

Factors Predicting Good Response to Plastic Stent in Patients with Inoperable Malignant Biliary Tract Obstruction

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ABSTRACT

Background: Biliary drainage is a cornerstone in the management of inoperable malignant biliary tract obstruction. Although self-expandable metallic stent (SEMS) was accepted for better patency, but it costs much higher, whereas some patients may have comparable drainage with plastic stent. This concept leads us to conduct a retrospective study to define patients who will be appropriate for plastic stent insertion.

Methods: Eighty-eight patients with inoperable malignant biliary tract obstruction were included. Clinical data, laboratory results, and survival times were evaluated and compared.

Results: Seventy-two patients (81.82%) had cholangiocarcinoma (CCA), 16 cases (18.18%) had biliary tract obstruction from metastatic tumor. Single 7 Fr plastic stents were inserted in 32 cases (36.36%) and 10 Fr stents in 52 cases (59.09%). Patients younger than 70 years had better median survival than the older (77 vs 33 days, $p < 0.001$). At the end of 2 weeks, patients whose total bilirubin level decreased to $< 50\%$ of initial had better median survival (78 days) than those who did not (50 days) ($p = 0.011$). Although, 10 Fr stent insertion could achieve this level better than 7 Fr stent (51.43% vs 22.73%, $p = 0.024$), the survival times were not different. The 30-day mortality was higher in patients with Bismuth type II-IV (41.67%) and pancreatic cancer (57.14%) than in patients with Bismuth type I and distal CCA (17.30%) ($p = 0.014$), but overall survival was not different. Baseline total bilirubin had no effect on survival.

Conclusions: Median survival was longer in patients younger than 70 years, patients with Bismuth type I and distal CCA, and those whose total bilirubin level decreased to $< 50\%$ of initial level after two weeks. Thirty-day mortality was higher in patients with Bismuth type II-IV and pancreatic cancer. Therefore, proper selection of patients may improve the outcome of plastic stent in patients with inoperable malignant biliary tract obstruction.

Key words : Cholangiocarcinoma (CCC), ERCP, biliary plastic stents

[*Thai J Gastroenterol* 2010; 11(2): 90-96.]

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INTRODUCTION

Biliary obstruction from the malignant lesions in the biliary trees, pancreas, gallbladder or metastatic lesions from other organs are clinical problems which are commonly seen in the north and north eastern parts of this country⁽¹⁾. However, most of the patients show up when they are in the conditions unfit for surgical treatment, the management is inevitably only palliative in this late stage⁽²⁾. Biliary drainage is therefore an appropriate method for this palliation, it reduces not only the degree of jaundice, pruritus, but it also improves other associated symptoms, and enhances quality of life^(3,4). At present, there are 3 methods for biliary drainage, namely, surgical drainage, internal drainage by endoscopic placement of stent, percutaneous biliary drainage. Internal drainage by the endoscopic stent has been accepted widely by the patients especially those who are not fit for major operation, since the procedure is relatively safe, inexpensive, and consumes less time, and in general with fewer complications⁽⁵⁾. However, the post-procedure infection is a major drawback that makes the usefulness and merit of stent insertion less than it should be.

There are 2 types of stents, namely, the plastic and the self expandible metallic stent (SEMS). In hilar obstruction, unilateral plastic stent had comparable median survival with bilateral plastic stent (143 vs 144 days)⁽⁶⁾ and the study from the same investigators also showed that unilateral SEMS drainage had the median survival of 140 days⁽⁷⁾. So, it seems that there was no benefit from using SEMS over plastic stents. Since the plastic stent is much cheaper than the SEMS, and there may be some patients who would have comparable benefit from the plastic stents, we therefore analyze the factors which will be predictors to identify this group of patients.

METHODS

Endoscopic retrograde cholangio-pancreatography (ERCP) reports and the medical records of these patients from the hospital statistical department during the year 2000 to 2005 were reviewed. There were 1,514 cases received the ERCP examinations, 128 cases had malignant obstruction in the biliary system and 40 cases with operable condition were excluded, leaving 88 inoperable cases for analysis.

