Medical Policy Manual Medicine, Policy No. 151

Confocal Laser Endomicroscopy

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Confocal laser endomicroscopy (CLE), also known as confocal fluorescent endomicroscopy and optical endomicroscopy, allows *in vivo* microscopic imaging of cells during endoscopy. CLE is proposed for a variety of purposes, especially as a real-time alternative to histology during colonoscopy and for targeting areas to undergo biopsy in patients with inflammatory bowel disease and Barrett esophagus.

MEDICAL POLICY CRITERIA

Use of confocal laser endomicroscopy is considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12
2. In Vivo Analysis of Colorectal Polyps, Medicine, Policy No. 104
3. Electromagnetic Navigation Bronchoscopy, Surgery, Policy No. 179

BACKGROUND

CLE involves using light from a low-power laser to illuminate tissue and, subsequently, the same lens detects light reflected from the tissue through a pinhole. The term confocal refers to having both illumination and collection systems in the same focal plane. Light reflected and scattered at other geometric angles that is not reflected through the pinhole is excluded from detection, which dramatically increases the special resolution of CLE images.

Endoscope-based and probe-based systems have been cleared by the U.S. Food and Drug Administration (FDA). Endoscope-based systems incorporate a confocal probe onto the tip of a conventional endoscope. Image collection scan rates vary by device. Probe-based systems place a probe through the biopsy channel of a conventional endoscope. Depth of imaging and field of view varies by device. As pointed out in review articles, the limited viewing area emphasizes the need for careful conventional endoscopy to target the areas for evaluation. Both CLE systems are optimized using a contrast agent. The most widely used agent is intravenous fluorescein, which is FDA-approved for ophthalmologic imaging of blood vessels when used with a laser scanning ophthalmoscope.

Unlike techniques such as chromoendoscopy, which are primarily intended to improve the sensitivity of colonoscopy, CLE is unique in that it is designed to immediately characterize the cellular structure of lesions. CLE can thus potentially be used to make a diagnosis of polyp histology, particularly in association with screening or surveillance colonoscopy, which could allow for small hyperplastic lesions to be left in place rather than removed and sent for histologic evaluation. This would reduce risks associated with biopsy and reduce the number of biopsies and histologic evaluations. Another key potential application of CLE technology is targeting areas for biopsy in patients with Barrett esophagus undergoing surveillance endoscopy. This is an alternative to conducting random biopsies during surveillance and has the potential to reduce the number of biopsies and/or improve the detection of dysplasia. Other potential uses of CLE under investigation include better diagnosis and differentiation of conditions such as gastric metaplasia, lung cancer, and bladder cancer.

As noted previously, limitations of CLE systems include a limited viewing area and depth of view. An additional limitation is the lack of standardized systems for classifying lesions viewed with CLE devices. Although there is not currently an internationally accepted classification system for colorectal lesions, two systems have been developed that have been used in a number of studies conducted in different countries. These are the Mainz criteria for endoscopy-based CLE devices and the Miami classification system for probe-based CLE devices.[1] Lesion classification systems are less developed for non-gastrointestinal lesions viewed by CLE devices, e.g., those in the lung or bladder. Another potential limitation of CLE is the learning curve for obtaining high-quality images and classifying lesions. Although several recent studies have found that the ability to acquire high-quality images and interpret them accurately can be learned relatively quickly, these studies were limited to colorectal applications of CLE.[2, 3]

Regulatory Status

Several CLE devices have been cleared for marketing by the FDA. These include:

Cellvizio® (Mauna Kea Technologies): This device consists of a confocal laser system, proprietary software, a flat-panel display and miniaturized fiber optic probes. Since 2006, Mauna Kea has received ten FDA approvals for Cellvizio® systems, most recently in May 2016

(FDA no.'s: K160416, K150831, K151593, K141358, K133466, K132389, K123676, K122042, K120208, K111047, and K061666).

EC-3870CLIK Confocal Video Colonoscope (Pentax Medical Company): This is an endoscopy-based CLE system which consists of the EC-3870CLIK, Confocal Video Colonoscope (K042741) and the ISC-1000 Pentax Confocal Laser System (K042740). The device must be used with a Pentax Video Processor. According to FDA materials, the intended use of the device is to provide optical and microscopic visualization of and therapeutic access to the lower gastrointestinal tract.

EVIDENCE SUMMARY

COLORECTAL LESIONS

Ideally, the evaluation of the safety and efficacy of confocal laser endomicroscopy (CLE) as a diagnostic tool would be based on randomized controlled trials (RCTs) comparing CLE to conventional diagnostic methods, such as biopsy with histology for analysis of colorectal lesions. The evidence for the use of CLE is best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. Validation of the clinical use of any diagnostic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting abnormal histology that is present or in excluding an abnormality that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Multiple studies have evaluated the diagnostic accuracy of CLE for patients undergoing screening or surveillance colonoscopy. Several systematic reviews of studies evaluating the diagnostic accuracy of CLE compared to a reference standard have been published. Descriptions of several systematic reviews and representative diagnostic accuracy studies are included below.

