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ENDOSCOPIC MANAGEMENT
OF PANCREATICO-BILIARY CANCER
AND PRECANCEROUS CONDITIONS
Endoscopic transpapillary approach to the pancreatico-biliary ductal system (ERCP) for diagnosing and treating biliary and pancreatic diseases has a long history starting in the 1970s of the last century.

Over years, ERCP has become the standard practice in the management and palliation of non-resectable malignant biliary and pancreatic disorders. The development of advanced imaging technologies and new devices for endoluminal diagnosis and therapy has markedly expanded the yield of ERCP in pancreatico-biliary oncology.

Moreover, the introduction of endoscopic ultrasound has further expanded both diagnostic and therapeutic perspectives, allowing not only to have access to the pancreatic and biliary ductal systems in case of ERCP failure, but also to reach the ducts and fluid collections through the stomach and gut wall, with unexpected successful results and outcomes.

Early diagnosis of intraductal tumors is today feasible by confocal endomicroscopy, an advanced imaging technique providing real-time histology (optical biopsy) and allowing to identify the neoplasia at a very early stage or confirming it in doubt cases, even in the pancreas by transpapillary or EUS-guided approach, with successful rates that are superior than those obtained by brush cytology or FNA.

New technologically-advanced devices and materials allow endoluminal therapy to treat lesions that until few years ago could only be treated by surgery, as bilio- or pancreatico-digestive EUS-guided anastomosis or debidement of necrotic collections occurring after a severe acute pancreatitis, with significant improvement in patients’ morbidity, hospital costs, and a significant cost-saving for the health care system, if routinely adopted in clinical practice outside referral centers.

Palliation by ERCP or EUS has a lower complication rate as compared to surgery, and improves the quality of life of patients permitting to start chemo-/radiotherapy earlier than after surgery. In this field a number of newly designed stents made with new materials have markedly improved the efficacy of biliary and pancreatic stenting and drainage.

In the last years ultrasound endoscopy has faced a tremendous growth and nowadays plays a pivotal role in the diagnosis and treatment of pancreatic focal lesions, even in adjunct to chemotherapy, with promising expectations on the treatment of locally advanced pancreatic cancer.

In this book, unique for its completeness and specificity, the Editors have brought together the world’s top experts and asked them to address all present and future aspects of the endoscopic management of pancreatico-biliary tumors, from the advanced diagnostics to therapy, with the aim of providing the reader with the state of the art in the field and future perspectives.

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Biliary strictures can be caused by various inflammatory and neoplastic diseases, both benign and malignant. Currently, the preoperative histologic diagnosis of biliary stenosis, and in particular of cholangiocarcinoma, is associated with low accuracy, making the decision to perform high risk surgery or radio chemotherapy or chemotherapy a difficult one to make. Even after a multidisciplinary decision, 10% to 15% of patients operated for malignant stenosis turn out to have a benign stenosis on the surgical piece. The preoperative diagnosis of biliary stenosis and in particular cholangiocarcinoma (CCK) is associated with a low sensitivity. CCK occurs in the hilar region in about 65% of cases, in the distal common bile duct in 20%, and as an intrahepatic lesion in 15%. Macroscopically, CCK is usually categorized into three types: exophytic or mass-forming, infiltrative or periductal, and polypoid or intraductal. Patients with hilar and extrahepatic CCKs usually present with symptoms of biliary obstruction, including painless jaundice, pale stools, dark urine, and pruritus. In patients with primary sclerosing cholangitis, CCK can be suspected when the patient complains of increasing jaundice, pruritis, weight loss, and abdominal pain, or when a rapidly increasing serum bilirubin level is observed. However, these symptoms are not more frequent in patients with CCK than in those without malignancy, except when CCK is detected within one year of the diagnosis of primary sclerosing cholangitis.

MRI with magnetic resonance cholangiopancreatography (MRCP) is usually considered the modality of choice in the diagnosis of CCK because of its high contrast resolution, multiplanar capability, and its ability to determine the parenchymal, biliary, and vascular extension. Several studies, including a meta-analysis, have shown that MRI has a sensitivity and a specificity of 90% in diagnosing biliary obstruction. The accuracy of MRI in diagnosing a malignant biliary stricture is lower and variable according to the authors (sensitivity of 48% to 88% and specificity of 71% to 95%).

