

Quality of Life in Patients with Unresectable Complex Hilar Cholangiocarcinoma Receiving Endoscopic Biliary Stent

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ABSTRACT

Background: Most cholangiocarcinoma patients present at an advanced stage of the disease. Palliative treatment options include PTBD and ERCP with biliary stenting. Although quality of life (QOL) is of importance in terminal or advanced malignancy, a number of studies on palliative ERCP and biliary stenting focus mostly on stent patency and survival, with limited data on QOL outcomes. The present study was aimed to assess QOL in patients with unresectable complex hilar cholangiocarcinoma who had undergone endoscopic biliary drainage.

Patients and Methods: Twenty-seven patients with unresectable Bismuth type II-IV hilar cholangiocarcinoma were prospectively treated with either plastic or metallic stent. QOL was assessed at baseline (prior to treatment) and 2-4 weeks after endoscopic biliary stent insertion, using the format of the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep). QOL scores for the pre-treatment and the post-treatment groups were analyzed.

Results: Biliary drainage was associated with post-treatment reduction of serum bilirubin by 14.68 mg/dL ($p > 0.05$). Patients reported improved social and domestic, emotional, functional, and hepatobiliary cancer subscale scores, but decreased physical well-being scores. Total FACT-Hep scores improved 5.62 points after treatment. No statistical significance was detected. Patients with successful drainage ($n = 22$) showed more QOL improvement, especially regarding emotional well-being in which statistical significance was detected ($p < 0.05$). The majority (46%) exhibited clinically significant improvement of FACT-Hep scores.

Conclusion: Palliative unilateral biliary drainage can decrease symptoms of jaundice and improved QOL of the patients. Statistical improvement of emotional well-being was shown in patients with successful drainage. Further study with larger sample size is needed.

Key words : FACT-Hep scores, quality of life, cholangiocarcinoma, biliary drainage

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Cholangiocarcinoma is the most common malignancy in North-Eastern Thailand. The incidence in Khon Kaen province is 36.8-84.6 per 100,000⁽¹⁾. Median survival ranges from 3 to 7 months. Most cholangiocarcinomas are located in hilar (60-70%)⁽¹⁾. Surgical resection by complete tumor excision and negative margins may offer cure and improve long-term survival. Unfortunately, only 32% of cases are potentially resectable at the time of diagnosis, and the prognosis in the remaining is very poor⁽²⁾. The benefits of chemotherapy and/or radiation are unproven in patients with unresectable hilar cholangiocarcinoma. Endoscopic biliary drainage, percutaneous transhepatic biliary drainage (PTBD) and surgical bypass are palliative treatment options for patients with ascending cholangitis or obstructive jaundice. Endoscopic biliary drainage and PTBD are associated with comparable success rates for the relief of jaundice. However, patients who treatment with PTBD suffer from having the catheter placed on the abdomen. Those treatment with a surgical bypass, on the other hand, are at a higher risk from the operation, and from a high post-operative morbidity and mortality^(3,4). Endoscopic biliary stent drainage is thus a treatment of choice for palliative drainage.

The aims of palliative treatment in unresectable hilar cholangiocarcinoma are to relieve symptoms of pruritus and jaundice, as reflected from reduction of serum bilirubin, and to improve the quality of life (QOL)⁽⁵⁾. Drainage of biliary contents equivalent to 25% of the liver volume can be about adequate palliation as well as improvements in biochemical parameters⁽¹⁰⁾. However, regarding QOL, there have been only a few studies assessing this aspect. The aim of the present study was to assess QOL in patients with unresectable hilar cholangiocarcinoma who had undergone endoscopic biliary drainage.

