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Clinical Outcome of Biliary Drainage for Obstructive Jaundice Caused by Colorectal and Gastric Cancers

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Objective: To clarify the prognostic factors for patients with obstructive jaundice due to advanced colorectal and gastric cancers who had undergone percutaneous transhepatic biliary drainage.
Methods: Baseline variables and clinical outcomes were evaluated for 92 consecutive patients treated with percutaneous transhepatic biliary drainage.
Results: Of the 92 patients, 32 (35%) had colorectal cancer and the remaining 60 (65%) had gastric cancer. Percutaneous transhepatic biliary drainage was successfully achieved in 74 (80%) patients, and 39 of them could receive subsequent chemotherapy. The median survival after percutaneous transhepatic biliary drainage was 273 days in the 39 patients who had undergone successful percutaneous transhepatic biliary drainage and subsequent chemotherapy, 65 days in 35 patients who had undergone successful percutaneous transhepatic biliary drainage but who had not received subsequent chemotherapy and 34 days in the remaining 18 patients who had undergone unsuccessful percutaneous transhepatic biliary drainage ($P < 0.001$). Multiple liver metastases and hepatic hilar bile duct stricture were independently associated with unsuccessful percutaneous transhepatic biliary drainage. Poor performance status, multiple liver metastases, presence of ascites, multiple prior chemotherapy administrations, undifferentiated type histology and high serum CA19-9 level were independently associated with a poor prognosis. A prognostic index calculated based on the number of these six factors was used to classify the patients into a good-risk group (index ≤ 2) ($n = 56$) and a poor-risk group (index ≥ 3) ($n = 36$). The median survival time and 2-month survival rate for the two groups were 163 and 44 days, respectively, and 85.7 and 33.3%, respectively ($P < 0.001$).
Conclusions: As regards the introduction of percutaneous transhepatic biliary drainage in patients with obstructive jaundice due to colorectal and gastric cancers, careful patient selection might be necessary. A prognostic model seems to be useful for making decisions as to whether percutaneous transhepatic biliary drainage is indicated for particular patients.

Key words: obstructive jaundice – stomach neoplasms – colorectal noplasms – drainage

INTRODUCTION

Obstructive jaundice sometimes occurs in patients with advanced or recurrent gastrointestinal cancer as well as in those with primary hepatobiliary and pancreatic cancer due to metastasis to abdominal lymph nodes, hepatoduodenal peritoneum or the liver.

Percutaneous transhepatic biliary drainage (PTBD) is now widely used for patients with obstructive jaundice and it is useful in improving hepatic function (1,2). PTBD is an effective method to achieve biliary decompression, and it makes it possible for these patients to undergo chemotherapy safely, because chemotherapeutic agents are often implicated in causing liver damage.

Irinotecan, known as a key chemotherapeutic agent in gastrointestinal (GI) cancer (3–6), is activated by hydrolysis to SN-38, which is lost into the bile and feces, but it is contraindicated at high levels of serum bilirubin for safety reasons (7). Accordingly, achieving normal or near-normal hepatic function by successful PTBD is especially important for those patients in order to avoid excessive SN-38 toxicity.

On the one hand, the prognosis for patients with obstructive jaundice due to advanced colorectal and gastric cancers is generally poor (4–24 weeks) and colorectal and gastric cancers are major causes of obstructive jaundice from non-biliary and non-pancreatic cancers in previous reports (1,8–10). Prospective clinical trials typically enroll patients with normal hepatic function and omit patients with hepatic dysfunction such as obstructive jaundice. So it is not clear whether PTBD and subsequent chemotherapy after achieving improved hepatic function in such patients improve their clinical outcomes. Some reports revealed that biliary drainage was effective for relief of symptoms (1,10). On the other hand, some cases did not improve their liver functions after PTBD and had poor prognoses (10). So we are often in doubt on whether to recommend an invasive PTBD intervention or settle for best supportive care for gastric and colorectal cancer patients with biliary obstruction. To solve this clinical question, we reviewed our experiences with PTBD cases and analyzed factors that affect clinical outcomes after PTBD procedures. The purpose of the present study is to investigate clinical outcomes of patients treated with PTBD due to advanced colorectal and gastric cancers and to identify patients who would not receive benefits from PTBD: patients who did not achieve relief from jaundice even after PTBD or who had a poor prognosis even after successful PTBD.

