Surgical strategies in the management of hilar cholangiocarcinoma

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CHAPTER 3

Evaluation of clinical and radiological findings in patients with benign biliary obstruction at the hepatic hilum, resected for presumed proximal bile duct carcinoma

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Abstract

Background: Among 132 consecutive patients with a resected tumor mass at the hepatic hilum, 20 patients (15%) had a histopathologically proven benign tumor. The aim of this study was to re-evaluate all clinical and radiographical characteristics in these patients, in order to define (non)suspicious features of a hilar stricture, which could result in future reduction of false-positive diagnosis of cholangiocarcinoma.

Patients and Methods: A panel of specialists, all experienced in hepato-pancreatobiliary disorders, blindly re-assessed all medical files and radiological examinations of these patients. Suspicion was graded on a 0/+/++ scale: no suspicion = 0, suspicious = +, highly suspicious = ++.

Results: The combination of symptoms was considered not suspicious in 3/19 (16%) patients. At US, only 1/16 (6%) patients had no suspicious features. In 4/18 (22%) patients the cholangiography images were considered not suspicious. However, the overall index of suspicion was + in 10 patients and ++ in the other 10 patients.

Conclusions: Careful review of all preoperative information confirmed the initial diagnosis. Only the grade of suspicion differed but would have had no influence on the choice of treatment. Therefore, due to limitations of current diagnostic tools, a false-positive preoperative diagnosis of malignancy cannot be excluded, resulting in a 15% resection rate of benign lesions in this series of suspicious hilar strictures.
Introduction

Cameron previously stated that cholangiographic demonstration of a stricture at or near the hepatic duct confluence, with proximal dilatation and with a normal or collapsed distal biliary duct, is virtually pathognomonic for the diagnosis of a proximal cholangiocarcinoma. He also stated that, even if the pathologist has difficulty to confirm the diagnosis after resection, the subsequent clinical course will prove the cholangiographic diagnosis being correct in the vast majority of these patients. And, although segmental sclerosing cholangitis may be confused with the diagnosis of proximal bile duct carcinoma, localized sclerosing cholangitis at the hilar region is distinctly unusual. However, because of the incidence of benign lesions at the hepatic hilum, previous reports have warned for just inappropriate surgical treatment of suspicious lesions in this area, without histological diagnosis. In an earlier study during the period 1984 till 1990, we reported a 13% false-positive preoperative diagnosis of malignancy in patients resected for a suspicious hilar obstruction. Therefore, as long as a malignant lesion has not been proven by histological examination, unnecessary extended operations to achieve a radical resection are preferably avoided.

The aim of this study was firstly, to determine if preoperative diagnosis and staging of hilar bile duct tumors after 1990, resulted in a reduction of false-positive diagnoses of malignancy. Secondly, if it would be possible to define suspicious features of a hilar stricture, during re-evaluation of all clinical and radiographical characteristics in these patients. Thirdly, to analyze the complications and follow-up in this particular group of patients that had undergone resection of a benign proximal bile duct lesion, presumed to be malignant.
Patients and Methods

Between 1983 and 1998, 132 consecutive patients underwent resection of a hilar stricture that was suspicious of a proximal bile duct carcinoma. In 20 patients (15%), final histopathological assessment of the specimen showed a benign lesion, diagnosed as chronic fibrosing or erosive inflammation, sclerosing cholangitis, or a granular cell tumor. These patients (7 women and 13 men) had a median age of 50 years (range: 24-72 years).

The medical files and radiological examinations of these 20 patients were re-assessed. In one patient who emigrated postoperatively, the peri-operative clinical findings as well as follow-up data could not be retrieved. The clinical history was re-evaluated paying special attention to the presentation and duration of the following symptoms: jaundice, abdominal pain and weight loss. Furthermore, histories of gallstone disease, inflammatory bowel disease and former abdominal operations were also evaluated in this study.

