Name of Journal: *World Journal of Gastrointestinal Endoscopy*

ESPS Manuscript NO: 33720

Manuscript Type: Original Article

Retrospective Cohort Study

Dear Editor and Reviewer;

Thanks for the revision of our manuscript entitled: "**Clinical impact of confocal laser endomicroscopy probe (p–CLE) in the management of gastrointestinal lesions"**

We perform the revision and we modify the text in accordance to your suggestions that we will explained point by point as follow:

REVIEWER 02551224:
ANSWER: Thanks for your review and comments. The discussion was slightly modified in accordance to your observations. Moreover, an important English grammar revision was done by a language editing service. (The final paper submitted had the language correction)

REVIEWER 00058340
ANSWER: The title was modified from: to:

1. Title: "Clinical impact of confocal laser endomicroscopy probe (p–CLE) in the management of gastrointestinal lesions". Please modify it reflect better authors' main contention. Please delete "probe" because probe alone without entire CellVizio system does not work.

ANSWER: The title was modified from: "**Clinical impact of confocal laser endomicroscopy probe (p–CLE) in the management of gastrointestinal lesions"** to: "**Clinical impact of confocal laser endomicroscopy (CLE) in the management of gastrointestinal lesions with uncertain diagnosis"**

2) The paper requires extensive linguistic revisions: e.g. Abstract : "Endoscopic and histopathology findings don't always correlate to certainty, leading to diagnostic and therapeutic inaccuracy. Confocal laser endomicroscopy

probe (p-CLE) allows in-vivo cellular evaluation with a diagnostic accuracy above 90% for neoplastic (N) and non – neoplastic (NN) lesions" should be changed to: Endoscopic and histopathology findings don't always closely correlate, leading to diagnostic and therapeutic inaccuracy. Confocal laser endomicroscopy (CLE) allows in-vivo tissue evaluation with a diagnostic accuracy over 90% for neoplastic (N) and non – neoplastic (NN) lesions" CONCLUSION: "p-CLE seems to be an essential diagnostic tool for patients with uncertain diag-nosis with a significant clinical impact on the diagnosis and treatment". should be changed to: CLE is a new diagnostic tool for patients with uncertain diagnosis and has a significant clinical impact on the diagnosis and treatment. Entire text require careful linguistic revisions.

ANSWER: Totally agree. The entire text was send to a company of language editing service as is specified in the language editing certificate. The conclusion of the abstract was changed in accordance to your suggestions to: "CLE is a new diagnostic tool for patients with uncertain diagnosis and has a significant clinical impact on the diagnosis and treatment."

3) Please remove from the entire text" p-CLE" and change it to CLE for the reason I mentioned before.

ANSWER: Totally agree. "p-CLE" was removed from the entire text and was changed to "CLE"

4) All figures require more detailed description and labeling with arrows. In Fig. 1c "Hystological" should be corrected to histological. Figure 1 B shows image in green color. Is this a pseudocolor? Regular CellVizio systems show black and white picture. Only CellVizio Dual band show color pictures. Please clarify this also for Fig 2B and 2C.

ANSWER: A detailed description was performed. The word "Hystological" was corrected by "Histological", but as I already mentioned the article was reviewed by a company of language editing service in this resubmission. Regarding the color of figures, it was explained in each figure how was obtained the color of the cellvizio, by using cellvizio viewer software, as well as was specified the type of image color palette used in each one.

Figure 1b. CLE showing dysplasia (image optimized by image color palette green-white by using Cellvizio® viewer software)

Figure 2c. CLE showing dark clumps suspected for malignancy (image optimized by image color palette "black-red-yellow" by using Cellvizio® viewer software)

In the next pages you can find the step by step correction remarked previous to the language editing service. (The final paper submitted had the language correction)

REVIEWER 01467632:
ANSWER: Thanks for your review and for considered our paper as a "very attractive topic". Regarding the appearance of carcinoid tumors are the same of malignant lesions for gastrointestinal tract as has been proposed by other authors, and is already mentioned in the methods of this paper. The parasites findings appearance as is mentioned in the results section was observed as an inflammatory area at confocal in accordance to the Paris classification (already mentioned in the methods of this paper).
Regarding the summarized results of the paper, the objective of this is not to determine the accuracy of each classification as has been reported by several studies, this paper was performed to determine the "global accuracy of CLE" to determine malignancy and non-malignancy in the clinical practice. Moreover, the clinical impact of this report is not only measured by the summarized results. The clinical impact was measured also by the "change in management", that is well explained in the material and methods part of the paper and the results. Finally, as a large confocal user of Cellvizio, I do not agree that the accuracy of CLE is correlated with the different probes, because all probes had an standard deep penetration on the mucosa (20μm) as you can see in all images obtained by Cellvizio. The probes had different diammeters due to its own use (for example cholangio flex and aq-flex are 0.8 mm in diameter, but still have the same penetration). Moreover, any study performed until now do not demonstrated that the characteristic of the probes had an impact on the accuracy of the method. All tables were edited and improved for better understand as you can see in this revision.

Below you can find the draft of the manuscript with the modifications suggested by the reviewers without English grammar correction:

Name of Journal: *World Journal of Gastrointestinal Endoscopy*
ESPS Manuscript NO: 33720
Manuscript Type: Original Article
Retrospective Cohort Study

Clinical impact of confocal laser endomicroscopy (CLE) in the management of gastrointestinal lesions with an uncertain diagnosis.

批注 [CR1]: The title was modified in accordance to the reviewer 00058340

Robles-Medranda C *et al.* **Clinical impact of CLE in GI**

批注 [CR2]: p-CLE was modified by the suggestion of the reviewer 00058340 here and in the rest of the manuscript

~~**Clinical impact of confocal laser endomicroscopy probe (p-CLE) in the management of gastrointestinal lesions**~~

~~Robles-Medranda C *et al.* **Clinical impact of p-CLE in GI**~~

带格式的: 英语(美国)

Carlos Robles-Medranda, Maria Vargas, Jesenia Ospina, Miguel Puga-Tejada, Manuel Valero, Miguel Soria, Gladys Bravo, Carlos Robles-Jara, Hannah Pitanga Lukashok

Carlos Robles-Medranda, Maria Vargas, Jesenia Ospina, Miguel Puga-Tejada, Manuel Valero, Miguel Soria, Gladys Bravo, Carlos Robles-Jara, Hannah Pitanga Lukashok, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas (IECED), University Hospital OMNI, Guayaquil 090505, Ecuador

Author contributions: Carlos Robles-Medranda and Maria Vargas wrote the paper; Gladys Bravo Velez collected data; Jesenia Ospina, Carlos Robles-Jara, Miguel Soria Alcívar and Miguel Puga-Tejada collected and analyzed the data; Manuel Valero analyzed data; Hannah P. Lukashok and Carlos Robles-Medranda designed the study, analyzed data and revised the manuscript for important intellectual content and final approval the version of the article to be publish.

Supported by: The study did not receive financial support from any institution.

Institutional review board statement: Ecuadorian Institute of Digestive Disease Institutional review board

Informed consent statement: Informed and written consent was provided to all study participants, or their legal guardians, prior to study enrollment

Conflict-of-interest statement: The authors have no conflict of interests.

Data sharing statement: No additional unpublished data are available.

批注 [W用3]: Please offer separate pdf files for the four statements and sign them in handwritten. Thank you!

批注 [CR4]: Separate Pdf files were attached

带格式的: 英语(美国)

~~Correspondance~~Correspondence **to:**

Carlos Robles-Medranda, MD, **Head of the Endoscopy Division**, Instituto Ecuatoriano de Enfermedades Digestivas – IECED, OMNI Hospital, Av. Abel Romeo Castillo y Av. Juan Tanca Marengo, Torre Vitalis, Mezanine 3, Guayaquil 090505, Ecuador. carlosoakm@yahoo.es

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Revised:

Accepted:

Article in press:

Published online

Abstract

~~Endoscopic and histopathology findings don't always correlate to certainty, leading to diagnostic and therapeutic inaccuracy. Confocal laser endomicroscopy probe (p-CLE) allows in vivo cellular evaluation with a diagnostic accuracy above 90% for neoplastic (N) and non – neoplastic (NN) lesions. Few studies have determined the clinical impact of p-CLE for the diagnosis and management of patients with uncertain diagnosis.~~

AIM: To evaluate the clinical impact of p-CLE for the diagnosis and management of patients with uncertain diagnosis.

METHODS

Retrospective chart review including patients with poor correlation between endoscopic and histological findings, whom underwent p-CLE between Nov 2013 and Oct 2015. Baseline characteristics, indications, previous diagnostic studies, findings at p-CLE, clinical management and histological results were described. Interventions based on p-CLE findings were analyzed. The diagnostic accuracy of p-CLE compared to target biopsies or the surgical specimen was also measured.

