Detection of benign hilar bile duct stenoses — A retrospective analysis in 250 patients with suspicion of Klatskin tumour

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ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form
1 May 2016
Accepted 3 May 2016

Keywords:
Klatskin tumour Mimicking lesions Benign hilar stenosis Diagnostic Surgical procedure

ABSTRACT

Introduction: The aim of this study was to identify clinical, laboratory and radiological parameters to distinguish benign from malignant strictures of the proximal bile duct.

Methods: Between 1997 and 2011, 250 patients were referred to our clinic with hilar bile duct stenoses suspicious for Klatskin tumour. Medical histories, clinical data, pre-interventional laboratory tests, imaging findings, as well as therapeutic approach and patient outcome were compared to final histological results. All data were retrieved from our prospectively maintained database and analysed retrospectively.

Results: We found benign bile duct lesions in 34 patients (13.6%). Among the entire study population, uni- and multivariate analyses of 18 clinicopathological parameters revealed that patient age, serum alkaline phosphatase, tumour marker CA19-9 and presence of tumour mass in computed tomography were independent predictors for malignant biliary stenoses (p < 0.05). Receiver operator characteristic curve showed that a CA19-9 serum level of 61.2 U/ml or more has a sensitivity, specificity and diagnostic accuracy for predicting the malignant nature of the hilar biliary stenoses of 74.6%, 80.0% and 83.5%, respectively. Surgical resection could be avoided by preoperative work-up and surgical exploration in 10 out of 34 patients with benign lesions. Rates of major liver resections performed were 66.7% in the benign lesion group and 90.7% in the Klatskin tumour group.

Conclusion: Despite improvements of preoperative diagnostics, it remains difficult to differentiate between benign and malignant hilar bile duct stenosis. Even explorative laparotomy was not able to safely exclude Klatskin tumour in all cases and therefore major liver resection was inevitable.

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mimicking lesions represents an important surgical challenge.

The crucial questions are: What are the preoperative diagnostic procedures required in order to provide information for reliable differentiation? What are the most common causes of benign ductal stenoses mimicking Klatskin tumours? In this retrospective analysis, we attempt to address these questions in patients presenting with suspected diagnosis ‘Klatskin tumour’ at our institution.

2. Patients and methods

Between January 1997 and December 2011, 250 patients with hilar biliary stenosis suspicious of Klatskin-Tumours were referred to the Department of Transplantation and Hepatobiliarypancreatic Surgery at the University Medical Centre Mainz for further diagnostic work-up and therapy. Patients suffering from intrahepatic cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma and hepatic metastasis with biliary obstruction were excluded from this study.

2.1. Diagnostic work-up

As described previously [6], patients underwent the following standardised diagnostic pathway in order to confirm the suspected diagnosis ‘Klatskin tumour’, to assess operability and to identify the required surgical intervention: (1) ERC including stent extraction from the bile duct if necessary (2) Spiral computed tomography (CT)-scan of the abdomen and lung for tumour staging and to exclude vascular invasion. (3) Percutaneous transhepatic cholangiography (PTC) combined with a subsequent implantation of a silicon drainage (PTCD, Yamakawa drainage) to maintain bile flow.

In comparison to ERC, PTC allows a better visualisation of longitudinal tumour growth, which is crucial to plan and perform a more aggressive surgical approach [7–9]. PTCD can remain in place and may subsequently be used for palliative treatment like photodynamic therapy. Endoscopically placed stents were not removed when longitudinal tumour involvement was adequately pictured by previous ERC. In cases which remained uncertain after these procedures or tumour mass was ill-defined or invisible in computed tomography a magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatographic (MRCP) was performed.

Imaging findings analysed were masses or thickening of the wall of the common bile duct and lymph nodes enlargement (CT). In this study any suspicious primary tumour mass >1 cm and lymph node enlargement >1 cm were considered.

Because of the risk of tumour cell dislocation, endoscopic brush cytologies and biopsies were not considered as standard procedures. Endosonography was applied only in single cases with suspicion of tumour infiltration of the distal bile duct and adjacent structures. Due to small numbers, these examination methods could not be considered for statistical analysis.

