Biochemical and radiological predictors of malignant biliary strictures

Ibrahim A. Al-Mofleh, Abdulrahman M. Aljebreem, Saleh M. Al-Amri, Rashed S. Al-Rashed, Faleh Z. Al-Faleh, Hussein M. Al-Freihi, Ayman A. Abd, Arthur C. Isnani

INTRODUCTION
Biliary stricture (BS) may result from an intra or extra-luminal benign or malignant process. Although history, laboratory investigations and imaging techniques may help to differentiate benign from malignant biliary strictures, it remains a clinical challenge. Endoscopic retrograde cholangiopancreatography (ERCP) has been considered the method of choice for the diagnosis of BS as a result of its accuracy in establishing the site and cholangiographic features of stricture[1]. Cytology specimens can be obtained, which has a sensitivity rate of only 35% but a specificity rate approaching 100% for the diagnosis of malignancy[2].

Recently, new imaging techniques with increased diagnostic yield have emerged. For instance, magnetic resonance cholangiopancreatography (MRCP) as a non-invasive method has similar or even better diagnostic yield with the advantage of avoiding complications of ERCP[3,4]. Also, with the advent of multislice CT (MS-CT), it has been possible to detect minute biliary and pancreatic tumours as well as small lymph nodes and vessels[5]. MS-CT cholangiography has become valuable in pre-operative evaluation and determining unresectability[6]. Therefore, CT has maintained as the method of choice for pancreatic and biliary tumours imaging[7,8]. Furthermore, intraductal ultrasonography (IDUS) has been valuable in the differentiation of MBS from BBS. It has increased the accuracy of ERC-tissue sampling, but it has not been suitable for staging lymphadenopathy-associated MBS[9].

The aim of this study was to identify the clinical, biochemical and or radiological predictors of malignant biliary strictures.

MATERIALS AND METHODS
All patients with biliary strictures from March 1998 to August 2002 who had ERCP or PTC in case of unsuccessful ERCP were included. Demographic characteristics, presenting features, laboratory data, imaging technique findings and management modalities were analyzed.

Definition of biliary strictures was suggested by cholangiographic features and it was supported by brush cytology, fine needle aspiration (FNA), the presence of mass or metastases by imaging and or clinical follow-up.

ERCP was performed by three experienced gastroenterologists using 4.2 mm channel duodenoscopes (Pentax or Olympus). All patients received diazepam and demerol as premedication. In addition, patients with biliary dilatation received cefuroxime prophylaxis. Endoscopic and cholangiographic findings were recorded.

Biopsy and brushing materials were obtained when feasible, strictures dilated with balloon or Soehendra dilator and large 10-12 F stent inserted.

Data collected were entered into the computer using Microsoft Excel. After all data were checked for completeness, statistical analysis was performed using Stat Pac gold analysis software and Microsoft Excel programs. Two-tailed P values of less than 0.05 were considered statistically significant. A receiver operator characteristic (ROC) curve was constructed.
to determine the optimal laboratory diagnostic criterion threshold (i.e., total bilirubin, ALT, AST and alkaline phosphatase) in predicting a malignant biliary stricture. A ROC curve displayed the false positive rate on the x axis (specificity), and the true positive rate on the y axis (sensitivity) for varying test thresholds, thus plotting the performance of a diagnostic test[10]. The ideal cut-off criteria for the laboratory results were chosen by determining the point lying geometrically closest to an ideal test with 100% specificity and sensitivity[11].

RESULTS
One hundred twenty six patients were included, 54 of those had a BBS while 72 had a MBS. The main causes of BBS were related to stone disease (choledocholithiasis, Mirizzi syndrome or postcholecystectomy). In 22 patients the cause could not be identified. Cholangiocarcinoma and pancreatic head carcinoma were the most common causes of MBS. Other causes of BS are shown in Table 1.

The mean age of patients with MBS (62.4±11.7 years) was significantly higher than that of patients with BBS (53±18 years) (P=0.0006). Fifty percent of BBS were proximal (P=0.01) and approximately 50% of MBS were distal (P<0.001). There were no significant gender differences (Table 2). Jaundice was found in more than 80% of patients with BBS and MBS; and right upper quadrant (RUQ) pain in 50% of patients. Anorexia, weight loss and fever were less common and no significant differences were observed when both groups were compared (Table 3).