RESULTS

144 patients were included, 51% (74/144) were female. Mean age was 51 years old. A total of 41/144 (28. 4%) lesions were neoplastic (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic). The sensitivity, specificity, PPV, NPV and observed agreement of CLE to detect N-lesions were 85.37%, 87.38%, 72.92%, 93.75% and 86.81% respectively. Cohen Kappa was 69.20%, which results in a good agreement. Changes in management were noticed in 54% of cases.

批注 [W用5]: Please delete this section. Thank you!

批注 [CR6]: This section was removed in accordance to your suggestions and the suggestions of the reviewer 00003557

批注 [CR7]: Statistics were reviewed. For kappa value there was a mistake that was corrected in this final version

~~Out of 144 patients included, 51% (74/144) were female. Mean age was 51 years old. A total of 41/144 (28. 4%) lesions were neoplastic (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic). The sensitivity, specificity, PPV, NPV and accuracy of p-CLE to detect N lesions were 85.37%, 87.38%, 72.92%, 93.75% and 86.8 respectively. The observed agreement was 90.6% with a Kappa value of 0.80, which results in a substantial agreement. Changes in management were noticed in 54% of cases.~~

CONCLUSION

~~p-~~CLE ~~seems to be an essential~~is a new diagnostic tool for patients with uncertain diagnosis ~~with~~ and has a significant clinical impact on the diagnosis and treatment.

批注 **[CR8]:** Conclusion was modified in accordance to the suggestion of reviewer 00058340

Key words: Confocal laser endomicroscopy; in-vivo microscopy; barret esophagus; gastrointestinal cancer; pancreatic cyst, biliary strictures~~, confocal laser endomicroscopy probe (p-CLE)~~

Abbreviations: Confocal laser endomicroscopy ~~probe~~ (~~p-~~CLE), neoplastic (N), non – neoplastic (NN), Ecuadorian Institute of Digestive Diseases (IECED), positive predictive value (PPV), negative predictive value (NPV), gastrointestinal (GI), computer tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), upper endoscopy(UE), inflammatory bowel disease (IBD),

Core tip: Endoscopic and histopathology findings don't always correlate to certainty, leading to diagnostic and therapeutic inaccuracy.

The use of confocal laser endomicroscopy ~~probe~~ (~~p-~~CLE) to evaluate patients with uncertain diagnosis changes significantly the clinical impact on the diagnosis and treatment.

Robles-Medranda C, Vargas M, Ospina J, Puga-Tejada M, Valero M, Soria M, Bravo G, Robles-Jara C, Lukashok HP. Clinical impact of confocal laser endomi-

croscopy probe (p-CLE) in the management of gastrointestinal ~~neoplastic and non-neoplastic~~ lesions with uncertain diagnosis

Audio Core Tip

批注 [W用9]: Please offer the audio core tip, the requriment are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:
Acceptable file formats: .mp3, .wav, or .aiff
Maximum file size: 10 MB
To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

批注 [CR10]: Audio core tip was done

INTRODUCTION

Conventional histology is the gold standard procedure to evaluate lesions in the gastrointestinal tract, however poor correlation between endoscopic and histological findings have been described. This can lead to inability to achieve an accurate diagnosis and subsequent inadequate clinical management [1-5]. It has been described a 20-30% probability of sampling errors, second to several factors such as inadequate macroscopic interpretation and minimal biopsy acquisition [6].

Confocal laser endomicroscopy (CLE) is a technique which allows in-vivo evaluation during endoscopy of the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts [5,7]. Furthermore, it provides dynamic information like blood flow and contrast up-take [8].

Multiple studies have shown that CLE has a diagnostic accuracy above 90% employing standardized parameters for the evaluation of specific lesions features [9-17]. However, there is minimal information on the literature about the influence of CLE in the evaluation and management of patients with uncertain diagnosis of GI lesions. The aim of this study is to evaluate the clinical impact of CLE in this group of patients.

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~~Probe based confocal laser endomicroscopy (p-CLE) is a technique which allows in-vivo evaluation during endoscopy of the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts [5,7]. Furthermore, it provides dynamic information like blood flow and contrast up-take [8].~~

~~Multiple studies have shown that p-CLE has a diagnostic accuracy above 90% employing standardized parameters for the evaluation of specific lesions features [9-17]. However, there is minimal information on the literature about the influence of p-CLE in the evaluation and management of patients with uncertain diagnosis of GI lesions. The aim of this study is to evaluate the clinical impact of p-CLE in this group of patients.~~

MATERIALS AND METHODS

Study design

The study was an observational, analytic, retrospective, cross sectional single-center study, with prospective data collection performed at the Ecuadorian Institute of Digestive Diseases - IECED, Omni Hospital Academic Tertiary Care Center, Guayaquil, Ecuador, from November 2013 to September 2015. The study protocol was approved by the Institutional Ethical and Review Board and was conducted according to the declaration of Helsinki.

批注 **[MÁPT11]:** COMPLETÉ UN POCO EL TIPO DE ESTUDIO, Y ORGANICÉ EL PÁRRAFO.

~~A retrospective, single-center study, with prospective collection of data from November 2013 to September 2015, performed at the Ecuadorian Institute of Digestive Diseases – IECED, Omni Hospital Academic Tertiary Care Center,~~

~~Guayaquil, Ecuador. The study protocol was approved by the Institutional Review Board and was conducted according to the declaration of Helsinki.~~

Demographic data, indications, previous diagnostic studies, ~~p-~~CLE findings, clinical management and histological results were described. Records from previous endoscopies [upper endoscopy (UE) and colonoscopy with high definition magnification and digital chromoendoscopy, endoscopic retrograde cholangio-pancreatography (ERCP) with brushing sample and endoscopic ultrasound (EUS)], computer tomography (CT), magnetic resonance imaging (MRI) cholangio-pancreatography and tumor markers were analyzed.

Population selection

Inclusion criteria:

1. Patients that underwent ~~p-~~CLE (Cellvizio®, Mauna Kea Technology, France), due to an uncertain diagnosis (absence of endoscopic and histological correlation) of gastrointestinal diseases including neoplastic (N) or non-neoplastic (NN) lesions (Table 1).
2. Age≥18 years old
3. Acceptance to participate
4. No previous p-CLE

Exclusion criteria:

1. Pregnancy.
2. Allergies and/or contraindication to fluorescein.

Endoscopy and ~~p-~~CLE procedures

All participants underwent ~~p-~~CLE according to the standard protocol. Sedation was provided using propofol for UE and colonoscopy, and general anesthesia for ERCP and EUS. For UE and colonoscopy the ~~p-~~CLE was performed using Gastroflex® and Coloflex® probes (Cellvizio®, Mauna Kea Technology, France) through the working channel of the standard video-endoscopes. For ERCP pro-

cedures ~~p-~~CLE was performed through cholangioscopy (Spy Glass® system, Boston Scientific®) and for EUS ~~p-~~CLE through a 19G needle (Expect® needle, Boston Scientific) using the Cholangioflex® and AQ-flex® probes (Cellvizio®, Mauna Kea Technology, France).

After inspection of the GI mucosa, the areas of suspected pathology were studied. The probe was carefully approached to the mucosa and in-vivo microscopy images at 1000x magnification were scanned by ~~p-~~CLE, and transmitted in a real-time video into a screen situated next to the endoscopy monitor. For tissue contrast, an injection of 5 ml of 10% fluorescein was performed in all patients.

The analysis of all lesions was done in real-time following endoscopic assessment. Microscopy images and videos obtained with ~~p-~~CLE were stored for further examination. The interpretation of the images was fulfilled according to previous published studies for esophageal [18,19], gastric [14,20,21] and colonic [22-24] lesions. The Miami [25,26], Paris [13], and CONTACT [11] studies criteria using ~~p-~~CLE were used for bilio-pancreatic tract and cystic pancreatic lesions.

Definitions

Uncertain diagnosis of gastrointestinal lesions was defined as lack of correlation between the histological report and findings on initial endoscopy (UE, colonoscopy, ERCP, EUS).

N lesions included dysplasia, adenomas and carcinomas located at any level of the GI tract, pancreas or biliary duct.

Any other lesion was defined as a NN lesion (Figures 1, 2).

We defined "change in management" by ~~p-~~CLE when it allowed--in cases of uncertain diagnosis --to target the biopsy site, with results that changed the management initially proposed based on the initial biopsy or avoided further diagnostic methods.

