

New Techniques in Endoscopy: Confocal Laser Endomicroscopy

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1. Introduction

In the last decades many technologic advances have been done in the field of endoscopic imaging in order to achieve, from one side a better visualisation of mucosal layer to distinguish neoplastic vs non-neoplastic tissue, and, on the other side, to obtain valuable tissue specimen for pathologist to improve diagnostic rate of the procedure. Indeed one of the fundamental features of endoscopic procedures consists in the possibility to perform direct biopsies in order to achieve histological diagnosis. Although histology is highly accurate, it has few limitations: false negative results, delay in reaching the final diagnosis and the decision of the correct and best treatment and increased costs in pathology procedures with, consequently, the need of repeated procedures. In addition sensitivity and specificity of histology are variable for difficulty to reach specimen adequacy, like in biliary duct and pancreatic cysts. Moreover the presence of flogosis or ulcers could alter the mucosal architecture and give some false negative/positive results to pathology examination. Nevertheless another important limitation of histology is that is a post-mortem analysis and it is not able to give us information about in-vivo processes (blood flow, mucosal junction exchanges).

New advances in endoscopic imaging have led, through high resolution endoscopy to magnification endoscopy but even if improved they are not able to give us a specific diagnosis and, up to now, international guidelines still suggest repeated biopsies and histology for surveillance protocol because new techniques are not strong enough to replace biopsies.

Confocal laser endomicroscopy (CLE), a recent advance of endoluminal imaging, allows an in-vivo visualization of mucosal layer with a detailed visualization of tissue and subcellular structures.

Since 2004 many papers have been published about the potential role of this new technique, have been published and many studies have been introduced to validate this technique.

CLE has the potential to anticipate the final diagnosis (neoplastic vs non-neoplastic) and consequently to guide next therapeutic steps in clinical practice without the delay of a pathology response. Moreover it offers the possibility to study mucosal layer to a micron resolution giving us an “optical biopsy” and future applications about a role of in-vivo study of physiologic and then pathologic processes, like tumoral angiogenesis, flogosis in healthy or neoplastic tissue are “work in progress”.

2. Physics

The physical principle of the CLE consists in the principle of light interaction with tissue. Light interacts with tissue in five different ways (Fig.1): 1- reflection, 2- absorption, 3- single scattering, 4- diffuse scattering, 5- absorption and re-emission at a different wave length of fluorescence.

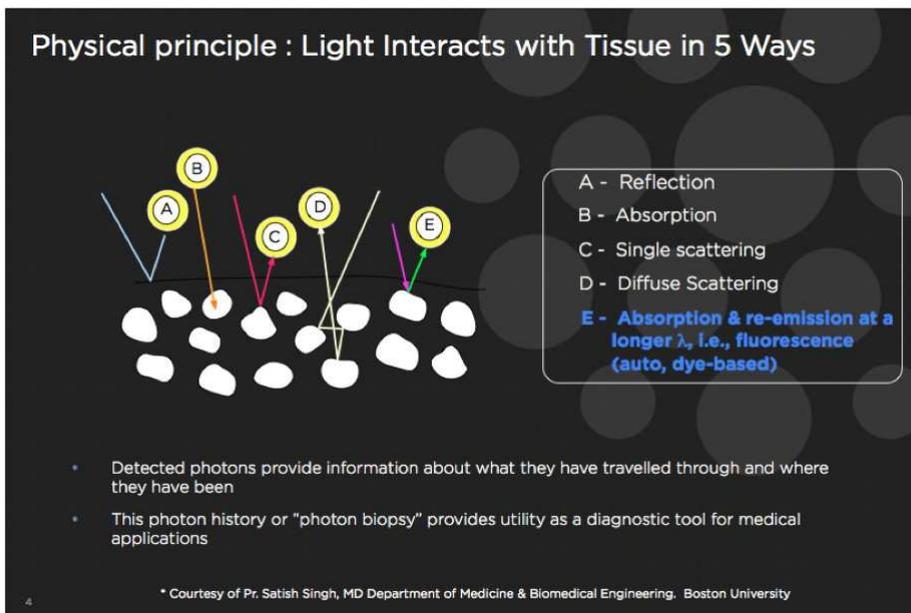


Fig. 1. 1- reflection, 2- absorption, 3- single scattering, 4- diffuse scattering, 5- absorption and re-emission at a different wave length of fluorescence.

This last phenomenon can be tissue auto-fluorescence or dye based fluorescence. The light source is a blue laser source light with variable wavelength (488 nm - 660 nm). Once the light arrives to the tissue a fluorescence signal returns back. Then this fluorescence signal is converted in imaging signal from a converter (detector) and then corrected in stabilized images from a system software. The last principle, absorption and re-emission at a different wavelength of fluorescence, is the basis of CLE and CLE mandates use of fluorescent agents. Most studies in humans have been performed with intravenous administration of fluorescein sodium. Fluorescein quickly distributes within all compartments of the tissue can be visualized after few second after fluorescein injection. It contrasts cellular and subcellular details, connective tissue and vessels architecture at high resolution but does not stain nuclei. The safety of the fluorescein as contrast agent had been demonstrated in ophthalmology because it has been used for years for ophthalmological imaging of blood vessels. Wallace et al. (1) reported a cross-sectional survey study about the safety of fluorescein in CLE procedures. 2272 patients were enrolled and no serious adverse events were reported. Minor adverse events occurred in 1.4 % (transient hypotension, nausea, injection site erythema, mild epigastric pain) but none of them required additional intervention than observation. Acriflavine, another contrast agent, is applied topically and

predominantly stains nuclei for human use, in USA and Europe the only FDA and EMEA approved contrast is fluoresceine because without nuclear stain it isn't prone to mutagenic effects.