We categorized the patients into 4 groups, the first group (Group 1) included carcinoma of ampulla of

Vater, distal cholangiocarcinoma (CCA) and hilar CCA with communication between the right and left hepatic ducts (Bismuth type I), the second group (Group 2) were those who had the malignant hilar lesions involving the confluence and/or invading into hepatic or intrahepatic ducts (Bismuth type II-IV), the third group (Group 3) were patients with tumor of pancreas. The fourth group (Group 4) were miscellaneous, namely, carcinoma of gallbladder, hepatoma which extended or metastasized to the hilum, and metastatic tumor to hilum from the tumor of other organs. The survival analyses were based on demographic data, types of malignant tumor, level of obstruction using Bismuth's classification, laboratory results, and sizes of the stents.

Statistical Analysis

SPSS version 15 was used for statistical analysis. Descriptive statistics was used for demographic data. Kaplan-Meier curve, Cox proportional hazard ratio and Log rank test were used for survival analysis. The one way ANOVA, Mann-Whitney test and Kruskal-Wallis test were used for analysis quantitative data and Fisher's exact test was used for qualitative data.

RESULTS

Eighty-eight patients were included in the analysis, 57 were male (64.77%), 31 were female (35.23%), median age 61.50 years (range 30-99 years). Seventy-two patients (81.82%) had cholangiocarcinoma (CCA), 16 cases (18.18%) had biliary tract obstruction from metastatic tumor. Of these 88 patients, 37 cases had CCA of common bile duct (CBD) (42.05%), 11 cases had hilar CCA of Bismuth type I (12.50%), 24 cases had Bismuth type II-IV (27.27%), 7 cases had carcinoma of pancreatic head (7.95%), 4 cases had carcinoma of ampulla of Vater (4.54%), 2 cases had carcinoma of gallbladder (2.27%), 1 case had hepatoma extending to hilum (1.14%), 1 case had colonic cancer metastasis to hilum (1.14%) and 1 case had hepatoma metastasis to distal CBD (1.14%).

At baseline, the average direct bilirubin was 15.60 ± 19.68 mg/dL and average total bilirubin was 24.93 ± 28.96 mg/dL. Thirty-two patients received 7 Fr stents (36.36%), 52 patients received 10 Fr stents (59.09%), 1 patient received 12 Fr stent (1.14%); 3 patients received two 7 Fr stents (3.41%) as shown in Table 1.

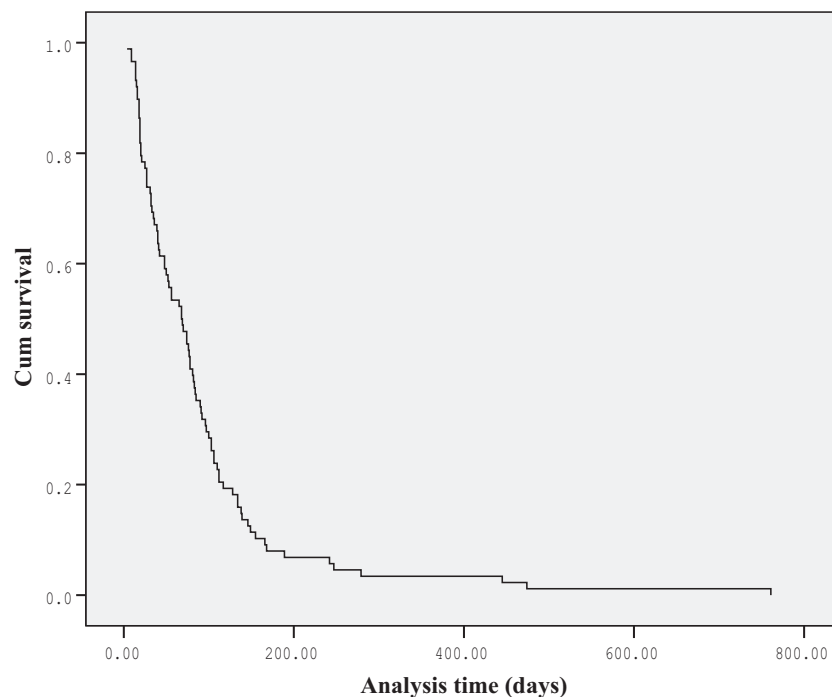
The overall median survival was 68.5 days (4 - 761 days) (Figure 1). From Cox proportional hazard

Table 1. Demographic data, characteristics, baseline laboratory results and size of stents