Preoperative diagnostic work-up consisted of abdominal US with (color) Doppler flow assessment of the portal venous system and hepatic artery in 16 patients, all performed by a single radiologist. Conventional CT was considered as a less useful modality in the evaluation of proximal bile duct tumors and therefore, was not routinely used in our institution. However, in 9 patients a CT scan was performed in the referring center. In 16 patients, ERCP was performed. In one patient, cholangiography was performed via the T-tube, which was left after a CBD exploration (patient no.14, see further) and two patients (no.5 and no.7) underwent a PTC procedure. One of the ERCP procedures, which was performed elsewhere, was not re-evaluable (patient no.3). Biliary drainage was established during all ERCP procedures by positioning of one or more endoprostheses into the right and/ or left biliary system. Brush cytology studies were done in 14 patients.

Visceral angiography, more frequently used in the past, was performed in 4 patients. Since 1992, laparoscopy in combination with intra-abdominal US was used in 6 patients. Results of endoscopic-US (EUS), in the past performed in a minority of the patients and MRCP (magnetic resonance cholangio-pancreaticography), which was used only occasionally since 1997, were not included in this analysis.
A panel consisting of two surgeons, two radiologists, and one gastroenterologist, all experienced in hepatopancreatobiliary disorders, blindly re-evaluated the clinical history and re-examined the radiological examinations of each patient. In order to prevent a bias because of the knowledge of dealing with only benign lesions, six patients with histopathologically proven malignant lesions were arbitrarily mixed with the above mentioned patients. Suspicion on malignancy regarding clinical presentation as well as radiological investigations was graded on a 0/+/++ scale: no suspicion = 0, suspicious = +, highly suspicious = ++.

Concerning clinical presentation, the following combination of signs and symptoms was considered suspicious: jaundice, pruritus and/or discoloration of stools with symptoms of weight loss and abdominal pain. The combination of painless jaundice and weight loss was thought to be highly suspicious of a malignancy.

When US showed a tumor mass with extraductal extension at the hepatic confluence, the lesion was considered highly suspicious of a malignancy. Although infrequent, a tumor mass at CT with proximal bile duct dilatation was considered highly suspicious. A stenosis and/or proximal (intrahepatic) bile duct dilatation without a tumor mass, was considered suspicious at US and/or CT.

During re-evaluation of cholangiography, an irregular and eccentric pattern and/or blunt ending was considered to be typical of a malignant lesion (++). In contrast, a smooth and concentric pattern and/or tapering of the duct was thought to be a feature of a benign lesion (0). In case of a combination of malignant and benign features, the benign signs were overruled and the lesion was considered suspicious (+).

At color-Doppler US, increase of flow compatible with stenosis or absence of flow compatible with occlusion, as well as vascular stenosis or occlusion during visceral angiography, was considered highly suspicious of malignancy.

On the basis of re-assessment of all clinical and radiographic data, an overall index of suspicion on malignancy was determined for each patient by weighing the scores of all investigations of the patient. However, the final suspicion score was not derived from the exact mean or sum of scores of the individual tests but was primarily based on the
investigations giving the highest suspicion. The final suspicion score in most cases was dictated by the outcome of cholangiography.

Furthermore, in this series of patients, also the type of resection, intra-operative suspicion on malignancy and definitive histological examination, were analyzed. Early and late postoperative complications during follow-up were also studied.
Results

Clinical presentation
Jaundice was the most frequently recorded symptom at first presentation and was present in 16 patients (84%). Eleven patients (58%) suffered from upper abdominal pain. Pain, usually prominent in the right upper abdomen or epigastric region, was mostly vague and not persistent. In all 13 patients with retrievable data concerning weight, only one had no weight loss. In all other patients weight loss varied between 3 and 15 kilograms, with a mean of 7 kilograms. The duration of symptoms until presentation at our department varied between one week and one year, with a mean period of 21 weeks. For patients whose symptoms started with non-persistent mild abdominal pain (in two patients it existed for years), we considered the moment of development of jaundice as starting-point of symptoms.