To overcome this limitation, a new imaging modality was evaluated to detect neoplasia in vivo in the biliary tract. Probe-based confocal laser endomicroscopy (pCLE) is an imaging technology which enables optical biopsy or in vivo histology applied in the bile duct with promising results. In what follows, we present the technique and the results of biliary pCLE in patients with biliary stenosis, comparing optical biopsies in the bile duct with definitive histology.

**pCLE procedure**

After selective cannulation of the common bile duct (CBD) using a cannulotome or a sphincterotome, a 0.035 guide wire was introduced in the CBD above the stenosis. Sphincterotomy was systematically performed allowing for the introduction of the guide wire with the 8 Fr double channel Teflon catheter (Cook Endoscopy®, Winston Salem, NC, USA). The CholangioFlex probe (Figure 1.1-1.2) was pre-loaded and guided in the bile duct using the X-Ray fluoroscopic control. The confocal miniprobe (CholangioFlex; Mauna Kea Technologies, Paris, France) used for the study has the following characteristics: a confocal plane from 40 µm to 70 µm, a lateral resolution of 3.5 µm, and a total field of view of 325x325 µm. The diameter of the probe is 0.94 mm. This probe has a magnification of 400 times and a depth of penetration into the tissue of 40 µm. The probe was then advanced until the tip was visible under fluoroscopy. Images
were obtained by placing the tip of the probe in contact with the mucosa. Intraductal images were recorded on the hard disk of a computer connected to the pCLE system. IV injection of 2.5 mL of 10% fluorescein (Novartis) was needed. Images were reviewed by an experienced pathologist in GI diseases and compared to ERCP findings, CBD biopsies performed during ERCP and in 5 patients to the resected specimen (Wipple resection). Systemic antibiotic prophylaxis was administered to all patients (amoxicillin-clavulanic acid-1 g).

Identification of patterns of normal bile duct

Images were obtained in patients treated endoscopically for CBD stones. Benign findings were characterized by reticular arrangement of dark-grey bands on a light-grey background and showed normal vessels (thin and regular); no gland was visible. These images were the normal aspect of the chorion of the wall of the CBD. The normal mucosa, which is very thin, was not visible because the depth of penetration of the pCLE system light is larger than the thickness of the mucosa (Figure 1.1).

Identification of patterns indicative of malignancy

pCLE interpretation criteria

pCLE images were interpreted prospectively using the Miami classification, in vivo and in real time.\textsuperscript{10} Criteria characteristic of malignancy are listed below (Figure 1.2):
- loss of reticular pattern of epithelial bands of less than 20 µm;
- thick white bands (>20 µm);
- thick dark bands (>40 µm);
- dark clumps;
- epithelium.

Characteristics of normal bile duct are listed below (Figure 1.2):
- reticular network of thin dark branching bands (<20 µm);
- light grey background;
- blood vessels <20 µm.

White bands correspond to blood vessels. Dark bands correspond to lymphatics.\textsuperscript{11}
DISCUSSION

Suspicious bile duct stenoses are often operated on with unclear preoperative histology. As a result, 10% to 15% of patients who undergo surgery for malignant stenosis turn out to have a benign stenosis on the surgical piece.3-6 Preoperative histology is mandatory if such highly morbid surgery is to be avoided. In spite of technical improvements such as FISH or DIA, endobiliary biopsies unfortunately have low accuracy. With pancreatic masses, accuracy can be good,12 but unnecessary surgical procedures exist in the same proportion as with bile duct stenoses.13-16 All preoperative histologies have a low negative predictive value (NPV). The highest NPV was obtained with endoscopic ultrasound (EUS), with recent progress in needles permitting a negative predictive value up to 78%.12 This low NPV explains the frequency with which suspicious lesions, during surgery, prove to be benign. Previous studies have used cpCLE for imaging gastrointestinal neoplasia.17-21 Meanwhile, this technique has been miniaturized further to enable in vivo histopathology via confocal miniprobes in the pulmonary system22 or urinary system.23