Sex	
Male	57 (64.77%)
Female	31 (35.23%)
Age (yrs.)	
Mean \pm 2SD	61.15 \pm 27.70
Median (range)	61.50 (30-99)
Diagnosis	
Distal cholangiocarcinoma	37 (42.05%)
Hilar cholangiocarcinoma (Bismuth II-IV)	24 (27.27%)
Hilar cholangiocarcinoma (Bismuth I)	11 (12.50%)
Pancreatic cancer	7 (7.95%)
Cancer of ampulla	4 (4.54%)
Cancer of gallbladder	2 (2.27%)
Hilar hepatocellular carcinoma	1 (1.14%)
Hilar metastatic tumor	1 (1.14%)
Distal metastatic tumor	1 (1.14%)
Baseline laboratory results	
Mean direct bilirubin (mg/dL) \pm 2SD	15.6 \pm 19.68
Mean total bilirubin (mg/dL) \pm 2SD	24.93 \pm 28.96
Number of patients with stents (%)	
7 Fr	32 (36.36%)
10 Fr	52 (59.09%)
12 Fr	1 (1.14%)
Bilateral 7 Fr	3 (3.41%)

model, only decrease of direct and total bilirubin to less than 50% of baseline was associated with longer survival ($p = 0.005$ and $p = 0.001$, respectively). The median survival in patients whose total bilirubin decreased to level less than 50% of baseline at the end of 2 weeks was 78 days (95% CI 43.19-112.81) while the median survival in patients who could not achieve this level was only 50 days (95% CI 25.01-74.99) (Figure 2). Moreover, the patients whose total bilirubin increased at the end of 2 weeks had a very short survival of 27 days (range 16-90 days) (Table 2). Although age was not associated with overall survival, when we categorized the patients into those over and under 70 year-old groups and compared the survival curve with Log rank test, the younger group also had better survival (77 days, 95% CI 63.68-90.32) than the older group (33 days, 95% CI 14.29-51.71) ($p < 0.001$) (Figure 2).

The overall survivals between patients in group 1 and group 2 were not different ($p = 0.877$) but the 30-day mortality in group 2 (41.67%) and group 3 (57.14%) were significantly higher than the patients in group 1 (17.30%) and group 4 (0%) ($p = 0.014$) (Table 3). Although the 10 Fr stent could decrease the bilirubin level at 2 weeks to less than 50% of baseline better than 7 Fr stent (51.43% vs 22.73%, $p = 0.024$) (Table 4), the sizes of the stents were not associated with sur-

**Figure 1.** Kaplan-Meier survival curve of patients.

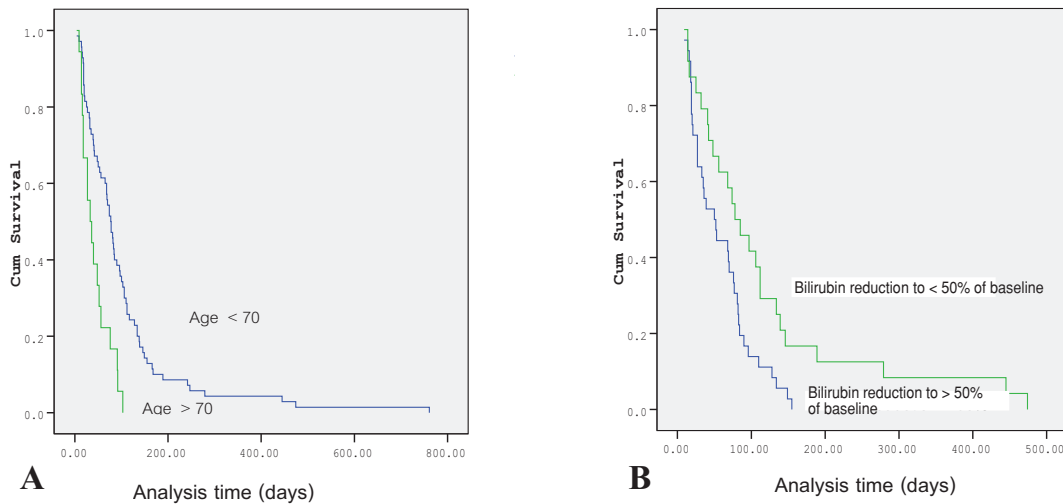


Figure 2. Kaplan-Meier survival curve of patients with age < 70 and > 70 years-old (A) and of patients with bilirubin reduction to > 50% and < 50% of baseline at 2 weeks (B).

