

## ORIGINAL ARTICLE

## Increase in serum bilirubin levels in obstructive jaundice secondary to pancreatic and periampullary malignancy – implications for timing of resectional surgery and use of biliary drainage

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### Abstract

**Background.** Routine preoperative biliary drainage in cases of jaundice secondary to pancreatobiliary malignancy is associated with a significant risk of complications, failure and stent occlusion. It may be possible to avoid biliary drainage in those patients who are not deeply jaundiced. **Aims.** To measure presenting serum bilirubin and its rate of increase in patients with malignant obstructive jaundice. To predict the urgency with which surgery should be performed to avoid preoperative biliary drainage. **Patients and methods.** Prospective data collection for all pancreatic and periampullary malignancies over a period of 18 months was carried out. Serum bilirubin levels before successful drainage were recorded. Rates of increase in bilirubin and the number of days for bilirubin to reach different thresholds were calculated. **Results.** Of 111 patients, 66 (59%) had resectable disease on imaging investigations. Median serum bilirubin on presentation was 160  $\mu\text{mol/l}$ . Median increase was 13.1  $\mu\text{mol/l/day}$  or approximately 100  $\mu\text{mol/l/week}$ . The predicted number of days for bilirubin levels to reach a variety of thresholds varied significantly. For a patient presenting with a serum bilirubin of 160  $\mu\text{mol/l}$ , the mean number of days for it to rise to 200  $\mu\text{mol/l}$ , 300  $\mu\text{mol/l}$ , 400  $\mu\text{mol/l}$  and 500  $\mu\text{mol/l}$  was 3, 13, 22 and 31 days, respectively. **Conclusions.** There is a variable window of opportunity in jaundiced patients with pancreatic and periampullary malignancy during which surgery may be performed to avoid biliary drainage procedures, depending on the threshold for operating on the jaundiced patient.

**Key Words:** *biliary drainage, serum bilirubin, jaundice, pancreatobiliary malignancy*

### Introduction

In patients undergoing surgical procedures for pancreatic and periampullary malignancy the presence of jaundice has been shown to be associated with a higher incidence of septic, renal and nutritional complications [1–3]. The depth of jaundice has been shown to correlate positively with mortality after surgical intervention in benign disease [1]. It seems likely that the same is true for malignant pathology, particularly as increasing jaundice has been shown to be associated with the same nutritional and septic sequelae that have adverse effects on surgical outcome [4].

Conventional management of jaundiced patients with pancreatic and periampullary malignancy has included the use of biliary drainage procedures, particularly endoscopic retrograde cholangiopancreatography (ERCP) followed by further assessment and

resectional surgery when possible. ERCP performed for purely diagnostic reasons has, more recently, been superseded by other imaging techniques such as CT, MRI and endoscopic ultrasound. Biliary instrumentation also carries a significant risk of morbidity and mortality from complications such as perforation, cholangitis, haemorrhage and acute pancreatitis. ERCP is associated with a complication rate of 1–25% and a mortality rate of 0.2–1% [5–15]. In addition, the procedure has a failure rate of between 3 and 30% [5,6,11,12,15–18]. Percutaneous transhepatic cholangiography (PTC) is associated with a complication rate of 27–67% with a mortality rate of up to 6% [15,19,20]. It also carries the additional risk of tumour seeding along the drain track rendering potentially curable tumours unresectable [21]. Even in patients who successfully undergo a complication-

free drainage procedure, recurrent jaundice and cholangitis due to stent occlusion is common [22].

Several studies have either shown no effect of preoperative drainage on outcome after resection [5,19,22–25,34] or a detrimental effect with increased morbidity, mortality or costs [26–28]. Improved postoperative morbidity has been demonstrated in other studies [29–32], with one also showing evidence of improved cardiac function after biliary drainage [33]. None of these studies were randomized trials and none advocating preoperative biliary drainage suggested a degree of hyperbilirubinaemia beyond which drainage should be mandatory.