Statistical analysis

Baseline characteristics as demographic data, indications, CLE findings, histological results and change in management were described through percentages and ranges, mean and standard deviation, as appropriate. The CLE overall diagnostic accuracy for an N-lesion was determined by the comparison between CLE findings and final histopathological report after CLE (biopsy or surgical specimen). Measures used for this purpose were: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), simple percent agreement (observed agreement) and inter-rater agreement (Cohen Kappa). Cohen Kappa was interpreted according to Landis & Koch-Kappa's Benchmark Scale. Change in management and redirection of biopsy samples were described through percentages. Characteristics between N-lesions and NN-lesions groups were compared using Student's t-test for continuing variables, chi-squared and Fisher test for categorical variables. A p value <0.05 was considered to be statistically significant. Statistical methodology of this study were reviewed by the IECED institutional Biostatistician. Statistical calculations were performed in SPSS software suite v.22. ~~Diagnostic yield was determined by the comparison between p-CLE and final histopathological findings after p-CLE. Measures used for this purpose were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and match measurement. The primary endpoint of malignant diagnosis was based on a positive histopathology report after p-CLE. Diagnostic and therapeutic management, redirection of biopsy samples and the need for further diagnostic methods was evaluated.~~

~~The observed concordance was evaluated according to Landis & Koch criteria.~~

~~The statistical methods of this study were reviewed by the IECED institutional statistician. Statistical calculations were performed in SPSS software suite v.22.~~

批注 [MÁPT12]: HACE FALTA CITAR ESTO???

批注 [CR13]: ok

批注 [MÁPT14]: AUMENTÉ LA PARTE DEL VALOR P… ESTO LO HICE LUEGO DE SU REVISIÓN.

批注 [MÁPT15]: VOLV ÍA ESCRIBIR EL ANÁLISIS ESTAD ÍSTICO.

RESULTS

One hundred and forty-four patients were included with a mean age of 51.33 years old (range 18 – 86). 51.4% (74/144) were female. There were 41/144 N-lesions: 13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic) (Table 1). Findings included Barrett esophagus

with and without dysplasia, adenocarcinomas and mucosal inflammation of different segments of the digestive tract, gastric metaplasia and dysplasia, carcinoid tumors, ampulloma, mucinous and serous pancreatic cysts, pseudocyst, adenoma and adenocarcinoma of the biliary tract and inflammation related to parasites.

CLE sensitivity, specificity, PPV and NPV detecting N-lesions compared with target biopsies or surgical specimen were 85.37%, 87.38%, 72.92% and 93.75%, respectively. The observed agreement was 86.81%, with a Cohen Kappa value of 69.20%, which results in a good agreement (Table 2). Changes in management were noticed in 78/144 (54.2) cases (Table 3), due to better acquisition of targeted biopsies by CLE, thus avoiding further diagnostic methods.

~~One hundred and forty four patients were included with a mean age of 51 years old (range 24-83). 51% (74/144) were male. 41/144 lesions were neoplastic (N) (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal and 1 rectal, 1 ampulloma and 1 pancreatic). (Table 1)~~

~~Findings included Barrett esophagus with and without dysplasia, adenocarcinomas and mucosal inflammation of different segments of the digestive tract, gastric metaplasia and dysplasia, carcinoid tumors, ampulloma, mucinous and serous pancreatic cysts, pseudocyst, adenoma and adenocarcinoma of the biliary tract and inflammation related to parasites.~~

~~The sensitivity, specificity, PPV, NPV and accuracy of p-CLE to detect N lesions compared with target biopsies or surgical specimen were 85.37%,87.38%, 72.92%, 93.75% and 86.8 respectively.~~

~~The observed agreement was 90.6% with a Kappa value of 0.80, which results in a substantial agreement. Changes in management were noticed in 54% of cases, second to better acquisition of targeted biopsies by p-CLE, thus avoiding further diagnostic methods.~~

批注 [CR16]: Table 2 was mentioned in the text in accordance to your suggestions

批注 [CR17]: Table 3 was mentioned in the text in accordance to your suggestions

DISCUSSION

CLE is an imaging method that has shown substantial benefit in the diagnosis of GI tract, bile duct and pancreatic lesions. Several publications support this statement by showing a considerable correlation between CLE and histology [15-17]. Recent studies [11,18] have demonstrated that CLE has a high accuracy in differentiating benign from malignant lesions, with a mean accuracy of 81% in bile duct and pancreas pathology [21], 94-96% for malignant gastric lesion [20] and 82% in polyp features evaluation [22]. In addition, the American Society for Gastrointestinal Endoscopy, reported that CLE had at least 90% sensitivity and 98% NPV for the detection of Barrett's esophagus associated dysplasia [18]. The Miami classification criteria for bile duct lesions have demonstrated a higher accuracy diagnosing malignant strictures compared to biopsy sample (81% vs. 75%) [12]. However, it had some limitations for differentiating inflammatory from malignant strictures, leading to false positive results. Based on this findings, Caillol et al. developed the Paris Classification, which has the ability to increase sensitivity and specificity in the characterization of indeterminate bile duct strictures [13,27]. Also in colonoscopy, CLE has proven to be very useful. Neumann et al. described that in inflammatory bowel disease (IBD) surveillance, CLE is a simple technique that facilitates an accurate and early detection of related lesions [23,24].

Our study focuses on the clinical impact and management change generated by the use of CLE in the evaluation of GI (upper and lower) lesions, including the bile duct pathology and pancreatic cysts, in a subgroup of patients with uncertain diagnosis due to non-conclusive previous studies.

CLE proved to have a high accuracy to detect neoplastic bilio-pancreatic lesions, which represented 80% of lesions found in the bile ducts and pancreas. In 54% of those cases, the use of CLE led to a change of the diagnostic and thera-

peutic approach. On the other hand, 71% of the overall lesions in patients with inconclusive diagnosis, were non-neoplastic benign lesions and CLE showed an observed agreement, PPV and NPV of 86%, 72% and 93%, respectively. These results are similar to previous publications concerning the upper and lower portions of the gastrointestinal tract. [1, 22-30]

The main advantage noted, by using CLE, was its ability to differentiate in-vivo lesions and guide targeted biopsies avoiding possible complications due to unnecessary endoscopic mucosal resections (e.g. perforation or bleeding). Also it prevented the use of further unnecessary invasive and noninvasive diagnostic methods (repeated endoscopy, ERCP, EUS, or other imaging modalities as CT and MRI), reducing patient risks and economical burden.

However, our study had limitations due to the fact that it was a single-center retrospective study with lack of randomization.~~p-CLE is an imaging method that has shown substantial benefit in the diagnosis of GI tract, bile duct and pancreatic lesions. Several publications support this statement by showing a considerable correlation between p-CLE and histology [15-17]. Recent studies [11,18] have demonstrated that p-CLE has a high accuracy in differentiating benign from malignant lesions, with a mean accuracy of 81% in bile duct and pancreas pathology [21], 94-96% for malignant gastric lesion [20] and 82% in polyp features evaluation [22]. In addition, the American Society for Gastrointestinal Endoscopy, reported that p-CLE had at least 90% sensitivity and 98% NPV for the detection of Barrett's esophagus associated dysplasia [18]. The Miami classification criteria for bile duct lesions have demonstrated a higher accuracy diagnosing malignant strictures compared to biopsy sample (81% vs. 75%) [12]. However, it had some limitations for differentiating inflammatory from malignant strictures, leading to false positive results. Based on this findings, Caillol et al. developed the Paris Classification, which has the ability to increase sensitivity and specificity in the characterization of indeterminate bile duct strictures [13,27]. Also in colonoscopy, CLE has proven to be very useful. Neumann et al. described that in inflammatory bowel disease (IBD) surveillance, CLE is a simple technique that facilitates an accurate and early detection of related lesions [23,24].~~

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~~However our study had limitations due to the fact that it was a single-center retrospective study with lack of randomization.~~

CONCLUSION

Our study suggests that ~~p-~~CLE represents an essential diagnostic tool for patients with uncertain diagnosis (neoplastic or non-neoplastic). It allows a real-time evaluation of the GI mucosa allowing endoscopists to target their biopsies leading to a significant clinical impact by improving and modifying diagnosis and treatment.

COMMENTS

(1) Background

批注 [W用18]: Please write the comments.
Writing requirements for each subsection
(1) Background
To summarize concisely and accurately the relevant background information so that readers may gain some basic knowledge about your study's relevance and understand its significance for the field as a whole.
(2) Research frontiers
To introduce briefly the current hotspots or important areas in the research field as related to your study.
(3) Innovations and breakthroughs
To summarize and emphasize the differences, particularly the advances, achievements, innovations and breakthroughs, as compared to other related or similar studies in the literature, which will allow the readers to assimilate the major points of your article.
(4) Applications
To summarize the practical applications of your research findings, so that readers may understand the perspectives by which this study will affect the field and future research.
(5) Terminology
To describe concisely and accurately any terms that may not be familiar to the majority of the readers, but which are essential for understanding your article.