Laboratory check-up included tumour markers (carcinembryonic antigen CEA, carbohydrate antigen 19-9 CA19-9), total serum bilirubin level and liver enzymes (aspartate transaminase AST, alanine transaminase ALT, alkaline phosphatase AP, gamma-glutamyl transpeptidase GGT). Laboratory values mentioned were determined before interventions. Autoimmune antibodies (lgG4, ANCA, ANA inter alia) were analysed in case of suspected auto immune pancreatitis and associated cholangitis.

If preoperative diagnostic failed to prove a benign cause of hilar stenosis, explorative laparotomy was carried out.

2.2. Surgical procedures

During surgical exploration, ultrasonography was routinely used in order to exclude any undiscovered lesions and to assess tumour localization, extension and position to relevant structures. Intraoperative criteria for unresectability were the presence of peritoneal or intrahepatic dissemination and extensive vascular involvement, precluding curative surgery. En bloc tumour resection with (extended) hemihepatectomy including liver segment one represented the standard procedure. Sole hilar resection was performed in patients with considerable comorbidity contraindicating extensive resection and Bismuth Type I and II tumours [6]. Resection margins of the bile ducts, suspicious tissue and lymph nodes were investigated by frozen sections in order to assess surgical radicality and determine the surgical approach.

2.3. Follow-up

The follow-up end point was October 2014. Median follow up was 17.8 months (range 1–140 months) in the Klatskin tumour group and 52.3 months (range 1–146 months) in the Klatskin mimicking group with underlying benign lesions. After hepatectomy the patients were followed at intervals of three months in the first two years and subsequently twice a year for the first five years following intervention. The follow-up examinations included CT or MRI scan, clinical examination and routine blood tests, including serum levels of tumour markers. Postoperative mortality was considered as in-hospital mortality in all cases.

2.4. Statistical analysis

Drawn from a prospectively collected database (Microsoft Access Database 2003) demographic data, preoperative diagnostics, resection’s technique used and results of the histopathological specimens were retrospectively analysed. All statistical analyses were performed using SPSS program 21.0 for Windows (SPSS, Chicago, IL, USA). Differences between values were analysed using the unpaired, two-sided t-test for continuous variables and by the chi-square test for categorical variables. Multivariate analysis was performed with logistic regression analysis. Variables to be entered into the multiple logistic regression analysis were chosen on the basis of the results of univariate analysis. P values < 0.05 were regarded as significant. Patient survival was calculated according to Kaplan-Meier. The time of surgery or final diagnosis was defined as the starting point of all calculations.

Receiver operator characteristic (ROC) curves were generated for laboratory values and imaging findings to determine the optimal diagnostic criterion threshold in predicting a malignant biliary stenosis. A ROC curve displayed the false positive rate on the x axis (specificity), and the true positive rate on the y axis (sensitivity) for varying test thresholds, thus plotting the performance of a diagnostic test. The ideal cut-off for the laboratory results were chosen by determining the point lying geometrically closest to an ideal test with 100% specificity and sensitivity. Diagnostic accuracy was measured by the area under the ROC curve (AUC). Higher AUC values represent greater accuracy. An AUC of 1.0 represents perfect sensitivity and specificity; an AUC of 0.5 represents an essentially worthless test.
3. Results

3.1. Baseline characteristics

Patient's characteristics, history, clinical symptoms and laboratory data at time of admission, as well as findings of preoperative imaging and interventions performed are summarized in Table 1. The receiver operator characteristic (ROC) test results of parameters in predicting malignant proximal bile duct stenosis are shown in Table 2.

3.2. Diagnostic and therapeutic approaches

Fig. 1 shows the diagnostic and therapeutic procedures in all patients. At admittance, most of these patients (81.6%) had previously undergone endoscopic retrograde cholangiography (ERC) with (69.1%) or without (30.9%) receiving bile duct stents due to cholestasis and jaundice. 72.4% of patients underwent the standard preoperative approach with percutaneous transhepatic cholangiography (PTC) and percutaneous drainage implantation. 39.6% of patients (99 out of 250 patients) received a magnet resonance imaging (MRI)-scan in addition to 'standard' spiral computed tomography (CT)-scan for clarification of biliary stenosis. Overall, 110 biopsies were taken, which showed in two cases malignant cells proved to be benign after surgical resection (sensitivity 43.0%, specificity 88.2%).

