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Intraductal biopsies in indeterminate biliary stricture: Evaluation of histopathological criteria in fluoroscopy- vs. cholangioscopy guided technique

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ABSTRACT

Background: Differentiating malignancy from benign disease in indeterminate biliary stricture by imaging modalities is limited. Definite diagnosis relies on histopathological diagnosis.
Aims: To assess accuracy of histopathological diagnosis of fluoroscopy-guided vs. cholangioscopy-directed intraductal biopsies in indeterminate biliary stricture.
Methods: All patients with indeterminate biliary stricture and fluoroscopically ($n = 68$) or cholangioscopy-directed (working channel 2 mm, $n = 38$) biopsies were included. Histopathological results of biopsies were classified into inflammatory lesion (class 1), dysplasia/intraepithelial neoplasia (class 2) and malignancy (class 3) and results as well as macroscopic diagnosis were compared with final diagnosis.
Results: Sensitivity and specificity of fluoroscopy-guided vs. cholangioscopy-directed biopsies were 22.9% and 100% vs. 25.0% and 100% for class 1 + 2 vs. class 3 lesions, respectively. Sensitivity for class 1 vs. class 2 + 3 lesions was 45.7% ($p = 0.044$) vs. 58.3% ($p = 0.214$) for fluoroscopy-guided vs. cholangioscopy-directed biopsies, respectively, while specificity was 100% in both. There was no difference in size of the obtained sample ($p = 0.992$). True positive diagnosis rate increased with the number of biopsies taken ($p = 0.028$).
Conclusion: Fluoroscopy-guided and cholangioscopy-directed intraductal biopsies are equally limited in establishing the diagnosis of malignancy in indeterminate biliary stricture.
Categorizing dysplasia or intraepithelial neoplasia as malignancy increases sensitivity without decrease in specificity. By taking more biopsies, diagnostic yield is increased.

1. Introduction

Definite diagnosis of indeterminate biliary strictures (IBS) is limited even if advanced non-invasive imaging is applied [1]. Preoperative diagnosis therefore typically involves collection and analysis of tissue or cells. Endoscopic retrograde cholangiography (ERC) is the standard approach to obtain material for cytology or histopathology in non-operative cases or prior to surgery, but cholangioscopy and endoscopic ultrasonography (EUS) are increasingly used for this purpose.

By way of ERC, positive results for malignancy are obtained in about 30–60% of cases in retrospective series. The diagnostic yield depends on patient selection and on the extent and localization of the tumor, but also on histopathological criteria applied to assess neoplasia. A diagnostic yield of 30–50% is typically reported for brush cytology [2–5]. Combining transpapillary biopsy with brush cytology does not significantly increase the diagnostic yield [6]. Prospective studies report even less favorable results from taking intraductal biopsies, i.e. sensitivity for fluoroscopy-guided biopsy was only 36% in an tertiary expert group [7], and sensitivity of cholangioscopy guided biopsies was no more than 31% in another highly experienced expert group [8]. In a recent meta-analysis, a pooled sensitivity of 60.1% was reported for cholangioscopy-guided biopsies in preselected patients [9]. One reason for low

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sensitivity of intraductal biopsies in comparison to percutaneous biopsy technique might be the small size of the specimen, which does not allow for explicit pathological findings [10]. However, extrahepatic cholangiocarcinomas are rarely amenable to percutaneous puncture.

To improve diagnostic yield of intraductal biopsies cholangioscopy techniques have been increasingly used: A miniature endoscope is passed through the working channel of a commercially available duodenoscope in the so called 'mother-baby' cholangioscopy technique; biopsies are thereby taken by a miniature biopsy forceps (diameter of 0.5 mm) [11]. In contrast, in direct retrograde cholangioscopy (DRC), an ultra-slim endoscope is inserted directly into the common bile duct (CBD) and a conventional biopsy forceps is passed through the working channel of this endoscope (diameter 2 mm) [12–14].

We therefore aimed to identify any factors that might improve diagnostic yield of intraductal biopsies in fluoroscopy-guided vs. cholangioscopy-directed technique.

2. Methods

2.1. Data collection

This is a retrospective study, which included patients with IBS who presented for diagnostic workup and further management at Frankfurt University Hospital from 2009 to 2015. All patients had undergone previous diagnostic work-up with abdominal ultrasonography and cross sectional imaging (magnetic resonance imaging (MRI) and/or computed tomography (CT)). ERCP was performed for endoscopic treatment, i.e. insertion of a stent to bridge the biliary stricture. In all patients, at least one biopsy was taken by way of ERCP or DRC. We identified the patients via our internal database (search criteria: Performance of ERCP in 2009 to 2015 with biopsies taken) and included only technically successful procedures.

