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Differentiation between benign and malignant hilar obstructions using laboratory and radiological investigations: A prospective study

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Abstract
Background: Preoperative determination of the aetiology of bile duct strictures at the hilum is difficult. We evaluated the diagnostic accuracy of laboratory parameters and imaging modalities in differentiating between benign and malignant causes of hilar biliary obstruction. *Patients and methods:* Fifty-eight patients (26 men) with a history of obstructive jaundice and liver function tests (LFTs) and ultrasound suggestive of biliary obstruction at the hilum were studied. They were evaluated by tumour marker assay (CA19-9), CT and MRI/MRCP. A single experienced radiologist, blinded to the results of other tests, evaluated the imaging. The final diagnosis was made either from histology of the resected specimen, operative findings or image-guided biopsy in inoperable patients. A receiver operator characteristic (ROC) curve was constructed for each laboratory parameter to determine optimal diagnostic cut-off to predict malignant biliary stricture (MBS). *Results:* In all, 34 patients had a benign and 24 had malignant aetiology. The mean age of benign patients was 38 years compared with 54 years for MBS. Forty-seven patients were treated with surgery while 11 had ERCP/PTC and stenting. The ROC curve showed that preoperative bilirubin level $>$8.4 mg/dl (sensitivity 83.3%, specificity 70%), alkaline phosphatase level $>$478 IU (sensitivity 63%, specificity 49%) and CA19-9 levels $>$100 U/L (sensitivity 45.8%, specificity 88.2%) for predicting MBS. The sensitivity, specificity and diagnostic accuracy of MRI/MRCP (87.5%, 85.3%, 82.7%, respectively) was marginally superior to CT (79.2%, 79.4%, 79.3%, respectively). *Conclusions:* Patients with a bilirubin level of $>$8.4 mg% and CA19-9 level $>$100 U/L were more likely to have malignant aetiology. MRI/MRCP was a better imaging modality than CT.

Key Words: *hilar biliary obstruction, MRCP, CECT, CA19-9, bilirubin*

Introduction

The differentiation of benign from malignant strictures in the proximal bile duct is difficult [1,2]. Benign biliary tumours and strictures such as an inflammatory stricture secondary to choledocholithiasis, Mirizzi syndrome, extrahepatic localized form of primary sclerosing cholangitis (PSC) and idiopathic benign focal stricture are the possible differential diagnoses of a bile duct carcinoma [3–6]. The clinical findings and laboratory values including tumour marker levels are not specific enough to determine the precise cause of a biliary stricture of the proximal bile duct [7–9]. The accuracy of alkaline phosphatase isoenzyme in differentiating benign from malignant extrahepatic biliary obstruction has been reported to be up to 80% [7]. CA19-9 has been used to differentiate between cholangiocarcinoma and other benign causes of obstruction, but it has a variable sensitivity and specificity [10,11]. The radiological modalities for evaluation of these patients include ultrasonography, contrast-enhanced CT scan, MRI and magnetic resonance cholangiopancreaticography (MRCP). These non-invasive diagnostic methods provide useful information about the level of obstruction, extent of biliary dilatation and the presence of a mass or distant metastasis [12–16]. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) are more accurate imaging tests for bile duct evaluation and allow a tissue diagnosis through brush biopsy and cytology studies. However, these are associated

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with a significant risk of morbidity [17,18]. Moreover, a preoperative histological assessment using biopsies or brush cytology has limited sensitivity (30–60%) in spite of high specificity (>95%) [19,20].

Hence, we carried out a study to identify the diagnostic markers that help in differentiating a benign from a malignant cause of proximal bile duct stricture (within 2 cm of the confluence) using laboratory tests and non-invasive imaging modalities before planning surgery or an invasive interventional procedure.

