

Saturday April 9th to Sunday April 10th

ICCU 2011 Nice

3rd International Conference of Cellvizio[®] Users

P R O C E E D I N G S
H I G H L I G H T S

Scientific symposium supported by an unrestricted educational grant from



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P R O C E E D I N G S

ICCU 2011 Highlights

Probe-Based Confocal Laser Endomicroscopy (pCLE): Discussion and Debate over Current Practice and Applications.

The third annual International Conference of Cellvizio Users (ICCU), organized by Pr. Jean-Paul Galmiche of the University Hospital of Nantes, France, and Pr. Prateek Sharma of the Kansas City Medical Center in the United States, took place April 8th to 10th in Nice. A community and discussion forum dedicated to endomicroscopy, ICCU brought together over 100 gastroenterologists and pulmonology specialists to discuss the impact of pCLE in both gastroenterology and pulmonary medicine, as well as future potential applications.

Through a variety of sessions held over three consecutive days, users had the chance to present their work (31 oral presentations and 26 posters), and debated the use of pCLE in current practice, with a particular focus on gastroenterology. Different strategies for the use of pCLE in patient management were discussed, more specifically: improving the diagnostic and therapeutic yield of patients with indeterminate bile and pancreatic duct strictures, detecting precancerous lesions in the esophagus and colon, but also the ability to make real-time decisions, driving endoscopic treatment and improving the management of patients overall.

Probe-Based Confocal Laser Endomicroscopy (pCLE) in Gastroenterology: Making it Common Practice

Improving the management of patients with indeterminate strictures of the bile and pancreatic ducts

Indeterminate biliary strictures are particularly difficult to diagnose. Histological results after biopsies or cytological results after brushing remain disappointing. Using pCLE for this indication is a solution to increase diagnostic accuracy.

The results of an international multicenter study of 102 patients (Cellvizio ERCP Registry, Yang Chen et al.¹) were presented at ICCU. The study showed that pCLE considerably improved the detection sensitivity of malignant strictures by detecting 98% of malignant patients in real-time during ERCP with a negative predictive value of 97% (diagnosis confirmed by pathology or by a one-year follow-up in the case of benign stricture).

With a relatively short learning curve, pCLE is a very accessible technique easily put into practice. Image interpretation criteria, called the Miami criteria (Figure 1), were also tested and validated during this study. In healthy tissue, pCLE images contain regular reticulum of fine black bands and fine white bands (vessels). However, in the case of malignancy, we see thick black bands with a more irregular reticulum, thickened vessels with slowed or inverted flow, dark clusters, and epithelial visualization. In one retrospective study on the use of these combined criteria, their sensitivity was 97%, but specificity was 33%. These figures improve when only the most significant criteria are accepted. However, these results need to be refined because other series show the possibility of thick black bands or dark clusters in benign strictures after liver transplantation (M. Pelisse, Barcelona) and in primary sclerosing cholangitis (G. Costamagna, Rome).

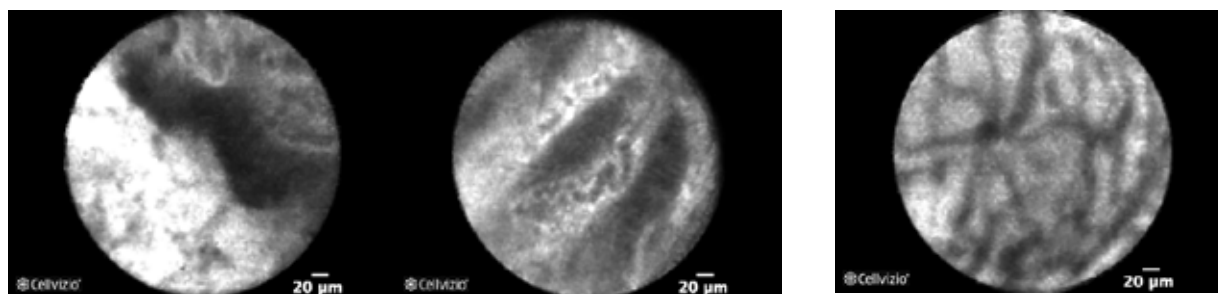
The confocal miniprobe delivery method (CholangioFlex™) has also been studied: there appears to be no significant difference in results, but a mere inclination toward less specificity (76% vs. 62%) with the catheter.



Dr. Marc Giovannini (Marseilles) illustrated the results of this study by presenting a clinical case: a patient with jaundice and a mass that appeared on an endoscopic ultrasound, with no histological proof of malignancy, underwent pCLE and was found to meet the Miami criteria for malignancy. Based on pCLE findings, Dr. Giovannini decided to refer the patient for surgery. The specimen removed turned out to be a pancreatic adenocarcinoma. In conclusion, pCLE provided an accurate diagnosis and spared this patient additional diagnostic testing.

