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 CA 19-9 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, intrahepatic 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 intrahepatic biliary obstruction has been reported to be up to 80% [7]. CA 19-9 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 cholangiopancreatography (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...
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, stricture 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 CA 19-9); 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 x 256: scan time 18s), axial and coronal T2W TRUFISP (TR/TE 4.5/2.2 ms, matrix 128 x 256: scan time 18s) 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 x 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 multislice 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
cholangiographic findings at ERC/PTC in inoperable patients. The patency of the confluence on imaging was compared with operative findings or cholangiographic findings at ERC/PTC in inoperable patients.

Statistical analysis

Paired Student's $t$ test was used to compare continuous variables. The $X^2$ test was used for pair-wise comparison of dichotomous variables. The sensitivity, specificity, negative and positive predictive value and diagnostic accuracy were used to compare the imaging investigations. For all tests, a $p$ value $<0.05$ was considered significant. The receiver operative characteristic (ROC) curve was used to obtain the cut-off values for laboratory parameters.

Results

Fifty-eight patients with a hilar block based on LFTs and ultrasonography were included in the study. All 58 patients were evaluated with serum CA 19-9 levels, CT and MRCP.

Clinical features

The patients with malignant strictures were significantly older compared with those with benign strictures ($p<0.001$) and malignant strictures were seen more frequently in men while benign strictures were more common in women. The incidence of pain was not significantly different between the two groups. Anorexia and weight loss were significantly more common in patients with malignant stricture ($p < 0.001$). Twenty-seven patients in the benign group and seven patients in the malignant group had a history of previous cholecystectomy. In the benign group, 27 patients had a history of cholecystectomy while none of the 7 patients without a previous cholecystectomy had a distended gall bladder. Presence of mass and enlarged lymph nodes on CT were significant findings that helped in determining the nature of the stricture (Table II). The presence of atrophy-hypertrophy complex did not help in making the diagnosis. CT provided additional information about the vascular involvement in eight patients with malignant strictures, thus helping in management. The images in Figure 2a, b and c show the characteristics of benign and malignant stricture seen on CT.

Of 34 patients with benign strictures, 27 patients were correctly diagnosed on CT, while 7 patients were incorrectly diagnosed because of the presence of a mass alone (2 patients), lymphadenopathy alone (4 patients) and a mass associated with enlarged lymph node (1 patient). Of 24 patients with a malignant stricture, 19 were diagnosed correctly. Four patients did not have any mass or enlarged lymph nodes, but had either a history of previous cholecystectomy or gallstones along with a patent confluence. One patient, who was a known case of sarcoidosis, had a stricture at the confluence with no mass and hence was diagnosed to have a benign stricture. On follow-up, he developed liver metastasis. The sensitivity of

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Benign</th>
<th>Malignant</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>38±14</td>
<td>54±9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>25 (73%)</td>
<td>7 (29%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Men</td>
<td>9 (27%)</td>
<td>17 (71%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>27 (79%)</td>
<td>15 (62%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Weightloss</td>
<td>13 (38%)</td>
<td>21 (87%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13 (38%)</td>
<td>18 (75%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>8.6±8.8</td>
<td>17.4±9.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>595±393</td>
<td>823±569</td>
<td>0.98</td>
</tr>
<tr>
<td>SGOT (IU/L)</td>
<td>124±84</td>
<td>113±60</td>
<td>0.566</td>
</tr>
<tr>
<td>SGPT (IU/L)</td>
<td>92±57</td>
<td>107±91</td>
<td>0.482</td>
</tr>
<tr>
<td>CA 19-9 (U/ml)</td>
<td>31±61</td>
<td>189±267</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Imaging

Ultrasonography showed biliary dilatation and correctly identified the level of obstruction in all patients. Whether the confluence was blocked or not was correctly ascertained in 22 of 24 patients with malignant and in all patients with benign strictures (compared with operative findings/cholangiographic findings at ERC/PTC). Two patients with malignant stricture had a blocked confluence, which on ultrasound was erroneously thought to be patent. Ultrasonography showed a mass lesion in 8 of 24 patients in the malignant group and in 1 of 34 patients in the benign group.

