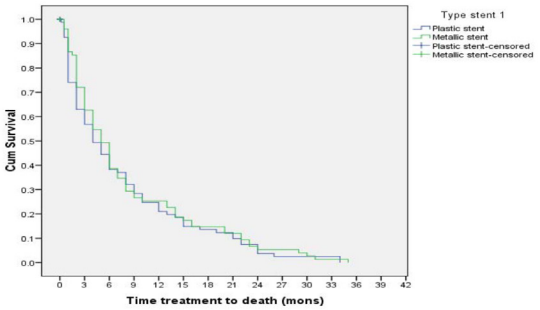

Figure 2. Survival Curves of Patients in the Present Study

Table 1. Patients' Demographic Data and Clinical Manifestations

Details	Plastic Stent (N=121)	SEMS (N=103)	p value
Age (mean±SD)	58.30±11.63	65.40±11.66	<0.001*
Males	70	62	0.414
Occupation			0.387
Government officer	18	18	
Businessman	12	15	
Farmer	19	11	
Employee	51	40	
Unemployed	21	19	
Native habitat			0.761
Central	69	52	
Eastern	5	5	
Northern	7	4	
Northeastern	25	26	
Western	8	11	
Southern	0	0	
Clinical manifestations			
Jaundice	121	101	0.21
Abdominal pain	82	71	0.484
Weight loss	105	89	0.992
Cholangitis as the first presentation (fever with jaundice)	9	11	0.483
Duration of symptoms (months)	2.61±2.05	1.96±1.62	0.010*
Positive cytology	59	36	0.154
CA19-9 level (mean ± SD) U/mL	12,560.48±91,705.24	22,240.47±138,46083	0.53
CA 19-9 more than 100 U/mL	65	57	0.405
CCA classifications			0.466
Distal	13	7	
Intrahepatic	18	13	
Hilar (types II-IV)	89	83	
PTBD needed during follow-up	14	5	0.058
Stent Occlusion	26	11	0.022*
Early stent occlusion (within 4 weeks for plastic stent and within 12 weeks for SEMS)	21	11	0.246

Table 2. Clinical Outcomes of the SEMS and Plastic Stent Groups

Details	Plastic stent (N=103)	SEMS (N=121)	P value
Stent occlusion	26.00	11.00	0.03*
Average number of stents used	1.38	1.19	0.02*
Complications	24.00	12.00	0.07
Median survival time (months)	4.93	5.87	0.41
Number of patients alive at the end of the study	4.00	1.00	0.42

(Kaplan-Meier method), was 4.93 months (95%CI: 2.24-5.76 months) for patients who received plastic stents and 5.87 months (95%CI: 3.57-6.41 months) for patients who received SEMSs, as shown in Figure 2.

The patients were classified into plastic stent and SEMS groups. The baseline characteristics of these 2 groups were found to have no statistically significant differences in terms of the sex distribution, type of CCA, underlying diseases, native habitat, and clinical manifestations. However, the duration of symptoms before diagnosis and the average age of patients were different between the groups. The patients' baseline characteristics and clinical manifestation were shown in table 1 and the clinical outcomes of these groups are also shown in Table 2.

Significantly more stents were used during the follow-up period in the plastic stent group (1.38 vs. 1.19, p=0.03). The stent occlusion rate was also higher in the plastic stent group (26 vs. 11, p=0.03). The median survival time was not statistically different between these groups in the present study.

Discussion

CCA is a malignant disease of the epithelial cells in the intrahepatic and extrahepatic bile ducts that is related to O. viverrini infestation. This study compared the clinical manifestations of different CCA types in an Eastern population, and similar comparisons in Western populations were reported previously. This study revealed that weight loss occurs in as many as 85.8% of patients with CCA in Eastern populations, compared with a rate of 35% in Western populations, but the brush cytology positivity rate was similar between Eastern and Western populations (42.6% vs. 9-24%) (Klatskin, 1965; Nagino et al., 2008; Friman, 2011; Kawakami et al., 2011; Moon and Choi, 2011; Khan et al., 2012). In this study, serum CA19-9 levels exceeding 100 U/mL were detected in 54.0% of the patients. As expected for a clinically silent disease, most of the patients presented with obstructive jaundice in the late stage of disease, and consequently, three-fourths of the patients were not candidates for radical resection (Friman, 2011; Moon and Choi, 2011; Khan et al., 2012). Ascending cholangitis as the first manifestation was present in less than 10% of patients in the present study. The mean duration of symptoms before diagnosis was 2.3 months. This duration was slightly longer because of the feasibility of performing advanced investigations; in particular, cross-imaging studies were more difficult to perform in some areas of Thailand, a finding that depended on the patients' socioeconomic status. CCA is a liver malignancy with a very high mortality rate. Even for patients with resectable disease, the 5-year survival rate has been reported as only 25-43%. In this study, more than 75% of the patients were diagnosed with hilar CCA, and this anatomical type has the worst prognosis. Therefore, almost all the patients died within 3 years. The overall mean survival time in this study was 5.5 months, which was much lower than the rates reported in studies from Europe and USA, which reported overall median survival times for unresectable CCA of approximately

13-16 months (Akamatsu et al., 2011; Aslanian and Jamidar, 2011; Anderson et al., 2012; Ruys et al., 2012). The number of patients in our study was not significantly different from those in retrospective studies by Nagino et al. (2008) and Kawakami et al. (2011), in which the overall median survival times were approximately 5-9 months. This result was substantially different from that of a prospective randomized control trial from Thailand by Sangchan et al. (2012) that reported a median survival time for unresectable CCA of only 1.3-4 months. Based on the aforementioned data, we hypothesized that the difference in the etiology of CCA between Western and Asian countries or in different parts of Thailand (primary sclerosing cholangitis and parasitic infestation respectively) including disease severity might reasonably explain the discordant median survival times of patients worldwide. For patients whose diseases were too advanced for surgery, which was an interesting issue in this study, palliative biliary stenting was another treatment method that improved the quality of life of patients. However, there were different risks and benefits regarding the drainage strategies. Many studies comparing the clinical outcomes of surgical bypass, PTBD, and endoscopic drainage have indicated that endoscopic biliary drainage was superior to PTBD and surgery (Nagino et al., 2008; Kawakami et al., 2011; Kogure et al., 2011; Hwang et al., 2012) in terms of the number of complications and morbidity. Most patients exhibited clinical improvement after the first procedure but gradual deterioration during a long-term follow-up due to disease progression. After comparing the clinical outcomes between the plastic stent and SEMS groups, we found that the number of stents used during the follow-up period and the stent occlusion rate were significantly lower in the SEMS group, whereas the overall median survival times for both groups were not statistically different. It is likely that the survival time is primarily related to the progression and aggressiveness of the diseases, whereas the efficacy of the drainage had no direct impact on the survival time. The results of the present study was different from those of Sangchan, 2012 et al. , who found that SEMS significantly improved the overall median survival of the patients compared to the effects of plastic stents (126 vs. 49 days, p=0.002 by intention-to-treat analysis). However, the short median survival time and low stent patency rates of both treatment groups in this study should be considered. Additional studies regarding the benefit of using SEMSs over plastic stents including cost-effectiveness studies should be conducted in the future. The present study did have some limitations. Due to its retrospective nature, many factors that might have affected the clinical outcomes could not be controlled such as bilateral or unilateral drainage of the biliary system and the inner diameter of the stents. To the best of our knowledge, there has been only 1 randomized controlled trial on this topic. Thus, more prospective studies are needed.

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