Table 2. Correlation between percent decrease of bilirubin at 2 weeks and mortality

Percentage decrease of bilirubin at 2 weeks	Number	Median survival (range) (days)
<50%	23	81.5 (14-474)
50-100%	24	68 (9-155)
>100%	13	27 (16-90)
Total	60	68 (9-474)
Data not available	28	76 (4-761)

$p = 0.0241$ (ANOVA), 0.0482 (Kruskall Wallis Test)

Table 3. Correlation between diagnosis and 30-day mortality

	Total	Survival time		30-day mortality*
		< 30 days	>30 days	
Group 1. Cancer of ampulla Distal cholangiocarcinoma Hilar cholangiocarcinoma (Bismuth I)	52	9	43	17.30
Group 2. Hilar cholangiocarcinoma (Bismuth II-IV)	24	10	14	41.67
Group 3. Cancer of pancreas	7	4	3	57.14
Group 4. Others	5	0	5	0
Total	88	23	65	26.14

* $p = 0.014$

Table 4. Correlation between sizes of stents and percent decrease of bilirubin at 2 weeks

Sizes of stents (Fr)	Percent decrease of bilirubin at 2 weeks		
	<50%	50-100%	>100%
7	8 (34.78%)	5 (20.83%)	9 (69.23%)
10	14 (60.87%)	18 (75.00%)	3 (23.07%)
12	1 (4.35%)	0 (0%)	0 (0%)
7, Bilateral	0 (0%)	1 (4.17%)	1 (7.69%)

vival time. The median survival of patients receiving 7 Fr, 10 Fr and bilateral 7 Fr plastic stents were 50 days (95% CI 13.97-86.03), 77 days (95% CI 54.58-99.42), and 36 days (95% CI 3.99-68.01) ($p = 0.17$), respectively. The gender, baseline bilirubin level, albumin, ALT were not associated with survival time ($p > 0.05$).

DISCUSSION

Biliary obstruction from CCA is the problem worldwide, but the prevalence is different from region to region. In western countries, most of the biliary obstruction is the results of carcinoma of the head of pancreas causing obstruction of the distal CBD. Studies have shown that cancer of pancreas causing obstruction of distal CBD were 62.6-70%, and only 9.9-12.5% were CCA of distal CBD^(8,9). For obstruction at the hilar region, CCA was found in 57.32-60%^(6,10), in our study, we found CCA in 81.8%, and carcinoma of pancreas in only 8%.

The management of obstruction of biliary system should ideally be the removal of the malignant lesion, and when the case is inoperable, the median survival is only 6 to 12 months⁽¹¹⁾. However, biliary decompression or drainage of the bile must be done; this will alleviate jaundice, itching, abnormal liver function, infection of the biliary system which usually brings to sepsis, abnormal intestinal absorption of fat, and coagulation defect. Therefore, biliary drainage by any method will improve the symptoms or at least the quality of life^(3,12-14). The rationale of biliary drainage in this inoperable cases is different from that of preoperative biliary drainage in hilar and pancreatic cancer obstructing the biliary system which is still controversial and seems to be unfavorable^(15,16).

In general, factor which favored the survival time as reported in other studies was the cancer itself, in the primary cancer with smaller size, chance to survive was better when comparing to larger metastatic lesions from the other organs^(7,12,17). Other important factors which affected survival time to be shorter were older age⁽¹⁸⁾, male sex⁽¹⁸⁾, hypoalbuminemia⁽¹⁹⁾, poor performance status⁽²⁰⁾, white bile⁽²¹⁾ and the choice not to administer chemotherapy for certain patient group⁽²²⁾.

Our study had demonstrated that the factors affecting prognosis were age, diagnosis, total bilirubin level, size of the inserted stent, proportion or percentage of decreased bilirubin level at the end of second

week. We found that the unfavorable factors were the age over 70 years, the slow decline of total bilirubin level to less than half of the initial value by the end of the second week, and CCA at the hilum which extended to the confluence (Bismuth type II-IV), obstruction from cancer of pancreas.

The explanation for poorer outcome for patients over 70 years is that these older age patients had more concomitant illness and less strong with poorer physical performances.