PATIENTS AND METHODS

Patients

This study included 92 consecutive patients who underwent PTBD due to obstructive jaundice with advanced GI cancer at our institution between March 2005 and January 2011. All of the patients had histologically confirmed adenocarcinoma of the stomach or colon or rectum, and they had obstructive jaundice (intrahepatic bile duct dilation on both ultrasound and computed tomography and laboratory data shows a transaminase value over five times of the upper normal limit or a serum total bilirubin of 2 mg/dl or greater) due to metastasis to abdominal lymph nodes, hepatoduodenal peritoneum or liver according to clinical and imaging findings.

PTBD Procedure and Subsequent Chemotherapy

We obtained written informed consent from all patients before PTBD. Following conventional percutaneous transhepatic cholangiography (11), we placed stents. Under ultrasound or fluoroscopic guidance, we punctured a peripheral bile duct with a 21-gauge needle, and confirmed the position with the injection of a small volume of contrast material. Then we inserted a guidewire through the needle into a central bile duct, and passed a plastic drainage cannula over the guidewire. The insertion of the cannula may require the use of sheaths and dilators to distend the tract. A catheter can then be inserted through the cannula and advanced across an obstruction into the duodenum, thereby draining bile internally and externally. Adequate drainage is usually confirmed by a steady decline in serum bilirubin concentrations. After adequate drainage, self-expanding metal stents were inserted to treat malignant biliary strictures. Placement of multiple stents was considered in hepatic hilar bile duct stricture cases, because better drainage effects were reported compared with those brought about by single-stent placement (12). In the current study, successful PTBD is defined as achieving a serum total bilirubin concentration of <3 mg/dl and a transaminase value within five times of the upper normal limit after PTBD. After successful PTBD, if performance status of patients is good (i.e. ECOG PS 0–2) and useful anti-cancer agents are available, we start subsequent chemotherapy.

Factors Analyzed

The relationships between pre-PTBD clinical variables and successful PTBD and survival after PTBD were investigated by univariate and multivariate analyses. Individual clinical data were collected from all medical records of the study patients. Pre-PTBD clinical variables included the age, sex, present illness, prior chemotherapy before PTBD, computed tomography findings, histological type, laboratory data including the tumor markers CEA and CA19-9 before PTBD and outcomes after PTBD. Undifferentiated type of histology means poorly differentiated adenocarcinoma and signet ring cell carcinoma. Liver metastasis was evaluated according to the latest General Rules of the Japanese Classification of Colorectal carcinoma published by the Japanese Society for Cancer of Colon and Rectum (13,14), i.e. H0 (no liver metastasis), H1 (the number of liver metastatic lesions: <4, the largest diameter: <5 cm), H2 (other than H1 and H3) and H3 (the number of liver metastatic lesions: >5, the largest

diameter: >5 cm). Changes in the laboratory data after PTBD were the differences from the minimum values within 1 month after PTBD. Each of the variables was divided into two subgroups in accordance with the median values for easy application in clinical practice. Statistical analyses were carried out using the chi-square tests and Fisher's exact test, and various factors were also evaluated simultaneously using logistic regression to determine the most significant variables related to successful PTBD.

The time to development of obstructive jaundice was measured for non-chemo-naïve patients from the date of initial chemotherapy to the date of development of obstructive jaundice. Survival after PTBD was measured for all the patients from the date of PTBD to the date of death or last follow-up.