Four patients had undergone a cholecystectomy. In 3 patients (no.2, 4 and 18) cholecystectomy was performed one year before presentation of symptoms and they now had recurrent episodes of jaundice. In one patient (no.14) cholecystectomy had been performed in another hospital, 3 months earlier. During this operation the CBD was explored for a suspected bile duct stone, which could not be identified. Instead, a hilar stenosis suspicious of a malignancy was found in which case a T-tube was left. With this T-tube still in situ, this patient was referred to our hospital for further management.

Except for one patient (no.3) who had a prior history of alcohol abuse, and also had suffered from hepatitis-A 21 years earlier, no other relevant history was recorded. None of the patients was known with inflammatory bowel disease. Except for 3 patients (16%) who had no jaundice as first symptom, the combination of symptoms was considered suspicious of malignant disease in all remaining 16 evaluable patients (84%) (+ in 10 patients and ++ in 6 patients) (table 1).
### TABLE 1. PREOPERATIVE FINDINGS IN 20 PATIENTS WITH A HILAR BILE DUCT TUMOR, PREOPERATIVELY DIAGNOSED AS CHOLANGIOCARCINOMA

<table>
<thead>
<tr>
<th>Patient (Gender, Age)</th>
<th>Clinical presentation</th>
<th>US</th>
<th>CT</th>
<th>ERCP/PTC</th>
<th>Doppler (D)/Angio (A)</th>
<th>Brush cytology</th>
<th>Laparoscopy</th>
<th>Type</th>
<th>Overall suspicion score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (M,45)</td>
<td>NA</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>2 (M,42)</td>
<td>++</td>
<td>ND</td>
<td>0</td>
<td>0</td>
<td>0 (A)</td>
<td>Atypical</td>
<td>ND</td>
<td>IIIA</td>
<td>+</td>
</tr>
<tr>
<td>3 (M,56)</td>
<td>+</td>
<td>ND</td>
<td>0</td>
<td>NA</td>
<td>0 (A)</td>
<td>Atypical</td>
<td>ND</td>
<td>IIIA</td>
<td>+</td>
</tr>
<tr>
<td>4 (M,55)</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND</td>
<td>Benign</td>
<td>ND</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>5 (M,59)</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++ (PTC)</td>
<td>0 (D/A)</td>
<td>ND</td>
<td>ND</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>6 (M,67)</td>
<td>+</td>
<td>++</td>
<td>ND</td>
<td>+</td>
<td>++ (D/A)</td>
<td>Benign</td>
<td>ND</td>
<td>II</td>
<td>++</td>
</tr>
<tr>
<td>7 (F,41)</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td>0 (PTC)</td>
<td>0 (D)</td>
<td>Atypical</td>
<td>ND</td>
<td>IIIA</td>
<td>+</td>
</tr>
<tr>
<td>8 (F,48)</td>
<td>+</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>0 (D)</td>
<td>Benign</td>
<td>ND</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>9 (F,51)</td>
<td>++</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++ (D)</td>
<td>ND</td>
<td>ND</td>
<td>II</td>
<td>++</td>
</tr>
<tr>
<td>10 (F,72)</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++ (D)</td>
<td>Atypical</td>
<td>ND</td>
<td>I</td>
<td>+</td>
</tr>
<tr>
<td>11 (F,23)</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++ (D)</td>
<td>ND</td>
<td>ND</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>12 (F,43)</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>0 (D)</td>
<td>Benign</td>
<td>ND</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>13 (M,62)</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++ (D)</td>
<td>Benign</td>
<td>ND</td>
<td>I</td>
<td>+</td>
</tr>
<tr>
<td>14 (M,62)</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>0 (D)</td>
<td>ND</td>
<td>ND</td>
<td>I</td>
<td>+</td>
</tr>
<tr>
<td>15 (M,36)</td>
<td>0</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++ (D)</td>
<td>ND</td>
<td>++</td>
<td>IIIB</td>
<td>++</td>
</tr>
<tr>
<td>16 (M,38)</td>
<td>++</td>
<td>+</td>
<td>ND</td>
<td>+</td>
<td>0 (D)</td>
<td>Benign</td>
<td>++</td>
<td>II</td>
<td>+</td>
</tr>
<tr>
<td>17 (F,35)</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>0 (D)</td>
<td>Malignant</td>
<td>0</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>18 (F,53)</td>
<td>++</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>0 (D)</td>
<td>Benign</td>
<td>+</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>19 (M,57)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>0 (D)</td>
<td>Benign</td>
<td>++</td>
<td>IIIA</td>
<td>++</td>
</tr>
<tr>
<td>20 (M,38)</td>
<td>+</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>0 (D)</td>
<td>Benign</td>
<td>++</td>
<td>II</td>
<td>++</td>
</tr>
</tbody>
</table>