Table 1 Causes of biliary strictures (n=126)

| Causes of BS          | Benign | % | Malignant | % | P value |
|-----------------------|--------|---|-----------|---|---------|
| Choledocholithiasis   | 12     | 22| 31        | 43|         |
| Mirizzi syndrome      | 7      | 13| 23        | 32|         |
| Postcholecystectomy   | 6      | 11| 5         | 7 |         |
| Sclerosing cholangitis| 3      | 5.5| 5         | 7 |         |
| Choledochal cyst      | 2      | 3.7| 4         | 5.5|        |
| Chronic pancreatitis  | 1.9    | 2.7| 2         | 2.7|         |
| Juxtapapillary diverticulum | 1 | 1.9| 2         | 2.7|         |
| Non-specified         | 22     | 40.7| 40.7 | 72|         |

Table 2 Demographic data of patients with biliary strictures (n=126)

| Causes of BS          | Benign | % | Malignant | % | P value |
|-----------------------|--------|---|-----------|---|---------|
| Number of patients    | 54     | 72 |           |   |         |
| Mean age              | 53±18  | 62.4±11.7| 0.0006 |   |         |
| Males                 | 25 (46)| 41 (56.9)| 0.2255 |   |         |
| Females               | 29 (54)| 31 (43.1)| 0.2255 |   |         |
| Sites of biliary stricture | 27 | 50 | 20 (27.7) | 0.0107 |   |         |
| Proximal              | 22 (41)| 17 (23.6)| 0.0394 |   |         |
| Middle                | 9 (17) | 35 (48.6) | <0.001 |   |         |
| Distal                |        |         |          |   |         |

Table 3 Presenting symptoms of patients with biliary strictures (n=126)

| Symptoms of BS          | Benign | % | Malignant | % | P value |
|-------------------------|--------|---|-----------|---|---------|
| Jaundice                | 44 (81)| 61 (84.7)| 0.5894  |   |         |
| RUQ pain                | 27 (50)| 30 (52.8)| 0.7561  |   |         |
| Weight loss             | 4 (7)  | 11 (15.3)| 0.1326  |   |         |
| Fever                   | 3 (5)  | 7 (9.7)  | 0.3066  |   |         |
| Anorexia                | 4 (7)  | 7 (9.7)  | 0.5843  |   |         |

Mean serum values of bilirubin, alkaline phosphatase, ALT and AST were significantly higher in patients with MBS. However GGT levels were not significantly different in both groups (Table 4).

As shown in Table 5 and Figure 1, ROC analysis identified total bilirubin of 84 umol/L as the best cut-off value for predicting a malignant biliary stricture with a sensitivity of 98.6%, a specificity of 59.3% and a positive likelihood ratio of 2.42 (area under the curve=0.735, SE=0.044, 95% CI=0.649-0.810). On the other hand, ROC analysis showed that other laboratory tests including ALT, AST and alkaline phosphates to have a poor sensitivity and specificity.

Proximal biliary dilatation was more frequently encountered in MBS compared to BBS, 73.8% vs 39.5% (P=0.0001). Majority of patients, 87% of BBS and 78% of MBS were treated endoscopically.

Table 4 Laboratory data of patients with biliary strictures (n=126)

| Parameters              | Benign | Malignant | P value |
|-------------------------|--------|-----------|---------|
| Total bilirubin (umol/ L) | 142.6±98.4 | 184.6±120.8 | 0.0389 |
| Direct bilirubin (umol/ L) | 102.4±95.3 | 138.10±98.5 | 0.0433 |
| Alkaline phosphatase (IU/ L) | 108.5±98.5 | 145.50±97.5 | 0.0002 |
| GGT (IU/ L)             | 397.0±96.5 | 436.50±325.1 | 0.591 |
| ALT (IU/ L)             | 52.7±88.3  | 66.94±85.6  | 0.0339 |
| AST (IU/ L)             | 76.5±43.2  | 107.80±45.7 | 0.0002 |

Table 5 Receiver operator characteristic (ROC) test results in predicting malignant biliary strictures