3.3. Non-surgical treatment

In five patients, the detected lesions could be determined as benign based on the medical history and preoperative work-up, rendering any surgical intervention redundant. In this group of patients, no suspicious tumour mass or enlarged lymph nodes were found in CT or MRI. Anamnestic information underlined the suspected diagnoses (Fig. 1). In three patients, endoscopic biopsies were taken which did not reveal any malignancy. In one patient ERC demonstrated massive intrahepatic cholelithiasis responsible for the observed symptoms. In close-meshed follow-up checks (median follow-up: 118 months) there were no symptoms indicating malign diseases.

Table 1

Baseline characteristics of the overall study population and patients resected suspicious for Klatskin tumour. Due to the small number imaging findings of MRI could not be included in multivariate analysis. OR odds ratio; CI confidence interval; SD standard deviation; NS not significant; AST aspartate transaminase; ALT alanine transaminase; GGT gamma-glutamyl transpeptidase; AP alkaline phosphatase; CEA carcinoembryonic antigen; CA19-9 carbohydrate antigen 19-9; NI no information. The receiver operator characteristic (ROC) test results of parameters in predicting malignant proximal bile duct stenosis are shown in Table 2.

| Variables | Overall study population | Patients after surgical resection |
|-----------|--------------------------|----------------------------------|
| Demographics | | |
| Median age, years (range) | 59 (31-82) | 65 (39-85) |
| Gender | Male, female | 16, 18 | 142, 74 |
| Prior cholecystectomy | Jaundice | 18 | 173 |
| Clinical presentation | Jaundice | 12 | 82 |
| Laboratory tests | Total bilirubin mg/dl | 1.8 ± 3.5 | 6.5 ± 8.3 |
| | AST U/l | 57.5 ± 78.5 | 90 ± 96.9 |
| | ALT U/l | 78 ± 160 | 111.5 ± 152.5 |
| | GGT U/l | 356.5 ± 548 | 530 ± 585 |
| | AP U/l | 260 ± 177.7 | 435.5 ± 476.7 |
| | CEA ng/ml | 1.5 ± 0.9 | 1.8 ± 38.5 |
| | CA19-9 U/ml | 20.5 ± 52 | 141 ± 3300 |

| Imaging | Computed tomography | 30 | 206 |
| | Presence of tumour mass (NI) | 30 (3) | 129 (16) |
| | Suspect lymph node | 7 | 72 |
| | MRI/MRCP | 16 | 97 |
| | Presence of tumour mass (NI) | 6 (1) | 64 (6) |

| Variables | Univariate analysis p value | Multivariate analysis p value, OR (95%CI) |
|-----------|---------------------------|------------------------------------------|
| Demographics | | |
| Median age, years (range) | <0.001 | 0.019, 0.274 (0.93–0.807) |
| Gender | Male, female | 0.036 | NS |
| Prior cholecystectomy | Jaundice | 0.007 | NS |
| Clinical presentation | Jaundice | 0.001 | NS |
| Laboratory tests | Total bilirubin mg/dl | 0.003 | NS |
| | AST U/l | 0.343 | NS |
| | ALT U/l | 0.759 | NS |
| | GGT U/l | 0.006 | NS |
| | AP U/l | 0.001, 0.189 (0.053–0.673) | NS |
| | CEA ng/ml | 0.455 | 0.001, 0.121 (0.035–0.411) |
| | CA19-9 U/ml | 0.031 | 0.001, 0.121 (0.035–0.411) |

| Imaging | Computed tomography | | |
| | Presence of tumour mass (NI) | 10 (3) | 129 (16) |
| | Suspect lymph node | 7 | 72 |
| | MRI/MRCP | 16 | 97 |
| | Presence of tumour mass (NI) | 6 (1) | 64 (6) |