Survival curves were calculated by the Kaplan–Meier method and the differences were evaluated by the log rank test. The Cox proportional hazards model was used to determine the significant variables related to survival after PTBD. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine the major independent predictors of survival after PTBD. All patients were then assigned a prognostic index value, calculated based on the number of the major independent predictors of survival. The stratification of the patients was carried out based on this prognostic index. All statistical analyses were performed using SPSS (version 17.0; SPSS Inc., IL), and differences at $P < 0.05$ were considered to be significant.

This retrospective study was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee at our institution.

RESULTS

Patient Characteristics

The baseline characteristics of all the 92 patients are shown in Table 1. Of the 92 patients, 32 patients (35%) have colorectal cancer and the remaining 60 (65%) have gastric cancer. Twenty-six patients (28%) were chemo-naïve and the remaining 66 (72%) had prior chemotherapy. A total of 74 patients (80%) underwent successful PTBD, and liver dysfunction due to obstructive jaundice improved after PTBD (Table 2).

Subsequent Chemotherapy after PTBD

Of the 74 patients who underwent successful PTBD, 39 received subsequent chemotherapy, but the remaining 35 could not receive chemotherapy after PTBD because of general deterioration. Of the 39 patients with subsequent chemotherapy, 13 received irinotecan-based chemotherapy, 10 received paclitaxel, 8 received platinum-based chemotherapy, 5 received S-1 alone and the remaining 3 received other drugs.

Table 1. Baseline characteristics of 92 patients just before percutaneous transhepatic biliary drainage (PTBD)

	No. of patients (%)
Age (years)	59.9 ± 11.2
Gender	
Male	64 (69.6)
Female	28 (30.4)
ECOG performance status	
0	36 (39.1)
1	40 (43.5)
2	12 (13.0)
3	4 (4.3)
Primary cancer	
Colorectal cancer	32 (34.8)
Gastric cancer	60 (65.2)
Histology	
Differentiated type	36 (39.1)
Undifferentiated type	56 (60.9)
Prior chemotherapy	
Chemo-naïve	26 (28.3)
First line	29 (31.5)
Second line	31 (33.7)
Third line	3 (3.3)
Fourth line	3 (3.3)
Liver metastasis	
H0	47 (51.1)
H1	9 (9.8)
H2	14 (15.2)
H3	22 (23.9)
Tumor marker	
CEA (ng/ml)	357 ± 1390.9
CA19-9 (IU/ml)	6219.2 ± 14 463.7

Table 2. Laboratory data just before and after PTBD

	Before PTBD	After PTBD[a]
Total bilirubin (mg/dl)*	7.5 ± 4.5	2.5 ± 3.6
AST (IU/l)*	141.5 ± 112.1	57.9 ± 65.7
ALT (IU/l)*	162.4 ± 170.4	39.0 ± 38.7
ALP (IU/l)*	1715.2 ± 1075.8	906.6 ± 730.4
γGTP (IU/l)*	589.4 ± 392.9	214.9 ± 184.2

[a]A minimum value within 1 month after PTBD.
*$P < 0.001$.

Time to Obstructive Jaundice in Non-Chemonaive Patients

A total of 66 patients received PTBD during the front-line chemotherapy. Of these 66 patients, 42 patients have gastric cancer, and the remaining 24 have colorectal cancer; 53 patients (80.3%) received successful PTBD and the remaining 13 (19.7%) received unsuccessful PTBD. The median time to obstructive jaundice was 259 days in the patients with gastric cancer and 306 days in those with colorectal cancer ($P = 0.017$). The median survival time after PTBD was 65 days in the patients with gastric cancer and 95 days in those with colorectal cancer, and there was no difference between them ($P = 0.395$).

Survival After PTBD

The median survival time after PTBD was 273 days in the patients with successful PTBD and subsequent chemotherapy ($n = 39$), 65 days in those with successful PTBD but without subsequent chemotherapy ($n = 35$) and 34 days in those with unsuccessful PTBD and without subsequent chemotherapy ($n = 18$) ($P < 0.001$) (Fig. 1). The difference between the latter two groups, successful PTBD without subsequent chemotherapy and unsuccessful PTBD, was not significant ($P = 0.296$).