CT showed biliary dilatation in all the patients. The confluence was patent in 23 patients with benign and 3 patients with malignant strictures. Of 24 patients with malignant strictures, the gall bladder was collapsed in 14, distended in 3 and the remaining 7 had a history of cholecystectomy. In the benign group, 27 patients had a history of cholecystectomy while none of the 7 patients without a previous cholecystectomy had a distended gall bladder. Presence of mass and enlarged lymph nodes on CT were significant findings that helped in determining the nature of the stricture (Table II). The presence of atrophy-hypertrophy complex did not help in making the diagnosis. CT provided additional information about the vascular involvement in eight patients with malignant strictures, thus helping in management. The images in Figure 2a, b and c show the characteristics of benign and malignant stricture seen on CT.

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CT in predicting the nature of the stricture was 79.2%, specificity 79.4%, positive predictive value 73.1%, negative predictive value 84.4% and diagnostic accuracy 79.3%.

The MRI/MRCP images were of good quality in all patients. Both the intra- and extrahepatic biliary radicals were visualized completely including the proximal and distal extent of the stricture. The confluence was patent in 23 and 3 patients with benign and malignant stricture, respectively. The primary confluence was involved in 5 patients while the secondary confluence of either side was involved in 13 patients in the malignant group. Of 24 patients with malignant strictures, gall bladder was collapsed in 14, distended in 3 and absent in 7 patients. Atrophy-hypertrophy complex did not differ significantly and was seen in four and eight patients in the benign and malignant group, respectively. The presence of a mass and a stricture with an irregular margin, asymmetric dilatation or long length had a significant predictive value in determining the nature of the lesion (Table III). Abrupt narrowing was present at a similar frequency in both groups. The images shown in Figure 3a, b and c show the characteristics of a malignant stricture seen on MRI and MRCP.

Of 34 benign patients, 29 were correctly diagnosed as having a benign stricture on MRI/MRCP, while 5 patients were diagnosed as having a malignant stricture either because they had a mass (3 patients) or the stricture morphology was suggestive of a malignant stricture (5 patients). Of the three patients with Mirrizzi's syndrome, two were correctly diagnosed on MRCP. The images in Figures 4 and 5 show characteristics of a benign stricture and Mirrizzi syndrome, respectively, seen on MRI and MRCP. Of 24 patients with malignant stricture, 21 were diagnosed correctly, 3 patients were diagnosed as having a benign stricture as they had no mass and the stricture morphology was suggestive of a benign stricture. The sensitivity of MRCP for predicting the nature of the stricture was 87.5%, specificity 85.3%, positive predictive value 80.8%, negative predictive value 90.6% and diagnostic accuracy 82.7%.

The comparison of Bismuth type of stricture on MRCP with operative/ERC/PTC findings showed that four patients with type 3 stricture were incorrectly classified as type 2 and type 4 strictures in two patients each in the benign group. In the remaining 25 patients the MRCP classification was in concordance with the operative/ERC/PTC findings. While in the malignant group three patients with type 2 stricture were incorrectly classified as type 1 (n = 1) and type 3 (n=2), one patient with type 3 stricture was underestimated to have a type 2 stricture and one patient with type 4 stricture was considered to have type 3 stricture. The remaining 16 patients were correctly classified by MRCP.

Based on the gold standard, there were 34 patients with benign stricture and 24 patients with malignant stricture (Table IV). All patients in the malignant

### Table II. CT findings determining the nature of the stricture.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign (n=34)</th>
<th>Malignant (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>3 (8.8%)</td>
<td>15 (62.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymph node &gt; 1 cm</td>
<td>5 (14.7%)</td>
<td>11 (45.8%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Atrophy-hypertrophy</td>
<td>4 (11.7%)</td>
<td>8 (33.3%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

### Management of patients

Based on the gold standard, there were 34 patients with benign stricture and 24 patients with malignant stricture (Table IV). All patients in the malignant

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Figure 1. Receiver operator characteristic (ROC) curves of the laboratory parameters (bilirubin, alkaline phosphatase, CA 19-9) for predicting the nature of the hilar biliary stricture.
Differentiation between benign and malignant hilar obstructions

Figure 2. (a) CT showing dilated common bile duct at porta (arrow) with no mass suggestive of benign stricture. Final diagnosis: benign biliary stricture. (b) CT showing mass encasing left hepatic artery (arrow) with confluence block suggestive of Klatskin tumour. Final diagnosis: cholangiocarcinoma. (c) CT showing mass (arrow) involving confluence with dilated intrahepatic biliary radicles suggestive of a malignant stricture. Final diagnosis: cholangiocarcinoma.

group had histopathological diagnosis, while 14 patients in the benign group had a biopsy for confirmation of the diagnosis. Twenty patients in the benign group had post-cholecystectomy benign biliary stricture (BBS), and the surgical findings revealed no mass, hence no biopsy of the bile duct was taken. All these patients are on follow-up and are doing well.