M: male, F: Female

0: not suspicious; +: suspicious; ++: highly suspicious;

NA: not available; ND: not done

\(^1\)Cholelithiasis carcinoma with invasion into the hepatic duct
In 10 patients (63%), a tumor mass with extraductal extension at the hepatic hilum was shown during US, scored as highly suspicious (fig.1). In 2 patients (no. 5 and 11)(22%), CT scan showed a tumor mass. In only one patient (no.11), this mass was also seen on US. In contrast, a tumor mass was demonstrated on US in three more patients (no. 10, 12 and 13), while on CT scan this could not be confirmed. In 5 patients (no.5, 14, 16, 17 and 19) a stenosis and/ or proximal (intrahepatic) bile duct dilatation was seen during US. Mean tumor diameter at US was 26 millimeters with a range between 15 and 40 millimeters.

**FIGURE 1. ULTRASONOGRAPHY: A TUMOR MASS WITH EXTRADUCTAL EXTENSION AT THE HEPATIC DUCT CONFLUENCE (ARROWS).**

Histopathological examination after resection showed a benign lesion. L: Liver, BD: right intrahepatic bile ducts, PV: portal vein, IVC: inferior caval vein.
ERCP / PTC

Of 16 performed ERCP procedures, 3 were considered as not suspicious (fig.2), 5 as suspicious and 8 as highly suspicious (fig.3). One of the patients (no.5) who had undergone a PTC procedure, had highly suspicious images. In total, 14 of all cholangiographies (78%) were considered as (highly) suspicious. All tumors were classified according to the Bismuth-Corlette classification (table 1).13

At brush cytological examinations, no malignant cells were found in 9 patients. In 4 patients, atypical cells were found and in one patient (no.17), brush cytology revealed cells highly suspicious for cholangiocarcinoma (table 1).

FIGURE 2. ERCP: A LONG EXTRA-HEPATIC SMOOTH STENOSIS WITH TAPERING (ARROW), COMPATIBLE WITH A BENIGN LESION.

However, clinical presentation and ultrasound images were suggestive of malignancy tipping the scales toward resection. Histopathological examination after resection showed a benign, fibroizing lesion.
FIGURE 3. ERCP: AN IRREGULAR STENOSIS WITH BLUNT ENDING AT THE SITE OF THE BIFURCATION WITH PROXIMAL DILATATION, SUGGESTIVE OF A MALIGNANT LESION (ARROW).
Histopathological examination after resection showed a benign lesion (granular cell tumor).

Doppler flow assessment / Angiography
During (color-) Doppler assessment of the portal venous system and hepatic arterial system, increase of flow was found in 3 patients (no.9, 11 and 13) and absence of flow in 3 patients (no.6, 10 and 15). Angiography showed possible tumor involvement into the right hepatic artery in one patient (no.6). All 6 cases were found to be highly suspicious of a malignancy (table 1).
Diagnostic laparoscopy with intra-abdominal US (IAUS)

Diagnostic laparoscopy with intra-abdominal US was used in the last 6 patients (table 1). In 4 patients (67%), a tumor mass was found at the hepatic hilum. In one patient (no. 18), during IAUS, there was suspicion on a gallbladder carcinoma with extension into the cystic duct. None of the diagnostic laparoscopies revealed vascular involvement of the tumor.

