Probe confocal laser endomicroscopy in the therapeutic endoscopic management of Barrett’s dysplasia

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Abstract

Background Endoscopic management of Barrett’s esophagus (BE) depends on the histological stage of BE and includes the following: follow up, endotherapy with thermal ablation, and piecemeal or monobloc endoscopic resection (ER). We know that biopsies are unreliable in 20-75% of cases. The aim of our study was to evaluate the efficiency of probe confocal laser endomicroscopy (pCLE) in the diagnosis of the histological stage of BE, compared with the final histological results after ER.

Methods This retrospective study was based on a prospective registry of patients referred for management of BE-associated dysplasia. The inclusion criteria were dysplasia associated with BE on pre-resection biopsy and endoscopic resection of the examined areas. CLE examinations (pCLEs) were performed using the Gastroflex® probe (Maunakea company). ER was sufficient to ensure that the target area was resected. The following four potential diagnoses were considered: normal or inflammatory mucosa, metaplasia (BE), low-grade dysplasia (LGD), and high-grade dysplasia/esophageal adenocarcinoma (HGD/EAC).

Results The sensitivity, specificity, and accuracy in the detection of HGD/EAC were 92.9%, 71.4% and 80% for pCLE, and 78.6%, 61.9%, and 68.6% for histological biopsy, respectively. The differences in favor of pCLE were not statistically significant (P=0.2); however, in 13 patients with irregularities of the mucosa without elevated or depressed lesions (2 HGD/EAC and 11 non-HGD/EAC), pCLE led to positive redirection of therapy in 70% (9/13) of cases.

Conclusion In the absence of visible lesions, pCLE appears to lead to correct diagnoses and to aid real-time decisions regarding therapeutic management.

Keywords Probe confocal laser endomicroscopy, Barrett’s esophagus, endoscopic resection

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Introduction

Barrett’s esophagus (BE) involves the replacement of the squamous mucosa with specialized intestinal metaplasia that can evolve in the following sequence: metaplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), and esophageal adenocarcinoma (EAC) [1]. Endoscopic management depends on the histological stage of BE and includes the following: follow up; endotherapy with thermal ablation; and endoscopic resection (ER), either piecemeal with mainly cap-assisted endoscopic mucosal resection (EMR), monobloc with the use of submucosal dissection (ESD), or surgical management in cases with invasive lesions [2]. The therapeutic management of BE depends on biopsy results, and we know that biopsies are unreliable in 20-75% of cases [3,4]. Consequently, several techniques have been introduced to improve the diagnosis of the histological stage of BE. With improvements in imaging (i.e. high-definition [HD] vision, electronic coloration, and zoom) endoscopy permits the detection of dysplasia in nearly 90% of cases, but this has only been demonstrated in a handful of studies by teams of Asian experts who compared the results with those of biopsies [5]. In parallel, confocal laser endomicroscopy (CLE) allows a histological view of the
mucosa and has been demonstrated to result in an increase in HGD detection in BE [6-9].

In the present study, CLE was used to detect dysplasia. Patients were referred to our center for the therapeutic management of dysplasia in BE, and the aim of our study was to test whether CLE could be used to confirm the accuracy of the diagnoses based on biopsy, and, when biopsy proved inaccurate, permit changes in therapeutic management in real time.

**Patients and methods**

This was a retrospective study based on a prospective registry of patients referred for the management of BE associated with at least LGD on previous biopsies, i.e., all patients had at least LGD on the biopsies. Inclusion criteria were: presence of macroscopic BE; dysplasia associated with BE on pre-resection biopsy; a CLE examination of visible lesions in BE; and ER of the examined areas because of HGD or suspicious lesions with LGD on the pre-resection biopsies. The lack of a biopsy, CLE or ER was an exclusion criterion. The macroscopic aspects of the BE and the examined areas had to be described as elevated or non-elevated lesions.

The pre-resection biopsy followed the Seattle protocol associated with targeted biopsies in suspicious areas. The biopsies were read by pathologists from our hospital or from an external center experienced in gastrointestinal diseases. The biopsy results were known before the pCLE and ER, because the aim of the study was to determine the influence of pCLE examination before treatment. Only the worst histology was taken into account.