带格式的: 字体: 小四

带格式的: 列出段落, 编号 + 级别: 1 + 编号样式: 1, 2, 3, … + 起始编号: 1 + 对齐方式: 左侧 + 对齐位置: 0.63 厘米 + 缩进位置: 1.27 厘米

Confocal laser endomicroscopy (CLE) is a technique which allows in-vivo evaluation during endoscopy of the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts.

(2) Research frontiers

We evaluate the clinical impact of CLE in patients with uncertain diagnosis of gastrointestinal lesions.

(3) Innovations and breakthroughs

The observed agreement was 86.81%, with a Cohen Kappa value of 69.20%, which results in a good agreement. Changes in management were noticed in 78/144 (54.2) cases, due to better acquisition of targeted biopsies by CLE, thus avoiding further diagnostic methods.

(4) Applications

CLE is a new diagnostic tool for patients with uncertain diagnosis and has a significant clinical impact on the diagnosis and treatment.

(5) Terminology

Confocal laser endomicroscopy; in-vivo microscopy.

带格式的: 字体: 小四, 非加粗, 英语(美国)
带格式的: 列出段落
带格式的: 字体: 非加粗
带格式的: 字体: 小四
带格式的: 列出段落, 编号 + 级别: 1 + 编号样式: 1, 2, 3, … + 起始编号: 1 + 对齐方式: 左侧 + 对齐位置: 0.63 厘米 + 缩进位置: 1.27 厘米
带格式的: Cuerpo A, 缩进: 左侧: 1.27 厘米, 定义网格后自动调整右缩进, 调整中文与西文文字的间距, 调整中文与数字的间距
带格式的: 字体: 非加粗, 字体颜色: 文字 1
带格式的: 字体: 小四
带格式的: 列出段落, 编号 + 级别: 1 + 编号样式: 1, 2, 3, … + 起始编号: 1 + 对齐方式: 左侧 + 对齐位置: 0.63 厘米 + 缩进位置: 1.27 厘米
带格式的: 字体: 小四, 英语(美国)
带格式的: 列出段落
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FIGURES

Figure 1: Colonic polyp

批注 [W用20]: Please offer total title for figure 1. Thank you!

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Figure 1a. Sigmoid flat polyp with a pitt pattern suggesting hyperplastic lesion (by using digital chromoendoscopy with high definition by i-scan) in a patient with cirrhosis and important coagulation disorders

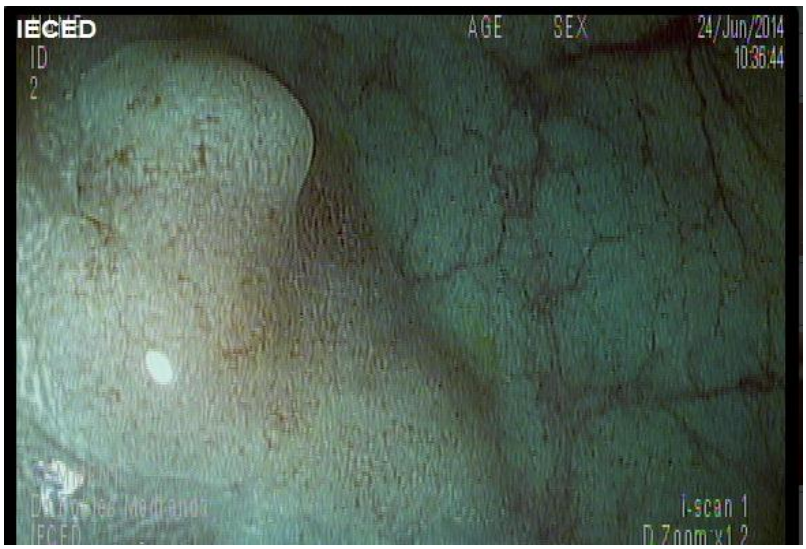

Figure 1b. ~~p~~-CLE showing dysplasia (image optimized by image color palette green-white by using Cellvizio® viewer software)

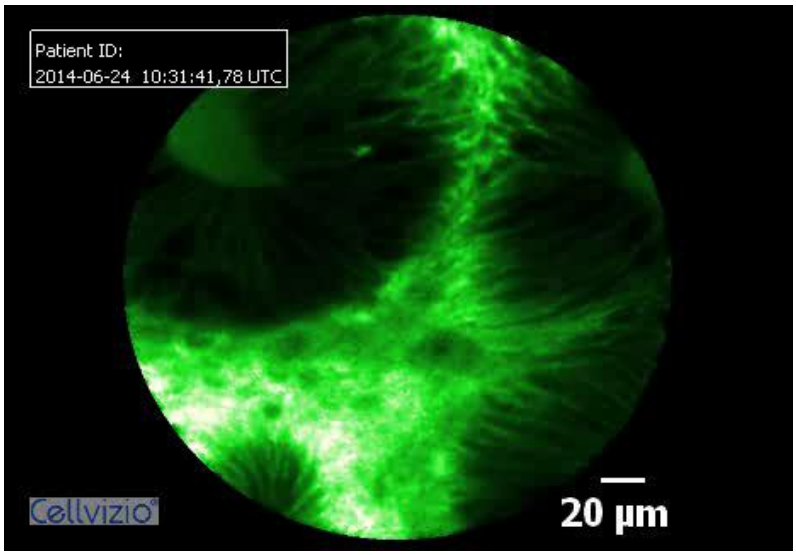

Figure 1c. Hiystological analysis of specimen confirming the dysplasia

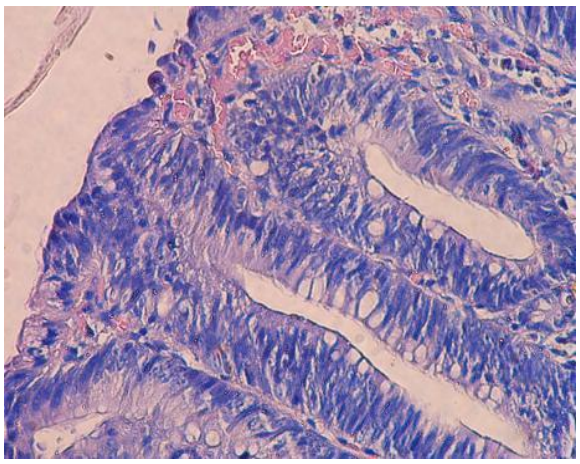

Figure 2: Undetermined stenosis of the biliary tract

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批注 [CR23]:

Figure 2a. ERCP of a patient with undetermined stenosis and citobrush negative for malignancy.

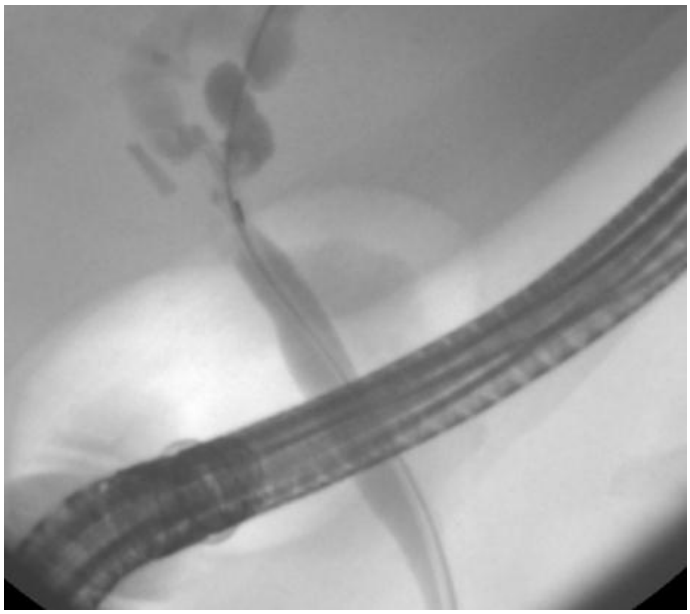

Figure 2b. Spyglass cholangioscopy showing a redish area non suspected for malignancy

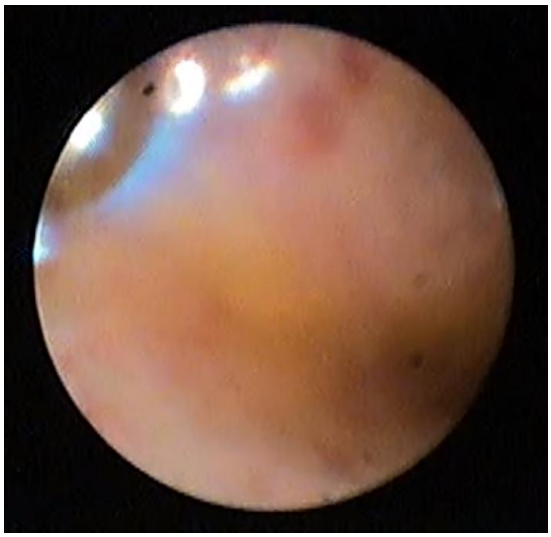

Figure 2c. CLE showing dark clumps suspected for malignancy (image optimized by image color palette "black-red-yellow" by using Cellvizio® viewer software)