Overall index of suspicion

Taking together the re-assessments of clinical presentation; ERCP/PTC; US (with Doppler flow assessment); angiography; diagnostic laparoscopy with IAUS and brush cytology, we determined an overall index of suspicion on malignancy for each patient, as shown in table 1. Ten cases were classified as suspicious and ten cases as highly suspicious according to the consensus of opinion of the reviewing panel.

Intraoperative findings and postoperative histologic examination

At laparotomy, an obviously suspicious tumor was found in 11 patients (55%) (table 2). In all other cases, there were doubts as to the nature of the fibrosing lesion, being malignant or benign. In two patients (no.6 and no.14) even bile duct stones were found and in one patient (no.17) a Mirizzi syndrome was diagnosed at laparotomy. In this series, all patients underwent local resection of the hepatic duct confluence to establish at least adequate biliary drainage, even when a lesion was thought to be benign during laparotomy. In 3 patients with a suspicious tumor, local resection was combined with an extended hemi-hepatectomy.

No biopsy specimens for frozen section examination were taken before resection had been accomplished, to avoid spilling of tumor cells in the operative field. During resection, frozen-section examinations of the surgical margins were performed to ensure a radical resection. In only one patient (no.18), frozen-section of the proximal surgical margin revealed adenocarcinoma and because of impossibility to resect more proximal into the liver, a presumed palliative local resection was performed. However, the diagnosis of malignancy was rejected after definitive pathological examination, revealing only fibrosis.
In all 3 patients after liver resection, definitive histopathological examination of the liver specimen showed signs of sclerosing cholangitis with concentric periductal fibrosis and focal formation of granulomatous tissue. In 2 patients, histopathology was compatible with a granular cell tumor, with cells displaying granular cytoplasm. In all patients, the specimen showed fibrosis with nonspecific mild to moderate chronic inflammation, consisting of mixed cells (lymphocytes, granulocytes and plasma cells), sometimes with signs of erosion.
### TABLE 2. PERI-OPERATIVE FINDINGS AND COMPLICATIONS IN PATIENTS (N=20) WITH BENIGN HILAR BILE DUCT TUMORS