Most clinicians would agree that the profoundly jaundiced patient should undergo biliary drainage before resection, particularly if septic or renal complications are encountered. However, many patients present with a mild degree of jaundice that would not, if it remained stable, preclude surgery from being performed without preoperative biliary drainage. Complications of drainage could thus be avoided and the degree of jaundice would not be severe enough to cause potential increases in postoperative complications.

Because most patients with mild obstructive jaundice of malignant aetiology will progress to severe jaundice if untreated, the surgeon may have a window of opportunity to perform a pancreatic resection without preoperative biliary drainage. This would assume that such patients could be identified early and management implemented before the jaundice progressed to a level that made drainage necessary. Consequently, a prospective study was carried out over an 18-month period, the aims of which were: (1) to determine the rate of increase of serum bilirubin levels in patients with pancreatic and periampullary malignancy and (2) to predict the length of time after presentation during which surgery could be carried out in order to avoid the use of biliary drainage procedures.

## Patients and methods

### Patients and measurements

Over the period of June 2002 to December 2003 inclusive, data were collected prospectively on all cases of suspected pancreatic and periampullary malignancy presenting with obstructive jaundice to a large cancer centre experienced in the treatment of such tumours. All serum bilirubin levels measured either by general practitioners, referring hospitals or within the cancer centre were recorded before successful biliary drainage or surgical intervention. All investigations and procedures were undertaken on purely clinical grounds.

### Statistical methods

*Rates of increase of serum bilirubin.* Bilirubin levels from presentation to maximum readings were first plotted

and seen to best fit to a linear model. Linear and logistic regression analysis was then carried out to determine the relationship between the level of serum bilirubin on presentation and the subsequent rate of increase. Rates of increase in bilirubin were calculated for each patient and compared on resectable and non-resectable patients using Student's *t* test.

*Calculating the window of opportunity for resection before drainage becomes necessary.* Given that there is little consensus as to a level of hyperbilirubinaemia above which biliary drainage is mandatory prior to resection, several threshold values were used: 200, 300, 400 and 500  $\mu\text{mol/l}$ . The calculated rate of increase in serum bilirubin was used to predict the number of days it would take for levels to rise from the presenting value to each threshold value if left untreated. Linear regression analysis was then performed using bilirubin on presentation ( $B_0$ ) as the predictor and number of days ( $D$ ) as the response with 95% confidence intervals being calculated. In this way it was hoped to identify the mean length of time that a patient with a specific bilirubin level would take to reach the threshold if biliary drainage were not performed. All calculations were made using Minitab Statistical Software.

## Results

### Demographics

In total, 111 patients with pancreatic or periampullary malignancy were included, 65 males and 46 females, with a median age of 69 years (range 34–89). Diagnoses were confirmed on histology/cytology ( $n=75$ ) or strong radiological evidence and raised tumour markers ( $n=36$ ). Resectable disease on staging by CT scan was found in 66 patients (59%).

### Bilirubin levels on presentation and rates of increase

Median serum bilirubin when first measured was 160  $\mu\text{mol/l}$  (9.4 g/dl) in all patients with an interquartile range (IQR) of 107–239  $\mu\text{mol/l}$ . This was not significantly different for those with resectable disease on staging in whom the median level was 166.5  $\mu\text{mol/l}$  (IQR 112.5–202  $\mu\text{mol/l}$ ,  $p=0.32$ , Student's *t* test). Table I shows the range of bilirubin levels when first

Table I. Serum bilirubin levels at first measurement.

Serum bilirubin ( $\mu\text{mol/l}$ )	Number (%) of patients (Total = 111)
$\leq 50$	10 (9%)
51–100	15 (14%)
101–150	29 (26%)
151–200	14 (13%)
201–250	19 (17%)
251–300	7 (6%)
>300	17 (15%)

measured. The subsequent median rate of increase in bilirubin levels was 13.1  $\mu\text{mol/l/day}$  (IQR 9.5–30.3). This did not vary significantly between resectable tumours (median 10.9) and non-resectable tumours (median 15.6) ( $p=0.25$ , Student's  $t$  test). In addition, linear and logistic regression analysis confirmed no relationship between the level on presentation and the subsequent rate of increase.