Of 58 patients, 47 were operated and 11 were managed using ERCP/PTC-guided intervention (Table V). Of the 34 patients with a benign aetiology, 32 underwent a surgical procedure while 2 patients were managed conservatively with stenting and anti-tubercular therapy. A histological diagnosis was obtained in both the latter patients by ERCP brush cytology and bile examination was done for demonstration of acid-fast bacilli. Fifteen patients in the malignant group underwent surgery while nine were stented. Of the 15 patients, 10 patients underwent curative resection and 7 of these had a frozen section done. Two patients in the malignant group and one patient in the benign group died. Both patients in the malignant group died of septic complications while the patient in the benign group died of aspiration.

Comparison of operative findings with imaging (Table VI)

Of the 32 patients in the benign group who underwent surgery, 3 patients had a mass during surgery similar to the findings on CT and MRCP and were treated as a presumed malignant lesion, but the final post-operative histopathology was suggestive of an inflammatory lesion in 2 patients and tuberculosis in 1 patient. Enlarged lymph nodes were seen in eight patients at surgery as compared to five patients on CT. The presence of atrophy-hypertrophy complex at surgery was in concordance with CT and MRCP. The confluence was patent in 25 patients at surgery as compared to 23 patients on MRCP.

Of the 15 patients in the malignant group who underwent surgery, a mass was seen in all patients during surgery, but only 11 of these patients were suspected to have a mass on CT and MRCP. Lymph nodes were found to be present in 14 patients at surgery, while CT detected lymph nodes in only 7 of them. The presence of atrophy-hypertrophy complex at surgery was in concordance with CT and MRCP. However, the vascular involvement was present in eight patients at surgery but detected in only three patients on CT. Of these eight patients, three patients underwent a curative resection, another three had a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign (n=34)</th>
<th>Malignant (n=24)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass</td>
<td>3 (8.8%)</td>
<td>16 (66.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irregular margin</td>
<td>4 (11.7%)</td>
<td>21 (87.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>4 (11.7%)</td>
<td>20 (83.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abrupt cut-off</td>
<td>28 (82.3%)</td>
<td>18 (75%)</td>
<td>0.793</td>
</tr>
<tr>
<td>Length of stricture (cm)</td>
<td>1.2±0.6</td>
<td>3.0±1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
palliative bypass and the remaining two patients had laparotomy, biopsy and closure.

Of the nine patients considered unresectable, five had vascular involvement (main portal vein), two had type 4 stricture and two developed septic complications following preoperative biliary drainage. Five patients were treated with bilateral PTBD and four patients had bilateral endoscopic drainage. Two
patients had metallic stents and the rest had plastic stents placed. Those who had a block just at the confluence with a patent secondary confluence had endoscopic drainage while the others were treated by the percutaneous route. Two patients in each group had cholangitis.

Follow-up

The mean follow-up of operated patients was 13.3 months (2-30 months) and for those who were stented it was 4.1 months (1-12 months) in the malignant group. On follow-up three patients died, one had cholangitis, two developed anastomotic stricture, two had local recurrence, two had systemic recurrence, two are doing well and one was lost to follow-up in the operated group. Seven of the nine stented patients died while two were lost to follow-up. Patients with anastomotic stricture were treated with percutaneous balloon dilatation and are on follow-up.

The mean follow-up of patients in the benign group was 10 months (6-30 months). On follow-up both patients with tubercular stricture treated with stenting and ATT were doing well. The stent was removed in one while the other was still stented. Two patients who had secondary biliary cirrhosis had developed ascites and were managed with diuretics. All the others are doing well.

Table V. Surgical and interventional procedures undertaken.

