

Confocal endomicroscopy: Is it time to move on?

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Abstract

Confocal laser endomicroscopy permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract and includes: Esophagus, stomach, small bowel, colon, biliary tract through and endoscopic retrograde

cholangiopancreatography and pancreas through needles during endoscopic ultrasound procedures. Many researches demonstrated a high correlation of results between confocal laser endomicroscopy and histopathology in the diagnosis of gastrointestinal lesions; with accuracy in about 86% to 96%. Moreover, in spite that histopathology remains the gold-standard technique for final diagnosis of any diseases; a considerable number of misdiagnosis rate could be present due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies. Theoretically; with the diagnostic accuracy rates of confocal laser endomicroscopy could help in a daily practice to improve diagnosis and treatment management of the patients. However, it is still not routinely used in the clinical practice due to many factors such as cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. These limitations are relative, and solutions could be found based on new researches focused to solve these barriers.

Key words: Confocal laser endomicroscopy; *In-vivo* microscopy; Barret esophagus; Gastrointestinal cancer; Confocal laser endomicroscopy probe

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Core tip: Confocal laser endomicroscopy (CLE) permits *in-vivo* microscopy evaluation during endoscopy procedures. It can be used in all the parts of the gastrointestinal tract with accuracy in about 86% to 96%. In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist. However, these limitations are relative, and solutions could be found

based on new research leading to increased consensus overcoming present barriers.

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INTRODUCTION

Confocal laser endomicroscopy (CLE) is an advanced endoscopic imaging modality that provides histology-like images at 1000-fold magnification for *in-vivo* microscopy evaluation^[1]. Since the first publication about the use of CLE in the gastrointestinal tract, ten years have passed^[2].

The technology was initially developed for an endoscope-integrated CLE system (e-CLE) (EC3870K, Pentax Medical, Japan) with specific applications to upper and lower endoscopy, and a few years later for a probe-based CLE system (p-CLE) (Cellvizio, Mauna Kea Technologies, France)^[1,2].

Nowadays only p-CLE is commercially available, with the advantage that it can be used in other parts of gastrointestinal tract as in bilio-pancreatic diseases through endoscopic retrograde cholangiopancreatography and endoscopic ultrasound.

Several studies have demonstrated a high correlation of results between CLE and histopathology in gastrointestinal lesions^[1,2]. In fact, CLE has overcome some of the limitations found in endoscopy (macroscopy) and histopathology (microscopy), thus improving patient management.

In spite of its high accuracy and several clinical applications, CLE is still not routinely used in the clinical practice due to many barriers.

CLINICAL EVIDENCE AND APPLICATIONS

It has been demonstrated that white light endoscopy is not accurate for predicting histological inflammation or other alterations such as nonspecific erythema, nodularity, erosions, *etc.*^[3].

Moreover, the limits between neoplastic and inflammatory areas are very narrow/unclear due to the coexistence of these processes together.

When using CLE during endoscopy we can clearly understand why the correlation between standard videoendoscopy and histopathology is not higher than 70% in most cases^[4].

Many studies evidence an accuracy of 81.5% using p-CLE for the diagnosis of dysplasia in Barrett esophagus^[5].

In gastric diseases, CLE has had an accuracy of 94%-96% for diagnosis of malignancy when compared directly with histological biopsies^[6]; and 88% for pre-malignant conditions such as intestinal metaplasia^[7].

In colon conditions, CLE has had an accuracy of 82%

for predicting polyp histology *in-vivo*, increasing to 94% if used in combination with digital chromoendoscopy with narrow band imaging during procedures^[8]. Moreover, in inflammatory bowel diseases (IBDs), various studies have examined the role of CLE in surveillance of IBD patients, assessing the extent of disease, targeting biopsies, earlier detection of dysplasia, assessment of mucosal healing, and defining treatment protocols^[9,10].

Recently, new applications in the biliary tract and for diagnosing subtypes of pancreatic cysts have been studied showing a mean accuracy of 85% for diagnosis of neoplastic and non-neoplastic lesions^[11,12].

IS IT TIME TO MOVE ON?

In spite of its high accuracy as well as several clinical applications, CLE is still not used in routine clinical practice. This could be correlated to many factors such as: cost of the procedure, lack of codification and reimbursement in some countries, absence of standard of care indications, availability, physician image-interpretation training, medico-legal problems, and the role of the pathologist.

However, these limitations are relative, and solutions could be found based on new research leading to increased consensus overcoming present barriers. Examples of this could be: cost-effective studies and analysis, meta-analysis, learning curve studies, *etc.*

A recent study performed at our institution demonstrated the benefit of using CLE in cases of "diagnostic doubts", causing changes in diagnostic and therapeutic approach in 40% of cases, in the performance of target biopsies in 100% of cases (17/17) and making other diagnostic or therapeutic methods unnecessary in all cases^[13].

In this regard, a patient with Barrett esophagus and dysplasia at histopathology but without dysplasia criteria at high definition with chromoendoscopy could have diagnosis benefits using CLE. Other examples are: patients with biliary tract stenosis of unknown origin where citobrush did not evidence neoplasia, and the difficult management during follow-up repetitions. In both cases, need of newer tests and examinations, biopsies, *etc.*, will be unnecessary, reducing the cost management of these patients.

One of the biggest problems when using CLE, is that histopathology remains the gold-standard technique for final diagnosis of diseases. However, histopathology could have a 20% to 30% misdiagnosis rate due to many factors such as interpretation mistakes, biopsy site inaccuracy, or number of biopsies^[4].

Another suggestion would be to use CLE in cases where other investigative procedures have shown an absence of malignancy as a method of confirmation of the negative results. This would eliminate many of the medical and cost-related problems mentioned above. The rationale for this is based on the fact that 9 out of 10 biopsies are benign and that the accuracy of CLE to confirm non-neoplastic lesions is higher than its

accuracy for confirming positive neo-plastic results.

FUTURE PERSPECTIVES

New studies focused on solving the relative barriers in using CLE are currently necessary. The results obtained during the last ten years validate the use of CLE in clinical practice, and the first step to doing this could be dealing with patients with diagnostic uncertainties. This could improve and solve many unclear diagnoses as well as improve therapeutic decisions and/or follow-up procedures in this kind of patient.

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