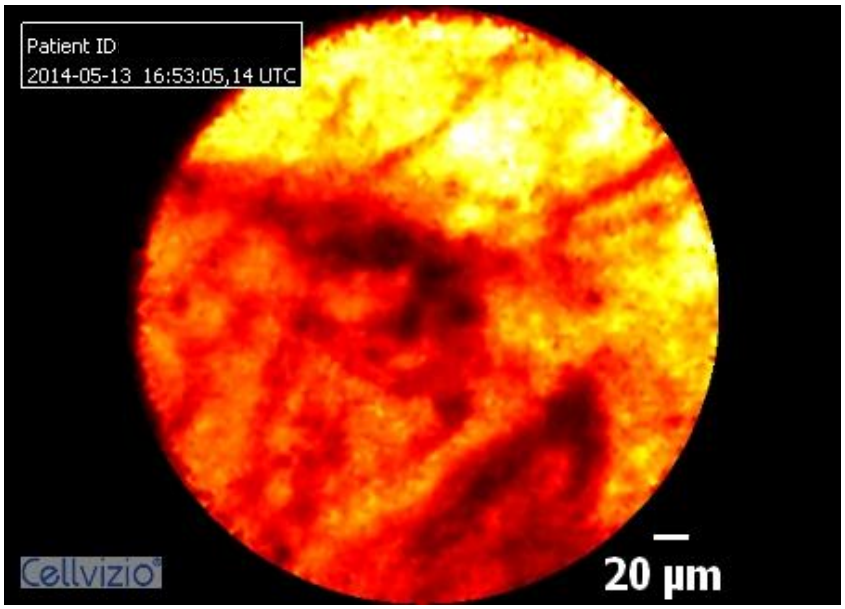

Figure 2d. Histological results from a target biopsy confirming a cholangiocarcinoma

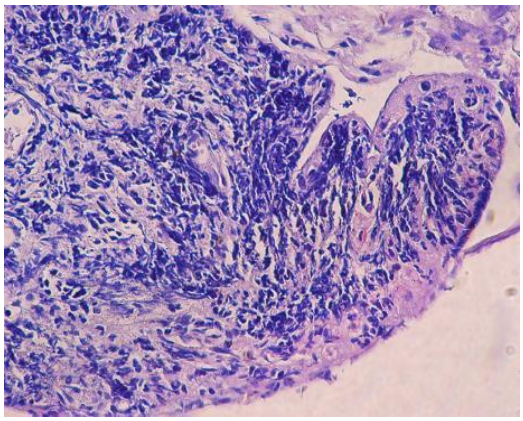

Table 1. Baseline characteristics.

-	Biopsy/Surgical specimen diagnosis						
	Total (n=144)		**Neoplastic lesions (n=41)**		**Non-Neoplastic lesions (n=103)**		***p* value**
Sex (female), n (%)	74	(51.4)	19	(46.3)	55	(53.4)	0.445
Age, years, mean ± SD	51.33	± 16.5	56.73	± 17.1	49.19	± 15.8	0.014
Initial endoscopy indication, n (%)							<0.001
Suspected tumor	70	(48.6)	32	(78.0)	38	(36.9)	
Other	74	(51.4)	9	(22.0)	65	(63.1)	
Location, n (%)							0.187
Vater ampulla	2	(1.4)	1	(2.4)	1	(1.0)	
Colon	14	(9.7)	6	(14.6)	8	(7.8)	
Duodenum	4	(2.8)	1	(2.4)	3	(2.9)	
Esophagus	24	(16.7)	8	(19.5)	16	(15.5)	
Stomach	59	(41.0)	10	(24.4)	49	(47.6)	
Ileum	1	(0.7)	0	(0.0)	1	(1.0)	
Pancreas	8	(5.6)	1	(2.4)	7	(6.8)	
Rectum	3	(2.1)	1	(2.4)	2	(1.9)	

Bile duct	29	(20.1)	13	(31.7)	16	(15.5)

SD: Standard Deviation.

Table 2. CLE overall diagnostic accuracy considering CLE target biopsy or surgical specimen as Gold Standard.

	Biopsy/Surgical specimen diagnosis						
	Total (n=144)		**Neoplastic lesions (n=41)**		**Non-Neoplastic lesions (n=103)**		***p* value**
CLE diagnosis, n (%)							<0.001
Neoplastic lesion	48	(33.3)	35	(85.4)	13	(12.6)	
Non Neoplastic lesion	96	(66.7)	6	(14.6)	90	(87.4)	
CLE overall diagnostic accuracy							
Sensitivity, n/T (%; 95% CI)				35/41	(85.37; 70.83 – 94.43)		
Specificity, n/T (%; 95% CI)				90/103	(87.38; 79.38 – 93.11)		
PPV, n/T (%; 95% CI)				35/48	(72.92; 61.46 – 81.97)		
NPV, n/T (%; 95% CI)				90/96	(93.75; 87.71 – 96.93)		
Observed Agreement, n/T (%)				125/144	(86.81)		
Cohen Kappa, % (95% CI)				69.20	(56.50 – 81.90)		

PPV: Positive Predictive Value. NPV: Negative Predictive Value. CI: confidence interval.

Table 3. Patients with change in management, according to biopsy/surgical specimen diagnosis, per location.

	Biopsy/Surgical specimen diagnosis						
	Total (n=78)		Neoplastic lesions (n=30)		Non-Neoplastic lesions (n=48)		*p* value
Location, n (%)							0.707
Vater ampulla	1	(1.3)	1	(3.3)	0		
Colon	9	(11.5)	4	(13.3)	5	(10.4)	
Duodenum	4	(5.1)	1	(3.3)	3	(6.3)	
Esophagus	10	(12.8)	5	(16.7)	5	(10.4)	
Stomach	17	(21.8)	5	(16.7)	12	(25.0)	
Ileum	1	(1.3)	0		1	(2.1)	
Pancreas	6	(7.7)	1	(3.3)	5	(10.4)	
Rectum	3	(3.8)	1	(3.3)	2	(4.2)	
Bile duct	27	(34.6)	12	(40.0)	15	(31.3)	

-		N (n=41)	NN (n=103)	Total (n=144)
Sex (F)				74
Age, years [mean]				51.53
INITIAL ENDOSCOPY INDICATIONS				
	Suspected tumor	32 (78)	38 (37)	70
	Other	9 (22)	65 (63)	74

N: neoplastic; NN: non neoplastic

Table 2. Results table.

Location	N	NN	TOTAL	*p* value	CM (N)	CM (NN)	TOTAL
Esophagus	8	16	24	0,187	5	5	10
Stomach	10	49	59		5	12	17
Vater am-	1	1	2		1	0	1

批注 [W用24]: For this table, please offer table title. Thank you!

批注 [CR25]: Tables were edited and organized in accordance to your suggestions. Insertion of location in the main text was performed in the results section. Statistical analysis was reviewed and the corrections were made.

批注 [W用26]: Please mark the location of tables 2 and 3. Thank you!

pulla							
Duodenum	1	3	4		1	3	4
Pancreas	1	7	8		1	5	6
Bile duct	13	16	29		12	15	27
Colon	6	8	14		4	5	9
Ileum	0	1	1		0	1	1
Rectum	1	2	3		1	2	3
Total	41	103	144		30	48	78

N: neoplastic result at p-CLE target biopsy

NN: non neoplastic result at p-CLE target biopsy

CM: change in management.

Table 3. p-CLE Diagnosis accuracy considering p-CLE target biopsy or surgical specimen as Gold Standard

Sensitivity	85,37%
Specificity	87,38%
PPV	72,92%
NPV	93,75%
Overall accuracy	86,80%
Change in management	54,16%

批注 [CR27]: Tables were edited and organized in accordance to your suggestions. Insertion of location in the main text was performed in the results section. Statistical analysis was reviewed and the corrections were made.

Below the manuscript edited with English grammar correction:

Name of Journal: *World Journal of Gastrointestinal Endoscopy*

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Retrospective Cohort Study

Clinical impact of confocal laser endomicroscopy (CLE) in the management of gastrointestinal lesions with an uncertain diagnosis.

Carlos Robles-Medranda, Maria Vargas, Jesenia Ospina, Miguel Puga-Tejada, Manuel Valero, Miguel Soria, Gladys Bravo, Carlos Robles-Jara, Hannah Pitanga Lukashok

Carlos Robles-Medranda, Maria Vargas, Jesenia Ospina, Miguel Puga-Tejada, Manuel Valero, Miguel Soria, Gladys Bravo, Carlos Robles-Jara, Hannah Pitanga Lukashok, Gastroenterology and Endoscopy Division, Instituto Ecuatoriano de Enfermedades Digestivas (IECED), University Hospital OMNI, Guayaquil 090505, Ecuador

Author contributions: Carlos Robles-Medranda and Maria Vargas wrote the paper; Gladys Bravo Velez collected data; Jesenia Ospina, Carlos Robles-Jara, Miguel Soria Alcívar and Miguel Puga-Tejada collected and analyzed the data; Manuel Valero analyzed the data; Hannah P. Lukashok and Carlos Robles-Medranda designed the study, analyzed the data, revised the manuscript for important intellectual content and provided final approval the version of the article to be published.