| Variables | Patients after surgical resection | Benign lesions (n = 24) | Klatskin tumours (n = 151) | Univariate analysis p value | Multivariate analysis p value, OR (95%CI) |
|-----------|---------------------------------|------------------------|--------------------------|---------------------------|------------------------------------------|
| Demographics | | 61 (32–78) | 64 (39–85) | 0.009 | NS |
| Gender | Male, female | 10, 14 | 105, 46 | 0.008 | NS |
| Prior cholecystectomy | Jaundice | 8 | 22 | 0.023 | NS |
| Clinical presentation | Jaundice | 12 | 118 | 0.003 | 0.038, 0.320 (0.108–0.941) |
| Laboratory tests | Total bilirubin mg/dl | 2.8 ± 3.9 | 5.9 ± 6.5 | 0.029 | NS |
| | AST U/l | 71 ± 73.4 | 84 ± 85.3 | 0.375 | |
| | ALT U/l | 88 ± 168.8 | 111 ± 148.9 | 0.886 | |
| | GGT U/l | 322.5 ± 627.6 | 490.5 ± 620.2 | 0.130 | |
| | AP U/l | 252.5 ± 196.3 | 434 ± 479.5 | 0.004 | 0.004, 0.108 (0.023–0.499) |
| | CEA ng/ml | 1.5 ± 1 | 1.6 ± 5.8 | 0.262 | |
| | CA19-9 U/ml | 21 ± 47.8 | 125.5 ± 2475 | 0.125 | |

| Imaging | Computed tomography | | |
| | Presence of tumour mass (NI) | 10 (1) | 88 (15) |
| | Suspect lymph node | 5 | 39 |
| | MRI/MRCP | 12 | 68 |
| | Presence of tumour mass (NI) | 4 (1) | 43 (6) | 0.056 | |
Table 2
ROC (receiver operator characteristic) test results in predicting malignant proximal bile duct stenosis. Only parameters with significance in univariate analysis are represented. For better representation and comparability ROC curves of laboratory parameters are shown additionally. n/a, not available; AUC, area under the curve; +LR positive likelihood ratio; -LR negative likelihood ratio; GGT, gamma-glutamyl transpeptidase; AP, alkaline phosphatase; CA19-9, carbohydrate antigen 19-9; CT, computed tomography; MRI, magnet resonance imaging.

| Variable                      | AUC    | Sensitivity (%) | Specificity (%) | Cut-off value | +LR  | -LR  |
|-------------------------------|--------|-----------------|-----------------|---------------|------|------|
| Age                           | 0.664  | 75.5            | 52.9            | 59 years      | 1.60 | 0.46 |
| Gender (male)                 | 0.593  | 65.7            | 52.9            | n/a           | 1.39 | 0.65 |
| Prior cholecystectomy         | 0.601  | 81.9            | 38.2            | n/a           | 1.33 | 0.47 |
| Jaundice                      | 0.636  | 80.1            | 47.1            | n/a           | 1.51 | 0.42 |
| Total bilirubin               | 0.657  | 42.5            | 86.2            | 6.0 mg/dl     | 2.43 | 0.61 |
| GGT                           | 0.741  | 57.9            | 85.7            | 685 U/l       | 3.08 | 0.67 |
| AP                            | 0.835  | 74.6            | 60.0            | 61.2 U/ml     | 3.73 | 0.32 |
| CA19-9                        | 0.658  | 68.8            | 63.0            | n/a           | 1.85 | 0.50 |
| CT Presence of tumour mass    | 0.646  | 69.6            | 60.0            | n/a           | 1.74 | 0.51 |

Fig. 1. Overview of patients with suspicion of Klatskin tumour in the period from January 1997 to December 2011. Reasons for irresectability in the Klatskin tumour group were extensive tumour infiltration of the portal vein and/or the hepatic artery (n = 10), adjacent organs (n = 4), and intrahepatic bile ducts (n = 10). Metastatic diseases included peritoneum (n = 17), distant lymph nodes (n = 5), pancreas (n = 1) and multiple/bilobular intrahepatic metastases (n = 6). Some patients showed several reasons for irresectability.
Based on the imaging, 19 patients had malignant diseases and were inoperable or unresectable because of advanced tumour mass with or without metastasis (Fig. 1). Biopsies (n = 12) were taken in order to justify adequate palliative approach including chemotherapy.