CLE examinations (pCLE: probe CLE) were performed on visible lesions with the Gastroflex® probe from the Maunakea company, Paris, France. A cap was inserted at the top of the endoscope to limit its movements, which made the pCLE examinations easier. After the injection of fluorescein, the pCLE examination was performed in real time in each case, based on the consensus of 2 experienced endoscopists who performed all of the ERs. CLE criteria were those described by Wallace et al [10], with the addition of the description of LGD (Table 1). LGD was defined by the lack of HGD/EAC and thickness and moderate irregularity of the glands. The examined area was unmarked so as not to hamper the ER and pathological readings.

ER was performed either using either a piecemeal (single snare or cap-assisted EMR with a Duette System® from Cook Medical) or an en bloc method (ESD). The ERs were at least semi-circumferential, and thus sufficiently large to ensure that the target area was resected.

We considered 4 potential diagnoses: normal or inflammatory mucosa, metaplasia (i.e., BE), LGD, and HGD/EAC. The primary endpoints were the sensitivities, specificities and accuracies for the detection of HGD/EAC by pCLE and pre-resection biopsies, compared with those of ER histology. The secondary endpoints were the sensitivities, specificities, and accuracies for the detection of LGD and BE without dysplasia by pCLE.

**Table 1 Miami criteria for Barrett's esophagus (BE) and dysplasia and added criteria for low-grade dysplasia (LGD)**

| Diagnosis | BE without dysplasia | BE with LGD | BE with HGD/EAC |
|-----------|----------------------|-------------|-----------------|
| Uniform villiform architecture | Regular thickened epithelial borders | Disorganized/loss of villiform structures and crypts |
| Columnar cells | Thickened epithelial borders | Dark, irregularly thickened epithelial borders |
| Dark goblet cells | Dilated vessels | Dilated irregular vessels |

HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma

**Statistical analysis**

The statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). The baseline characteristics were summarized using the following descriptive statistics: medians and ranges for continuous variables; numbers and percentages for categorical variables. The aims of this study were to evaluate the abilities of the confocal and biopsy techniques to determine the histologies (EAC, HGD, and BE). To this end, the concordances, sensitivities and specificities were calculated and then compared using non-parametric Cochran’s Q tests to determine whether there were significant differences in the diagnostic abilities of these two techniques.

**Results**

Data were collected from 35 examinations conducted during 35 endoscopic procedures in 31 patients from January 2013 to January 2015. The mean length of BEs was C2.77 [1-9] M4.03 [1-9]. The lesions were elevated (nodular) in 17 cases and non-elevated (or depressed) in 3 cases. There were 2 cases of post-therapeutic stenosis. In 13 cases, the lesions were only irregularities of the mucosa that were made visible thanks to the HD endoscopic vision. The ERs were semi-circumferential in 15 cases and circumferential in 20 cases. The ERs were performed with a single snare in 6 cases, with cap-assisted EMR in 23 cases, and with ESD in 6 cases. The histological results from the resections were normal/inflammatory in 3 cases, BE in 8 cases, LGD in 10 cases, and HGD/EAC in 14 cases. No complications were observed.

Correct diagnoses were made in 71% (25/35) of the cases by pCLE and in 43% (15/35) of the cases by pre-resection biopsy. The sensitivity, specificity, and accuracy for the detection of HGD/EAC was 92.9%, 71.4% and 80% for pCLE, and 78.6%, 61.9%, and 68.6% for histological biopsy, respectively. However, the differences in favor of pCLE were not statistically significant (P=0.25; Table 2).

Fourteen patients had HGD/EAC after ER. One case of HGD/EAC was missed by pCLE and 3 cases were missed by the pre-resection biopsies. In the cases of agreement between the pre-resection biopsies and pCLE (21/35), the sensitivity,
specificity and accuracy for HGD/EAC (12 HGD/EAC cases and 9 non-HGD/EAC cases) were 92%, 89%, and 90%, respectively.