3. Systems

Currently two devices are available and approved to perform CLE: one system is inserted in the tip of the scope (eCLE, Pentax Corporation, Tokyo, Japan) (Fig.2) and one, a probe-based system, is a separate device from the endoscope but capable to be introduced in the working channel of any standard endoscope (pCLE, Cellvizio, Mauna KeaTech, Paris, France) (Fig.3).

- *eCLE*: In this system, the miniaturized confocal scanner has been integrated into the distal tip of a new endoscope. A blue laser light source delivers an excitation wavelength of 488 nm and light emissions detected at 505- 588 nm. Successive points within the tissue are scanned in a raster pattern along X-axis and Y-axis to construct serial en-face optical section of 475 x 475 mm at user-controlled variable imaging depth. The optical slice thickness is 7 mm with a lateral resolution of 0.7 mm (2). Images on the screen approximate a 1000 fold magnification of the tissue in vivo. The advantage of this system is that the working channel of the scope is free and it can be used for target biopsies or for combined enhancement techniques such as chromoendoscopy. The limit of this system is that the calibre of the scope is bigger than a standard 11.8 mm upper scope and is stiff. Moreover the lens of the scope is not combined with HD software and virtual chromoendoscopy or other system (I-SCAN).

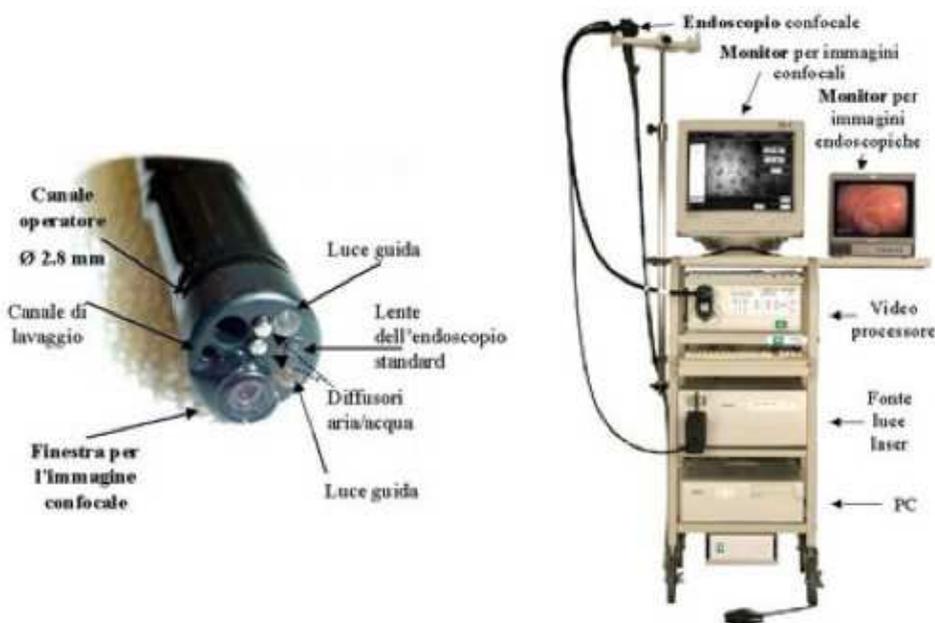


Fig. 2. eCLE system, Pentax Corporation, Tokyo, Japan



Fig. 3. pCLE, Cellvizio, Mauna KeaTech, Paris, France

- pCLE*: This system probe-based, can be used through the working channel of any standard endoscope (colonoscope, gastroscope, cholangioscope, bronchoscope, ureterscope...). The advantage of this pCLE is the versatility of the system and the possibility to combine it with other advanced “red flag” imaging modalities such as virtual chromoendoscopy or magnification. Scanning rates is 12 images/sec. The limits of this system pCLE are the slightly low power resolution compared to eCLE (1 mm vs 0.7mm) and a small field of view (240 – 600 mm). So pCLE system could not be well suited to surveying large areas of tissue such as long segments of BE and should ideally be combined with a red-flag technique for classification of tissue in a site already detected by enhanced endoscopy. However Mauna Kea has developed a post acquisition specifically-developed software (“mosaicing”) (fig.4) to paste images together and to obtain images similar to histology specimen.

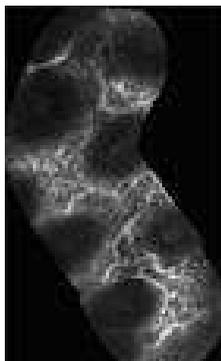


Fig. 4. "Mosaicing" in Cellvizio software

4. Clinical applications

Clinical applications of CLE include, potentially, all the current applications of biopsies for distinguishing neoplastic vs non-neoplastic tissue.

Early data suggests a role for CLE: 1- in surveillance program of chronic disease (Barrett's oesophagus and chronic inflammatory bowel disease), 2- in the definition of a known lesion (small colonic polyps, undetermined biliary strictures) 3- in therapeutic approach (definition of lesion's margin before EMR or ESD (in oesophagus, stomach or colon) and after resection procedure to detect residual tissue.

4.1 Gastroenterology

- *Barrett's oesophagus (BE)*: Barrett's oesophagus, considered as an abnormal change in squamous epithelium of the oesophagus into an intestinal columnar epithelium (Fig.5), is considered a pre-malignant lesion and the most important risk factor for the development of oesophageal adenocarcinoma.

