



BRIEF ARTICLE

## Factors relating to the short term effectiveness of percutaneous biliary drainage for hilar cholangiocarcinoma

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Received: August 16, 2009 Revised: September 21, 2009

Accepted: September 28, 2009

Published online: November 7, 2009

cutaneous biliary drainage was related to patient's prothrombin time or the extent of tumor involvement. It, however, had no impact on survival.

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**Key words:** Cholangiocarcinoma; Percutaneous biliary drainage; Treatment effectiveness

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Tsai HM, Chuang CH, Lin XZ, Chen CY. Factors relating to the short term effectiveness of percutaneous biliary drainage for hilar cholangiocarcinoma. *World J Gastroenterol* 2009; 15(41): 5206-5210 Available from: URL: <http://www.wjgnet.com/1007-9327/15/5206.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.5206>

### Abstract

**AIM:** To identify factors that were related to the short term effectiveness of percutaneous transhepatic biliary drainage in cholangiocarcinoma patients and to evaluate the impact of palliative drainage on their survival.

**METHODS:** Seventy-four patients with hilar cholangiocarcinoma who underwent percutaneous biliary drainage were enrolled in the study. The demographic and laboratory data as well as the imaging characteristics were retrospectively analyzed to correlate with the bile output and reduction rate of serum bilirubin 1 wk after drainage.

**RESULTS:** Patients with more bile duct visualized on percutaneous transhepatic cholangiography or absence of multiple liver metastases on imaging studies had more bile output after biliary drainage [odds ratio (OR): 8.471,  $P = 0.010$  and OR: 1.959,  $P = 0.022$ , respectively]. Patients with prolonged prothrombin time had a slow decrease in serum bilirubin (OR: 0.437,  $P = 0.005$ ). The median survival time was not significantly different in patients with low or high bile output (75 d vs 125 d,  $P = 0.573$ ) or in patients with slow or rapid reduction of serum bilirubin (88 d vs 94 d,  $P = 0.576$ ).

**CONCLUSION:** The short term effectiveness of per-

### INTRODUCTION

Cholangiocarcinoma is the second most common primary liver cancer, after hepatocellular carcinoma and the incidence is increasing<sup>[1,2]</sup>. Hilar cholangiocarcinoma with the tumor involving the biliary confluence or the right or left intrahepatic ducts is most common and accounts for 40%-60% of all cholangiocarcinomas<sup>[3]</sup>. About 80% of patients with hilar cholangiocarcinoma are unsuitable for curative surgical resection due to severe comorbidity for major surgery, metastases or advanced loco-regional disease<sup>[4]</sup>. Percutaneous or endoscopic biliary drainage is usually performed as a palliative treatment to relieve these patients from jaundice, pain, and cholangitis<sup>[5]</sup>.

A fluent bile output after percutaneous transhepatic biliary drainage (PTBD) reduces the biliary pressure and therefore, alleviates the cholangitis and pain of patients. The reduction of serum bilirubin is usually the hallmark of successful biliary drainage. Nonetheless, despite the drainage catheter being correctly positioned in the bile duct, there are still some patients who have scanty bile output and persistent elevation of serum bilirubin<sup>[6]</sup>. We retrospectively analyzed the clinical and imaging characteristics of these patients in an attempt to identify the factors related to bile output and reduction of serum bilirubin after PTBD. In addition, we also compared

the survival of patients with different bile output and reduction rates of bilirubin after PTBD to investigate if the short term effectiveness of biliary drainage had any impact on the long term survival.

## MATERIALS AND METHODS

### Patients

From January 1998 to June 2007, 74 consecutive patients with hilar cholangiocarcinoma who underwent PTBD in our hospital, a tertiary transferring center, were enrolled. The diagnosis of cholangiocarcinoma was confirmed either by pathologic diagnosis ( $n = 39$ ) or by imaging studies plus clinical follow-up which illustrated further tumor progression ( $n = 35$ ). These patients included 39 males and 35 females with a mean age of  $66.1 \pm 12.8$  and  $66.5 \pm 12.5$  years, respectively. All of the patients, irrespective of future treatment modality, underwent PTBD due to the presence of jaundice and a dilated biliary system and were further observed for at least 1 wk to evaluate the effectiveness of PTBD. Of them, 54 patients were unsuitable for surgical intervention on the basis of their comorbidity and/or tumor extent and were enrolled for survival analysis.