Parameter | Cut-off value | Sensitivity (%) | Specificity (%) | +LR | -LR |
-----------|---------------|-----------------|-----------------|-----|-----|
| Total bilirubin (umol/ L) | 84 | 98.6 | 59.3 | 2.42 | 0.02 |
| Direct bilirubin (umol/ L) | 63 | 91.7 | 61.1 | 2.36 | 0.14 |
| Alkaline phosphatase (IU/ L) | 136 | 59.7 | 83.3 | 3.58 | 0.48 |
| GGT (IU/ L) | 246 | 80.6 | 53.7 | 1.74 | 0.36 |
| ALT (IU/ L) | 68 | 45.8 | 81.5 | 2.47 | 0.66 |
| AST (IU/ L) | 85 | 76.4 | 74.1 | 2.95 | 0.32 |

+LR=positive likelihood ratio; -LR=negative likelihood ratio.

Figure 1 ROC analysis of total bilirubin.

DISCUSSION
The differentiation between benign and malignant biliary strictures can be difficult but is of obvious importance in regard to prognosis and planning optimal therapy.
In our study, majority of patients with BS presented with obstructive jaundice and half had right upper quadrant pain. Other less frequent symptoms included anorexia, weight loss and fever. In contrast to Tandon et al., who have encountered more anorexia and weight loss in MBS, we found no significant difference between MBS and BBS. This could be due to the early stage at presentation in our patients.

In our study, although statistically significant differences were found in most biochemical parameters, bilirubin was the best predictor of malignant biliary stricture. A serum bilirubin level of 84 µmol/L or greater was highly predictive of malignant biliary stricture with a sensitivity of 98.6%, a specificity of 59.3% and a positive likelihood ratio of 2.42. Furthermore, proximal biliary dilatation was more frequently encountered in MBS compared to BBS, 73.8% vs 39.5% (P=0.0001). Similarly, in a prospective study of 29 patients, Bain et al. have shown that a bilirubin of level of 75 µmol/L or greater or a stricture length of greater than 14 mm was highly predictive of malignant biliary stricture. In the same study, intrahepatic duct dilatation was present in 93% of malignant strictures versus 36% of BBS (P=0.002). In our study, we found that distal bile duct strictures were mainly due to a malignant process, 48.6% vs 9% in BBS (P<0.001), which is contrary to other studies. This is probably because we have rarely encountered BBS secondary to chronic pancreatitis which is commonly present with distal benign BS (we had only one patient).

ERCP remains to be an important imaging technique in the diagnosis and treatment of obstructive jaundice[14]. The yield of ERCP in differentiating MBS from BBS can be further improved with tissue sampling. Sensitivity of biliary fluid and brushing cytology is unsatisfactorily low. It can be improved by combining fine needle aspiration biopsy with intraductal forceps biopsy. This method has been known as triple tissue sampling[15,16]. Despite the triple tissue sampling, the sensitivity and negative predictive value have not exceeded 62% and 39%, respectively[16]. Furthermore, brushing cytology yield could be improved by stricture brushing after a 10F dilatation of malignant stricture[17]. Similar observation on improvement of bile cytology has been reported earlier by Mohandas et al.[18]. Evaluation of cytology specimens for aneuploidy and tumour markers, CA 19-9 and CEA might also increase the diagnostic yield[19].

Recently, intraductal ultrasonography (IDUS) has been evaluated in the differential diagnosis of MBS from BBS with conflicting results. While Gress et al. have not found reliable differentiation criteria[20], Inui et al. and Tamada et al., who used special biliary and pancreatic probes, have provided encouraging results[21,22]. However, its accuracy is still not exceeding 80%. IDUS has been reported to be superior to conventional endoscopic ultrasonography in terms of diagnostic accuracy, and prediction of tumour resectability[23].

Treatment of BS depends on the etiology, benign or malignant, magnitude of damage in post-surgical injuries and prediction of resectability of MBS. Endoscopic management of BBS has been considered the primary method before the decision of surgical intervention[24]. Major bile duct injuries require surgical construction. After initial evaluation of anatomy by direct cholangiogram and inserting a biliary drain, surgical reconstruction with Roux-en-Y hepaticojejunostomy has been associated with an overall success rate exceeding 90%[25]. It has been considered as the best treatment modality of BBS[26]. On the other hand Born et al. have considered endoscopic or percutaneous management as an adequate short and long-term alternative to surgery[27].