MATERIAL AND METHODS

Patients

This study was approved by the Khon Kaen University Ethics Committee for Human Research. Patients were recruited from Srinagarind Hospital between 31 December 2007 and 28 February 2009. All patients gave informed consent before entering the study. The diagnosis was made from a typical history and evidence of biliary ductal dilatation with or without a mass at the hepatic bifurcation on computed tomography (CT)

or magnetic resonance cholangiopancreatography (MRCP). The diagnosis was also supported by biochemical tests and tumor markers, such as carcinoembryonic antigen (CEA) and cancer antigen (CA19-9)^(11,12). Unresectable tumors were defined as follow: bilateral hepatic duct involvement up to secondary radicals, bilateral hepatic artery involvement, encasement of the portal vein proximal to its bifurcation, atrophy of one hepatic lobe with contralateral biliary radical involvement, distant metastases^(13,14) or patients unfit for operation because of advanced age or medical illness.

Material

The QOL was assessed by using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep). This is a reliable and valid measuring tool that is widely used in clinical studies of hepatobiliary cancer patients⁽¹⁵⁾. FACT has been validated in Thai patients, including the low educated population^(16,17). The FACT-Hep Thai version used in this study was first validated at Srinagarind hospital⁽¹⁷⁾.

The 45-item FACT-Hep consists of five subscales: (1) physical well-being (PWB) 7 items, (2) social and family well-being (SWB) 7 items, (3) emotional well-being (EWB) 6 items, (4) functional well-being (FWB) 7 items, and hepatobiliary cancer subscale (HepCS subscales) 18 items. The HepCS subscales are to assess specific symptoms of hepatobiliary carcinoma and side-effects of treatment. The FACT-General total score (FACT-G), representing total general QOL scores, is a summation of PWB, SWB, EWB and FWB. The FACT-Hep, representing total QOL scores specific to hepatobiliary carcinoma, is a summation of FACT-G and HepCS. All FACT items are rated on a 5-point scale ranging from 0 = not at all to 4 = very much, and total FACT-Hep scores are 180. Higher scores on all scales of the FACT-Hep reflect better quality of life.⁽¹⁸⁾

The Minimal Important Difference (MID) is defined as the smallest difference in score that patients perceive as beneficial, that is likely to be meaningful and lead the clinician to consider a change in the patient's management. A MID of all FACT domains, including FACT-Hep has also been established⁽¹⁸⁾.

Outcome measurement

Endoscopic biliary drainage with unilateral plastic or metallic stent was performed in patients diagnosed with unresectable complex hilar cholangiocar-

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cinoma. Patients were prospectively followed and QOL was assessed at baseline (prior to treatment) and at 2-4 weeks after stent insertion. All patients were followed up either to the end of study or to the time of death. The FACT-Hep was administered by a well-trained interviewer.

Successful biliary drainage was defined as a decrease in total bilirubin of more than 30% of the pretreatment value in 2 weeks, or 75% of pretreatment value in 4 weeks.

Statistics

Descriptive statistics were used for assessment of demographic characteristics and biochemical parameters. QOL data were checked and recorded according to the scoring guideline of FACT-Hep. Comparison of QOL scores before and after treatment was made using paired *t*-test. The functional well-being was used Wilcoxon signed ranks test, based on normality test of Kolmogorov-Smirnov. Statistical significance was set at *p*-value < 0.05.

To help determining clinically meaningful change of QOL score, MID was use as a cutoff point for the analysis. These were reported as 5-6 points for Hepatobiliary Cancer Subscale, 6-7 points for FACT-G, and 8-9 points for FACT-Hep⁽¹⁸⁾. The cutoff point scores used in this study were 5, 6 and 8 points for HCS, FACT-G and FACT-Hep respectively.

RESULTS

A total of 27 patients were included in the study. Most patients presented with jaundice and pruritus (96.3% and 100%). Three patients were classified as Bismuth II (11.1%), seventeen patients were classified as Bismuth III (63.0%), and seven patients were classified as Bismuth IV (25.9%). The 25.9% of patients had vascular involvement, and 40.7% had distant me-

Table 1. Clinical characteristics at baseline.