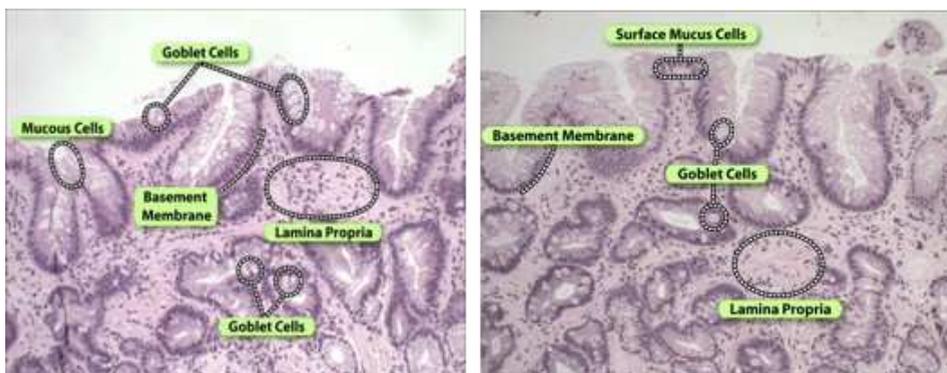


Fig. 5. Typical **Barrett glands** with **goblet cells** and regular arrangement of nuclei are visible. The lamina propria contains some **regular capillaries** and connective tissue and lymphocytes and plasma cells as well. The basement membrane is intact and thin. The density of the cells is potentially increased in conventional histology due to shrinking artefacts.

The incidence of oesophageal adenocarcinoma has been rapidly rising, increasing from 3-fold to 6-fold since 1990 (3). International guidelines suggest endoscopic surveillance of BE with random 4-quadrant biopsies every 1-2 cm through the extension of intestinal metaplasia for detection of dysplasia (high grade/low grade) or early intraepithelial cancer. However, surveillance endoscopy has several limitations because dysplastic changes occurring in Barrett's esophagus are not easily identifiable by standard endoscopy. Consequently, the current standard of endoscopic practice is to take multiple biopsies because there are no features on standard resolution endoscopy that distinguish Barrett's glandular metaplasia, dysplasia or early stage neoplasia. However, there is much controversy about the real efficacy of an intense four-quadrant biopsy sampling protocol in detecting Barrett's dysplasia and cancer because the accuracy of standard endoscopy and random biopsies is low and they may fail to detect neoplastic lesions. Moreover biopsies obtained using this technique are prone to sampling error and inter-observer agreement is low even between advanced operators and even among expert pathologists. Nevertheless, the need for histology confirmation of neoplasia eliminates the ability to direct therapy during the index endoscopy because the endoscopist cannot see the location of the disease. Thus repeated endoscopies are needed, the first for the diagnosis and then for the therapy. A multiple biopsies protocol could also interfere with next therapeutic steps; EMR or ESD could be more difficult without adequate "lifting sign" due to scar tissue after repeated biopsies.

This intense surveillance protocol has also many effects on healthcare economy for resource management and costs, considering that neoplastic progression in Barrett's oesophagus has a really low incidence (< 1 case in 200 per year).

Recent published data showed that pCLE was able to detect intraepithelial neoplasia with a sensitivity of 75% and specificity of 89-91% (4-8) Fig.6.

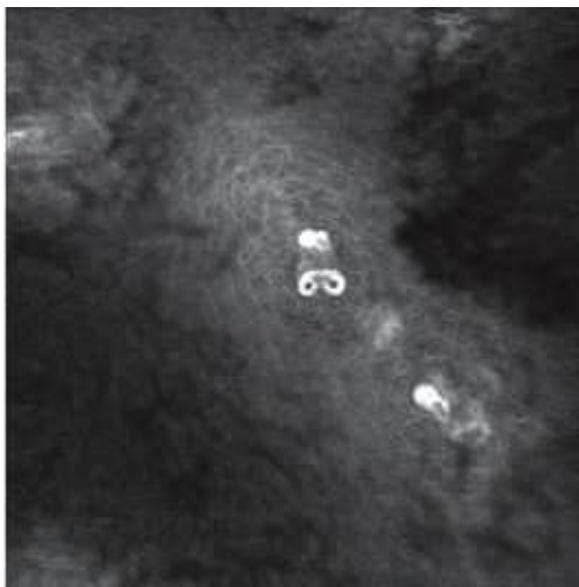


Fig. 6. pCLE images of healthy squamous epithelium with intrapapillary loop suitable for vessels with fluoresceine

In the same paper, ranking study population for disease-risk, in the low risk group population, pCLE has a NPV nearly 98.8% suggesting the possibility to avoid random biopsies. Fig. 7, Fig. 8.

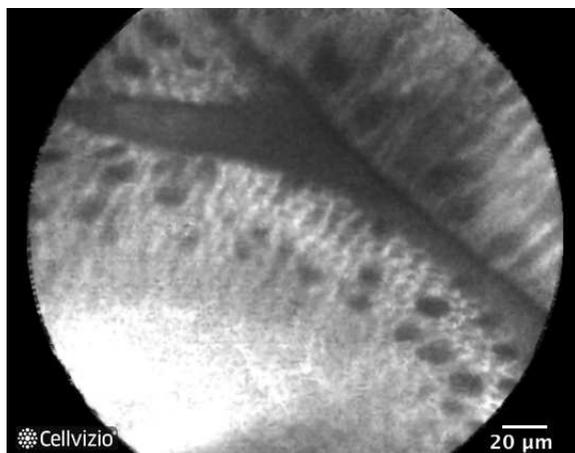


Fig. 7. pCLE images of Barrett's gland with regular columnar-lined epithelial surface. Dark mucin Goblet cells (round-shape black cells).