### Clinical characteristics

The medical records of each patient were retrospectively reviewed. Data collected from all patients on the day of, or 1 d before, biliary drainage included the initial serum levels of albumin, bilirubin, alanine aminotransferase (ALT), alkaline phosphatase and prothrombin time. The average daily bile output and the serum total bilirubin level 1 wk after drainage were recorded for the evaluation of drainage effectiveness. The overall survival time of patients who did not undergo surgical resection was also checked.

### Imaging characteristics analysis

Percutaneous transhepatic cholangiography (PTC), contrast enhanced computed tomography (CT) and/or magnetic resonance (MR) imaging were reviewed for imaging characteristics analysis. The liver tumors were classified as type I, II, IIIa, IIIb, and IV according to the system of Bismuth *et al.*<sup>[7]</sup>. The maximal diameter of the tumors was estimated on CT or MR imaging either by direct measurement of the tumor size if its margin could be clearly defined or indirect measurement of the distance between dilated ducts if the tumor was difficult to visualize. The maximal diameter of the intrahepatic duct punctured for biliary drainage was measured on CT, MR, or PTC imaging. The number of visualized intrahepatic bile ducts (first branches of right and left intrahepatic ducts) was counted later on a follow-up PTC as it may depend on the injection pressure of contrast and the radiologist usually injected less contrast media to avoid risk of cholangitis when performing PTBD. A follow-up PTC taken several days after the biliary drainage, although it may still have some limitation, should carry a lower risk of cholangitis and allow more contrast injection. In addition, CT or MR

imaging was checked for multiple liver metastases, locoregional lymphadenopathy and peritoneal involvement.

### Percutaneous transhepatic biliary drainage procedure

Before PTBD, the bleeding profile was checked and treated if abnormal, and antibiotic therapy was commenced. If CT or MR images showed dilated ducts were confined to a single lobe, PTBD was performed *via* that lobe. If the ducts of both lobes were dilated, our radiologists preferred to approach from the left side unless it was atrophied due to tumor invasion of the ipsilateral portal vein. The duct selected for drainage depended on the decision of the radiologist, who selected the most feasible duct to approach. PTBD was performed as a standard procedure. In brief, the biliary system was punctured and a guide wire (0.035 inch) was introduced into the bile duct. Through the guide wire, the puncture tract was dilated using a bougie, followed by the insertion of an 8-French pigtail catheter.

### The effectiveness of biliary drainage

The average daily bile output during the first week after PTBD was calculated. The reduction rate of serum bilirubin was calculated by dividing the reduction of total bilirubin level after 1 wk of drainage by the original level. For differentiating the effectiveness of biliary drainage, an average bile output of more or less than 300 mL/d and a reduction rate of serum bilirubin of higher or lower than 20% (i.e. the integer of median value of patient distribution) were chosen to further divide patients into two groups with similar sample size.

### Statistical analysis

Except for patient survival which was presented as median survival days, all the other data were expressed as mean  $\pm$  SD. The differences in demographic, biochemical, and imaging characteristics between patient groups were compared by Independent-Samples *t* test or  $\chi^2$  test as appropriate. Variables that achieved statistical significance ( $P < 0.05$ ) or were close to significance ( $P < 0.1$ ) in the univariate analysis were subsequently included in a multivariate analysis using a stepwise forward logistic regression. The survival of patients with different effectiveness of biliary drainage was compared by using the log-rank test. The statistical calculations were computed using the SPSS 12.0 program for Windows (SPSS Inc., Chicago, IL, US).