<table>
<thead>
<tr>
<th>Patient (Gender Age)</th>
<th>Overall suspicion score</th>
<th>Type of Resection</th>
<th>Intra-operative conclusion</th>
<th>Histologic Examination</th>
<th>Pre-operative Radiotherapy</th>
<th>Complications Early</th>
<th>Late</th>
<th>Alive</th>
<th>Foll. up period (months)</th>
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<tbody>
<tr>
<td>1 (M, 45)</td>
<td>+</td>
<td>Local</td>
<td>Malignant</td>
<td>Fibrosis</td>
<td>No</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>2 (M, 42)</td>
<td>+</td>
<td>Local</td>
<td>Malignant</td>
<td>Fibrosis</td>
<td>No</td>
<td>++/R</td>
<td>++</td>
<td>t</td>
<td>148</td>
</tr>
<tr>
<td>3 (M, 56)</td>
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<td>Local</td>
<td>Malignant</td>
<td>Scler. Chol(^1)</td>
<td>No</td>
<td>++/R(^t)</td>
<td>&lt;&lt;</td>
<td>&lt;&lt;</td>
<td>&lt;&lt;</td>
</tr>
<tr>
<td>4 (M, 55)</td>
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<td>Benign</td>
<td>Fibrosis</td>
<td>No</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5 (M, 59)</td>
<td>++</td>
<td>Local</td>
<td>Malignant</td>
<td>Scler. Chol(^1)</td>
<td>No</td>
<td>++/R</td>
<td>++</td>
<td>t(^t)</td>
<td>2</td>
</tr>
<tr>
<td>6 (F, 67)</td>
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<td>Benign</td>
<td>Fibrosis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>102</td>
</tr>
<tr>
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<td>Fibrosis</td>
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<td>++</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>8 (F, 48)</td>
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<td>Local</td>
<td>Benign</td>
<td>Fibrosis</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>Local</td>
<td>Benign</td>
<td>Fibrosis</td>
<td>No</td>
<td>+/R(^t)</td>
<td>+</td>
<td>+</td>
<td>60</td>
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<tr>
<td>10 (F, 72)</td>
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<td>Local</td>
<td>Benign</td>
<td>Fibrosis</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>88</td>
</tr>
<tr>
<td>11 (M, 23)</td>
<td>+</td>
<td>Local</td>
<td>Malignant</td>
<td>Fibrosis</td>
<td>Yes</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>46</td>
</tr>
<tr>
<td>12 (F, 43)</td>
<td>+</td>
<td>Local</td>
<td>Malignant</td>
<td>GCT(^2)</td>
<td>Yes</td>
<td>++/R(^t)</td>
<td>-</td>
<td>+</td>
<td>70</td>
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<td>Benign</td>
<td>Fibrosis</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>70</td>
</tr>
<tr>
<td>14 (M, 62)</td>
<td>+</td>
<td>Local</td>
<td>Benign</td>
<td>Fibrosis</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64</td>
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<td>Malignant</td>
<td>Scler. Chol(^1)</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>36</td>
</tr>
<tr>
<td>16 (M, 38)</td>
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<td>Malignant</td>
<td>Fibrosis</td>
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<td>++</td>
<td>++</td>
<td>+</td>
<td>31</td>
</tr>
<tr>
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<td>Fibrosis</td>
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<td>++</td>
<td>-</td>
<td>+</td>
<td>30</td>
</tr>
<tr>
<td>18 (F, 53)</td>
<td>++</td>
<td>Local</td>
<td>Malignant</td>
<td>Fibrosis</td>
<td>Yes</td>
<td>++/R(^t)</td>
<td>++</td>
<td>+</td>
<td>29</td>
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<tr>
<td>19 (M, 57)</td>
<td>++</td>
<td>Local</td>
<td>Benign</td>
<td>Fibrosis</td>
<td>Yes</td>
<td>++/R(^t)</td>
<td>++</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>20 (M, 38)</td>
<td>++</td>
<td>Local</td>
<td>Malignant</td>
<td>GCT(^2)</td>
<td>Yes</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>5</td>
</tr>
</tbody>
</table>

M: male, F: Female
0: not suspicious; +: suspicious; ++: highly suspicious; NE: not evaluable

Early complications: -; no; +: minor; ++: major; R: re-operation; t; death
Late complications: -; no; +: without re-admission; ++: with re-admission; R: re-operation

\(^1\) Extended right Hemi-hepatectomy; \(^2\) Extended left Hemi-hepatectomy;
Sclerosing Cholangitis; \(^3\) Granular cell tumor; \(^4\) Died during follow-up (see text);
This patient is waiting for a liver transplantation for primary sclerosing cholangitis;
Frozen section proximal resection margin (R. hepatic duct); adenocarcinoma
Postoperative complications

Postoperative complications were found in 13/19 patients (68%) (table 2). Fever, wound infection, and pneumonia, recorded as minor complications, occurred in 2 patients (10%) (table 2). Gastro-intestinal bleeding; leakage of anastomoses; intra-abdominal or liver abscesses or severe liver failure, recorded as major complications, occurred in 11 patients (58%). In 6 patients (32%), re-laparotomy was performed for lavage and drainage of abscesses, treatment of intra-abdominal bleeding or anastomotic leakage. One patient (no.3) died postoperatively due to sepsis and multi organ failure after a second re-laparotomy for a colon perforation. (Hospital mortality: 5%).