Thirteen patients exhibited irregularities of the mucosa without elevated or depressed lesions (2 HGD/EAC cases and 11 non-HGD/EAC cases). Among these 13 patients, pCLE led to positive redirections of therapy in 70% (9/13) of the cases. There was one misdiagnosis (8%), but no cases of HGD/EAC were missed by CLE. In these cases, pCLE exhibited a sensitivity, specificity, and accuracy for the detection of HGD/EAC of 100%, 82%, and 85%, respectively, compared with 55%, 50%, and 54%, respectively, for the pre-resection biopsies (P=0.02; Table 3). Among these 13 patients, 6 patients exhibited HGD/EAC on pre-resection biopsy. In one case, the pCLE and ER confirmed this finding, and in the other 5 cases, pCLE and ER revealed no HGD/EAC. Six other patients had LGD on the pre-resection biopsies, including 3 cases in which pCLE revealed HGD that was confirmed by ER in one case and invalidated in the 2 other cases (in one case the ER invalidated the pre-resection biopsy and pCLE results). In 2 cases, ER confirmed the pCLE findings of no dysplasia, and in 1 case, the ER confirmed pCLE validation of LGD. The last patient had BE without metaplasia on the pre-resection biopsy, and pCLE found LGD that was confirmed by ER. In this subgroup, we were able to avoid ERs in four cases (i.e. the HGD on the biopsies was not validated by the CLE), and in one case, we performed ER instead of applying ablative therapy.

The macroscopic visualizations of 14 elevated lesions (9 HGD/EAC and 5 non-HGD/EAC) resulted in a sensitivity, specificity, and accuracy for the detection of HGD/EAC of 64.7%, 81.3%, and 72.7%, respectively, and these values were significantly better than those for the non-visualized lesions (P=0.008). For these elevated lesions, pCLE resulted in a sensitivity, specificity, and accuracy of 100%, 40%, and 78.6%, respectively, whereas biopsy resulted in values of 89%, 60%, and 78.6%, respectively (P=0.2).

Regarding the detection of LGD, pCLE had a sensitivity, specificity, and accuracy of 70%, 84%, and 80%, respectively, whereas the pre-resection biopsies resulted in values of 40%, 60%, and 54.3%, respectively (P=0.5). Regarding the detection of BE without dysplasia, pCLE had a sensitivity, specificity, and accuracy of 62.5%, 100%, and 91.4%, respectively, whereas the pre-resection biopsies resulted in values of 0%, 96%, and 74%, respectively (P=0.02).

Regarding the 2 cases of stenosis, in one case, LGD was detected by pre-resection biopsy and pCLE and confirmed by ER. In the other case, pre-resection biopsy found the LGD, pCLE found the HGD/EAC, and ER invalidated these results with a diagnosis of BE without metaplasia (Figs. 1-3).

**Discussion**

Our study is an evaluation of the diagnostic efficacies of pre-resection biopsy and pCLE compared with histology obtained by ER and of the potential influence of pCLE in the management of BE.

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**Table 2** Sensitivity, specificity and accuracy of biopsies and CLE for HGD/EAC

| Diagnostic method | Endoscopic resection | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|-------------------|----------------------|----------------|----------------|--------------|
|                   |                      | HGD/EAC | No HGD/EAC | HGD/EAC | No HGD/EAC | HGD/EAC | No HGD/EAC | HGD/EAC | No HGD/EAC |
| CLE diagnosis     | 93                   | 74     | 82     | P=0.25 |
|                   | 13                   | 5      | 93     | 74     | 82     | P=0.25 |
| Biopsy diagnosis  | 79                   | 58     | 67     |
|                   | 11                   | 8      | 79     | 58     | 67     |
|                   | 3                    | 11     |

CLE, confocal laser endomicroscopy; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma

**Table 3** Sensitivity, specificity and accuracy of CLE and biopsies with non-elevated lesions (13 patients)

| Diagnostic method | Endoscopic resection | Sensitivity (%) | Specificity (%) | Accuracy (%) |
|-------------------|----------------------|----------------|----------------|--------------|
|                   |                      | HGD/EAC | no HGD/EAC | HGD/EAC | no HGD/EAC | HGD/EAC | no HGD/EAC | HGD/EAC | no HGD/EAC |
| CLE diagnosis     | 100                  | 82     | 85     | P=0.22 |
|                   | 2                    | 2      | 100    | 82     | 85     | P=0.22 |
| Biopsy diagnosis  | 50                   | 55     | 55     |
|                   | 1                    | 5      | 50     | 55     |
|                   | 1                    | 6      |

CLE, confocal laser endomicroscopy; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma
of Barrett’s dysplasia. We found greater histological reliability with pCLE than with pre-resection biopsies, although this difference was not statistically significant. Despite some limitations, this study has two strong points. First, benchmark histology can be obtained by ER and not by unreliable biopsies. Second, pCLE is potentially useful in the characterization of flat lesions found in BE, the incidence of which seems to increase with HD endoscopy. Thus, HD endoscopy offers the possibility of applying treatment in real time without waiting for new pathological findings.