### 3.4. Exploratory laparotomy

A total of 51 patients underwent an explorative laparotomy under the suspicion of Klatskin tumour without surgical resection. Surgery was interrupted, when frozen sections of suspicious tissue revealed advanced malignity and curative resection could not be taken into consideration. In five cases preoperative imaging showed highly suspicious hilar tumour masses (n = 3) and enlarged lymph nodes (n = 2) which could not be confirmed by explorative surgery (Fig. 1). Therefore, malignant origin of the hilar stenosis appeared to be highly improbable after exploration with multiple sampling of frozen sections and we abstained from major resection. All five patients were supplied with temporary transhepatic biliary drainages (n = 4) or endoluminal stents (n = 1) and were followed-up closely. All of them were alive and in good health at the point of their last follow-up consultation (median follow-up: 32.5 months).

### 3.5. Resection

The surgical procedures performed and underlying diseases are summarized in Table 3. Resection rate was 60.4% in all patients with Klatskin tumour (n = 216) and 76.6% among those undergoing exploration (n = 197). Rates of major resections (percentage of bile duct resection including hemihepatectomy) performed were 90.7% in the Klatskin-group and 66.7% in the benign lesion group, respectively. There were no statistical differences between the two groups considering the extension of resection (P = 0.661).

### 3.6. Benign Klatskin mimicking lesions

In summary, thirteen patients (38.2%) showed unspecific chronic fibrosing (n = 5) or florid erosive (n = 8) inflammation of the bile duct in histology, without a history of intervention on the biliary system. Thus, the cause of bile duct stenosis was assumed to be idiopathic. The second main reason (35.3%) turned out to be stenosis occurring after medical intervention such as cholecystectomy (n = 9), radiotherapy (n = 1), biliodigestive anastomosis (n = 1), pancreaticoduodenotomy (n = 1) or selective chemoembolisation (n = 1) of the liver. The diagnosis of autoimmune disease was always based on histopathological findings. Only in one out of three cases autoimmune serum antibodies were found positive.

### 3.7. Perioperative complications and long-term survival

The surgical outcome did not differ among the two groups in view of morbidity and mortality (Table 4). 10 of the 13 patients with Klatskin tumours who died in the postoperative course had

| Total | Explorative laparotomy | Bile duct resection (+ liver segm) | Hemihepatectomy |
|-------|------------------------|----------------------------------|-----------------|
|       | Right (extended) | Left (extended) | Right (extended) | Left (extended) |
| Klatskin tumours | 197 | 46 | 14 | 68 (43)* | 69 (5) |
| Benign lesions | 29 | 5 | 8 (1) | 12 (3) | 4 (1) |

| Chronic fibrosing cholangitis |       |       |       |       |       |
| Idiopathic | 13 | 1 | 2 (1) | 8 (2) | 2 (1) |
| Post-interventional | 9 | 2 | 3 | 3 (1) | 1 |
| PSC | 1 | – | – | 1 | – |
| PSC + autoimmune pancreatitis | 1 | 1 | – | – | – |
| PBC | 1 | 1 | – | – | – |
| AIDS-associated cholangiopathy | 1 | – | 1 | – | – |
| Neurofibroma | 1 | 1 | – | – | 1 |
| Caroli syndrome | 1 | – | – | – | 1 |
| Bile duct adenoma | 1 | – | 1 | – | – |

| Table 3 | Surgical procedures in patients with referral diagnosis Klatskin tumour. PSC, Primary sclerosing cholangitis; PBC, primary biliary cirrhosis. *One patient with additional Whipple procedure. |
|---------|---------------------------------------------------------------------------------------------------|
| Klatskin tumours | 197 | 46 | 14 | 68 (43)* | 69 (5) |
| Benign lesions | 29 | 5 | 8 (1) | 12 (3) | 4 (1) |