The decision of therapeutic modality for biliary or pancreatic tumours depends on the evaluation of resectability. It is important to determine preoperatively the spread of MBS. These events may help decide the appropriate treatment for each condition. Surgery has to be considered for the management of resectable tumours. However, at the time when the diagnosis of MBS has been established, it is often late for curable resection[29]. Therefore, endoscopic approach remains the method of choice for palliation. Majority of our patients (78%) had endoscopic palliation.

In a large series with 505 patients, Costamagna et al. strongly suggested ERCP in the diagnosis and palliation of all patients with suspected MBS[29]. ERCP has been considered as the optimal technique for diagnosis and palliation of MBS[30].

In conclusion, a serum bilirubin level of 84 µmol/L or greater is the best predictor of MBS. Older age, proximal biliary dilatation, higher levels of bilirubin, alkaline phosphates, ALT and AST are all associated with MBS. ERCP is the best imaging technique in demonstrating stricture and biliary dilation, and remains the method of choice in managing BBS and MBS.

REFERENCES

1. Hawes RH. Diagnostic and therapeutic uses of ERCP in pancreatic and biliary tract malignancies. Gastrointest Endosc 2002; 56(6 Suppl): S201-205.
2. Scudera PL, Koizumi J. Brush cytology evaluation of lesions encountered during ERCP. Gastrointest Endosc 1990; 36: 281-284.
3. Hall-Crapps MA, Allen CM, Owens CM, Theis BA, Donald J, Paley M, Wilkinson ID, Chong WK, Hatfield AR, Lees WR. MR Cholangiography: Clinical evaluation in 40 cases. Radiology 1993; 189: 423-427.
4. Soto JA, Barish MA, Yucel ED, Steinberg D, Ferucci JT, Chuttani R. Magnetic resonance cholangiography: Comparison with endoscopic retrograde cholangiography. Gastroenterology 1996; 110: 599-597.
5. Kim HJ, Kim MH, Lee SK, Yoo KS, Seo DW, Min YI. Tumour vessel: a valuable cholangioscopic clue of malignant biliary stricture. Gastrointest Endosc 2000; 52: 635-638.
6. O’Malley ME, Boland GW, Wood BJ, Fernandez-del-Castillo C, Warshaw AL, Mueller PR. Adenocarcinoma of the head of the pancreas: determination of surgical resectability with thin section pancreatic-cholecysto-phase CT. Am J Roentgenol 1999; 173: 1513-1518.
7. Cha HH, Han JK, Kim TK, Kim AY, Park SJ, Choi BI, Suh KS, Kim SW, Han MC. Preoperative evaluation of Klatskin tumour: Accuracy of spiral CT in determining vascular invasion as a sign of unresectability. Abdom Imaging 2000; 25: 500-507.
8. M o r t e l e K J , J i H , R o s P R . C T and magnetic resonance imaging in pancreatic and biliary tract malignancies. Gastrointest Endosc 2002; 56(6 Suppl): S206-212.
9. Farell RJ, Aagarwal B, Brandwein SL, Underhill J, Chuttani R, Pleskov DK. Intraductal US is useful adjunct to ERCP for distinguishing malignant from benign biliary strictures. Gastrointest Endosc 2002; 56: 681-687.
10. McNeil BJ, Keller E, Adelsleh BJ. Primer on certain elements of medical decision making. N Engl J Med 1975; 293: 211-215.
11. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983; 148: 839-843.
12. Tandon RK, Mehrorita R, Arrora A, Chakravary SK, Vashhisht S. Biliary strictures on ERCP. A study in Northern India. J Assoc Physicians India 1994; 42: 865-870.
13. Bain VG, Abraham N, Jiangri GS, Alexander TW, Henning RC, Hoskinison ME, Maguire CG, Lallo EA, Sadowski DC. Prospective study of biliary strictures to determine the predictors of malignancy. Can J Gastroenterol 2000; 14: 397-402.
14. Khurram M, Durrani AA, Hasun Z, Butt AA, Ashfaq S. Endoscopic retrograde cholangiopancreaticographic evaluation of patients with obstructive jaundice. J Coll Physicians Surg Pak 2003; 13: 325-328.
15. Fogel EL, Sherman S. How to improve the accuracy of diagnosis of malignant biliary strictures. Endoscopy 1999; 31: 758-760.
16. Jalilwala J, Fogel EL, Sherman S, Gottlieb K, Fluskiger J, Buckshot LG, Lehman GA. Triple tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc 2000; 51(4 Pt 1): 383-390.
17. Panasher VK, Huibregtse K. Endoscopic retrograde wire-guided...
cytology of malignant biliary strictures using a novel scraping brush. Gastrointest Endosc 1998; 48: 288-290