#### *Predicting the time for bilirubin levels to rise above threshold levels*

When the predicted length of time for bilirubin levels to rise above each threshold level was plotted against bilirubin on presentation, an inverse linear relationship was demonstrated. Figure 1 shows an example of this relationship for a threshold set at 300  $\mu\text{mol/l}$ . The mean predicted number of days, with 95% confidence intervals, for levels to rise to each threshold level is shown in Table II for several arbitrary bilirubin levels on presentation.

### Discussion

The presence of obstructive jaundice, if untreated, results in nutritional, metabolic and septic complications. Surgery in jaundiced patients has been shown to be associated with an increased risk of complications that increases with the depth of jaundice [1–4]. Less jaundiced patients are therefore more suitable for surgery without preoperative drainage. In our study, the median bilirubin on presentation was 160  $\mu\text{mol/l}$  and >60% of our patients with malignant distal biliary obstruction presented with a serum bilirubin of <200  $\mu\text{mol/l}$ . In only 15% of cases was the presenting serum bilirubin over 300  $\mu\text{mol/l}$ . Most patients therefore, present with a level of jaundice that would not necessarily preclude surgery without preoperative biliary drainage. Thus, a limited window of opportunity exists in which to diagnose and stage patients as quickly as possible so that early operation, if indicated, may be carried out before progressive jaundice makes drainage inevitable.

Choosing a threshold of hyperbilirubinaemia below which most surgeons would be happy to avoid biliary drainage prior to resection is difficult, since for individual patients other factors including co-morbid-

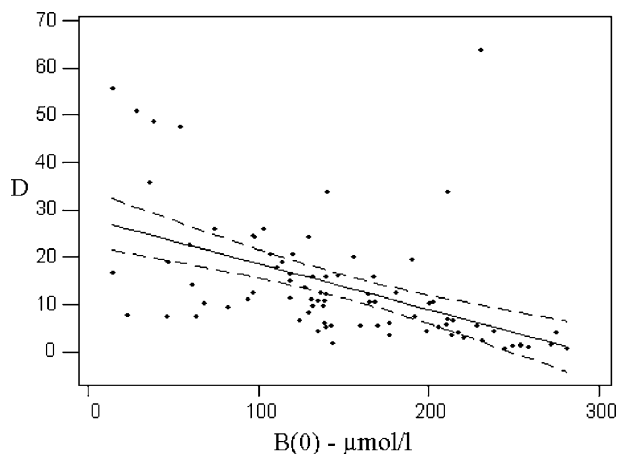


Figure 1. Linear regression plot of the number of days for serum bilirubin to rise above 300  $\mu\text{mol/l}$  (D) vs bilirubin levels on presentation ( $B_0$ ).

ity will need to be taken into account. Many studies have looked at the adverse effects of jaundice per se and shown a higher rate of nutritional, septic and subsequent surgical complications in more jaundiced subjects [1–4,34]; however, none has suggested a threshold below which surgery without drainage in the non-septic patient is universally acceptable. If, for example, a threshold of 300  $\mu\text{mol/l}$  is employed, the average patient would have <2 weeks from presentation to breaching this level. Even if one were to reject the idea of having a fixed threshold for surgery without preoperative biliary drainage, knowing that bilirubin increases by an average of approximately 100  $\mu\text{mol/l/week}$  is useful data and is argument in itself for prompt action and fast-track surgery if potentially hazardous drainage procedures are to be avoided.

We have demonstrated that there is significant variability in the rate of increase in serum bilirubin levels after presentation and that this is independent of the potential resectability of the obstructing tumour. The predicted number of days for bilirubin to breach each threshold level has wide confidence intervals and can therefore only be used as a guide. It does, however, reinforce the argument that in all cases prompt investigation, staging and surgery are essential if biliary drainage is to be avoided in as many cases as possible. Processing patients this quickly from presentation to definitive surgery offers a considerable challenge that has major resource implications in a

Table II. Predicted interval in days between presentation and serum bilirubin rising above different threshold levels.