Questions in this session involved mainly the fact that the current pCLE approach allows for two possibilities: normal or abnormal tissue (malignant). The reality is probably more complex and must include inflammatory or fibrous lesions. The image interpretation criteria will have to be refined, keeping these elements in mind as well as with post-transplantation series and studies on primary sclerosing cholangitis.

Figure 1: pCLE images of malignant and benign bile ducts (Cellvizio ERCP Registry)



Abnormal bile ducts (Cholangiocarcinomas):
Epithelial visualization and wide white bands (vessels)

Normal bile ducts:
Fine black bands

Can endoscopy alone detect neoplasia?

pCLE users tried to answer this question after reviewing all the work conducted in endomicroscopy to date for three different indications (Barrett’s esophagus, colorectal polyps, and inflammatory diseases of the colon).

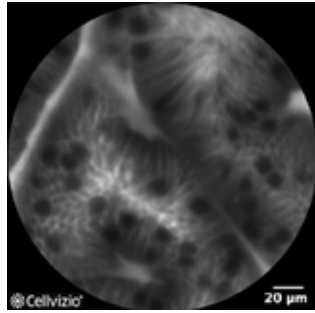
Impact of pCLE on randomized biopsies for Barrett’s esophagus patients

Surveillance of Barrett’s esophagus is currently based on the Seattle protocol, which, in general, is seldom followed due to its long and invasive nature. In this context, pCLE is of particular interest when combined with white-light endoscopy (WLE) and virtual chromoendoscopy techniques, such as NBI (Narrow Band Imaging, Olympus). An international multicenter study of 101 patients demonstrated that pCLE detects and characterizes twice as many neoplastic lesions as WLE and 1.7 times as many as NBI when pCLE imaging is conducted on suspect areas with both WLE and NBI and using four quadrant sampling methodology (Seattle protocol). Similarly, patients in whom neoplastic lesions were not found using any of the three methods (WLE, NBI, or pCLE) could forego biopsies (about 40% of the patients in the study) without the risk of “missing” a patient with neoplastic lesions.

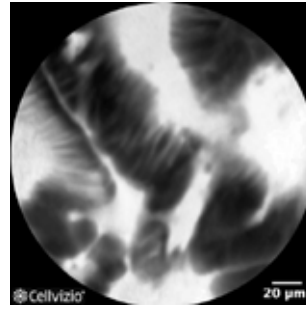
This study, in which the University Hospital of Nantes participated, was recently accepted for publication in GI Endoscopy².

To support these results, Dr. Bertani (Modena, Italy) shared her experience on the subject by presenting a case study on a patient for whom pCLE led to more neoplastic lesions to be detected, and in turn guiding decisions as to the most appropriate therapeutic approach to take.

Figure 2: pCLE images obtained in Barrett's esophagus (DONT BIOPCE Trial)



Intestinal metaplasia with visualization of caliciform cells



High-grade dysplasia

Colorectal polyps: what strategies for CLE?

Currently, two strategies are being discussed in the context of advanced optical diagnostic methods: 1) the “Diagnose, Resect, and Discard” strategy, which consists of limiting the cost of histological analysis by not performing pathology tests on small colorectal polyps previously characterized using an optical method (such as pCLE) during the endoscopic procedure, and 2) the strategy called “Leave a Polyp Behind” which consists of avoiding unnecessary resections by leaving small, non-adenomatous polyps in place. One of the current difficulties is to know which is the required threshold for new techniques, in terms of diagnostic performance, to be considered for such clinical practice.

The ASGE recently communicated an opinion³ mentioning that the negative predictive value (NPV) of an “endoscopic” diagnosis compared to a histological diagnosis needed to be greater than or equal to 90% in order to leave a polyp of less than 5 mm in place. In a prospective study, Wallace et al.⁴ demonstrated that a NPV of 94% could be achieved by combining NBI and pCLE (for polyps whose endoscopic diagnosis was qualified by observers as “very reliable”). According to this study, the sensitivity of pCLE is higher than that of NBI or FICE (91% as opposed to 77%). Another study on the learning curve for colorectal polyps demonstrates that pCLE can be mastered almost without a learning curve (whether with regard to image interpretation or acquisition) and that it should therefore very quickly result in highly reliable diagnosis⁵.

At this time, the lack of publications containing health-economic models makes it difficult to estimate the potential savings with these two strategies, and although the diagnostic performance of pCLE on colorectal polyps is probably high, it is worth confirming in a multicenter study.

Inflammatory diseases of the colon

The surveillance scheme for patients with Crohn's disease or ulcerative colitis consists of performing four-quadrant biopsies every 10 centimeters along the length of the colon, a long, painful, and ineffective procedure considering the high risk of sampling error. Several studies have assessed the benefits of eCLE in ulcerative colitis, particularly that of Kiesslich et al.⁶, which showed that chromoscopy combined with endomicroscopy could detect 4.75 as many dysplastic lesions as standard endoscopy. The study presented at ICCU by Neumann et al. seems to suggest similar results, as well as the possibility of showing histological lesions associated with Crohn's disease with a high degree of diagnostic accuracy. The current development of fluorescent probes combined with specific markers, although their use is currently limited to preclinical studies, gives us a glimpse of what the future may hold in the field of molecular marking.