Our phase I-II study 24 showed the feasibility of this new technique; no complications occurred and interpretable images were obtained in 33/37 patients (89.1%). Normal aspects of the CBD were described in patients of the control group A (CBD...
stones). Group B patients included bile duct stenosis, IDCM showed malignant changes in 25 cases, final diagnosis was malignant strictures in 23 cases and benign stenosis in 2 cases. False positive cases of IDCM included 2 chronic pancreatitis. Recently, Meining et al. 24 reported the first experience of IDCM using the cholangioscope technique. Fourteen patients with biliary strictures were examined. Mucosal imaging was performed with the same pCLE system introduced via the accessory channel of a cholangioscope. All strictures could be reached. Presence of irregular vessels on confocal laser microscopy enabled prediction of neoplasia with an accuracy rate of 86%, sensitivity of 83%, and specificity of 88%. The respective numbers for standard histopathology were 79%, 50%, and 100%. The mean signal-to-noise ratio of laser microscopic images acquired from malignant strictures differed significantly from those of benign origin (1.8 vs. 2.6, P=0.005).

Our preliminary study showed the same aspects of normal CBD and malignant biliary stenosis using IDCM as those published by Meining et al. 24 Angiogenesis has been reported as an essential step in the progression and development of carcinomas including cholangiocarcinomes, ampullary cancer and pancreatic carcinoma. 25, 26 These aspects explain the findings of increased neovascularization in malignant biliary strictures. Because abnormal vessels can be made visible by confocal miniprobe with fluorescein, the diagnostic accuracy for the detection of cholangiocarcinomes or malignant stenosis can be increased. In our study, it was possible to target all CBD stenosis and correctly identify all the malignant ones.

More recently, a cooperative study 27 confirmed the accuracy of the Miami classification. A total of 102 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) with pCLE to assess indeterminate pancreaticobiliary strictures were enrolled in a multicenter registry; 89 of these patients were evaluable. Information and data on the following were collected prospectively: clinical, ERCP, tissue sampling, pCLE, and follow-up. A uniform classification of pCLE findings (“Miami Classification”) was developed, consisting of a set of image interpretation criteria. Thereafter, these criteria were tested through blinded consensus review of 112 randomized pCLE videos from 47 patients, and inter-observer variability was assessed in 42 patients.

A consensus definition of the specific criteria of biliary and pancreatic pCLE findings for indeterminate strictures was developed. Single-image interpretation criteria did not have a high enough sensitivity for predicting malignancy. However, combining two or more criteria significantly increased the sensitivity and predictive values. The characteristics most suggestive of malignancy included the following: thick white bands (>20 µm), or thick dark bands (>40 µm), or dark clumps or epithelial structures. These provided sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 97%, 53%, 80%, and 80% compared with 48%, 100%, 100%, and 41% for standard tissue sampling methods. Inter-observer variability was moderate for most criteria. The Miami Classification enables a structured, uniform, and reproducible description of pancreaticobiliary pCLE. Combining individual characteristics improves the sensitivity for the detection of malignancy.

IDCM might be an ideal adjunct to ERCP with brush cytology or biopsy for characterization of CBD stenosis. These results indicated that this technology will increase the diagnostic accuracy of the detection and classification of biliary strictures in the future, but more multicenter studies are necessary in particular to differentiate inflammatory CBD stenosis (PSC or chronic pancreatitis) from CCK.

Last year, we presented during the DDW 2013 our latest experience of patients with indeterminate biliary stenosis. From July 2007 to May 2012, 61 patients with a biliary stricture were included (mean age 67 years old, 26 women, 33 men). 12 patients had a stent in place. Pre-operating imaging findings were available (MRI or scanner). An EUS had to be conducted before the ERCP procedure. No histology was available at the time of pCLE. For each pCLE procedure, a diagnosis of benign or malignant stenosis was reported. The aim of the study was to evaluate pCLE in bile duct stenosis. Results were compared to definitive histology. Benchmark histology (definitive histology) was obtained in the case of malignant lesions by endoscopy (endobiliary biopsy, EUS-FNA), percutaneous biopsies, or surgery. For benign lesions, benchmark histology was surgery or a follow-up of one year.