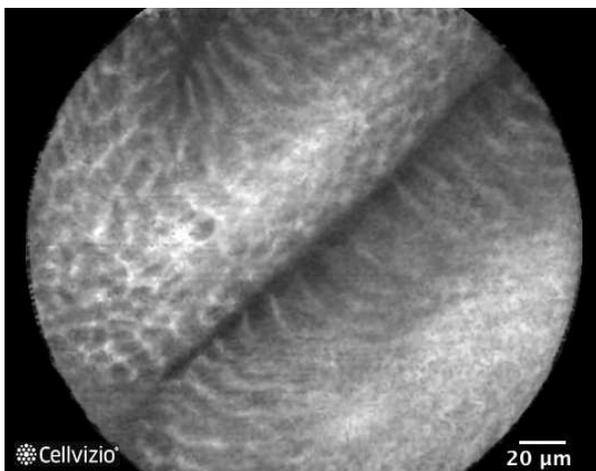


Fig. 8. pCLE images of Barrett's gland with regular columnar-lined epithelial surface. Dark mucin Goblet cells (round-shape black cells).

Another study by Bajbouj et al (5) did not confirm these data and the authors explain the differences with previous results with the low frequency of neoplasia detected in the study and secondly to strict adherence with diagnostic criteria for neoplasia in their data. The prevalence of neoplasia was lower than in the published data using the CLE system or other studies evaluating different imaging modalities, which have described prevalence of HG dysplasia or early cancers ranging between 24% and 59%. As changes in prevalence impact

on the variables measured, particularly on the PPV, the authors also face the problem of over-interpretation in those studies and the possibility of false positive pCLE findings. A prospective multicenter randomized trial had been presented in DDW 2010 with analogue results in a study population of around 100 patients.

An important study is about the inter-observer agreement and Wallace et al. reported a rate of 86% with a Kappa estimate of 0.72 (CI 95% 0.58-0.86) (6). The observers in this study also rated individual features suggestive of neoplasia, such as irregular epithelial thickness, epithelial inhomogeneity, dark epithelial structures (lack of fluoresceine uptake), crypt/villi fusion and irregular vessels. These individual features had good specificity but lower sensitivity than all together and none of them appeared to compete with the overall diagnostic assessment. Fig. 9, Fig.10.

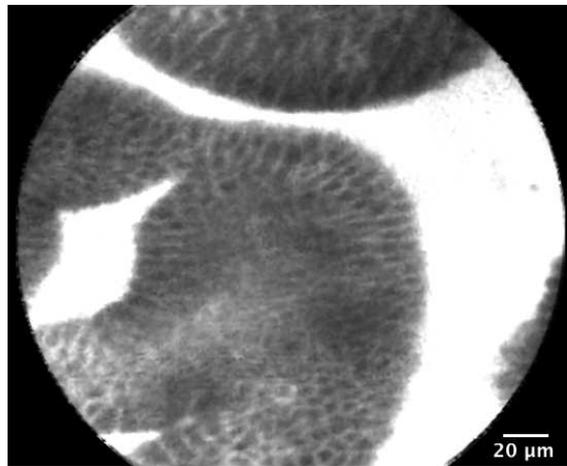


Fig. 9. pCLE images of Barrett's glands with loss of epithelial lining. No Globet cells suggestive for Dysplastic Barrett's esophagus

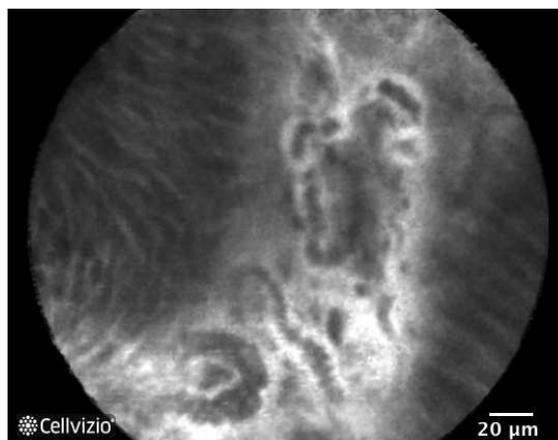


Fig. 10. pCLE images of irregular vessels suggestive for dysplastic Barrett's esophagus.

Another recent application of confocal endomicroscopy is a role in guiding therapeutic endoscopic procedures; 1- to localize and predict pathology, 2- to target biopsies and resections in surveillance and treatment, 3- to guide which therapy to use, 4- to assess treatment adequacy and gauge need for further treatment (7).

- *Early gastric cancer:* Gastric cancer remains the world's second leading cause of cancer-related deaths, with a mortality rate of 16.3 per 100,000 in men and 7.9 per 100,000 in women (9) and in eastern countries the risk of gastric cancer is dramatically high. One of the strategies to improve prognosis, essentially depends on earlier detection of pre-neoplastic changes in mucosal layer because intraepithelial neoplasia and early gastric cancer have a dramatically better prognosis than advanced one. The diagnosis of these lesions is currently based on pathologic assessment. Virtual chromoendoscopy and trimodal imaging endoscopy have demonstrated significant value for the detection of early gastric neoplasia whereas the detection of intraepithelial gastric neoplasia (GIN) has been less mentioned and investigated. Considering the higher incidence of GIN compared with early gastric carcinoma especially in eastern countries a new technique is highly desirable. Furthermore, given the different progression risk of GIN if the dysplasia is a low-grade or high-grade in screening and surveillance population

CLE provide an excellent definition of the gastric pit pattern with high diagnostic accuracy on detection gastric atrophy and gastric intestinal metaplasia Fig 11.