Threshold of serum bilirubin level ( $\mu\text{mol/l}$ )	Mean predicted days until levels rise above threshold (95% confidence interval) at different presenting levels of serum bilirubin				
	50 $\mu\text{mol/l}$ (2.9 g/dl)	100 $\mu\text{mol/l}$ (5.8 g/dl)	160 $\mu\text{mol/l}$ (9.4 g/dl)	200 $\mu\text{mol/l}$ (11.7 g/dl)	250 $\mu\text{mol/l}$ (14.6 g/dl)
200	14 (10–18)	9 (5–14)	3.5 (0–10)	NA	NA
300	23 (16–31)	19 (9–28)	13 (1–25)	9 (0–22)	4 (0–19)
400	32 (17–47)	28 (9–46)	22 (0–45)	18 (0–44)	14 (0–42)
500	41 (19–64)	37 (9–65)	31 (0–65)	28 (0–66)	23 (0–66)

modern health service. It does, however, have the potential to reduce complications of biliary drainage and to reduce days in hospital waiting for drainage procedures or in treating complications.

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### References

- [1] Armstrong CP, Dixon JM, Taylor TV, Davies GC. Surgical experience of deeply jaundiced patients with bile duct obstruction. *Br J Surg* 1984;71:234–8.
- [2] Dixon JM, Armstrong CP, Duffy SW, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. *Gut* 1983;24:845–52.
- [3] Lacaine F, Fourtanier G, Fingerhut A, Hay JM. Surgical mortality and morbidity in malignant obstructive jaundice: a prospective multivariate analysis. *Eur J Surg* 1995;161:729–34.
- [4] Blamey SL, Fearon KCH, Gilmour WH, Osborne DH, Carter DC. Prediction of risk in biliary surgery. *Br J Surg* 1983;70:535–8.
- [5] Lai EC, Mok FP, Fan ST, Lo CM, Chu KM, Liu CL, et al. Preoperative endoscopic drainage for malignant obstructive jaundice. *Br J Surg* 1994;81:1195–8.
- [6] Varghese JC, Liddell RP, Farrell MA, Murray FE, Osborne DH, Lee MJ. Diagnostic accuracy of magnetic resonance cholangiopancreatography against direct cholangiography in the detection of choledocholithiasis. *Clin Radiol* 2000;55:25–35.
- [7] Halme L, Doepel M, von Numers H, Edgren J, Ahonen J. Complications of diagnostic and therapeutic ERCP. *Ann Chir Gynaecol* 1999;88:127–31.
- [8] Sica GT, Braver J, Cooney MJ, Miller FH, Chai JL, Adams DF. Comparison of endoscopic retrograde cholangiopancreatography with MRCP in patients with pancreatitis. *Radiology* 1999;210:605–10.
- [9] Seifert E. Endoscopic retrograde cholangiopancreatography. *Am J Roentgenol* 1977;68:542–9.
- [10] Kessler RE, Falkenstein DB, Clemett AR, Zimmon DS. Indications, clinical value and complications of endoscopic retrograde cholangiopancreatography. *Surg Gynecol Obstet* 1976;142:865–70.
- [11] Ciriza C, Dajil S, Jimenez C, Urquiza O, Karpman G, Garcia L, et al. Five years analysis of endoscopic retrograde cholangiopancreatography in the hospital del Bierzo. *Rev Esp Enferm Dig* 1999;91:693–702.
- [12] Bilbao MK, Potter CT, Lee TG, Katon RM. Complications of endoscopic retrograde cholangiopancreatography (ERCP): a study of 10,000 cases. *Gastroenterology* 1976;70:314–20.
- [13] Zinsser E, Hoffman A, Will U, Koppe P, Bossekert H. Success and complication of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography: a prospective study. *Z Gastroenterol* 1999;37:707–13.
- [14] Vitale GC, George M, McIntyre K, Larson GM, Wieman TJ. Endoscopic management of benign and malignant biliary strictures. *Am J Surg* 1996;171:553–7.
- [15] Speer AG, Cotton PB, Russel RC, Mason RR, Hatfield AR, Leung JW, et al. Randomised trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. *Lancet* 1987;8550:57–62.