## RESULTS

### Events associated with the biliary drainage

There was no procedure associated mortality or significant morbidity, except two cases of transient hemobilia and two cases of cholangitis. Most of our patients who did not undergo surgical intervention were maintained on PTBD and only 12 (16.2%) of them were switched to external-internal biliary drainage. The drainage was further revised if the initial PTBD drainage had unsatisfactory function during the follow up. Of the 26 patients

**Table 1** The clinical characteristics of patients with high and low bile output (mean  $\pm$  SD)

	Bile output		P-value <sup>1</sup>
	> 300 mL (n = 33)	< 300 mL (n = 41)	
Age (yr)	64.5 $\pm$ 10.3	67.7 $\pm$ 14.2	0.25
Sex (male:female)	20:13	19:22	0.35
Biochemical data			
Albumin (g/dL)	3.4 $\pm$ 0.6	3.0 $\pm$ 0.5	0.01
Total bilirubin (mg/dL)	12.2 $\pm$ 7.4	12.0 $\pm$ 8.5	0.92
ALT (U/L)	132.5 $\pm$ 184.5	142.6 $\pm$ 115.2	0.77
Prolonged prothrombin time (s)	1.0 $\pm$ 1.1	1.2 $\pm$ 1.3	0.42
Bilirubin reduction rate (%)	22.5 $\pm$ 41.2	13.6 $\pm$ 29.7	0.31
Alkaline phosphatase (U/L)	463.9 $\pm$ 301.8	552.9 $\pm$ 373.8	0.297
Imaging characteristics			
Visualized bile ducts on PTC	2.7 $\pm$ 1.2	1.7 $\pm$ 1.0	0.001 <sup>2</sup>
Tumor size (cm)	5.3 $\pm$ 2.9	4.6 $\pm$ 2.5	0.31
Diameter of bile duct (mm)	10.5 $\pm$ 6.1	11.1 $\pm$ 5.9	0.65
Approach side (right:left)	9:24	10:31	0.79
Bismuth type I / II / IIIa / IIIb/IV <sup>3</sup>	8/6/5/3/7	2/6/11/11/5	0.03
Lymphadenopathy	10	9	0.59
Liver metastasis	4	14	0.03 <sup>2</sup>
Peritoneal involvement	7	8	1.00

<sup>1</sup>By Independent-Samples *T* test and  $\chi^2$  test as appropriate; <sup>2</sup>Only the absence of multiple liver metastases and more intrahepatic bile ducts visualized on PTC were statistically significant in multivariate analysis; <sup>3</sup>Eleven patients with ambiguous imaging that cannot be confidently classified were not included for analysis. PTC: Percutaneous transhepatic cholangiography.

who underwent palliative treatment only and survived longer than 90 d, 20 patients (77%) received at least one drainage revision.

### Bile output after drainage

There were 33 patients with and 41 patients without an average bile output of more than 300 mL/d. As shown in Table 1, among the biochemical data, only a higher serum albumin concentration was associated with higher bile output in patients undergoing PTBD. Higher bile output was, however, not associated with a more rapid reduction of serum bilirubin as it was not significantly different between both groups. Patients who had fewer intrahepatic bile ducts shown on PTC, hence a more advanced Bismuth classification, or multiple liver metastases had lower bile output after biliary drainage. The size of tumor, the diameter of bile duct, the approach side of PTBD, and the presence of lymphadenopathy or peritoneum involvement were all unrelated to the amount of bile output.

In multivariate analysis, the absence of liver metastases and a greater number of intrahepatic bile ducts visualized on PTC were still significantly associated with a higher bile output. The odds ratios (ORs) were 8.471, (95% CI: 1.675-42.835,  $P = 0.010$ ) for negative metastasis and 1.959, (95% CI: 1.103-3.481,  $P = 0.022$ ) for more intrahepatic bile ducts on PTC.