In the situation that the bilirubin level decreased only slightly, this reflected that the obstruction was not effectively relieved, at the same time, in some cases, the bilirubin level increased higher than the initial value after the procedure, this could be explained that the lumen of the stent was relatively inadequate for the passage of bile, especially when it was in infected condition which the sticky bile clogged more easily in the lumen.

When the disease extended to the confluence causing obstruction of bile flow from both hepatic lobes, the procedure to insert more than one stent to decompress the biliary obstruction in both lobes was technically more difficult than putting only one stent, since the tumor tissue is usually firm or hard. Drainage in a single lobe might not be adequate to drain the biliary system, especially when the bile was infected. Moreover, when injected contrast media filled the biliary system in both lobes during endoscopic examination, and only one lobe drainage was achieved, this would be more harmful to the patients⁽¹⁰⁾.

Usually, the patients who had 10 Fr stents inserted had a more significant number of decreasing bilirubin level comparing to the patients who were inserted with 7 Fr stents, this was due to the better patency of the larger stent lumens^(23,24). However, the analysis for the sizes of stents may had some biases, since the patients were not allocated to which sizes, normally, the endoscopist would try to use a larger stent if it could be inserted, and changed to a smaller one after failure of putting the larger one, since the obstruction from the CCA was usually firm, even after the endoscopic dilatation of bile duct, quite often the procedure was still difficult to insert a larger stent as the endoscopist intended at the beginning.

In the analysis of our patients, the pre-procedural level of total bilirubin and the size of stent were not statistically significant, but they showed a trend that the pre-procedural level of bilirubin which was >10

mg/dL had a poorer prognosis, which might be due to longer time of obstruction or the patient had suffered through a longer disease process. For the sizes of the stents, the 10 Fr stent had a trend of better capacity for drainage than the 7 Fr in group 1 patients; this was consistent with the previous studies^(23,24). But for the patients in group 2, the 10 Fr stent was not better than the 7 Fr stent; this was also shown by previous studies even using the SEMs, the median survival time was not better than using the plastic stents^(6,7).

Our patients showed a median survival period at 68.5 days, comparing to those of other studies which were found at 140-160 days^(6,9,10). These might be due to our the patients sought treatment rather late in course of illness, and quite often after certain complications occurred, and they were usually in poor physical performance.

The data from this study would be of benefit for us to consider an appropriate management of older patients, especially those with age more than 70 years, obstruction from hilar CCA extending to confluence (Bismuth type II-IV), or cancer of the pancreas invading the biliary system. Since we have to reconsider our techniques of demonstration the level of obstruction at the time of endoscopic examination, which may be the use of guidewire to determine the level of obstruction or using air cholangiogram which is practically not so easy to get clear images due to interference from the air in the bowel loops making it difficult to determine the level of obstruction, or preferably, selective injection of contrast media into only the lobe determined to be drained which ideally is safer for the patients, therefore, to have magnetic resonance cholangio-pancreatography (MRCP) to determine the lobe to be drained in certain cases may be helpful to serve this purpose, but this will add costly expense to the patients.

For the evaluation of the bilirubin level, we found that the decrease of bilirubin to at least 50% by the end of 2 weeks after stenting was as good as evaluation at one month to the decrease of at least 75% as the previous recommendations^(6,7). We found the median survival in our study to be 81.5, 68 and 27 days in patients whose total bilirubin level decreased to the level less than half, more than half, and increased above the initial value, respectively. Therefore, in the cases of poorly decreased or increased level of bilirubin at the end of the second week, we should consider other alternative way to drain the bile or even try to exchange

the stent to a larger one if possible with the expectation to have a better drainage, but these also depend on the conditions and performances of the patients whether they will be fit enough for any additional procedures of drainage.

In conclusion, patients who showed better result from the endoscopic plastic stent drainage were those under 70 years of age, obstruction were Bismuth type I or distal CCA, while those with Bismuth II-IV and obstruction due to pancreatic cancer had poorer prognosis. And for all patients, the decreased level of bilirubin to less than half of baseline by the end of the second week would be a good prognostic sign. However, due to the poor result of treatment and short survival for all types of inoperable CCA, the less costly plastic stent is still an appropriate choice for consideration in patients with poor response (group 2 and 3), if the estimated survival is relatively short and the repeated procedure is not expected.

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