Most authors use pCLE to target biopsies [6,7]. In the meta-analysis conducted by Gupta et al [11], which included 8 studies with 345 patients, a per-lesion analysis revealed a pooled sensitivity of 68% and a pooled specificity of 88%, while a per-patient analysis revealed a pooled sensitivity of 86% and a pooled specificity of 83%. All of the included series used biopsies for the benchmark histologies. In a study by Canto et al (which was not included in the above-mentioned meta-analysis), pCLE was analyzed for its value in the detection of HGD [8]. The benchmark histologies for the 94 patients who were studied with pCLE were ER for 22 patients and biopsies for 72 patients, but the results were combined. This group yielded very good results for the detection of HGD. A per-biopsy analysis of 192 patients found the BE neoplasia rate to be significantly higher when pCLE was used (86% compared to 10% with white-light endoscopy [WLE]). pCLE also significantly increased the negative predictive value (NPV) from 94% with WLE to 98%. However, the specificity was lower in the pCLE group (93% vs. 99%), but the accuracies were similar (92% and 93%). A per-patient analysis revealed that, with the addition of pCLE, the sensitivity increased significantly from 40% to 95%, the NPV increased significantly from 90% to 98%, while the specificity decreased (from 98% to 92%). As Gupta et al reminded us, the Preservation and Incorporation of Valuable Endoscopic Innovation that was implemented in 2012 by the American Society of Gastroenterology states that
to replace the Seattle protocol, a technique should have a per-
patient sensitivity of at least 90%, an NPV of at least 98%, and
a specificity of at least 80% for the detection of HGD/EAC. The
meta-analysis did not obtain these results, although the study
of Canto et al did.

All of these studies relied on biopsy results. However, as
the study by Wani et al demonstrated, ER results contradict
biopsy results in 30% of cases [12]. The goal of our study was
to compare pCLE results with more reliable histology results.

One limitation of our study lies in the pathological readings
of the biopsies. While all pre-resection biopsies were subjected
to a double reading, not all of the readings were performed in
our center. We are aware of difficulties of diagnosing dysplasia,
particularly LGD, in BE [13]. Because of the admitted difficulty
of reading pathological findings in BE, the confirmation of pathological findings by 2 specialized gastrointestinal
pathologists is recommended [14]. Nevertheless, the term "gastrointestinal pathologist" is not well defined.
Moreover, there are only very limited data regarding the
interobserver variability between general and gastrointestinal
pathologists [15].

In contrast, we have some data that demonstrate low
interobserver agreement in diagnoses between gastrointestinal
pathologists. Montgomery et al [13] demonstrated poor agreements for LGD (K=0.65) and indefinite dysplasia
(K=0.15) among these pathologists. We also know that the risk
of progression from LGD to carcinoma ranges from 2-40%
depending on the study. This variability is probably due to
the poor interobserver reproducibility [15]. In a study that
included 168 patients, pre-resection biopsies were reviewed by
7 gastrointestinal pathologists, after histologic consensuses had
been reached for 5 of the 168 patients. Agreement among all
7 pathologists was observed in only 12/163 (7.4%) of the cases. In
10 of these 12 cases, invasive carcinomas could not be excluded.
The overall kappa score for all diagnoses defined in this study
(i.e. HGD, HGD or intramucosal carcinoma, intramucosal
adenocarcinoma, and submucosal adenocarcinoma) was fair
(K=0.30), the highest score (for HGD) was moderate (0.47),
and the lowest score (for submucosal carcinoma) was very
poor (0.14) [16]. Consequently, it can be concluded that
pathological readings by gastrointestinal pathologists do not
resolve controversies related to the readings of pathological
biopsies in BE.

We should remind the reader that there is discordance
between pre-resection biopsy and EMR-based pathologies.
EMR can be considered as the gold standard relative to pre-resection biopsy, given its better interobserver concordance [17,18]. Recently, another publication found that
the accuracy of pre-resection biopsies compared with that
of ER pathology in 142 cases was only 61% (downgrades in
16% and upgrades in 23% of cases) after the gastrointestinal
pathologists' readings. Some cases exhibited no dysplasia on
the pathology resections (6 cases), which was consistent with
the results of studies by others and our own study [19].