- [16] Georgopoulos SK, Schwartz LH, Jarnagin WR, Gerdes H, Breite I, Fong Y, et al. Comparison of magnetic resonance and endoscopic retrograde cholangiopancreatography in malignant pancreaticobiliary obstruction. *Arch Surg* 1999;134:1002–7.
- [17] Rieuer R, Wayland W. Yield of prospective non-invasive evaluation of the CBD combined with selective ERCP/sphincterotomy in 1,930 consecutive laparoscopic cholecystectomy patients. *Gastrointest Endosc* 1995;42:6–12.
- [18] Hoyuela C, Cugat E, Bretcha P, Collera P, Espinos J, Marco C. Must ERCP be routinely performed if choledocholithiasis is suspected. *Dig Surg* 1999;16:411–4.
- [19] Pitt HA, Games AS, Lois JF, Mann LL, Deutsch LS, Longmire LP. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? *Ann Surg* 1985;201:545–53.
- [20] Carrasco CH, Zornoza J, Bechtel WJ. Malignant biliary obstruction: complications of percutaneous biliary drainage. *Radiology* 1984;152:343–6.
- [21] Charnley RM, Banerjee AK, Whitaker SC, Spiller RC, Doran J. Peritoneal seeding of pancreatic cancer following transperitoneal biliary procedures. *Br J Surg* 1995;82:393.
- [22] Karsten TM, Allema JH, Reinders M, van Gulik TM, de Wit LT, Verbeek PC, et al. Preoperative biliary drainage, colonisation of bile and postoperative complications in patients with tumours of the pancreatic head: a retrospective analysis of 241 consecutive patients. *Eur J Surg* 1996;162:881–8.
- [23] Bakkevold KE, Kambestad B. Morbidity and mortality after radical and palliative pancreatic cancer surgery. Risk factors influencing the short-term results. *Ann Surg* 1993;217:356–68.
- [24] Pellegrini CA, Allegra P, Bongard FS, Way LW. Risk of biliary surgery in patients with hyperbilirubinaemia. *Am J Surg* 1984;154:111–7.
- [25] Norlander MD, Kalin B, Sundblad R. Effect of percutaneous drainage upon liver function and postoperative mortality. *Surg Gynecol Obstet* 1982;155:161–6.
- [26] Povoski SP, Karpeh MS, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. *Ann Surg* 1999;230:131–42.
- [27] Pisters WT, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S, et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001;234:47–55.
- [28] Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH, Brennan MF. A preoperative biliary stent is associated with increased complications after pancreaticoduodenectomy. *Arch Surg* 1998;133:149–53.
- [29] Marcus SG, Dobryansky M, Shamamian P, Cohen H, Gouge TH, Pachter HL, et al. Endoscopic biliary drainage before pancreaticoduodenectomy for periampullary malignancies. *J Clin Gastroenterol* 1998;26:125–9.
- [30] Nakayama T, Ikeda A, Okuda K. Percutaneous transhepatic drainage of the biliary tract: technique and results in 104 cases. *Gastroenterology* 1985;74:545–53.
- [31] Gundry SR, Strodel WE, Knol JA, Eckhauser FE, Thompson NW. Efficacy of preoperative biliary tract decompression in patients with obstructive jaundice. *Arch Surg* 1984;119:703–8.
- [32] Lygidakis NJ, Van der Heyde MN, Lubbers MJ. Evaluation of preoperative biliary drainage in the surgical management of pancreatic head carcinoma. *Acta Chir Scand* 1987;153:665–8.
- [33] Padillo J, Puente J, Gomez M, Dios F, Naranjo A, Vallejo JA. Improved cardiac function in patients with obstructive jaundice after internal biliary drainage. Haemodynamic and hormonal assessment. *Ann Surg* 2001;234:652–6.
- [34] Sewnath ME, Karsten TM, Prins MH, Rauws EJA, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. *Ann Surg* 2002;236:17–27.