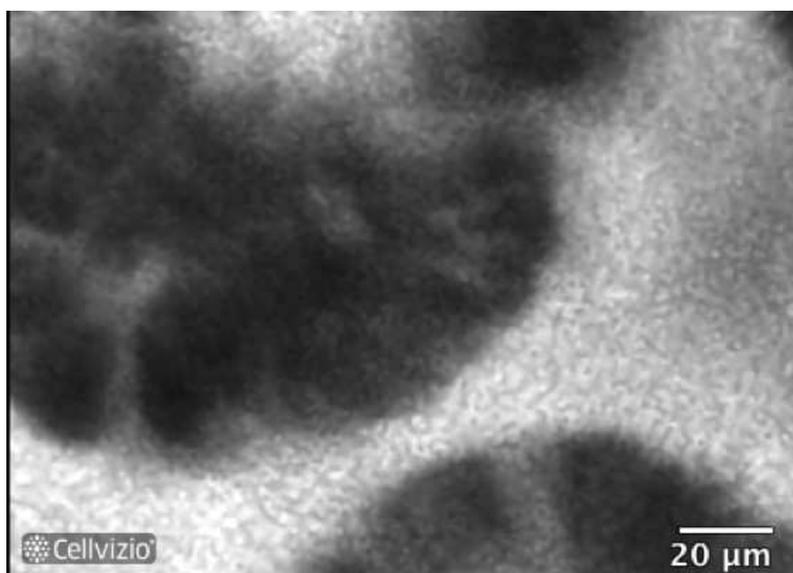


Fig. 11. pCLE images of “early gastric cancer with loss of typical honey-comb structures

Recently one study has been published to evaluate the role of pCLE before ESD to reduce disease recurrence (10).

- *Celiac disease:* Many papers have been published about the role of CLE in the study of jejunal mucosa in Celiac disease. Alterations of villa in terms of length, numbers and distribution are easily recognized. Fig. 12.

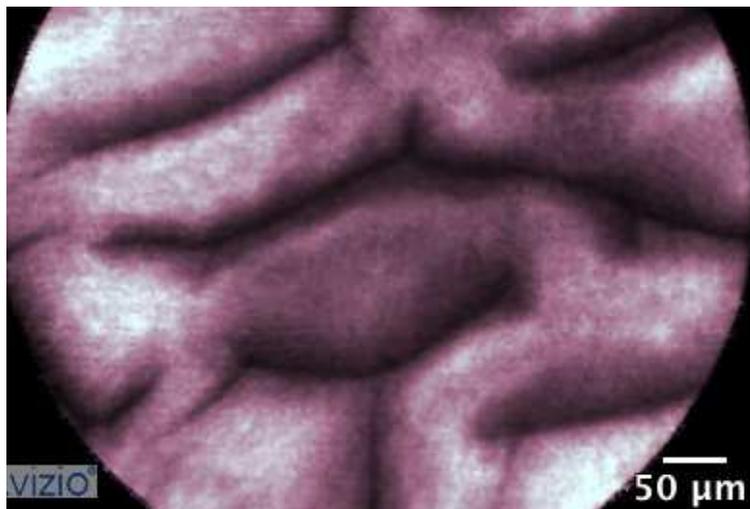


Fig. 12. pCLE images of duodenal villi in healthy duodenum

- *Whipple Disease*: Whipple's disease is a rare, systemic infectious disease caused by the bacterium *Tropheryma whipplei*. Diagnosis is made by intestinal biopsy, which reveals the presence of the organism as PAS-positive macrophage inclusion. Endoscopy of the duodenum and jejunum can reveal pale yellow shaggy mucosa with erythematous eroded patches in patients with classic intestinal Whipple's disease, hypercellularity of the lamina propria with "foamy macrophages", and a concurrent decreased number of lymphocytes and plasma cells, per high power field view of the biopsy. A case report about the use of CLE in the diagnosis of Whipple's Disease has been published (11). CLE showed pseudoatrophy and dilation of the villi, the presence of crypts within the villi, significant infiltration with inflammatory cells, and the presence of vacuoles or signal absence in the tip of the villi. CLE demonstrated moreover foamy macrophages in the lamina propria. However, all of these features are not specific for Whipple's disease because they could be found also in *Mycobacterium Tuberculosis* and other infectious disease; the possibility to target biopsies could play a potential role of this technique even if the correct diagnosis is reached with the visualization of the *bacteria* with electron microscopy.
- *Inflammatory Bowel disease*: The use of CLE in colon disease ranges from classifications of colorectal polyps between hyperplastic to neoplastic (adenomatous) to the study of inflammatory bowel disease (IBD). In particular patients affected by Ulcerative Colitis (UC) are at increased risk of developing colorectal cancer, so guidelines recommend endoscopic surveillance including targeted biopsies of suspected lesions and multiple random biopsies. However the sensitivity of this protocol for detection of neoplasia is still low and is therefore desirable to replace the inefficient procedure by a more efficient method. Chromoendoscopy and virtual chromoendoscopy (NBI) can be used to improve detection of dysplastic lesions and can be used to predict histology whereas pCLE is an in-vivo histology. Kiesslich et al, using the CLE system reported a sensitivity of 97.4%, specificity of 99.4% accuracy of 99.2% to predict the presence of neoplastic changes (1) Fig 13.

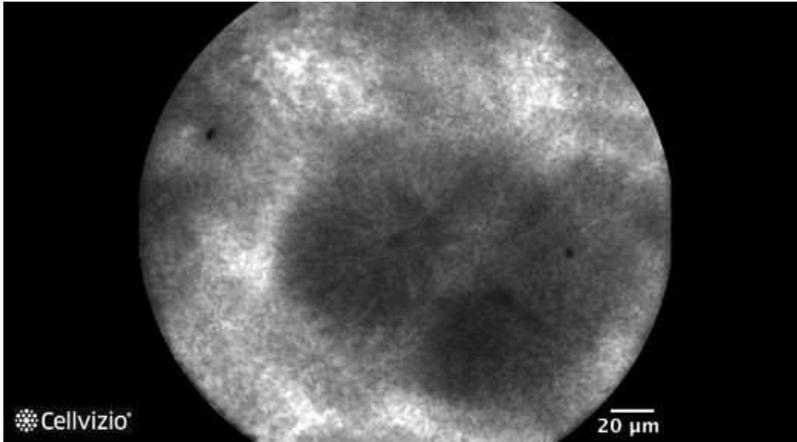


Fig. 13. pCLE images of typical UC mucosa with fusion of the glands.