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Informed consent statement: Informed written consent was obtained from all study participants or their legal guardians prior to study enrollment.

Conflict-of-interest statement: The authors have no conflict of interests.

Data sharing statement: No additional unpublished data are available.

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Abstract

AIM: To evaluate the clinical impact of CLE in the diagnosis and management of patients with an uncertain diagnosis.

METHODS

A retrospective chart review was performed. Patients who underwent CLE between Nov 2013 and Oct 2015 and exhibited a poor correlation between endoscopic and histological findings were included. Baseline characteristics, indications, previous diagnostic studies, findings at the time of CLE, clinical management and histological results were analyzed. Interventions based on CLE findings were also analyzed. We compared the diagnostic accuracy of CLE and target biopsies of surgical specimens.

RESULTS

A total of 144 patients were included. Of these, 51% (74/144) were female. The mean age was 51 years old. In all, 41/144 (28. 4%) lesions were neoplastic (13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and observed agreement when CLE was used to detect N-lesions were 85.37%, 87.38%, 72.92%, 93.75% and 86.81%, respectively. Cohen's Kappa was 69.20%, thus indicating good agreement. Changes in management were observed in 54% of the cases.

CONCLUSION

CLE is a new diagnostic tool that has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnosis.

Key words: Confocal laser endomicroscopy; *in vivo* microscopy; Barret esophagus; gastrointestinal cancer; pancreatic cyst, biliary strictures

Abbreviations: Confocal laser endomicroscopy (CLE), neoplastic (N), non–neoplastic (NN), Ecuadorian Institute of Digestive Diseases (IECED), positive predictive value (PPV), negative predictive value (NPV), gastrointestinal (GI), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), upper endoscopy (UE), inflammatory bowel disease (IBD).

Core tip: Endoscopic and histopathological findings are not always certain, thus potentially leading to inaccurate diagnoses and inappropriate therapeutics. The use of confocal laser endomicroscopy (CLE) has a significant clinical impact on the diagnosis and treatment of patients with uncertain diagnoses.

Robles-Medranda C, Vargas M, Ospina J, Puga-Tejada M, Valero M, Soria M, Bravo G, Robles-Jara C, Lukashok HP. Clinical impact of confocal laser endomicroscopy (CLE) in the management of gastrointestinal lesions with an uncertain diagnosis.

Audio Core Tip

INTRODUCTION

Conventional histology is the gold standard procedure in evaluating lesions in the gastrointestinal tract. However, endoscopic and histological findings are sometimes poorly correlated, thus hindering accurate diagnosis and subsequent clinical management [1-5]. The probability of sampling error has been found to be 20-30% and is affected by several factors, such as inadequate macroscopic interpretation and minimal biopsy acquisition [6].

Confocal laser endomicroscopy (CLE) is a technique that is used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts [5,7]. Furthermore, it provides dynamic information including blood flow and contrast up-take [8].

Multiple studies have shown that CLE has a diagnostic accuracy above 90% when standardized parameters are used to evaluate specific lesion features [9-17]. However, there is minimal information in the literature regarding the influence of CLE on the evaluation and management of patients with GI lesions of uncertain diagnosis. The aim of this study was to evaluate the clinical impact of CLE in this group of patients.

MATERIALS AND METHODS

Study design

This study was an observational, analytical, retrospective, cross-sectional single-center study. Prospective data from November 2013 to September 2015 were collected at the Ecuadorian Institute of Digestive Diseases (IECED) Omni Hospital Academic Tertiary Care Center, Guayaquil, Ecuador. The study protocol was approved by the Institutional Ethical and Review Board and conducted according to the guidelines in the declaration of Helsinki.

Demographic data, indications, previous diagnostic findings, CLE findings, clinical management and histological results are described. Records from previous endoscopies [i.e., upper endoscopy (UE), colonoscopy with high definition

magnification and digital chromoendoscopy, endoscopic retrograde cholangiopancreatography (ERCP) with brushing sample and endoscopic ultrasound (EUS)], computed tomography (CT), magnetic resonance imaging (MRI) cholangiopancreatography and tests for tumor markers were analyzed.

Population selection

Inclusion criteria:

5. Patients who underwent CLE (Cellvizio®, Mauna Kea Technology, France) as a result of an uncertain diagnosis (an absence of correlation between endoscopic and histological findings) in gastrointestinal diseases, including neoplastic (N) or non-neoplastic (NN) lesions (Table 1).
6. Patients ≥18 years old
7. Patients who agreed to participate
8. Patients with no previous p-CLE

Exclusion criteria:

3. Pregnant patients
4. Patients with allergies and/or contraindication to fluorescein

Endoscopy and CLE procedures

All participants underwent CLE according to the standard protocol. Sedation was accomplished with propofol in UE and colonoscopy and general anesthesia in ERCP and EUS. In UE and colonoscopy, the CLE was performed with Gastroflex® and Coloflex® probes (Cellvizio®, Mauna Kea Technology, France) through the working channel of a standard video-endoscope. In ERCP procedures, CLE was performed through cholangioscopy (Spy Glass® system, Boston Scientific®), and in EUS, CLE was performed through a 19G needle (Expect® needle, Boston Scientific) with Cholangioflex® and AQ-flex® probes (Cellvizio®, Mauna Kea Technology, France).

After the GI mucosa was inspected, the areas with suspected pathology were further examined. The probe was carefully advanced to the mucosa, and *in vivo* microscopy images were scanned at 1000x magnification by using CLE. These video images were transmitted in a real-time onto a screen situated next to the endoscopy monitor. For tissue contrast, 5 ml of 10% fluorescein was injected in all patients.

All lesions were analyzed in real-time after an endoscopic assessment. Micrographs and videos obtained during CLE were stored for further examination. The images were interpreted according to methods previously published in esophageal [18,19], gastric [14,20,21] and colonic [22-24] lesions. The Miami [25,26], Paris [13], and CONTACT [11] study criteria for using CLE were used in biliopancreatic tract and cystic pancreatic lesions.

Definitions

An uncertain diagnosis in a case of gastrointestinal lesions was defined as a lack of correlation between a histological report and findings on initial endoscopy (e.g., UE, colonoscopy, ERCP, EUS).

Neoplastic (N) lesions included dysplasia, adenomas and carcinomas that were located at any level of the GI tract, pancreas or biliary duct.

Any other lesion was defined as a non-neoplastic (NN) lesion (Figures 1, 2).

We defined a "change in management" resulting from CLE in cases of uncertain diagnosis when the results of CLE changed the management strategy that was initially based on the original biopsy or when no further diagnostic methods were used.

Statistical analysis

Baseline characteristics, including demographic data, indications, CLE findings, histological results and changes in management, were described as percentages and ranges or means and standard deviations, as appropriate. The overall diagnostic accuracy of CLE in an N-lesion was determined by comparing the CLE

findings to the final post-CLE histopathological report (e.g., biopsy or surgical specimen). The following measurements were used for this purpose: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), simple percentage agreement (observed agreement) and inter-rater agreement (Cohen's Kappa). Cohen's Kappa was interpreted by using Landis & Koch-Kappa's Benchmark Scale. Changes in management and redirected biopsy samples were described as percentages. The characteristics of N-lesions and NN-lesions groups were compared using Student's t-test for continuing variables and chi-squared and Fisher's test for categorical variables. A p value <0.05 was considered to be statistically significant. The statistical methodology used in this study was reviewed by the IECED institutional Biostatistician. Statistical calculations were performed in SPSS software suite v.22.

RESULTS

A total of 144 patients were included. The mean age of the patients was 51.33 years old (range 18 – 86), and 51.4% (74/144) were female. There were 41/144 N-lesions, including 13 bile duct, 10 gastric, 8 esophageal, 6 colonic, 1 duodenal, 1 rectal, 1 ampulloma and 1 pancreatic lesion (Table 1). The findings included Barrett's esophagus with or without dysplasia, adenocarcinomas and mucosal inflammation in different segments of the digestive tract, gastric metaplasia and dysplasia, carcinoid tumors, ampulloma, mucinous and serous pancreatic cysts, pseudocysts, adenoma and adenocarcinoma of the biliary tract and inflammation related to parasites.