During follow-up (mean period: 56 months, range: 2-148 months), 10 patients (56%) had recurrent episodes of cholangitis and 2 patients had jaundice without fever (11%), which both were recorded as late complications (table 2). Three patients were treated with oral antibiotics and 9 patients (50%) required re-admission for intra-venous antibiotic treatment and/or PTBD, in one patient combined with repeated efforts of pneumodilatation of the hepatico-jejunostomy. In two patients, a re-laparotomy was needed for bending of the Roux-en-Y loop with obstruction (patient no.4) and for revision of the hepatico-jejunostomy (patient no.9), respectively (table 2).

Three patients died during the follow-up period. One patient (no.2) died of postoperative complications after a liver transplantation for secondary biliary cirrhosis, 12 years postoperatively. The second patient (no.5) died two months postoperatively, due to respiratory insufficiency, exacerbation of Kahler disease and cardiac failure, for which he was re-admitted. The third patient (no.9) died of a second primary tumor (a hepatocellular carcinoma) with lung metastases, 4 years postoperatively.
Discussion

Reports about benign lesions at the hepatic hilum are scarce. Wetter et al. found among 98 consecutive patients, all diagnosed as having a cholangiocarcinoma, 8 patients with a benign lesion (8%). He reported many other causes of focal hilar obstruction such as other malignant tumors (gallbladder carcinoma or metastatic lesions); lymphoid tumors; apudoma; carcinoid; granular cell myoblastoma; an extrahepatic localized form of sclerosing cholangitis or an inflammatory stricture secondary to choledocholithiasis.

Due to the relative inexperience with these benign lesions and the inability to demonstrate these lesions with the current preoperative diagnostic tools, the chance for (under-) or over-treatment of these patients is considerable. In the present study, a false-positive preoperative diagnosis of malignancy was found in 15% of patients. This percentage is comparable with our previous results. When focussing only on the period after the previous study (1991-1997), a period in which IAUS was used routinely, 9 patients with a benign lesion were found among 50 patients (18%), showing that the incidence of diagnostic errors did not decrease. Consequently, despite the fact that 2 patients had a granular cell tumor for which also a resection was needed, 7 patients (14%) underwent, besides for establishing at least adequate biliary drainage, an unnecessary resection.

The issue is that, in the absence of previous biliary surgery or stones, any tumor mass obstructing the hepatic confluence should be considered malignant. Application of improved diagnostic methods, such as intra-abdominal ultrasonography (IAUS) and also thin-section multiphasic spiral CT scan and MRCP, possibly are more efficient in the preoperative diagnosis of a benign lesion, but the value of these tools awaits further assessment. Preoperative histologic or cytologic examination by means of biopsies or brush is often difficult, is liable to false-negative results and carries a potential risk of implantation metastases. Therefore, in order to improve diagnostic accuracy, we examined the possibility of using an objective suspicion index.

Painless jaundice with weight loss was thought to be highly suspicious of a malignancy and was seen in six patients (32%). Otherwise, re-evaluation of the clinical
presentation did not really contribute to the suspicion index.

At ultrasonography (US), cholangiocarcinomas are usually isoechogenic and small. The differential diagnosis of these tumors differs according to the US appearance. For nodular mural thickening, inflammation should be considered and infiltrative lesions can mimic sclerosing cholangitis. In this series, a tumor mass at the hepatic hilum with extraductal extension was considered highly suspicious, whereas proximal (intrahepatic) bile duct dilatation alone or a stenosis at the hepatic hilum was considered suspicious. However, using these criteria during re-evaluation of US, only one patient could be excluded of having a possible malignancy.

As discussed in another study, in which CT was more sensitive (44%) than US (31%) in detecting a hilar mass, the additional value of CT over US can be questioned. In the present study, CT scan had no additional value, probably due to the fact that all ultrasound investigations were done by one single radiologist who was very experienced in US of the hepatobiliary tract. In contrast, most CT scans were performed before referral by different radiologists and spiral CT scan was not applicable at that time.