In the therapeutic management of BE, biopsies are essential
for selecting the appropriate treatment, but several studies have
demonstrated that biopsies lack reliability. In a series published
in 2011, 55 patients (58%) who were referred for T1 lesions
with HGD/intramucosal cancer on biopsy had an invasive Sm2
lesion [20]. In another series, while biopsies revealed HGD,
9 patients (78%) with visible lesions had EAC on ER pathology,
and the value for patients with no visible lesions was 32%
(7/22) [21]. In a surgical series, the authors found that 12%
(3/25) of the cases had EAC with submucosal invasion without
endoscopic lesions [22]. Regarding previous endoscopic
studies involving evaluations of pre-resection biopsies and the
pathological results of ERs, we found ER without dysplasia or
without BE in 4/75 patients in the study by Moss et al [23],
7/19 patients in the study by Ahmad et al [24], 4/25 patients
in the study by Nijhawan et al [25], and 2/12 patients in the
study by Seewald et al [26]. All of these studies were performed
after pre-resection biopsies with HGD. It is not so surprising
that, with the improvement of the scope, we found more
lesions; however, they were not systematic with dysplasia and
consequently needed to be better characterized.

The Seattle protocol is used to minimize sampling errors and
not only requires many biopsies of suspicious lesions, but also
a very high number of systematic biopsies. Indeed, the number
is so high that the protocol is not well applied. The protocol
is probably not very efficient in the detection of dysplasia [27,28].

With improvements in endoscopic imaging, several authors
have attempted to decrease the numbers of biopsies required.
HD imaging with targeted biopsies should allow a level of
dysplasia detection that is equivalent to that of the Seattle
protocol [29]. Likewise, targeted biopsies with electronic
enhancement allow for significantly better detection of HGD
than white-light HD endoscopy using the Seattle protocol
(21 vs. 30%) [30].

By improving detection, HD endoscopy also increases the
number of lesions observed by the endoscopist, which, in this
context, explains the increase in ER in the English Registry
of Radiofrequency Ablation (RFA). This registry revealed
an increase in ER from 48% to 60% between 2008 and 2013 and
a parallel decrease in relapse rates from 13% to 2% [31].
Thus, the problem arising in therapeutic management is one of
characterizing lesions that are undetected by biopsy. Although
the effect was not significant in our study, pCLE could help us
improve the in vivo characterization of histology. In this respect,
our subgroup of patients without elevated or depressed lesions
is important. In this subgroup, pCLE corrected the diagnoses
in 70% of cases. In other words, using pCLE, a patient who is
referred for RFA with LGD can be upgraded to ER based on the
detection of HGD/EAC in real time.

Our study had some limitations. Major limitations are the
retrospective design and the small number of patients. This
small sample size could explain why our results did not reach
significance, despite the trend toward a difference (i.e., 92.9%
and 78.6% sensitivities for the detection of HGD with pCLE
and biopsy, respectively). Another limitation is that the
endoscopists were not blinded to the pre-resection biopsy
results. However, it is common practice for endoscopists
to know the pathology results before ER, and we sought to
maintain this condition in our study. With this non-blinded
method, the decision for ER included an account of the pre-
In the absence of visible lesions, pCLE appears to correctly diagnose close to 70% of cases. pCLE could be applied before thermal ablation in the therapeutic management of LGD to detect HGD/EAC, which would provide greater scope for altering the path of ongoing therapy. Technical progress still needs to be made, but real-time decision making using pCLE could aid in the management of BE.

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**Summary Box**

**What is already known:**

- Endoscopic treatment is the first-line therapy of dysplasia in Barrett’s esophagus
- Endoscopic treatment is based on pre-endoscopic biopsy
- Biopsies for pre-endoscopic treatment are not reliable

**What the new findings are:**

- Confocal laser endomicroscopy (CLE) is a relatively new technique used for gastrointestinal disease
- CLE assumes a comparison with pre-endoscopic biopsies
- CLE can positively change therapeutic endoscopic treatment, in real time, avoiding repeat diagnostic endoscopy
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