18 Mohandas KM, Swaroop VS, Gullar SU, Dave UR, Jagannath P, DeSouza LJ. Diagnosis of malignant obstructive jaundice by bile cytology: results improved by dilating the bile duct strictures. Gastrointest Endosc 1994; 40(2 Pt 1): 150-154

19 Ryan ME, Baldauf MC. Comparison of flow cytometry for DNA content and brush cytology for detection of malignancy in pancreaticobiliary strictures. Gastrointest Endosc 1994; 40(2 Pt 1): 133-139

20 Gress F, Chen YK, Sherman S, Savides T, Zaidi S, Jaffe P, Lehman G, Wonn MJ, Hawes R. Experience with a catheter-based ultrasound probe in the bile duct and pancreas. Endoscopy 1995; 27: 178-184

21 Inui K, Nakazawa S, Yoshino J, Wakabayashi T, Okushima K, Nakamura Y, Hattori T, Miyoshi H. Ultrasound probes of biliary lesions. Endoscopy 1996; 30 (Suppl 1): A 120-123

22 Tamada K, Hagai H, Yasuda Y, Tomiyama T, Ohashi A, Wada S, Kanai N, Satoh Y, Ido K, Sugano K. Transpapillary intraductal US prior to biliary drainage in the assessment of longitudinal spread of extrahepatic bile duct carcinoma. Gastrointest Endosc 2001; 53: 300-307

23 Menzel J, Poremba C, Dietl KH, Domshke W. Preoperative diagnosis of bile duct strictures. Comparison of intraductal ultrasonography with conventional endosonography. Scand J Gastroenterol 2000; 35: 77-82

24 Al-Karawi MA, Mohamed AES. Endoscopic management of benign biliary strictures. Saudi Med J 1994; 15: 56-60

25 Lillemoe KD, Melton GB, Cameron JL, Pitt HA, Campbell KA, Talomini MA, Sauter PA, Coleman J, Yeo CJ. Postoperative bile duct strictures: Management and outcome in the 1990s. Ann Surg 2000; 232: 430-441

26 Tocchi A, Mazzoni G, Liotta G, Costa G, Lepre L, Miccini M, DeMasi E, Lamazza MA, Fiori E. Management of benign biliary strictures: biliary enteric anastomosis vs endoscopic stenting. Arch Surg 2000; 135: 153-157

27 Born P, Rosch T, Bruhl K, Sandschin W, Allescher HD, Frimberger E, Classen M. Long-term results of endoscopic and percutaneous transhepatic treatment of benign biliary strictures. Endoscopy 1999; 31: 725-731

28 Sugiyama M, Atomi Y, Kuroda A, Muto T. Bile duct carcinoma without jaundice: Clues to early diagnosis. Hepatogastroenterology 1997; 44: 1477-1483

29 Costamagna G, Gabrielli A, Mutignani M, Perri V, Bunonato M, Crucitti F. Endoscopic diagnosis and treatment of malignant biliary strictures: review of 505 patients. Acta Gastroenterol Belg 1993; 56: 201-206

30 Al-Mofleh IA, Rashed RS, Al-Amri SM, Al-Ghamdi AS, Al-Faleh FZ, Al-Freih HM, Isnani AC. Malignant biliary strictures: Diagnosis and management. Saudi Med J 2003; 24: 1360-1363

Edited by Wang XL Proofread by Xu FM