Patients and methods

Study design

This prospective study was conducted from October 2003 to August 2005. Fifty-four patients who attended the GI surgery and gastroenterology outpatient departments with a history suggestive of obstructive jaundice underwent preliminary work-up with liver function tests (LFTs) and an abdominal ultrasound. Patients with liver function tests suggestive of obstructive jaundice and an ultrasound showing high biliary obstruction were included in the study. High biliary obstruction was defined as obstruction to the normal flow of bile due to an extrinsic or intrinsic block involving a biliary tract within 2 cm of the confluence. Patients with a diagnosis of carcinoma gall bladder with biliary obstruction, strictured hepaticojejunostomy, portal biliopathy, hepatic metastasis with biliary dilatation and hepatocellular carcinoma with biliary dilatation were excluded from the study, as the cause of hilar obstruction was obvious. Patients assessed as being unfit to undergo a major surgical procedure were also excluded.

These patients were then evaluated with a) biochemical parameters (total bilirubin and alkaline phosphatase); b) tumour marker (serum CA19-9); c) imaging (contrast-enhanced helical computed tomography (CECT) and MRI with MRCP).

The whole abdomen was scanned with special reference to the hepatobiliary and pancreatic region by ultrasound using a Phillips HDI 3000/5000 scanner with a 3 MHz convex transducer after 6 h of fasting in all patients.

CECT was performed in all patients using a Somatom Plus-4 scanner (Siemens, Erlangen, Germany). The patients were kept fasting for 6 h before the procedure. Non-ionic iodinated contrast material (20 ml in 750 ml of water) was given orally. Another 100 ml of contrast was injected into an antecubital vein with a pressure injector at 3 ml/s. Helical CT was performed with 5.0 mm thick collimation and a table speed of 7.5 mm/s (1.5:1 pitch) for scanning from the dome of the diaphragm to the third lumbar vertebra and images were reconstructed at 5 mm intervals. Immediately afterwards the rest of the abdomen and pelvis were scanned with 10 mm collimation, 15 mm/s table speed and 10 mm reconstruction interval.

MRI/MRCP was performed on a Siemens Sonata Maestro class Magnetom 1.5 tesla MR scanner. Phased array flexible torso coils were used. Before MRCP, an axial T1W FLASH (TR/TE 104/4.8 ms: flip angle 75°, matrix 128 × 256: scan time 18 s), axial and coronal T2W TRUFISP (TR/TE 4.5/2.2 ms, matrix 128 × 256: scan time 18 s) and a heavily T2W HASTE sequence (echo space of 10.9 ms, effective TE 83 ms, one excitation, flip angle of 150° and matrix of 240 × 256) were taken. Fat suppression was used in some patients to suppress the signal from the peritoneal fatty tissue. Axial and coronal thin (two to four) sections were taken with HASTE sequence through the entire biliary and pancreatic tree. This was followed by a thick slab MRCP at slice thickness of 30–50 mm (imaging time 1.4–2 s) with careful optimization of the slice position and orientation by using axial T2-weighted images. The slab was placed in such a manner that it did not include the renal pelvis, spine and fluid in the duodenum or stomach. Multiple angulations at increments of 10° were used to achieve the best visualization of the biliary tree. Negative contrast in the form of ferric ammonium citrate 1200 mg dissolved in 70 ml of water was given orally just before or during examination. The multi-slice MRCP technique was used if satisfactory images were not obtained by the thick slab single slice method.

The parameters that were analysed included: a) preoperative bilirubin level and serum alkaline phosphatase level; b) serum CA 19-9 level; c) CT findings including any mass/thickening of the wall of the common bile duct (CBD), lymph node > 1 cm and atrophy-hypertrophy complex; and d) MRI/MRCP findings including any thickening of the wall of the CBD/mass, abrupt cut-off/gradual tapering, separation of ducts, length of the stricture and presence of atrophy-hypertrophy complex.

Image analysis

CECT and MRI/MRCP were evaluated by a single experienced radiologist. The radiologist was blinded to the results of all other tests. Histopathology or operative findings were considered as the gold standard. The final diagnosis was made either from histology of the resected specimen and/or operative findings, or image-guided biopsy in inoperable patients. In those patients where no tissue for histology could be obtained, their subsequent clinical course was used as the gold standard to ascertain whether they had a benign or malignant cause for the obstruction to the biliary tract. Any patient with post-cholecystectomy biliary stricture, who had suspicion of a malignancy at surgery, underwent a biopsy. The classification of strictures into Bismuth type on MRCP was compared with operative findings or