During re-assessment, cholangiography (ERCP or PTC) showed 4 patients (22%) with lesions at the hepatic hilum, not particularly suspicious for a proximal cholangiocarcinoma. In two patients, a smooth stricture, probably due to compression from outside the common hepatic duct, was seen. In two other patients, with type IIIb strictures, the cholangiographic appearance was found not suspicious, because the obstruction which was situated more proximal into the left intrahepatic biliary radicals was more suggestive of sclerosing cholangitis. It is remarkable that during re-evaluation of cholangiography, none of the type I strictures were deemed suspicious, whereas all 6 tumors classified as type IIa tumors were considered highly suspicious.

Doppler flow assessment and angiography were used when a resection for (highly) suspicious tumors was considered. Six patients were found to have signs of vascular involvement, however during laparotomy no evidence of vascular involvement was found, showing that preoperative signs of vascular involvement can also be falsely present in benign lesions. This has been reported before for benign intrahepatic bile duct strictures.
The routine use of IAUS, in addition to conventional US, has the advantage of providing more specific images of the biliary tract and surrounding tissues. However, in this study, the value of IAUS was limited and had additive value in only one patient. While all other examinations showed a (highly) suspicious lesion, IAUS revealed a Mirizzi syndrome, which was confirmed during laparotomy. Nevertheless, because brush cytology in this patient showed cells suspicious of malignancy, resection followed.

As has been stated by others, due to the mainly extraluminal growth pattern, brushing of hilar bile duct tumors is a relatively ineffective diagnostic procedure. However, of all 14 brush cytology studies in this series, 4 patients had atypical cells and in one patient (7%), for cholangiocarcinoma suspicious cells were even found. Therefore, brush cytology was not very helpful in ruling out a malignant lesion.

As discussed in a previous study of pancreatic head cancer and benign inflammatory pancreatic disease, it proved to be difficult to achieve a final suspicion score based on calculation of the separate scores of each investigation. Even careful review of all preoperative information and radiographic images confirmed the initial diagnosis. Therefore, the decision to undertake resection was not an error in judgement, but reflects a consistent policy in the management of proximal bile duct lesions. Reassessment, resulted in only a difference in the gradation of suspicion in several cases, which otherwise would not have resulted in a different choice of treatment.

There was no correlation between the overall suspicion score and the intra-operative findings. Even during laparotomy, in the majority of cases (55%), the tumor was considered to be malignant. Obviously, resection of the lesion is still the most reliable way to rule out malignancy.

In this study, resection of these presumed malignant lesions by local resection, if necessary combined with a liver resection, was associated with substantial hospital morbidity (68%) and even mortality (5%). The morbidity rate is comparable with that of patients resected for histopathologically proven cholangiocarcinoma. However, the hospital mortality rate is lower. Furthermore, during follow-up, only 6 patients were completely symptom free, with a maximum period of 81 months. Three patients with
recurrent episodes of cholangitis were treated with oral antibiotics. All remaining patients had to be re-admitted at one time or another, clearly influencing their quality of life.

In conclusion, due to limitations of current diagnostic tools and based on the intention of not wanting to miss a potentially curable cancer, resection of a benign lesion mimicking a malignant stricture at the proximal bile duct, cannot be avoided. In at least 15% of patients in this series, an inflammatory lesion or other benign tumor masquerading as cholangiocarcinoma, was diagnosed by histopathologic analysis of the surgical specimen. Furthermore, the price of these resections regarding postoperative and late complications is high and therefore, at least (extended) liver resections have to be reserved for only highly suspicious cases and should be performed in specialized centers. Nowadays, in uncertain cases, we prefer to wait for frozen section analysis of the resection margins of the local resection specimen, before continuing with an extended liver resection.
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