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

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HIGHLIGHTS

- Identification of clinical, laboratory and radiological parameters to distinguish benign from malignant strictures of the proximal bile duct.
- Retrospective analysis in 250 patients with suspicion of Klatskin tumour.
- Patient age, alkaline phosphatase, CA19-9 and presence of tumour mass in CT scan are predictors for malignant stenosis of the proximal bile duct.

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ABSTRACT

Introduction: The aim of this study was to identify clinical, laboratory and radiological parameters to distinguish benign from malignant stenoses 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.

1. Introduction

Klatskin tumour is a common referral diagnosis in patients with hilar bile duct stenosis. However, there are numerous different diseases leading to hilar biliary stenosis mimicking Klatskin tumours. Up to 15% of patients resected for Klatskin tumours reveal benign proximal biliary obstruction on final histology [1–5].

Currently, complete surgical resection represents the only curative treatment of Klatskin tumours. Due to the invasion of the

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tumour into the intrahepatic bile duct, mostly a major liver resection is necessary. Major liver resections are associated with a higher postoperative complication rate and mortality. Therefore, the differentiation between Klatskin tumours and benign Klatskin 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 this 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 cholangiopancreaticography (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 (carcinoembryonic 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 (IgG4, 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.