Van den Broek et al (12) reported similar data but lower sensitivity (65%), specificity (82%) and accuracy (81%) due probably to a different system, a learning curve in providing images and technical skills. Hurlstone et al. (13) assessed the clinical feasibility and predictive power of CLE for in-vivo differentiation between ALM and DALM in UC. The study evidenced high accuracy of the technique and consequently the possibility to differentiate patients eligible for endoscopic treatment from patients fit for surgery. Recently, De Palma et al. (14) reported the use of CLE applied in real-time inflammation activity assessment. The inflammation activity assessment includes polyps architecture, cellular infiltration and vessel architecture. These studies showed that images taken with CLE provide information that are equivalent to conventional histology, differentiating between active and non-active UC during ongoing colonoscopy Fig 14.

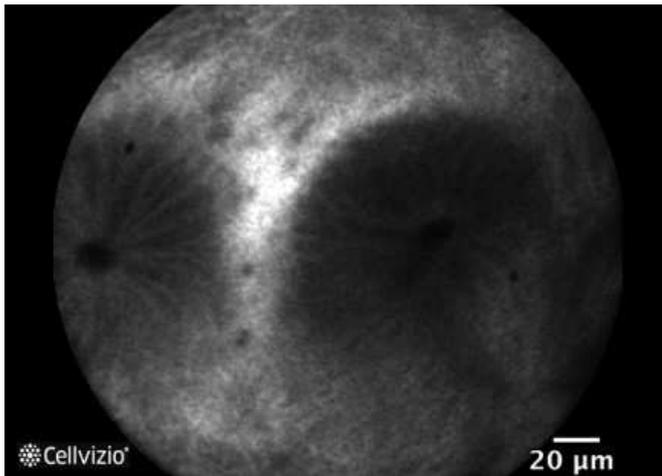


Fig. 14. pCLE images in a patient with long-standing UC. Increased intercrypt distance due to glands atrophy

Recently the use of CLE has been applied also to functional studies in IBD, to evaluate epithelial gaps resulting from intestinal cell shedding rate higher than in healthy patients undergoing colonoscopy. Liu et al (15) reported that patients with IBD had a significantly higher epithelial gap density in the terminal ileum compared with controls without IBD.

- *Polyps*: Colorectal cancer has been recognized as the second most common cause of cancer related death in the United States (16). It progresses through various morphological stages, including polyp formation and malignant transformation. Different type of polyps have been classified, hyperplastic and adenomatous polyps with a malignant potential. Standard endoscopic inspection cannot by itself distinguish between neoplastic and non-neoplastic lesions. Thus all detected lesions need to be removed and then evaluated by pathologist and this approach still remains the gold standard. Almost half of the polyps removed are hyperplastic and this standard approach results in unnecessary polypectomies with consequently increased risks and costs. The first report of the potential role of CLE in predicting pathology of the colon polyps was by Kiesslich et al (1). They reported that intraepithelial neoplasia was predicted by CLE with an accuracy of 92% (sensitivity of 97% and specificity of 99%). Hurlstone et al (17) subsequently confirmed Kiesslich data, in particular confirmed the role of CLE in visualization of high-quality cellular, subsurface vascular and stromal imaging enabling prediction of intra-epithelia neoplasia with high level of accuracy (99%). Polgase et al (18) also confirmed similar results. Recently Xie published that in polyps with diameter > 10 mm the sensitivity of CLE was 97.1% specificity 100% (19). A study by Gomez et al (20), reported also a moderate to good interobserver agreement between international collaborative colleagues for distinguishing neoplasia from non-neoplastic tissue. Buchner et al, (21) defined also a learning curve of the technique to predict colorectal neoplasia. They reported accuracy of 82% after 60 procedures. Fig. 15-fig 16.

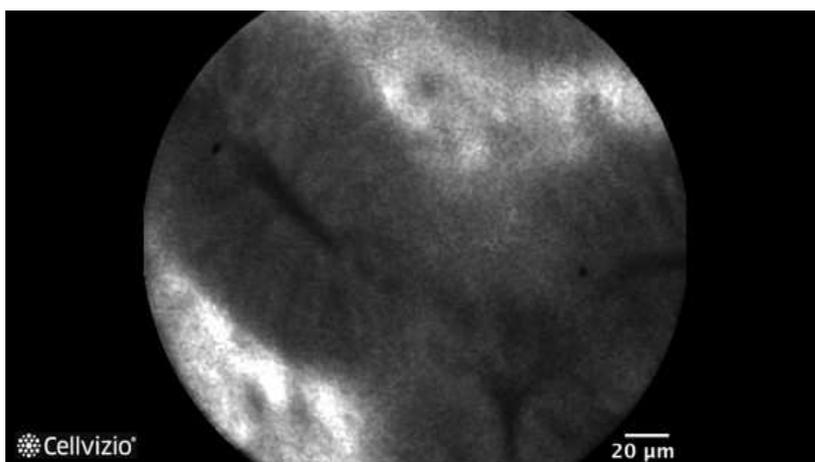


Fig. 15. pCLE images showing glands with star-opening of the crypts typical of hyperplastic polyps

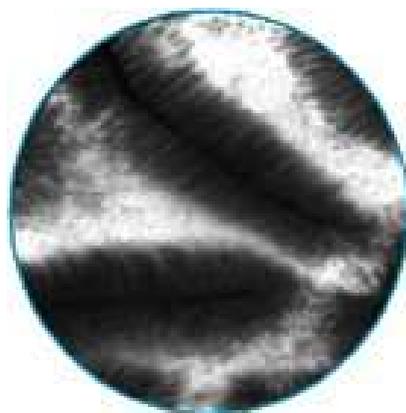


Fig. 16. pCLE images with long finger-like glands typical of adenomatous polyps.