Characteristics	n = 27	(%)
Sex (male : female)	21 : 6	77.8 : 22.2
Age (yrs)	58.78 ± 10 (range 44-81)	
Pruritus	26	96.3
Jaundice	27	100
Fever	8	29.6
Abdominal pain	7	25.9
Ascites	3	11.1
Bismuth classification		
- II : III : IV	3 : 17 : 7	11.1 : 63.0 : 25.9
Portal vein involvement	7	25.9
Distant metastases	11	40.7
Acute complication		
- Acute pancreatitis	4	14.8
- Ascending cholangitis	3	11.1

Table 2. Biochemical parameters and QOL at baseline (n = 27).

	Reference range	Mean ± SD	Median (range)
Biochemical parameters			
Albumin (g/dL)	3.8-5.4	2.95 ± 0.80	3.1 (1.5-4.2)
TB (mg/dL)	0.25-1.5	25.19 ± 10.44	25.17 (8.7-50.0)
ALP (U/L)	42-121	510.88 ± 364.89	414.00 (120-1740)
CA19-9 (U/mL)	0-37	544.83 ± 464.25	400.50 (4.12-1609)
CEA (ng/mL)	0-0.25	16.76 ± 34.12	5.88 (1.41-171)
QOL			
Physical well-being (PWB)	0-28	18.59 ± 5.17	19.00 (7-25)
Social and family well-being (SWB)	0-28	17.48 ± 4.54	19.00 (8-26)
Emotional well-being (EWB)	0-24	14.40 ± 5.92	15.00 (2-24)
Functional well-being (FWB)	0-28	11.70 ± 5.73	10.00 (4-28)
Hepatobiliary cancer subscale (HCS)	0-72	41.29 ± 12.44	41 (13-64)
FACT-G	0-108	62.18 ± 15.89	61 (30-102)
FACT-Hep	0-180	103.48 ± 26.55	100 (43-166)

Note: SD;standard deviation, TB;serum total bilirubin, ALP;alkaline phosphatase, CA19-9;cancer antigen 19-9, CEA;carcinoembryonic antigen, QOL;quality of life, FACT-G;Functional Assessment of Cancer Therapy-General, FACT-Hep; Functional Assessment of Cancer Therapy-Hepatobiliary

tastases (Table 1). Baseline biochemical parameters and FACT-Hep scale are shown in Table 2.

Serum bilirubin was 14.68 mg/dL difference between pre-treatment and post-treatment values (mean 25.19 ± 10.44 at baseline, and 10.51 ± 12.21 at time of follow up). After biliary stent drainage, the social and family well-being, emotional well-being, functional well-being and hepatobiliary cancer subscale improved with average score of 0.92, 1.88, 1.03 and 2.44 respectively. Physical well-being, however, decreased by 0.66 point. There was no statistical difference between pre-treatment and post-treatment in all parameters (Table 3). The total FACT-Hep scores were improved 5.62

points after treatment with no statistical difference between pre-treatment and post-treatment.

To interpret clinical significance of QOL outcome, the patients were classified according to the changes of QOL scores as "improved" (improved > MID points), "worse" (decreased > MID points) and "stable" (change < MID points). Thus, there were 44.4% improved, 22.2% stable and 33.3% worse using FACT-Hep scores after treatment. Table 4 displays subgroup analysis of patients with successful biliary drainage. There was more improvement of QOL for these patients, especially emotional regarding well-being, which significantly improved by 2.5 points. The

Table 3. QOL outcomes after 2-4 weeks of biliary stent placement.