| Chronic fibrosing cholangitis |       |       |       |       |       |
| Idiopathic | 13 | 1 | 2 (1) | 8 (2) | 2 (1) |
| Post-interventional | 9 | 2 | 3 | 3 (1) | 1 |
| PSC | 1 | – | – | 1 | – |
| PSC + autoimmune pancreatitis | 1 | 1 | – | – | – |
| PBC | 1 | 1 | – | – | – |
| AIDS-associated cholangiopathy | 1 | – | 1 | – | – |
| Neurofibroma | 1 | 1 | – | – | 1 |
| Caroli syndrome | 1 | – | – | – | 1 |
| Bile duct adenoma | 1 | – | 1 | – | – |

| Table 4 | Postoperative complications and outcome after resection. ICU, intensive care unit. |
|---------|----------------------------------------------------------------------------------|
| Benign lesions (n = 24) | Klatskin tumours (n = 151) |
| Median ICU stay days (range) | 1 (0–29) | 1 (0–118) |
| Morbidity |       |       |
| Abscess | 4 | 16 |
| Bleeding | 1 | 7 |
| Biliary fistula/bilom | 3 | 14 |
| Pleural effusion | 4 | 18 |
| Ascites | 2 | 19 |
| Arterial thrombosis | – | 1 |
| Occlusion of the portal vein | 1 | 1 |
| Pancreatic fistula | – | 2 |
| Reoperation | 3 | 18 |
| In-hospital mortality |       |       |
| Total | 2 (8.3%) | 13 (8.6%) |
| Liver failure | 1 | 6 |
| Septic shock | 1 | 3 |
| Multi organ failure | – | 4 |
| Survival rates |       |       |
| 1-, 3-, and 5-year (%) | 87, 87, 81 | 71, 39, 22 |
undergone right or extended right hemihepatectomy, the remaining three had received left hemihepatectomy. Median overall survival of patients with Klatskin tumours was 26 months.

Two patients in the ‘benign group’ died within the first 30 days after receiving right hemihepatectomy. One patient suffered from fulminant liver failure. Second patient developed a liver abscess and died in the course of a septic shock and consecutive cardiac failure. One patient in the group of benign bile duct stenosis died following cardiac surgery performed four years after hepatic resection.

4. Discussion

Resection still represents the only curative approach to Klatskin tumours. In consideration of the high postoperative complication rate including mortality, performance of major liver resection is a difficult decision to make [6,10–15]. Malignant origin of a tumorous stenosis can be proven but never be excluded definitely without complete resection. Therefore, the decision towards surgery remains mandatory in questionable cases as it has been demonstrated that resection is the only chance for long-term survival in patients with Klatskin tumour. Even in patients undergoing palliative surgery, survival is superior to patients without resection [6].

Approximately 14% of all patients with Klatskin tumours referred to our centre turned out to suffer from benign lesions which is comparable to previous studies [1–5]. And, hilar biliary stenosis mimicking Klatskin tumours form a heterogeneous group of diseases.

4.1. Patient history, age and gender

Iatrogenic induced stenosis of the bile duct, especially after cholecystectomy, are one of the most frequent lesions mimicking Klatskin tumours [4,16,17]. In our series, 38.2% of patients with a benign stenosis and 18.1% of patients with a malignant stenosis had a past history of cholecystectomy.

Considering age, patients with benign stenosis have been reported to be, on average, younger compared to those presenting with malignant hilar stenosis [16,17]. In the literature, age of patients suffering from benign stenosis ranges from 38 to 64 years [1,2,4,16,17] compared to 54–68 years in patients with Klatskin tumours [6,10–16]. The majority of patients with Klatskin tumours appears to be male [6,10–16,18]. In the present study, in the overall population and resection subgroup patient age, gender and a history of cholecystectomy showed significance in univariate analyses (p < 0.05) and provided an indication of dignity. Weight loss in combination with painless jaundice, as described by Corvera et al. [1], was no predictor for malignant origin in our series (p = 0.152, data not shown).