### Reduction rate of serum bilirubin after drainage

Of the 70 patients available for analysis of bilirubin

**Table 2** Clinical characteristics between the patients who had rapid and slow bilirubin reduction rates after drainage (mean  $\pm$  SD)

	Reduction		P-value <sup>1</sup>
	> 20% (n = 37)	< 20% (n = 33)	
Age (yr)	67.6 $\pm$ 12.5	65.4 $\pm$ 12.3	0.515
Sex (male:female)	19:18	18:15	1.000
Biochemical data			
Albumin (g/dL)	3.4 $\pm$ 0.5	3.0 $\pm$ 0.6	0.016
Total bilirubin (mg/dL)	10.6 $\pm$ 5.9	15.0 $\pm$ 5.1	0.022
ALT (U/L)	172.3 $\pm$ 190.2	102.1 $\pm$ 70.0	0.048
Prolonged prothrombin time (s)	0.7 $\pm$ 0.7	1.7 $\pm$ 1.4	0.001 <sup>2</sup>
Alkaline phosphatase (U/L)	499.5 $\pm$ 268.6	543.8 $\pm$ 428.8	0.630
Imaging characteristics			
Visualized bile ducts on PTC	2.2 $\pm$ 1.2	2.1 $\pm$ 1.2	0.815
Tumor size (cm)	4.9 $\pm$ 2.6	4.9 $\pm$ 3.0	0.968
Diameter of bile duct (mm)	11.0 $\pm$ 5.9	10.4 $\pm$ 5.9	0.670
Approach side (right:left)	10:27	8:25	1.000
Bismuth type I / II / IIIa / IIIb/IV <sup>3</sup>	5/7/10/5/6	5/5/6/9/5	0.657
Lymphadenopathy	11	7	0.583
Liver metastasis	12	5	0.159
Peritoneal involvement	10	5	0.379

<sup>1</sup>Abbreviations as in Table 1; <sup>2</sup>In multivariate analysis, only the prothrombin time was significantly associated with bilirubin reduction; <sup>3</sup>Abbreviations as in Table 1.

reduction (four patients did not have a serum bilirubin check 1 wk after drainage), 37 patients had a bilirubin reduction of more than 20% after 1 wk of drainage and 33 patients did not. The reduction rate of bilirubin was significantly more rapid in patients who had a less prolonged prothrombin time or a better serum biochemical profile including higher serum albumin, lower serum bilirubin or ALT (Table 2). None of the imaging characteristics such as tumor size, Bismuth classification, liver metastasis and lymphadenopathy had an impact on the rate of serum bilirubin reduction after biliary drainage.

In multivariate analysis, only prolonged prothrombin time was significantly associated with a slower reduction rate of serum bilirubin. The OR was 0.437 (95% CI: 0.245-0.780,  $P = 0.005$ ), compared to those with normal prothrombin time.

### Short term effectiveness of biliary drainage and patients' survival

Most of the patients who were unsuitable for surgical resection died of cholangitis and/or liver failure. Only one patient was still alive at the time of analysis. The median survival time of these patients was 94 d. Although 12 patients received additional drainage due to scanty biliary output or persistent hyperbilirubinemia, the median survival of patients with bilateral biliary drainage was similar to that of patients who received only unilateral drainage (66 d *vs* 94 d,  $P = 0.358$ ). In addition to biliary drainage, 10 of the 54 patients who had unresectable tumors also underwent external beam radiation therapy. The median survival was, however, not significantly longer

in these patients (103 d) than in those who received drainage only (88 d,  $P = 0.493$ ). These patients were therefore, combined for survival analysis.

The serum bilirubin reduction rate, whether it was more rapid or slower than 20% did not affect the median survival time of patients (94 d *vs* 88 d,  $P = 0.576$ ). The median survival time was also similar between patients with a bile output less than 300 mL (75 d) and those with a bile output more than 300 mL (125 d,  $P = 0.573$ ).

## DISCUSSION

As shown in our previous and current studies, bile output was not correlated with the reduction rate of bilirubin<sup>[8]</sup>. Both liver cells and ductular cells contribute to the formation of bile<sup>[9]</sup>. Biliary obstruction results in proliferation of bile ducts and ductules. The increased amount of bile after relief of obstruction can be caused by excretion of water and electrolytes from the proliferated biliary epithelial cells (i.e. the secretin choleresis)<sup>[9]</sup>. Nevertheless, the reduction of serum bilirubin is dependent on bilirubin excretion by liver cells which can be impaired as a result of cholestasis<sup>[10]</sup>. Prolonged biliary obstruction in these patients results in bile duct proliferation and hepatocyte damage, which explains the discrepancy between bile output and bilirubin reduction rate. A high bile output is therefore, not associated with a rapid reduction in serum bilirubin if most of the bile comes from the bile ducts rather than liver cells.