QOL	Treatment outcome (n = 27)						
	at baseline (means ± SD)	at follow up (means ± SD)	mean different of score	clinical meaningful interpretation			
				improved (%)	stable (%)	worse (%)	
PWB	18.59 ± 5.17	17.92 ± 5.60	-0.66	NA	NA	NA	
SWB	17.48 ± 4.54	18.40 ± 4.81	0.92	NA	NA	NA	
EWB	14.40 ± 5.92	16.29 ± 5.86	1.88	NA	NA	NA	
FWB	11.70 ± 5.73	12.74 ± 5.70	1.03	NA	NA	NA	
HCS	41.29 ± 12.44	43.74 ± 13.23	2.44	10 (37.0)	8 (29.6)	9 (33.3)	
FACT-G	62.18 ± 15.89	65.37 ± 17.44	3.18	11 (40.7)	9 (33.3)	7 (25.9)	
FACT-Hep	103.48 ± 26.55	109.11 ± 29.33	5.62	12 (44.4)	6 (22.2)	9 (33.3)	

Note: PWB; physical well-being, SWB; social and family well-being, EWB; emotional well-being, FWB; functional well-being. HCS; the hepatobiliary cancer subscale, FACT-G; Functional Assessment of Cancer Therapy-General, FACT-HEP; Functional Assessment of Cancer Therapy-Hepatobiliary, NA; not available, Analysis of QOL scores before and after treatment using paired *t*-test. The functional well-being was using Wilcoxon signed ranks test.

Table 4. QOL outcomes in patients with successful biliary drainage.

QOL	Treatment outcome (n = 22)						
	at baseline (means ± SD)	at follow up (means ± SD)	mean different of score	clinical meaningful interpretation			
				improved (%)	stable (%)	worse (%)	
PWB	19.45 ± 4.78	18.90 ± 5.51	-0.54	NA	NA	NA	
SWB	17.59 ± 4.89	19.22 ± 4.88	1.63	NA	NA	NA	
EWB	15.04 ± 6.02	17.54 ± 5.12	2.50*	NA	NA	NA	
FWB	11.86 ± 6.16	13.18 ± 6.02	1.31	NA	NA	NA	
HCS	42.50 ± 13.19	46.59 ± 12.70	4.09	9 (40.9)	7 (31.8)	6 (27.3)	
FACT-G	63.95 ± 16.90	68.86 ± 16.49	4.90	9 (40.9)	8 (36.4)	5 (22.7)	
FACT-Hep	106.45 ± 28.08	115.45 ± 27.53	9.00	10 (45.5)	6 (27.3)	6 (27.3)	

Note: PWB; physical well-being, SWB; social and family well-being, EWB; emotional well-being, FWB; functional well-being. HCS; the hepatobiliary cancer subscale, FACT-G; Functional Assessment of Cancer Therapy-General, FACT-HEP; Functional Assessment of Cancer Therapy-Hepatobiliary, NA; not available, Analysis of QOL scores before and after treatment using paired *t*-test. The functional well-being was using Wilcoxon signed ranks test.**p* < 0.05

majority (45.5%) had clinical significant improvement of FACT-Hep scores.

DISCUSSION

It has been shown that successful biliary drainage is associated with improvement of QOL in patients with malignant biliary tract obstruction, most of whom with common bile duct obstruction⁽⁵⁾. The present study is the first to attempt evaluating QOL of complex hilar cholangiocarcinoma patients following unilateral hepatic duct drainage with plastic or metallic stent. The FACT-Hep Thai version employed in this study is a valid and reliable tool that has been validated in patients with hepatobiliary carcinoma as in this study⁽¹⁷⁾.

Palliative biliary drainage appears to reduce serum bilirubin level and improve QOL scores in most domains. Despite the trend of QOL improvement, the study fails to detect statistical significance. This could be from a limited power of the study, related to small sample size. We found, however, a significant improvement of emotional well-being in patients with successful drainage. It was somewhat surprising that physical well-being showed a slight deterioration. This could be because relieving jaundice and pruritus symptoms by biliary drainage did not really affect the patients' physical activity.

The majority of patients in the study were classified as Bismuth III (63.0%) and Bismuth IV (25.9%) and had more advanced disease (25.9% had vascular involvement, while 40.7% had distant metastases). It was therefore more difficult to achieve adequate biliary drainage, and could partly explain poorer QOL outcome in this population.