Histology of dysplasia on biopsies was considered as malignancy for endoscopic biopsies. Only histology of carcinoma was considered as a benchmark histology for endoscopic biopsies. Endoscopic
biopsies were brush cytology, endobiliary biopsies and EUS-FNA.

Six patients were excluded from the study, 5 because there was no definitive histology, 1 because of the failure of ERCP. Hence 55 patients were studied. 9 patients did not have endobiliary biopsies, 21 did not have brush cytology, 7 had neither.

No EUS was performed in 3 patients. Benchmark histology was obtained with endobiliary biopsies in 11 cases, with EUS in 22 cases, with surgery in 21, with percutaneous biopsies in 2, and in 7 cases with a follow-up of one year for benign lesions.

4 patients were operated with a malignant histology before surgery. 4 patients had both malignant endobiliary biopsies and malignant EUS-FNA histology.

There were 41 malignant lesions and 14 benign lesions. Among malignant lesions, we obtained 15 pancreatic adenocarcinoma, 12 CCK, 7 carcinoma of major papilla (ampulloma), 5 metastases (2 breast carcinoma, 1 lymphoma, 2 colonic cancers), 1 hepatocellular carcinoma (CHC), 1 gall bladder carcinoma. Among benign lesions, 6 were operated and 8 had follow-up of at least one year. Biliary stenosis were localized in the main bile duct in 35 cases, in the hilum in 9 cases and in the lower part of the bile duct in 11 cases.

Sensitivity, specificity, PPV, NPV, and reliability for pCLE, biopsies, and pCLE + biopsies are represented in table 1-I. There were two important points in our results. First, accuracy increased significantly (P <0.03) with a combination of pCLE + biopsies. Secondly, the NPV with combination of pCLE + biopsies was 100%.

19 patients had a biliary stricture without individualized mass on pre-operating imaging findings (6 malignant lesions, 13 benign lesions). Among malignant lesions we obtained 3 CCK, 1 ampulloma, 2 metastatic lesions (1 colonic metastasis, 1 breast metastasis). Among benign lesions, 6 patients underwent surgery and 7 had a follow-up of one year. Lesions were localized in the common bile duct (7 cases), in the hilum (6 cases), and in the lower part of the bile duct (6 cases).

Sensitivity, specificity, PPV, NPV, and reliability for pCLE, biopsies, and pCLE + biopsies are represented in table 1-II. Accuracy was lower for patients without mass on MRI or CT-scan. Nevertheless accuracy was good at 79% and, importantly, a NPV of 100%.

The fact that our study obtained an NPV of 100% represents a step forward, all the more because this figure extends to all stenoses including the subgroups of stenoses without mass and those excluding pancreatic adenocarcinoma. This very good NPV should be considered as a confirmation of the NPV of 100% obtained by Shah et al., in a study which concerned PSC and probably an improvement in therapeutic impact in the management of the patients.

In our study, high NPV was obtained not only with pCLE but also with other endoscopic procedures (EUS and ERCP). This was probably a limitation. These endoscopic procedures were able to be performed during the same anesthesia, however. Only 3 patients did not have EUS (1 with mass in the hilum, 2 without mass). 7 patients had neither brush cytology nor endobiliary biopsies. This lack of endobiliary histology was probably a limitation, but could also be profit of the usefulness of pCLE.

While evaluating a diagnostic tool necessarily involves studying the therapeutic impact, the aim of this study was to compare histological diagnoses

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**Table 1-I** Results of biopsies+ pCLE for histology of bile duct stenosis.

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCLE</td>
<td>88%</td>
<td>79%</td>
<td>92%</td>
<td>69%</td>
<td>85%</td>
</tr>
<tr>
<td>biopsies</td>
<td>76%</td>
<td>79%</td>
<td>91%</td>
<td>52%</td>
<td>76%*</td>
</tr>
<tr>
<td>pCLE + biopsies</td>
<td>100%</td>
<td>71%</td>
<td>91%</td>
<td>100%</td>
<td>93%*</td>
</tr>
</tbody>
</table>

* statistically significant difference (P=0.03).