Real-Time Decision-Making and Immediate Treatment

pCLE provides real-time detection of malignancy, thus allowing the patient's treatment to begin immediately, regardless of the indication involved.

The Impact of pCLE on Endoscopic Treatment and the Monitoring of Patients with Barrett's Esophagus

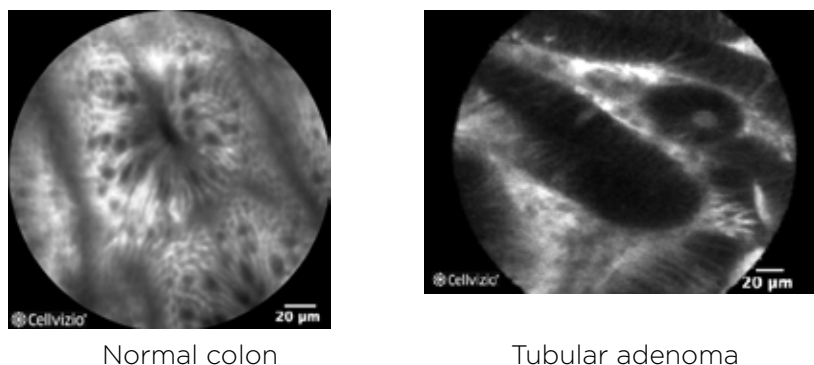
There are currently various therapeutic procedures for patients with a neoplastic Barrett's esophagus: EMR, ESD, photodynamic therapy, radiofrequency ablation, and cryotherapy. In this context, Dr. Konda presented a series of 7 cases demonstrating that pCLE guided the choice of treatment toward one or another of the currently available techniques. In fact, in 4 out of 7 patients studied, the use of pCLE alone or combined with NBI changed the endoscopic approach by detecting lesions invisible under WLE⁷.

pCLE could also play a role in guiding treatment by checking the resection margins or through early detection of neoplastic recurrences in the EMR scar.

Is it Possible to Avoid Systematic Retreatment of Colorectal Lesions?

After an EMR of a colorectal lesion, surveillance is recommended to detect and treat possible neoplastic recurrences within the scar. The main difficulty is that the time required to receive the biopsy results means the patients (many of whom are referred from far away for a very specific treatment) have to be called to come back in for treatment. Conversely, "blind" empirical treatment leads to a high number of overtreatments. Therefore, pCLE has the potential to play an important role in allowing real-time histological diagnosis and deciding during the same procedure whether to perform additional endoscopic treatment or not. An international multicenter study conducted by Mayo Clinic Jacksonville (Dr. Wallace), the University Hospital of Nantes (Dr. Coron), and AMC in Amsterdam (Dr. Fockens) assessed the role of pCLE in detecting neoplastic recurrences in 129 post-EMR or ESD scars⁸. pCLE detected 97% of recurrences while NBI detected only 72% (with a similar specificity). The negative predictive value obtained (99%) suggests the possibility of considerably reducing the number of empirical retreatments.

Figure 3: pCLE Images obtained in the colon (Dr. Coron, University Hospital of Nantes, France, and Dr. Meining, Klinikum rechts der Isar, Munich)



And soon: in vivo characterization of pancreatic cysts during an endoscopic ultrasound-guided needle biopsy

Another promising advance was presented during ICCU: nCLE ("needle-based confocal laser endomicroscopy"), i.e., a CLE approach using EUS-guided needle biopsy. In general technical terms, a confocal miniprobe has been specially manufactured for insertion inside ultrasound-guided biopsy needles. A multicenter study called INSPECT (and including 7 international centers) is currently being conducted cystic tumors of the pancreas, a disease for which current diagnostic techniques have limited sensitivity, from 34% to 75%. This study is aimed

at validating the feasibility of nCLE in this area and developing diagnostic criteria. The technique is in its early phases, but the first results presented seem promising and justify further discussion about other potential indications for nCLE.

Conclusion

These three days spent discussing the benefits of pCLE in current practice led to a consensus among Cellvizio users: pCLE is a tool that can improve the detection of neoplasia in various gastroenterology applications, particularly in the diagnosis of biliary and pancreatic strictures, Barrett's esophagus, and colic lesions. pCLE also helps the endoscopist to guide therapeutic decisions, whether it is to choose one resection technique over another, to make the decision to treat or not, or to provide additional diagnostic information, as we see in the cases of undeterminate biliary or pancreatic strictures.

pCLE users also discovered the new Cellvizio 100 series, which will soon replace the current Cellvizio system. The new system was said to be easier to use thanks to a design facilitating integration to the endoscopy suite. Although Cellvizio is now used in the digestive and pulmonary systems, it is without a doubt that Cellvizio, with all its clinical benefits has the potential to also help physicians in other areas such as urology and minimally invasive surgery.

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