This study employed FACT-Hep, which is a QOL measure specific to hepatobiliary carcinoma, rather than just FACT-G which is a general QOL measure. This tool is expected to be more sensitive and capable of capturing more changes after treatment. The study results are in keeping with this theory, as higher improvement scores were detected in FACT-Hep than FACT-G.

The study limitation is related to a small sample size. Further study with a larger sample size with more varied socioeconomic background is needed to confirm the findings. It is also warranted to determine the impact of stent type, metallic versus plastic, upon QOL of the patients. A longer follow up of patients' QOL

should also be evaluated.

CONCLUSION

Unilateral biliary drainage could improve QOL of patients with unresectable complex hilar cholangiocarcinoma. Significant improvement of emotional well-being was reported in patients with successful drainage. A limited sample size may preclude detection of statistical significance in most QOL domains, and a larger study is warranted.

REFERENCES

1. Parkin DM, Ohshima H, Srivatanakul P, *et al.* Cholangiocarcinoma: epidemiology, mechanisms of carcinogenesis and prevention. *Cancer Epidemiol Biomarkers Prev* 1993;2:537-44.
2. Launois B, Reding R, Lebeau G, *et al.* Surgery for hilar cholangiocarcinoma: French experience in a collective surgery of 552 extrahepatic bile duct cancers. *J Hepatobiliary Pancreat Surg* 2000;7:128-34.
3. Andersen JR, Sorensen SM, Kurse A, *et al.* Randomized trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. *Gut* 1989;30:1132-5.
4. Smith AC, Dowsett JF, Russell RC, *et al.* Randomized trial of endoscopic stenting versus surgical bypass in malignant low bile duct obstruction. *Lancet* 1994;344:1655-60.
5. Abraham NS, Barkun JS, Barkun AN. Palliation of malignant biliary obstruction: A prospective trial examining impact on quality of life. *Gastrointest Endosc* 2002;56:835-41.
6. Freeman ML, Overby C. Selective MRCP and CT - targeted drainage of malignant hilar biliary obstruction with self-expanding metallic stents. *Gastrointest Endosc* 2003;58:41-9.
7. De Palma GD, Pezzullo A, Rega M, *et al.* Unilateral placement of metallic stents for malignant hilar obstruction: A prospective study. *Gastrointest Endosc* 2003;58:50-3.
8. Cheng JLS, Bruno MJ, Bergman JJ, *et al.* Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: Efficacy of self-expanding metallic Wallstents. *Gastrointest Endosc* 2002;56:33-9.
9. De Palma GD, Galloro G, Siciliano S, *et al.* Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: Results of a prospective, randomized, and controlled study. *Gastrointest Endosc* 2001; 53:547-53.
10. Dowsett JF, Vaira D, Hatfield ARW, *et al.* Endoscopic biliary therapy using the combined percutaneous and endoscopic technique. *Gastroenterology* 1989;6:1180-6.
11. Anderson, Pinson, Berlin, *et al.* Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004;9:43-57.
12. Khan, Davidson, Goldin, *et al.* Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document: *Gut* 2002;51:1-9.

13. Bismuth H, Castaign D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. *World J Surg* 1998;23:39-47.
14. Burke EC, Jarnagin WR, Hochwald SN, *et al.* Hilar cholangiocarcinoma patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. *Ann Surg* 1998;228:385-92.
15. Heffernan N, Cella D, Webster K, *et al.* Measuring Health-Related Quality of Life in Patient With Hepatobiliary Cancers: The Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire. *J Clin Oncol* 2002;20:2229-39.
16. Ratanatharathorn V, Sirilerttrakul S, Jirajarus M, *et al.* Quality of life, Functional Assessment of Cancer Therapy-General. *J Med Assoc Thai* 2001;84:1430-42.
17. Pratheepawanit N, Lerkiatbundit S, Thienthong S, *et al.* Validation of FACT-G (Thai version) in low literate patients. *Patient Reported Outcomes Newsletter* 2005;34:9-10.
18. Steel JL, Eton DT, *et al.* Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Ann Oncol* 2006;17:304-12.