Clinicopathological Factors Associated with Unsuccessful PTBD

Univariate analysis showed that H3 liver metastasis, hepatic hilar bile duct stricture and CA19-9 >500 IU/ml were significantly associated with unsuccessful PTBD (Table 3). Multivariate analysis showed that hepatic hilar bile duct stricture and H3 liver metastasis were the independent factors significantly associated with unsuccessful PTBD (Table 4).

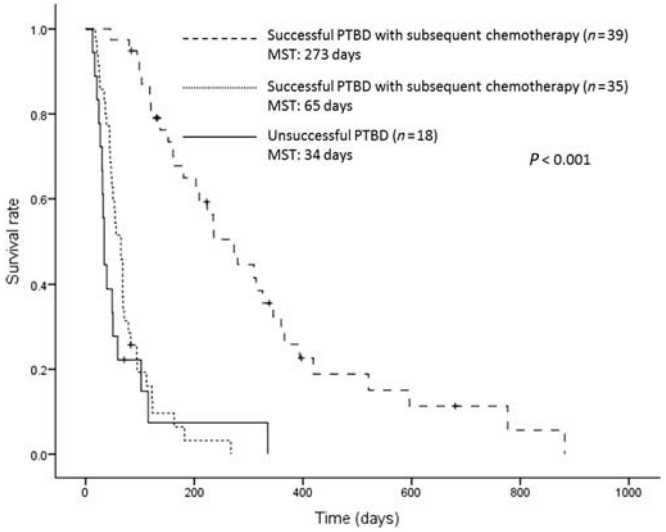

Figure 1. Survival after percutaneous transhepatic biliary drainage (PTBD); the median survival of patients who had a complete resolution of jaundice and received subsequent chemotherapy was significantly longer than that of those without subsequent chemotherapy ($P < 0.001$).

Poor Prognostic Factors for the Patient Treated with PTBD

The median survival times and P values for univariate analysis are shown in Table 5. Among these variables, ECOG poor performance status, prior chemotherapy beyond second

Table 3. Clinicopathological factors associated with unsuccessful PTBD

	Unsuccessful ($n = 18$)	Successful ($n = 74$)	P value
ECOG performance status			
0, 1	13	63	0.169
2, 3	5	11	
Primary cancer			
Colorectal cancer	6	26	0.886
Gastric cancer	12	48	
Histological type			
Differentiated type	8	28	0.606
Undifferentiated type	10	46	
Prior chemotherapy			
≤First line	8	47	0.139
>First line	10	27	
Liver metastasis			
H0, 1, 2	7	63	<0.001
H3	11	11	
Hepatic hilar bile duct stricture			
Absent	5	53	0.001
Present	13	21	
Ascites			
Absent	10	53	0.118
Present	8	21	
CEA (ng/ml)			
≤10	9	38	0.918
>10	9	36	
CA19-9 (IU/ml)			
≤300	6	44	0.046
>300	12	30	
Alb (g/dl)			
<3.5	13	39	0.134
≥3.5	5	35	
Total bilirubin (mg/dl)			
≤6.0	8	39	0.530
>6.0	10	35	
ALP (IU/l)			
≤1400	10	37	0.672
>1400	8	37	

Table 4. Multivariate analysis of factors associated with unsuccessful PTBD

Variable	Hazard ratio	95% confidence interval	*P* value
Liver metastasis, H3	5.893	1.750–19.840	0.004
Hepatic hilar bile duct stricture	4.049	1.173–13.977	0.027

