Establishing a Diagnosis in Indeterminate Pancreaticobiliary Strictures: Is Confocal Laser Endomicroscopy the Answer?

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Despite the advances that have been made in diagnostic modalities during recent years, the differentiation between benign and malignant pancreaticobiliary strictures remains a significant diagnostic challenge. Conventional cancer markers are of limited diagnostic utility and radiologic assessment with cross-sectional imaging may not provide a definitive diagnosis in the absence of a mass lesion [1–3]. Endoscopic evaluation has, for many years, relied heavily on cholangiographic appearance and biliary brush cytology, which, despite a specificity approaching 100 %, shows a low sensitivity of 15–57 % for malignancy [4].

Confocal laser endomicroscopy (CLE) provides microscopic information on mucosal tissue in real time and aims to enhance the diagnostic accuracy of endoscopic examination. Employing technology designed to prevent light scattering, CLE generates highly focused images of very small mucosal areas [5, 6]. It has been used in detecting dysplasia/cancer in various settings, such as colorectal polyps, inflammatory bowel disease, and Barrett's esophagus [7–9]. A CLE probe has been devised fitting in the working channel of a cholangioscope or in a catheter that can be inserted through the working channel of a standard duodenoscope under fluoroscopic or cholangioscopic guidance allowing examination of indeterminate biliary strictures. Fluorescein is given intravenously 2–3 min prior to mucosal imaging allowing also for visualization of blood vessels [10].

In recent years, a number of studies have attempted to determine the performance characteristics of this modality

for the differentiation of benign and malignant pancreaticobiliary strictures [10–13]. Also, data from a multicenter prospective study were used to reach a consensus definition of biliary and pancreatic probe-based CLE [13]. Characteristics most suggestive of malignancy included thick dark bands ($>40\text{ }\mu\text{m}$), thick white bands ($>20\text{ }\mu\text{m}$), dark clumps, or epithelial structures, whereas thin dark or white bands were suggestive of benign lesions (Miami classification criteria). It has been shown that combining two or more criteria for malignancy significantly increases the sensitivity and predictive values of the method [13]. In the largest study investigating the performance characteristics of CLE in indeterminate biliary lesions, a total of 89 patients were included [12]. Utilizing the Miami classification criteria, CLE was found to have a sensitivity of 98 %, a specificity of 67 %, and a negative and positive predictive value of 97 and 71 %, respectively. It compared favorably with conventional histopathology that had a sensitivity, specificity, negative and positive predictive values of 45, 100, 69, and 100 %, respectively [12]. The excellent sensitivity and negative predictive value of CLE in indeterminate pancreaticobiliary strictures suggest that it could be an important adjunct to ERCP for distinguishing benign from malignant disease and that it may be used to guide biopsy sampling.

Integrating this very promising new technology into every-day clinical practice involves defining not only its performance characteristics but also interobserver agreement for the perceived final diagnosis and for the different diagnostic criteria applied. In the initial validation of the Miami classification criteria, three criteria indicative of malignancy and one indicative of benign strictures showed moderate interobserver agreement as suggested by significant Fleiss kappa values between 0.40 and 0.60 [13]. Apart from these findings, however, data on interobserver

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agreement for the diagnostic criteria and final diagnosis (i.e., benign vs. malignant) in indeterminate pancreaticobiliary strictures assessed by means of CLE are lacking.

In the current issue of *Digestive Diseases and Sciences*, Talreja et al. [14] present the results of a study on interobserver agreement in interpretation of probe-based CLE imaging of pancreaticobiliary strictures. The authors asked six clinicians in five institutions to classify 25 video clips from indeterminate biliary strictures according to the Miami classification criteria and as benign or malignant. They found that interobserver agreement for all criteria and for final diagnosis ranged from poor to fair both for less experienced observers (≤ 10 cases), whose kappa values ranged -0.079 to 0.277 , and for more experienced observers (>11 cases), whose kappa values ranged 0.092 – 0.347 [14]. However, kappa values were higher in the more experienced compared to the less experienced group with regard to three out of five diagnostic criteria examined and final diagnosis [14]. Although previously published data indicate that the operating characteristics of CLE in indeterminate pancreaticobiliary strictures do not improve significantly with experience [12], the findings of the study published in the current issue of the journal [14], suggest that experience, and thus possibly training, may, potentially, improve interobserver agreement. The authors conclude that further standardization of the classification criteria used may also be needed to improve interobserver reliability and clinical utility of the method.

A limitation of the study of Talreja et al. [14] is that assessment of video clips was performed without knowledge of any clinical information, which is rarely the case in reality. In a recent report on the performance characteristics of CLE in indeterminate pancreaticobiliary lesions, its accuracy appeared to be enhanced by visually targeting mucosa via cholangioscopy as opposed to fluoroscopically guided catheter delivery of the CLE probe, although differences did not reach statistical significance (83 vs. 73 %, respectively) [12]. Thus, integrating clinical information, including cholangiogram and cholangioscopic data, and in particular targeting mucosal areas to be examined with CLE probes by means of cholangioscopy could, potentially, improve the diagnostic utility and interobserver agreement of CLE findings.

Furthermore, little research has been done to establish the utility of CLE in patients with chronic inflammatory biliary conditions, such as primary sclerosing cholangitis or IgG4-associated cholangitis, and indeterminate pancreaticobiliary lesions. Biliary strictures in this context could be notoriously difficult to differentiate from pancreaticobiliary malignancy [15–17] and it is conceivable that CLE could further improve our differential diagnostic capability. It is, however, unclear whether current classification criteria are applicable in this patient population.

In conclusion, CLE is a very promising modality that may be a useful adjunct to ERCP for the differential diagnosis of indeterminate biliary strictures. As the study of Talreja et al. [14] indicates, further standardization of classification criteria and training may be needed to improve interobserver agreement and integration of the method in clinical practice. Future studies should also aim to further delineate the clinical utility of CLE in chronic biliary conditions, such as primary sclerosing cholangitis, particularly in conjunction with cholangioscopy.

Conflict of interest None.

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