Cholangiocarcinoma with more advanced Bismuth classification implies a complicated biliary obstruction and is frequently found to have fewer intrahepatic bile ducts depicted on PTC<sup>[7]</sup>. Liver metastases also cause biliary obstruction by compressing the bile ducts externally. The presence of multi-site biliary obstruction, either caused by intra-luminal obstruction or external compression of the tumor, leads to fewer sources of bile flowing into the drained bile duct and was therefore, associated with less bile output after PTBD in our observations.

Accumulation of bile salts within the liver can cause necrosis and apoptosis of liver cells<sup>[10-13]</sup>. The liver may need more time to recover in cases with long lasting biliary obstruction. Prolonged prothrombin time in cholangiocarcinoma patients can be due to either vitamin K deficiency or impaired liver synthesis of coagulation factors, both sequelae of prolonged cholestasis. Weston reported that patients with prolonged prothrombin time took longer for bilirubin reduction after endoscopic biliary stenting<sup>[14]</sup>. Similarly, patients with a prolonged prothrombin time in our study also had a slow reduction of serum bilirubin.

Surgical resection is the standard treatment for intrahepatic cholangiocarcinoma<sup>[15]</sup>. Patients unsuitable for surgical resection live a significantly shorter time than those undergo curative tumor resection. Previous reports indicate that the method of drainage has no impact on patient survival<sup>[4]</sup>. Our data further showed that patient's survival was not related to the bile output

or the rate of bilirubin reduction after biliary drainage. This may be because even though the drainage provides good short term success in palliating symptoms, it is however associated with significant morbidity in the long term follow up including catheter clogging, catheter dislodgement, cholangitis, and liver failure<sup>[16]</sup>. As seen in our study, most of the patients who survived more than 90 d received multiple drainage revisions and as a consequence of tumor progression, most of them still died of cholangitis and liver failure. Therefore, the short term effectiveness of PTBD adds little benefit to survival unless other effective methods such as photodynamic therapy are available to retard the tumor progress and keep the biliary systems patent<sup>[17,18]</sup>.

In conclusion, our study identified factors that were related to the short term effectiveness of PTBD in patients with hilar cholangiocarcinoma. After biliary drainage, patients may have less bile output in the presence of multiple sites of biliary obstruction, and slower reduction of serum bilirubin if the prothrombin time is prolonged. A higher bile output was not associated with a more rapid bilirubin reduction. Although we only observed the drainage effect at 1 wk which may not reflect the ultimate result of drainage, we did find that a short term relief of biliary obstruction by PTBD was not associated with a better survival in patients with unresectable cancer.

## COMMENTS

### Background

Biliary drainage is performed as a palliative treatment of hilar cholangiocarcinoma. The reduction of serum bilirubin is usually the hallmark of successful biliary drainage. However, some patients may have persistent jaundice or scanty bile output after biliary drainage.

### Research frontiers

This paper analyzed factors relating to bile output and reduction of serum bilirubin after percutaneous biliary drainage. Furthermore, the impact of short term effectiveness of biliary drainage on long term survival was investigated.

### Innovations and breakthroughs

After percutaneous biliary drainage, high bile output was not associated with a rapid reduction of serum bilirubin. The bilirubin reduction was related to patient's prothrombin time and the bile output, to the extent of tumor involvement. Neither the amount of bile output nor the rate of bilirubin reduction had an impact on survival.

### Applications

The effectiveness of percutaneous biliary drainage can be properly estimated before the procedure. Patient should be observed for daily bile output as well as the reduction of serum bilirubin. An initially well functioning biliary drainage does not link to a longer survival of patients and further efforts to maintain biliary patency are required.

### Peer review

Chen *et al* found that the short term effectiveness of percutaneous biliary drainage was related to patient's prothrombin time or the extent of tumor involvement, but it had no impact on survival. The paper is informative.

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S- Editor Tian L L- Editor O'Neill M E- Editor Zheng XM