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Benign (n=34)</th>
<th>Malignant (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HJ</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>Cholecystectomy + HJ</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Hemi-hepatectomy + CBD excision + HJ</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cholecystectomy + CBD excision + HJ</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Cholecystectomy + cholecdochoplasty</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>CBD excision + Whipple’s procedure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Central hepatectomy + cholangiojejunostomy</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>CBD excision + HJ</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Exploratory laparotomy+biopsy</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Segment 3 bypass</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Endoscopic stenting</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Percutaneous stenting</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>CBD, common bile duct; HJ, hepaticojejunostomy</td>
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</tbody>
</table>

Table VI. Comparison of operative findings with CT and MRCP in both groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Benign stricture</th>
<th>Malignant stricture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT</td>
<td>MRCP</td>
</tr>
<tr>
<td>Mass</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Lymph node</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Atrophy/hypertrophy complex</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

NA, not applicable.

Discussion

Obstructive jaundice due to hilar biliary strictures can be a diagnostic dilemma, as preoperative differentiation between hilar Cholangiocarcinoma and benign biliary stricture is often difficult. We carried out a prospective study using laboratory and imaging tests to differentiate benign and malignant strictures.

In our study the patients with a malignant stricture were older than patients in the benign group. Similar results have been reported in the literature [21], except for a retrospective study by Kim et al. [13] in which they found that patients with both benign and malignant strictures belonged to similar age groups. In our study, the female preponderance in the benign group was due to a high incidence of post-cholecystectomy biliary strictures.

The clinical history and examination along with biochemical parameters and tumour markers were useful in arriving at a working diagnosis. The combination of painless progressive jaundice with weight loss and anorexia is thought to be highly suspicious of malignancy [7]. In our study we found anorexia and weight loss to be significantly more common in patients with malignant strictures. The incidence of pain was similar in both groups. Previous biliary surgery was an important factor in determining the nature of the lesion, as iatrogenic bile duct injury is the most common cause of benign strictures. In our study all patients who had a history of previous biliary surgery had had a Cholecystectomy. Of 34 patients who had a past history of Cholecystectomy, 27 had a benign stricture and 7 had a malignant stricture.

We found that a bilirubin level > 8.4 mg/dl and alkaline phosphatase levels > 478 IU/L were suggestive of a malignant lesion. Similar results have been reported by Al-mofleh et al. [21], Pasanen et al. [22] and Bain et al. [23]. As malignant lesions tend to have complete obstruction, these patients tend to have higher levels of bilirubin and alkaline phosphatase. However, similar values may be present in benign strictures in the presence of cholangitis or a long history, thereby decreasing the specificity of these two parameters.

The CA 19-9 level is useful in diagnosing Cholangiocarcinoma [24-27]. In our study, a CA19-9 level > 100 U/L had a sensitivity of 45.5% and
specificity of 88% in predicting the malignant strictures. These are comparable to the values reported in the literature [11, 24]. The level of CA 19-9 could be elevated in a variety of benign conditions, especially in patients with obstructive jaundice, thereby decreasing its specificity. Biliary obstruction and cholangitis can result in high serum levels of CA 19-9 thereby decreasing its predictive value [28]. Relief of jaundice decreases the serum levels to normal in benign conditions but not in the malignant group. Therefore, a repeat assay of CA19-9, 2-3 weeks after relief of jaundice, may help in differentiating malignant strictures from benign [11]. Biliary CA 19-9 levels are not of much diagnostic value, as the levels are raised in both benign and malignant conditions [10].

Imaging remains the cornerstone for the evaluation of the level of biliary obstruction and its underlying cause. In this study, ultrasound correctly determined the level of obstruction in all cases but the patency of the confluence was assessed correctly in 96% of cases. The accuracy of ultrasound to determine the level of biliary obstruction varies between 80% and 100% according to the literature [28,29]. Non-union of the right and left hepatic ducts, dilated intrahepatic biliary radicles and/or the presence of a mass at the hilum suggest a malignant aetiology. Variable sensitivities for detection of a mass have been reported based on the morphology of the stricture [28,29].

In our study CT had a sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of 79.2%, 79.4%, 73.1%, 84.4% and 79.3%, respectively, for predicting the nature of the stricture. Rosch et al. [12] found a sensitivity and a specificity of 77% and 63%, respectively, for CT to differentiate between benign and malignant strictures. The presence of a mass (62.5%) and lymph node enlargement > 1 cm (45.4%) were significant (p <0.001 and 0.009, respectively) findings in determining the malignant nature of the stricture. Han et al. [30] found a mass with hyper-enhancement in 17 of 21 patients with hilar cholangiocarcinoma. Choi et al. [31], in a retrospective analysis, found a wall thickening > 1.5 mm suggestive of a mass, rim-like contrast enhancement in either the arterial or portal phase (60%), long stricture (1.8 cm vs 0.7 cm), higher proximal dilatation (2.2 cm vs 1.8 cm) and lymph node enlargement > 1 cm as significant findings on multiphasic spiral CT to diagnose a malignant stricture.