4.2. Laboratory parameters

As previous studies already described, statistically significant differences were found in cholestatic parameters AP and GGT in patients with Klatskin tumours compared to patients with benign stenoses [16,17,19]. In our analyses, AP even showed to be an independent predictor of malignant bile duct stenosis. However, ROC curve analyses showed a limited sensitivity and specificity with only a “weak diagnostic evidence” (positive likelihood ratio 4.05, negative likelihood ratio 0.49).

In our study, CA19-9 was the best predictor of malignant biliary stenosis with a sensitivity of 74.6%, a specificity of 80.0% and a diagnostic accuracy of 83.5%. Saluja et al. found a significant difference of CA19-9 level in patients with benign and malignant proximal bile duct stenosis [16]. We could confirm this observation in the overall study population. In our series, patients with a CA19-9 level greater than 612 U/ml were more likely to have a malignant bile duct stenosis. CA19-9 represents a standard tumour marker indicating adenocarcinoma of the pancreatico-biliary system [18–22]. But it has to be born in mind, that elevated serum levels of CA-19-9 can also be associated with cholestasis, cholangitis or autoimmune diseases like primary sclerosing cholangitis and autoimmune pancreatitis [23–26]. Therefore, determination CA19-9 is not a reliable parameter to distinguish between benign or malignant dignity in all cases. Subgroup analysis illustrate this. In patients who underwent surgical resection, for example, preoperative CA19-9 does not achieve statistical significance. [4, our series].

4.3. Interventional sample taking

A preoperative histologic evaluation with biopsies or brush cytology has limited sensitivity in spite of high specificity [27,28]. Following applies: negative cytology from brushings does not exclude malignancy and occurrence of false-positive results cannot be excluded. Moreover, there is always a risk of tumour cell dislocation in course of sample taking.

4.4. Imaging

Among the entire study population, presence of tumour mass in CT or MRI show statistically reliable differences between malignant and benign proximal bile duct stenosis (P = 0.001, P = 0.018). In contrast, lymph node enlargement >1 cm fail to assist as a significant parameter on CT to diagnose a malignant stenosis, as described before [16]. But presence of tumour mass in imaging could not exclude benign dignity in all cases. And resection was always considered necessary when imaging showed typical patterns of malignant tumorous stenosis, even if there was no evidence of malignancy revealed by the corresponding frozen sections.

PTC provide information on the longitudinal expansion of the stenosis, which is crucial to plan surgical approach [7–9]. Furthermore, percutaneous transhepatic cholangiography (PTC) allows the placement of selective and multiple percutaneous drainages (PTCD), resulting in a more rapid removal of obstructive cholestasis [29]. In our experience, PTC contributed to prevent extended resection in 18 out of 34 patients with benign lesions when combined with CT and/or MRI. In five patients, major resection was obviated by preoperative work-up and surgical exploration. And finally, the surgical procedure could be restricted to bile duct resection (n = 7) and segmentectomy (n = 1) in another eight cases. In our study, we did not evaluate further imaging criteria of biliary stenosis - like shape of margins or kind of stenosis tapering-in PTC or ERC, making further investigations necessary.

4.5. Limiting factors

There are some limiting factors of this study. First of all, the limitations of our study are the low number of patients with benign bile duct stenosis (n = 34) and its retrospective nonrandomized design. Secondly, long investigation period and alterations in diagnostics restricted data evaluation, making further controlled and prospective studies necessary.

5. Conclusion

In conclusion, most of the patients with benign bile duct stenosis showing unspecific inflammation in final histology and have a history with previous medical intervention. Alkaline phosphatase and CA19-9, as well as presence of tumour mass in imaging
representing useful diagnostic guideposts to distinguish between benign or malignant dignity of hilar biliary stenosis. But even a combination of these parameters cannot exclude malign dignity in all cases and final proof of diagnosis is only possible after extended resection. Therefore, the decision towards major liver resection remains justified in patients with undefined hilar lesions in order to avoid mistreatment of a potentially curative tumour.

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