**Table 1-II** Results of sensitivity, specificity, PPV, NPV and accuracy for patients without mass on pre-operating imaging findings.

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCLE</td>
<td>83% (36-100)</td>
<td>77% (46-95)</td>
<td>62% (24-91)</td>
<td>91% (59-100)</td>
<td>79% (54-94)</td>
</tr>
<tr>
<td>Biopsies</td>
<td>50% (12-88)</td>
<td>77% (46-95)</td>
<td>50% (12-88)</td>
<td>77% (46-95)</td>
<td>68% (43-87)</td>
</tr>
<tr>
<td>pCLE + biopsies</td>
<td>100% (54-100)</td>
<td>69% (39-01)</td>
<td>60% (26-88)</td>
<td>100% (66-100)</td>
<td>79% (54-94)</td>
</tr>
</tbody>
</table>
obtained using pCLE with benchmark histologies, because the key here was that using pCLE should permit a histological and therefore certain diagnosis. Histologic accuracy of 79% in bile duct stenosis represents real progress in terms of preoperative histology, similar to previous studies.\(^7\)\(^9\) In our study, 11 out of 14 patients operated had malignant lesions. 4 of them had a preoperative malignant histology with biliary sampling. With pCLE, on the other hand, 10/11 of them did. With complex additional sampling methods, the accuracy of endobiliary sampling was between 47% and 67%.\(^18\)

A potential limitation was the definition of benchmark histology. Only 21 patients underwent surgery, and thus had what we consider as an unquestionable histology of reference. The specificity of endobiliary biopsy was considered as 100% with histology of carcinoma, as described in the literature.\(^1\)\(^,\)\(^2\) A follow-up of one year was considered sufficient for diagnosis of benign stenosis. One patient presented a duodenal carcinoma after 2.5 years of follow-up. The question is whether this patient had a new carcinoma or whether we missed the diagnosis during follow-up. Likewise, another question is whether surgery can be considered an unquestionable reference given that an anatomopathological procedure cannot entirely study the surgical piece.

Can we improve the use of pCLE in the bile duct, then? From the beginning of the study, we progressed in our description of inflammatory lesions.\(^14\) We now know that inflammatory lesions due mainly to previous stenting or cholangitis have an impact on the diagnosis of the nature of the lesions.\(^28\) Because we stopped inclusions in 2011, we were unable to use our new classification. A second point is that cholangioflex needs to be improved to have better quality images. Accuracy was significantly improved in an earlier retrospective study by improving the quality of images.\(^14\) This was confirmed by Shieh et al.\(^29\), who described how images are better with a gastroflex® probe, however is difficult to insert into the bile duct. Among the 3 benign lesions operated, one patient had a highly suspicious biopsy, and 2 others had malignant lesions with pCLE. With the new classification and with progress in imaging, we would hope not to misdiagnose these stenoses.

### CONCLUSION

The addition of a pCLE procedure in the diagnostic histological examination of a biliary stricture enables a significant increase in diagnostic reliability. The NPV of 100% is a very important point and it confirms previous published results. Of course techniques need to be improved further. Obtaining 85% of pre-operative histology and 93% diagnosis accuracy for malignancy in combination with routine endoscopic techniques is, however, very promising.

### REFERENCES

8. Boberg KM, Bergquist A, Mitchell S et al. Cholan-

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**Table 1-III**

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
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<tr>
<td>pCLE</td>
<td>83% (36-100)</td>
<td>77% (46-95)</td>
<td>62% (24-91)</td>
<td>91% (59-100)</td>
<td>79% (54-94)</td>
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<tr>
<td>Biopsies</td>
<td>50% (12-88)</td>
<td>77% (46-95)</td>
<td>50% (12-88)</td>
<td>77% (46-95)</td>
<td>68% (43-87)</td>
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<tr>
<td>pCLE + biopsies</td>
<td>100% (54-100)</td>
<td>69% (39-01)</td>
<td>60% (26-88)</td>
<td>100% (66-100)</td>
<td>79% (54-94)</td>
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