- *Common bile duct:* The pre-operative diagnosis of biliary stenosis and, in particular, cholangiocarcinoma is associated with low sensitivity. Cytological brushing and fine needle aspiration have a low diagnostic accuracy. Moreover, clinical onset of symptoms is often suspicious of malignancy but, if primary sclerosing cholangitis is the underlying disease, the final diagnosis is challenging. Few case reports and case series about the use of pCLE system (cholangioprobes) through a cholangioscope or a catheter (graduated dilation catheter) in the CBD have been published up to now showing promising results of the technique. Fig.17.

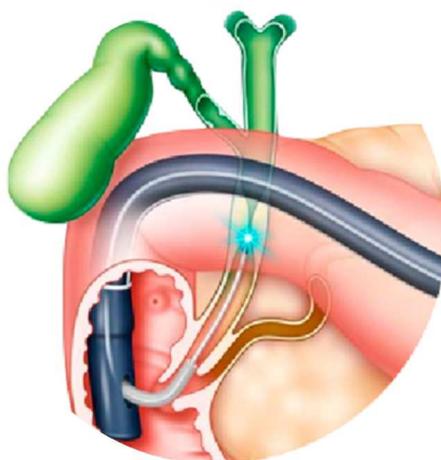


Fig. 17. Simulation of Cholangioflex probe introduced in common bile duct through a catheter

Recently, Giovannini et al, (22) reported a phase I-II study to evaluate the potential role of pCLE to detected neoplasia. The accuracy of pCLE was 100% for detection of ampullary tumors, 80% for pancreatic cancer and 81% for cholangiocarcinoma. Fig.18-Fig.19.

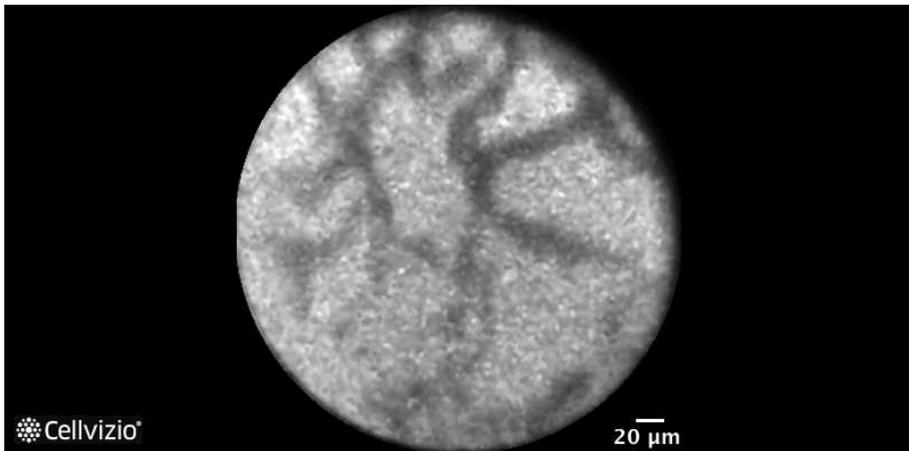


Fig. 18. pCLE images of biliary epithelium with regular dark thin branches. Healthy biliary epithelium

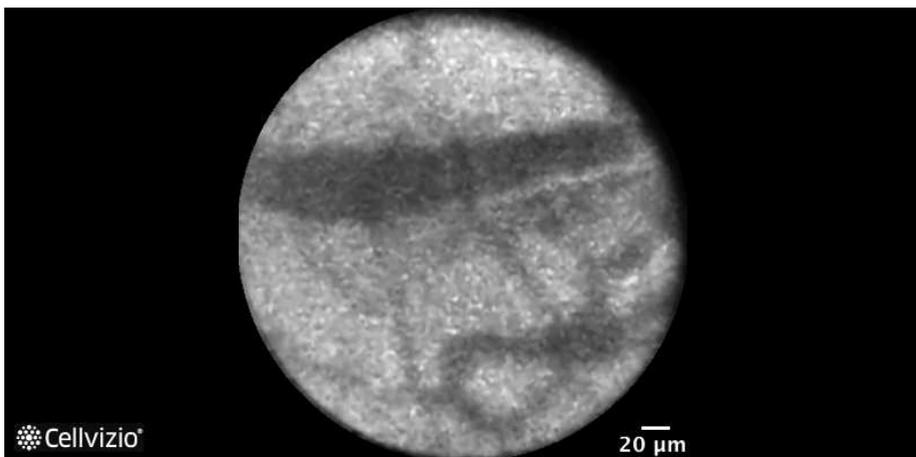


Fig. 19. pCLE images of cholangiocarcinoma with typical thick dark bands and different size of branches

Professor Yank Chen presented promising results in last DDW 2010, from a multicenter randomized trial from USA and Europe. He showed a sensitivity of pCLE of 97% with a NPV of 80%. Same results have been reported from dr. Meining from Munich in a pilot study. Their data are under publications.

- *Pancreas:* One of the major advantages of the probe-based system is the small diameter of the fibers that allows through a fine-needle system visualization of pancreatic cysts epithelium. Few case reports have been published (23) and presented in last UEGW 2010 from dr Meining group (Munich) with promising results in the definition of neoplastic vs non-neoplastic IPMN or pancreatic cystic lesion.