The electronic medical records and the endoscopic and pathological data were abstracted to standardized forms. The following data were extracted: age, gender, date of procedure, ERCP results including number of samples, histopathological findings including size of the specimen, clinical reports such as discharge letters and other histopathological findings as from transcutaneuous biopsies or surgery. The diameter of the biggest fragment was counted as specimen size. Macroscopic findings at ERCP were categorized into 'strong suspicion for malignancy' or 'no strong suspicion for malignancy' based on the fluoroscopy or cholangioscopy findings and the clinical assessment of the experienced interventionalist. Interventions were performed by highly experienced interventional endoscopists (>250 ERCP procedures per year). All histopathological specimens were investigated by at least two board certified pathologists.

Histopathological findings were categorized into non-malignant (class 1, e.g. normal bile duct tissue, inflammation), suspicious for malignancy (class 2, i.e. dysplasia, low or high grade intraepithelial neoplasia) and 'definite for malignancy' (class 3, invasive carcinoma).

We categorized all bile duct biopsies into three classes, reassessing the bioptical material in accordance to the Vienna classification of gastrointestinal neoplasia [15]. Thereby, Vienna category 1 (negative for neoplasia/dysplasia) and 2 (indefinite for neoplasia/dysplasia) were merged into class 1, category 3 (non-invasive low grade neoplasia) and 4 (non-invasive high grade neoplasia) were merged into class 2, and Vienna category 5 (invasive neoplasia, intramucosal carcinoma, submucosal carcinoma or beyond) was termed as class 3 lesion. During follow-up of the patient, the clinical course, further interventions and additional histopathological findings were evaluated. The final diagnosis (=gold standard) was determined by either definite histopathological diagnosis from surgical resection or transcutaneuous biopsy, or from clinical follow-up of at least twelve months duration. Only patients who fulfilled these criteria were included. If patients underwent repeated endoscopic evaluation with biopsies, only the first ERCP/DRC was assessed in this study. DRC was usually performed either (1) for patients referred to our hospital from secondary centers for dedicated cholangioscopy because of inconclusive results in former ERCP and cross sectional imaging, or (2) IBS was diagnosed at our hospital and the decision for DRC was made by the interventional endoscopist for inconclusive findings at ERC and cross sectional imaging. Patients underwent a mean of 1.5 diagnostic ERCP (SD 2.7, range 0–16) and 0.26 fluoroscopic guided biopsy or brush cytology (SD 0.45, range 0–1) before DRC-directed biopsy.

Macroscopic and microscopic findings were compared to the gold standard. Location of the lesions was evaluated for sensitivity of biopsies.

All procedures were performed at conscious sedation (propofol; optional combination with midazolam). For all DRC procedures, the GIF-N180 or the GIF-XP180 gastroscopes with a working channel of 2 mm diameter were used (Olympus Medical, Tokyo, Japan). Standard two-lumen 5F balloon catheters (MTW Endoskopie, Wesel, Germany; Endoflex, Voerde, Germany) and a guide wire (VisiGlide 0.025 in., Olympus Medical, Tokyo, Japan) were used to assist intubation of the CBD.

Standard duodenoscopes (Olympus V-Scopes, TJF 160VF, TJF-Q180V; Olympus Europe, Hamburg, Germany) were used for ERCP and the short-wire technique with locking the wire at the distal end of the duodenoscope was applied.

2.2. Statistics

Statistical analysis was carried out using BiAS (version 11.01, BiAS for Windows; Epsilon-Verlag, Frankfurt, Germany). Continuous variables are presented as mean ± SD and categorical variables as frequencies and percentages. Differences between unpaired groups were analyzed using Mann–Whitney U test for continuous variables and a χ^2 test (or Fisher exact test, if numbers were small) for nominal variables.

Sensitivity and specificity were calculated for each diagnostic method. Positive predictive value (PPV) and negative predictive value (NPV) were calculated adapting the prevalence to that of the study population. A two-tailed p-value < 0.05 was considered statistically significant.

The study protocol was approved by the institutional review board (No. 427/15) of the local ethics committee of the University Hospital Frankfurt, and written informed consent was obtained from all patients prior to all investigations that had been performed.

3. Results

3.1. Patient characteristics

There were 106 patients included into this study (66 male, 40 female; mean age 67 years). Biopsies were taken using fluoroscopy guidance in 68 patients and DRC in 38 patients. The final diagnosis of strictures was malignant in 47 and a benign in 59 patients. Malignancy was either confirmed via initial or follow-up intraductal biopsy ($n = 13$), percutaneous biopsy ($n = 2$) or histopathological specimen from surgical resection ($n = 23$). In nine patients, rapid radio-morphologic progress of the tumor and clinical deterioration confirmed malignancy. Final diagnoses were CCA ($n = 32$), cancer of the pancreatic head ($n = 11$), hepatocellular carcinoma ($n = 2$), and one patient each with metastasis and intraductal papillary mucinous neoplasia (IPMN), respectively.