Table 5. Univariate analysis of prognostic factors after PTBD

	n	Median survival (days)	*P* value
ECOG performance status			
0, 1	76	120	<0.001
2, 3	16	39	
Primary cancer			
Colorectal cancer	32	122	0.157
Gastric cancer	60	70	
Histological type			
Differentiated type	36	182	0.059
Undifferentiated type	56	69	
Prior chemotherapy			
≤1st line	55	122	0.010
>1st line	37	65	
Liver metastasis			
H0, 1, 2	70	118	0.001
H3	22	44	
Hepatic hilar bile duct stricture			
Absent	58	95	0.206
Present	34	99	
Ascites			
Absent	63	137	<0.001
Present	29	50	
CEA (ng/ml)			
≤10	47	115	0.048
>10	45	94	
CA19-9 (IU/ml)			
≤300	50	122	0.095
>300	42	79	
Alb (g/dl)			
<3.5	52	69	0.003
≥3.5	40	180	
Total bilirubin (mg/dl)			
≤6.0	47	95	0.713
>6.0	45	112	
ALP (IU/l)			
≤1400	47	115	0.592
>1400	45	95	

Table 6. Multivariate analysis of poor prognostic factors after PTBD

Variable	Hazard ratio	95% confidence interval	*P* value
Liver metastasis, H3	3.254	1.793–5.906	<0.001
ECOG performance status >1	2.830	1.538–5.209	0.001
Prior chemotherapy, >first line	2.661	1.554–4.556	<0.001
Ascites	2.381	1.383–4.101	0.002
Histology, undifferentiated type	2.402	1.398–4.128	0.002
CA19-9 (IU/ml) >500	1.663	1.043–2.653	0.033

line chemotherapy progression, H3 liver metastasis, presence of ascites and serum albumin level of <3.0 g/dl were significantly associated with a poor survival after PTBD. The results of the Cox proportional hazards model are shown in Table 6. ECOG poor performance status, H3 liver metastasis, prior chemotherapy beyond second-line chemotherapy progression, presence of ascites, undifferentiated type histology and high level of CA19-9 were independently associated with a poor prognosis.

For the clinical application of these findings, a prognostic index was calculated based on the number of these six variables identified by multivariate analysis. The prognostic index values ranged from 0 to 6. The median survival time after PTBD in the patients with index of 0 ($n = 5$), 1 ($n = 26$), 2 ($n = 25$), 3 ($n = 21$), 4 ($n = 13$), 5 ($n = 3$) and 6 ($n = 3$) were 236, 235, 120, 49, 44, 21 and 17 days, respectively ($P < 0.001$, log-rank test). The patients were then assigned to two groups according to their prognostic index, as follows: poor-risk group, prognostic index ≥3 ($n = 36$); and good-risk group, prognostic index ≤2 ($n = 56$). The median survival time was 163 days in the good-risk group and 44 days in the poor-risk group ($P < 0.001$, log-rank test). The 2-month survival rate was 85.7% in the good-risk group and 33.3% in the poor-risk group ($P < 0.001$).

DISCUSSION

Only a few reports have been published on the evaluation of clinical outcomes and prognostic factors in colorectal and gastric cancer patients who received biliary drainage for obstructive jaundice. Some studies showed that biliary drainage for obstructive jaundice due to gastrointestinal cancer was effective for relief of symptoms, but they evaluated only 13–21 patients (1,8–10). To the best of our knowledge, the current study is the first and largest report that assesses prognostic factors for survival of patients with obstructive jaundice due to colorectal and gastric cancers treated with PTBD.

Our results suggest that patients with obstructive jaundice with the poor prognostic factors that we described above

could not receive survival benefit from PTBD even though they achieved an improvement of their hepatic dysfunction. The median survival time and 2 months survival rate in the poor-risk group was 44 days and 33.3%, respectively. A prognostic model seems to be useful for deciding whether PTBD is indicated for these patients. In the previous reports (1,8,9), some patients who improved their hepatic function by PTBD and received subsequent chemotherapy survived relatively longer than did the patients with obstructive jaundice. Van Laethem et al. (10) also evaluated 16 patients with metastases from colorectal cancer and found that patients had additional chemotherapy after complete resolution of jaundice survived longer.