The sensitivity, specificity, PPV and NPV for detecting N-lesions between CLE and target biopsies or surgical specimens were 85.37%, 87.38%, 72.92% and 93.75%, respectively. The observed agreement was 86.81%, and Cohen's Kappa value was 69.20%, thus indicating good agreement (Table 2). Changes in management were noted in 78/144 (54.2) cases (Table 3). These changes resulted from the improved ability of CLE to acquire targeted biopsies, which avoided the need for further diagnostic methods.

DISCUSSION

CLE is an imaging method that has demonstrated substantial benefit for diagnosing GI tract, bile duct and pancreatic lesions. Several previous reports have supported CLE's efficacy by showing CLE and histological findings are well correlated [15-17]. Recent studies [11,18] have demonstrated that CLE has high accuracy in differentiating benign from malignant lesions in bile duct and pancreas pathology (mean accuracy, 81%) [21], malignant gastric lesions (94-96%) [20] and polyps (82%) [22]. In addition, the American Society for Gastrointestinal Endoscopy has reported that CLE has at least 90% sensitivity and 98% NPV when it is used to detect Barrett's esophagus-associated dysplasia [18]. The Miami classification criteria for bile duct lesions have been demonstrated to have a higher accuracy when they are used to diagnose malignant strictures rather than biopsy samples (81% vs. 75%, respectively) [12]. However, these criteria have some limitations when they are used to differentiate inflammatory from malignant strictures, thus leading to false positives. On the basis of this finding, Caillol et al. have developed the Paris Classification, which has increased sensitivity and specificity in characterizing indeterminate bile duct strictures [13,27]. Additionally, in colonoscopy, CLE has been demonstrated to be very useful. Neumann et al. have found that CLE, when used in inflammatory bowel disease (IBD) surveillance, is a simple technique that facilitates the accurate and early detection of related lesions [23,24].

Our study focused on the clinical impact and management changes resulting from the use of CLE to evaluate GI (upper and lower) lesions, including bile duct pathology and pancreatic cysts, in a subgroup of patients with uncertain diagnoses due to non-conclusive previous tests.

CLE was found to have a high accuracy in detecting neoplastic bilio-pancreatic lesions, which accounted for 80% of all lesions found in the bile ducts and pancreas. In 54% of such cases, the use of CLE resulted in a change in the diagnostic

and therapeutic approach. However, 71% of all lesions in patients with an inconclusive diagnosis were NN benign lesions, and CLE resulted in an observed agreement, PPV and NPV of 86%, 72% and 93%, respectively. These results were similar to those reported in previous publications that have explored lesions in the upper and lower portions of the gastrointestinal tract. [1, 22-30]

The main advantages of using CLE include its ability to differentiate *in vivo* lesions and guide targeted biopsies, thereby avoiding the potential complications associated with endoscopic mucosal resections (e.g., perforation or bleeding). Additionally, using CLE prevents a need for further unnecessary invasive and noninvasive diagnostic methods (e.g., repeated endoscopy, ERCP, EUS, or other imaging modalities, such as CT and MRI), thus decreasing patient risk and economic burden associated with such procedures.

However, our study has limitations, including its single-center retrospective design and lack of randomization.

CONCLUSION

The results of this study suggest that CLE is a valuable diagnostic tool for patients with an uncertain diagnosis (neoplastic or non-neoplastic). CLE can be used to perform real-time evaluation of the GI mucosa, thus allowing endoscopists to target biopsies and having a significant clinical impact when it is used to improve and modify diagnoses and treatment strategies.

COMMENTS

(6) Background

Confocal laser endomicroscopy (CLE) is a technique that can be used *in vivo* during endoscopy to evaluate the mucosal epithelium of the gastrointestinal tract, the bile duct and pancreatic cysts

(7) Research frontiers

We evaluated the clinical impact of CLE in patients with an uncertain diagnosis in gastrointestinal lesions.

(8) Innovations and breakthroughs

The observed agreement was 86.81% and had a Cohen's Kappa value of 69.20%, thus indicating good agreement. Changes in management were noted in 78/144 (54.2) cases and were associated with the improved acquisition of targeted biopsies, thus avoiding the need for further diagnostic tests.

(9) Applications

CLE is a new diagnostic tool that can be used in patients with uncertain diagnosis, in whom it has a significant clinical impact on diagnosis and treatment.

(10) Terminology

Confocal laser endomicroscopy; *in vivo* microscopy

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FIGURES

Figure 1: Colonic polyp

Figure 1a. A sigmoid flat polyp was viewed using digital chromoendoscopy with high definition by i-scan, which revealed a pit pattern suggestive of a hyperplastic lesion in a patient with cirrhosis and important coagulation disorders.

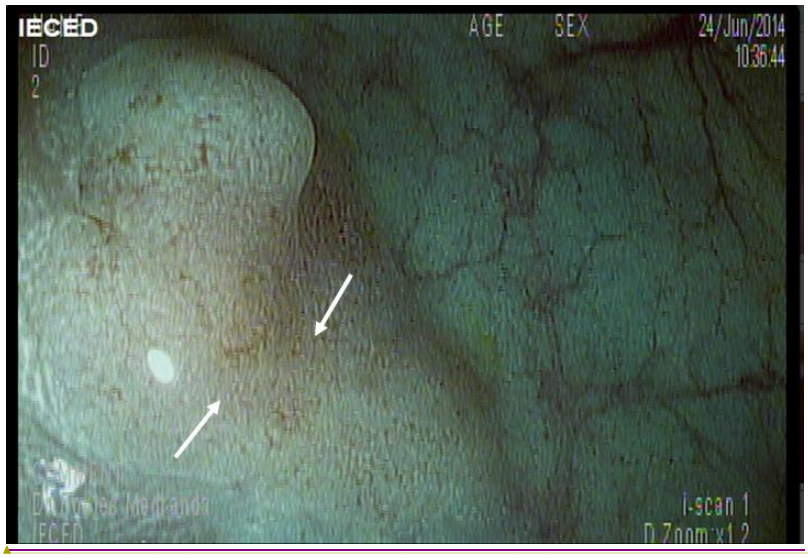

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Figure 1b. CLE showing dysplasia (image optimized by using a green-white image color palette in Cellvizio® viewer software).

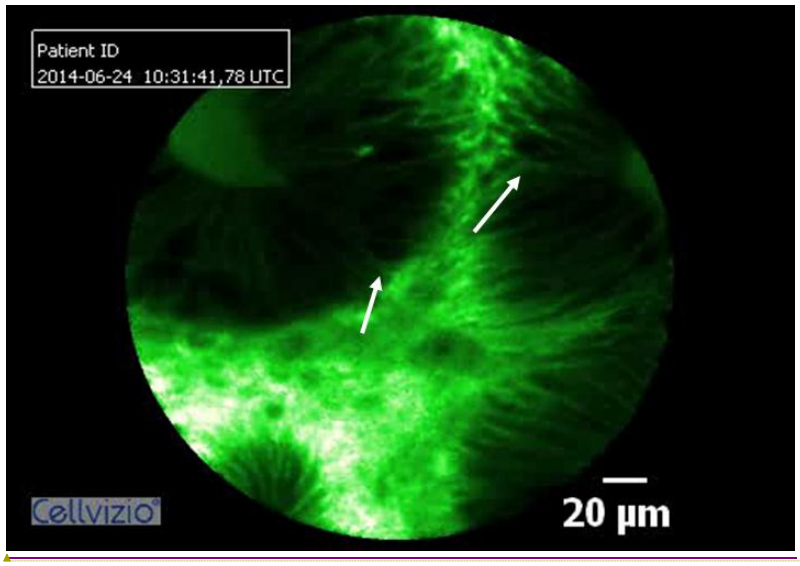

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Figure 1c. A histological analysis of the specimen confirmed the dysplasia.

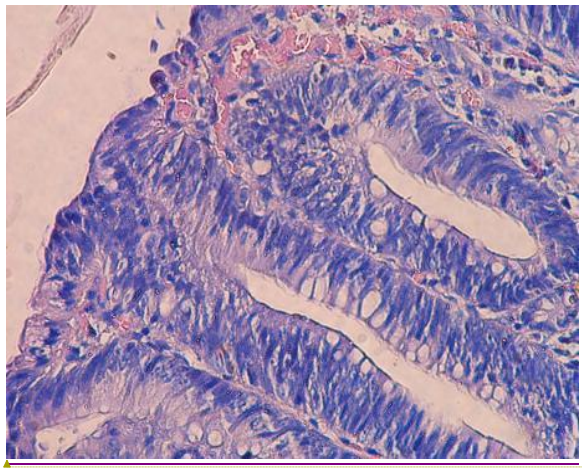

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Figure 2: Undetermined stenosis of the biliary tract

Figure 2a. ERCP was performed in a patient with undetermined stenosis who was citobrush-negative for malignancy.