We found that MRCP could demonstrate the level of obstruction correctly in all cases. MRCP with MRI had a sensitivity of 87.5%, specificity of 85.3%, positive predictive value of 80.8%, negative predictive value of 90.6% and diagnostic accuracy of 82.7% in predicting the nature of the stricture. MRCP/MRI can determine the level of obstruction in 85-100% of cases [32], while the sensitivity of differentiation of benign from malignant strictures varied widely from 30% to 98% in the literature [13,33,34]. Park et al. [35] found a sensitivity, specificity and accuracy of 81%, 70% and 76%, respectively, for MRCP/MRI to differentiate between benign and malignant stricture.

The criteria for differentiation were based on the findings observed during direct cholangiography and included an irregular margin, asymmetric dilatation of the biliary radicles, abrupt or gradual tapering of stricture, presence or absence of a mass and length of the stricture. Malignant strictures are usually long as they have an infiltrative growth pattern, which spreads intramurally beneath the epithelial lining. They are irregular with an asymmetric dilatation because of the nature of involvement of the bile duct by the tumour. We found that presence of a mass, stricture with long length (3 cm vs 1.2 cm) and an irregular margin and asymmetric dilatation of the bile ducts helped in making a diagnosis of a malignant stricture. Park et al. [35] found stricture length (3 cm vs 1.3 cm) with irregular margin and asymmetric narrowing of bile ducts to suggest a malignant aetiology. Bain et al. [22] found long stricture (3 cm vs 0.8 cm) and presence of intrahepatic duct dilatation (93% vs 36%) to suggest a malignant aetiology. The sensitivity of MRCP decreases in patients with a history of previous biliary intervention and cholangitis, as there is inflammatory thickening of the bile ducts and surrounding tissue, which can mimic a mass or produce bile duct wall enhancement on imaging.

Most of the previous studies done to evaluate the role of MRCP in differentiation of hilar strictures have used ERCP as the reference method [12,35,36]. We have compared the imaging modalities with surgical findings and biopsy in all operable cases and histopathological diagnosis by tissue sampling under ultrasound guidance or during ERCP/PTC in inoperable cases. Another drawback of these previous studies was that both lower and upper end strictures were evaluated together and a majority of the evaluated patients had lower end strictures [12,35,36]. We have analysed only hilar blocks, which makes our cohort homogenous.

Kim et al. [13], using conventional T1- and T2-weighted images and gadolinium-enhanced dynamic MR images, found that non-enhanced T1 and less heavily T2-weighted images with MRCP significantly improved the diagnostic accuracy, while gadolinium-enhanced images did not further improve the accuracy. We also looked at T1 and T2 images while interpreting the results of MRCP primarily to detect the presence of a mass.

Domagk et al. [36] showed that intraductal US can help in distinguishing malignant from benign strictures by demonstrating a heterogeneous and irregular bile duct thickening and invasion of the portal vein or hepatic artery on imaging. Klatskin tumours are small, fibrotic and hypocellular, resulting in false negative results and at times lesions may not be accessible at all. Preoperative brush cytology/biopsy, digital imaging analysis and fluorescent in situ

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hybridization has sensitivity between 30% and 60% [37,38]. The role of frozen section analysis is also limited, as well-differentiated cholangiocarcinoma are difficult to differentiate from benign lesions with the small amount of tissue obtained during surgery. Moreover it has a definite potential for implantation metastasis.

We conclude that although it is difficult to differentiate a benign biliary stricture from a malignant one preoperatively, it is possible to identify them with the help of laboratory parameters and imaging with reasonable accuracy. Malignant strictures are more common in patients with age more than 50 years and those with a history of anorexia and weight loss. Patients with bilirubin level > 8.4 mg/dl and CA 19-9 > 100 U/ml are more likely to have a malignant aetiology. MRI with MRCP has higher sensitivity and specificity rates than CECT. It is better than CT as it can provide a detailed map of the biliary tree above the stricture, which is helpful in formulating both surgical and interventional management in these patients. Overall, MRI with MRCP was the best modality for predicting the nature of hilar biliary stricture.

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