We reported a successful PTBD rate of 80%. In this study the proportions of H3 liver metastasis and hepatic hilar bile duct stricture are 24 and 37%, respectively. These factors were independent factors associated with unsuccessful PTBD. It is technically difficult to perform bile duct drainage in hepatic hilar bile duct stricture (12). We think these patient characteristics explain this rate.

H3 liver metastasis was an independent factor in both unsuccessful PTBD and poor prognosis. Poor performance status, multiple chemotherapy history, presence of ascites, undifferentiated type histology and high level of CA19-9 were independently associated with a poor prognosis in this study. The type of primary cancer and elevated levels of alkaline phosphatase (ALP) and total bilirubin were not associated with a poor prognosis in this study. A retrospective review of the radiology database revealed that 16.5% of the 297 patients had intrahepatic bile duct dilatation with colorectal liver metastasis (15). Macroscopic bile duct invasion was observed in 20% and microscopic bile duct invasion was observed in 40% of colorectal liver metastases in one previous study (16). So patients with obstructive jaundice with multiple liver metastases, such as H3, might have multiple macroscopic and microscopic bile duct invasions, and it might be difficult for them to achieve normal liver function and long survival after PTBD in this study. The question of whether chemotherapy benefits extend to patients with poor performance status is particularly relevant because performance status is an established strong prognostic factor in advanced colorectal and gastric cancers; thus, the median survival of poor performance status patients was less than half that of patients with good performance status at presentation (17–21). So even if patients improve liver function after biliary drainage, it may be difficult for those with poor performance status to benefit from the subsequent chemotherapy. A Phase 3 study showed a survival advantage of second-line chemotherapy for gastric cancer and of third-line chemotherapy for colorectal cancer (5,6,22,23). There is no evidence of survival advantages of the chemotherapy beyond progression after the second-line chemotherapy of gastric cancer and third-line chemotherapy of colorectal cancer. Systemic chemotherapy induces pathological changes in the non-tumorous liver, including sinusoidal dilatation, atrophy of hepatocytes and steatosis; and regimen-specific hepatic changes are described as 'blue' liver and 'green' liver and can affect the clinical outcome (24,25). These results can explain why patients with progression beyond second-line chemotherapy in this study had a poor prognosis and showed a tendency to fail to achieve normal liver function after PTBD. Elevated levels of CA19-9 are related to an unfavorable prognosis in colorectal and gastric cancers (26,27). Some reports revealed that patients with undifferentiated adenocarcinoma and the presence of ascites at the time of first-line chemotherapy had poor survival (21,28,29). The independent poor prognostic factors we describe here of the patients treated with PTBD are consistent with these previous reports evaluating patients receiving chemotherapy.

It is important to point out the limitations of this study. First, patients who received PTBD may have been more fit, better able to tolerate it and therefore more likely to derive benefit from it. Another potential limitation is that we did not evaluate clinical symptoms. The improvement of clinical findings such as pruritus, nausea and abdominal discomfort caused by obstructive jaundice were reported and fatigue was one of the difficult symptoms to improve in patients with non-biliary and non-pancreatic cancers (1,10). The survival times after PTBD of the patients with successful PTBD without subsequent chemotherapy and those with unsuccessful PTBD did not differ significantly in this study. Although PTBD might be useful for relief of symptoms caused by obstructive jaundice in patients with non-biliary and non-pancreatic cancers (1,10), our results suggest that PTBD and achievement of an improved hepatic dysfunction did not always lead to survival benefits. If patients with clinical symptoms caused by obstructive jaundice are unlikely to receive successful PTBD or survival benefits, we recommend non-invasive palliative treatments.

In conclusion, careful patient selection is necessary when introducing PTBD in order to avoid invasive procedures in patients with a poor prognosis. A prognostic model seems to be useful for making decisions on whether PTBD is indicated, because PTBD might not give survival benefits to the patients in the poor-risk group.

Conflict of interest statement

None declared.

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