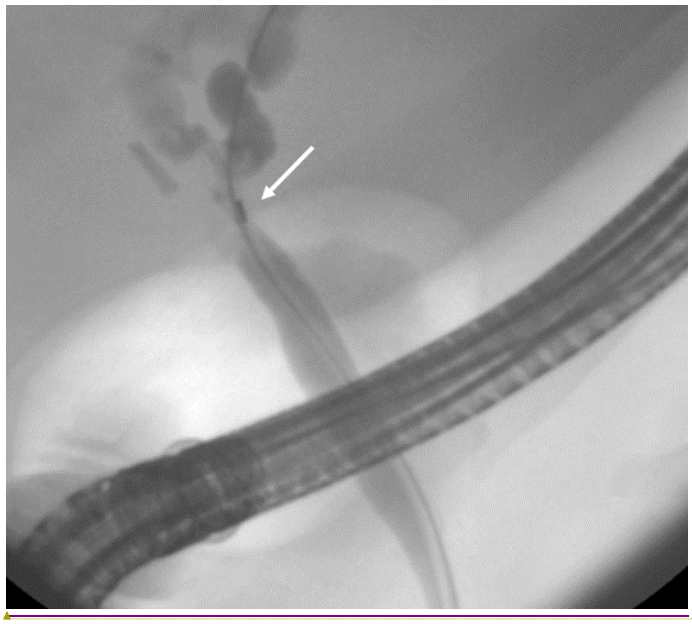

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Figure 2b. Spyglass cholangioscopy showing a reddish area that was not suspected of malignancy.

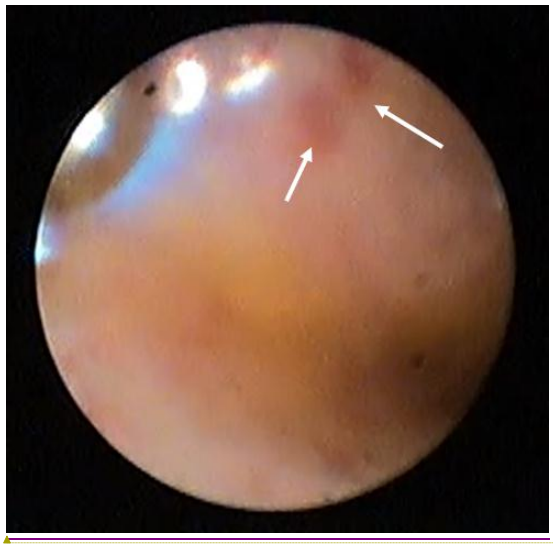

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Figure 2c. CLE showing dark clumps that were suspected of malignancy (image optimized using the "black-red-yellow" image color palette in Cellvizio® viewer software).

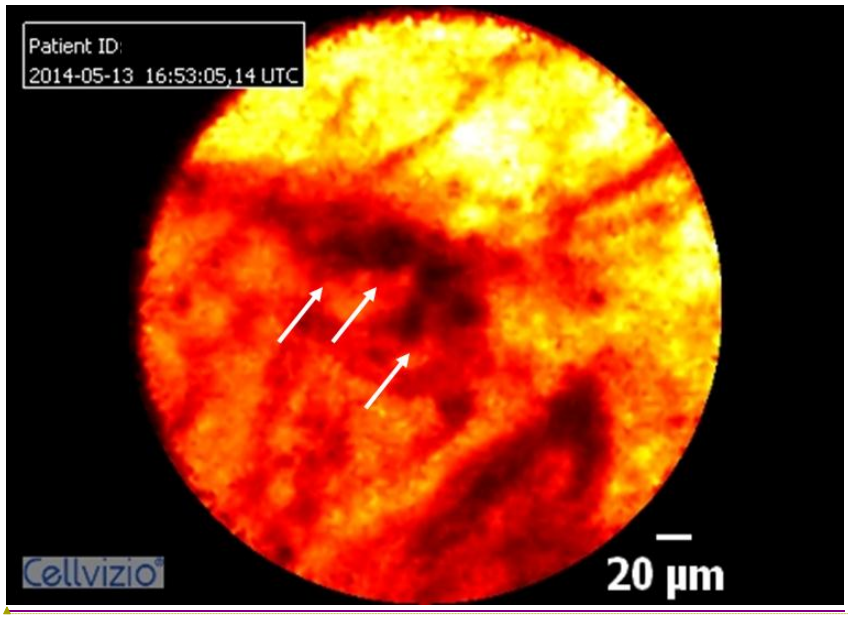

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Figure 2d. The histological results of a target biopsy confirmed a diagnosis of cholangiocarcinoma.

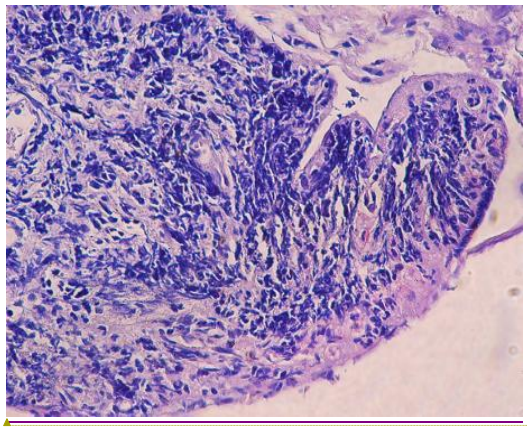

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Table 1. Baseline characteristics.

-	Biopsy/Surgical specimen diagnosis						
	Total (n=144)		**Neoplastic lesions (n=41)**		**Non-Neoplastic lesions (n=103)**		***p* value**
Sex (female), n (%)	74	(51.4)	19	(46.3)	55	(53.4)	0.445
Age, years, mean ± SD	51.33	± 16.5	56.73	± 17.1	49.19	± 15.8	0.014
Initial endoscopy indication, n (%)							<0.001
Suspected tumor	70	(48.6)	32	(78.0)	38	(36.9)	
Other	74	(51.4)	9	(22.0)	65	(63.1)	
Location, n (%)							0.187
Vater ampulla	2	(1.4)	1	(2.4)	1	(1.0)	
Colon	14	(9.7)	6	(14.6)	8	(7.8)	
Duodenum	4	(2.8)	1	(2.4)	3	(2.9)	
Esophagus	24	(16.7)	8	(19.5)	16	(15.5)	
Stomach	59	(41.0)	10	(24.4)	49	(47.6)	
Ileum	1	(0.7)	0	(0.0)	1	(1.0)	
Pancreas	8	(5.6)	1	(2.4)	7	(6.8)	
Rectum	3	(2.1)	1	(2.4)	2	(1.9)	

Bile duct	29	(20.1)	13	(31.7)	16	(15.5)

SD: Standard Deviation.

Table 2. CLE overall diagnostic accuracy with either CLE target biopsy or surgical specimens as the Gold Standard.

	Biopsy/Surgical specimen diagnosis						
	Total (n=144)		**Neoplastic lesions (n=41)**		**Non-Neoplastic lesions (n=103)**		***p* value**
CLE diagnosis, n (%)							<0.001
Neoplastic lesion	48	(33.3)	35	(85.4)	13	(12.6)	
Non-Neoplastic lesion	96	(66.7)	6	(14.6)	90	(87.4)	
CLE overall diagnostic accuracy							
Sensitivity, n/T (%; 95% CI)				35/41	(85.37; 70.83 – 94.43)		
Specificity, n/T (%; 95% CI)				90/103	(87.38; 79.38 – 93.11)		
PPV, n/T (%; 95% CI)				35/48	(72.92; 61.46 – 81.97)		
NPV, n/T (%; 95% CI)				90/96	(93.75; 87.71 – 96.93)		
Observed Agreement, n/T (%)				125/144	(86.81)		
Cohen's Kappa, % (95% CI)				69.20	(56.50 – 81.90)		

PPV: Positive Predictive Value. NPV: Negative Predictive Value. CI: confidence interval.

Table 3. Patients with changes in management following biopsy/surgical specimen diagnosis, listed according to organ.

	Biopsy/Surgical specimen diagnosis						*p* value
	Total (n=78)		Neoplastic lesions (n=30)		Non-Neoplastic lesions (n=48)		
Location, n (%)							0.707
Vater ampulla	1	(1.3)	1	(3.3)	0		
Colon	9	(11.5)	4	(13.3)	5	(10.4)	
Duodenum	4	(5.1)	1	(3.3)	3	(6.3)	
Esophagus	10	(12.8)	5	(16.7)	5	(10.4)	
Stomach	17	(21.8)	5	(16.7)	12	(25.0)	
Ileum	1	(1.3)	0		1	(2.1)	
Pancreas	6	(7.7)	1	(3.3)	5	(10.4)	
Rectum	3	(3.8)	1	(3.3)	2	(4.2)	
Bile duct	27	(34.6)	12	(40.0)	15	(31.3)	