- *Eosinophilic esophagitis*: The use of the confocal laser endomicroscopy for the diagnosis in-vivo of eosinophilic esophagitis has been reported only as case-report. Fluoresceine leakage revealed dilated intercellular spaces and capillary ectasia within the esophageal squamous epithelium. In addition, leakage demonstrated by extravasation of fluoresceine, became visible. Furthermore small cells within the intercellular spaces suspicious of eosinophilis and mild mucosal edema were demonstrated (24).

5. Future applications

Urology: Recently pCLE has extended its applications to urology. One in-vivo study has been published to date (25).

Pulmonary disease: Histopathological tissue assessment remains the gold standard for accurate diagnosis of many lung conditions. Lesions' biopsies are usually performed through blind transbronchial procedure with 1-12% risk of pneumothorax (26) and a 2-9% risk of significant bleeding. Transthoracic biopsy is preferred for peripheral lesions, either percutaneously or via thoracotomy or thoracoscopy. The recent miniaturization of the confocal laser-scanning microscope enables in vivo imaging of superficial tissue also in lung disease. The only commercial system is Cellvizio-Lung ®. CLE imaging of mucosal and epithelial layers within the body requires the topical or intravenous administration of fluorescent contrast agent such as fluoresceine or acriflavine, whereas elastin acts as an endogenous fluorescent agent. Thiberville et al. (27) described five distinct lattice arrangements of the connective tissue fibres of the normal basement membrane in separate areas of the bronchial tree Fig.20. These regular structures became disorganised with a decreased fluoresceine signal in pre-malignant and malignant condition.

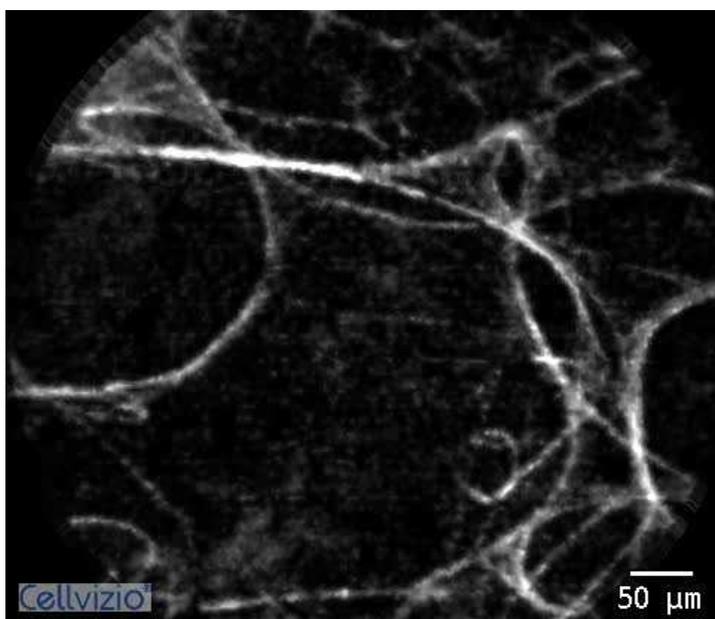


Fig. 20. pCLE images of healthy alveoli

Solid organs: A new generation of confocal miniprobes, narrow enough to be introduced through a needle have been developed for needle-based confocal laser endomicroscopy (nCLE). Their potential role is to perform virtual biopsies of solid organs (liver, pancreas and other intraperitoneal structures) accessible only through needle or during laparoscopy, EUS or NOTES. The first report by Goetz et al. (28) was in 2008. The authors reported the possibility to visualize, with different staining protocols, distinct aspects of the morphology and perfusion of the healthy and pathologic liver. A substantial correlation with histology was detected with additional information about in-vivo processes imaging: increased vessels permeability, common feature of inflammation. Its potential application in liver disease could be to perform multiple optical biopsies to find out the most appropriate site to obtain specimen to reveal pathognomonic changes potentially yielding instantaneous histopathological diagnosis. Mennone et al (29) also reported the use of nCLE in rat model liver. Images obtained provide sufficient detail to distinguish normal from cirrhotic livers in rat model.

Molecular imaging: Some case reports only in animals, about the use of novel biomarkers to study angiogenesis in-vivo and consequently to visualize fluorescence -tagged molecular agents.

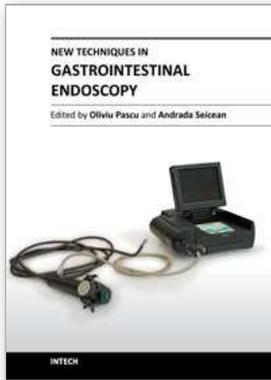
Bacterial recognition: Recently few case studies have shown that CLE can identify *Bacteria* on the mucosal surface during gastroscopy, *Helicobacter Pylori* (30) and colonoscopy (31). A new confocal endomicroscopy technique has been developed for the identification of *E.Coli* (32).

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As result of progress, endoscopy has become more complex, using more sophisticated devices and has claimed a special form. In this moment, the gastroenterologist performing endoscopy has to be an expert in macroscopic view of the lesions in the gut, with good skills for using standard endoscopes, with good experience in ultrasound (for performing endoscopic ultrasound), with pathology experience for confocal examination. It is compulsory to get experience and to have patience and attention for the follow-up of thousands of images transmitted during capsule endoscopy or to have knowledge in physics necessary for autofluorescence imaging endoscopy. Therefore, the idea of an endoscopist has changed. Examinations mentioned need a special formation, a superior level of instruction, accessible to those who have already gained enough experience in basic diagnostic endoscopy. This is the reason for what these new issues of endoscopy are presented in this book of New techniques in Gastrointestinal Endoscopy.

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