Systematic Reviews

A 2018 systematic review by Lord analyzed the diagnostic accuracy of several optical imaging techniques for in vivo lesion characterization in colonic inflammatory bowel disease (IBD).[4] A total of 22 studies were identified assessing performance of virtual chromoendoscopy, dye-based chromoendoscopy, magnification endoscopy, and confocal laser endomicroscopy. A bivariate meta-analysis was performed. Pooled sensitivities of real-time CLE, magnification endoscopy, virtual chromoendoscopy, and dye-based chromoendoscopy were 91% (95%CI 66% to 98%), 90% (95%CI 77% to 96%), 86% (95%CI 62% to 95%), and 67% (95%CI 44% to 84%), respectively. Pooled specificities were 97% (95%CI 94% to 98%), 87% (95%CI 81% to 91%), 87% (95% CI 72% to 95%), 86% (95%CI 72% to 94%), for the same methods, respectively. The authors concluded that real-time CLE is highly accurate for differentiating neoplastic from non-neoplastic lesions in patients with colonic IBD, but also note that most

CLE studies were performed by single expert users within tertiary centers, which may confound results.

In 2013, Su reviewed studies on the efficacy of CLE for discriminating colorectal neoplasms from non-neoplasms,[5] Studies needed to use histologic biopsy as the reference standard and in which the pathologist and endoscopist were blinded to each other's findings. Included studies also used a standardized CLE classification system. Patient populations included individuals at increased risk of colorectal cancer due to personal or family history, patients with previously identified polyps, and/or patients with IBD. Two reviewers independently assessed the quality of individual studies using the modified Quality Assessment Of Diagnostic Accuracy Studies (QUADAS) tool, and studies considered to be at high risk of bias were excluded from further consideration. A total of 15 studies with 719 adult patients were found to be eligible for the systematic review. All were single-center trials and two were available only as abstracts. In all the studies, suspicious lesions were first identified by conventional white-light endoscopy with or without chromoendoscopy and then further examined by CLE. A pooled analysis of the 15 studies found an overall sensitivity of CLE of 94% (95% CI 0.88 to 0.97) and specificity of 95% (95% CI 0.89 to 0.97), compared to histology. Six of the studies included patients at increased risk of colorectal cancer (CRC) who were undergoing surveillance endoscopy, five studies included patients with colorectal polyps and four studies included patients with IBD. In a predefined subgroup analysis by indication for screening, the pooled sensitivity and specificity for surveillance studies was 94% (95% CI, 90% to 97%) and 98% (95% CI 97% to 99%), respectively. For patients presenting with colorectal polyps, the pooled sensitivity of CLE was 91% (95% CI 87% to 94%) and specificity was 85% (95% CI 78% to 90%). For patients with IBD, the pooled sensitivity was 83% (95% CI 70% to 92%) and specificity was 90% (95% CI 87% to 93%). In other predefined subgroup analyses, the summary sensitivity and specificity was significantly higher ($p<0.001$) in studies of endoscopy-based CLE (97% and 99%, respectively) than studies of probe-based CLE (87% and 82%, respectively). In addition, the summary sensitivity and specificity was significantly higher ($p<0.01$) with real-time CLE in which the macroscopic endoscopy findings were known (96% and 97%, respectively) than with blinded CLE in which recorded confocal images were subsequently analyzed without knowledge of macroscopic endoscopy findings (85% and 82%, respectively).

Another systematic review was published in 2013 by Dong.[6] The investigators included studies that assessed the diagnostic accuracy of CLE compared with conventional endoscopy. They did not explicitly state that the reference standard was histologic biopsy, but this was the implied reference standard. A total of six studies were included in a meta-analysis. All of the studies were prospective, and at least five included blinded interpretation of CLE findings (in one study, it was unknown whether interpretation was blinded). In a pooled analysis of data from all six studies, the sensitivity was 81% (95% CI 77% to 85%) and the specificity was 88% (95% CI 85% to 90%). The authors also conducted a subgroup analysis by type of CLE used. When findings from the two studies on endoscopy-based CLE were pooled, the sensitivity was 82% (95% CI 69% to 91%) and the specificity was 94% (95% CI 91% to 96%). Two studies may not have been a sufficient number to obtain a reliable estimate of diagnostic accuracy. When findings from the 4 studies on probe-based endoscopy were pooled, the sensitivity was 81% (95% CI 76% to 85%) and the specificity was 75% (95% CI 69% to 81%).

A 2013 systematic review by Wanders searched for studies that reported diagnostic accuracy of studies on any of several new technologies used to differentiate between colorectal neoplasms and non-neoplasms.[7] To be included in the review, studies needed to use the technology to differentiate between non-neoplastic and neoplastic lesions and to use

histopathology as the reference standard. Blinding was not an inclusion criterion. Eleven eligible studies were identified that included an analysis of CLE. A pooled analysis of study findings yielded an estimated sensitivity of 93.3% (95% CI 88.4 to 96.2) and a specificity of 89.9% (95% CI 81.8% to 94.6%). A meta-analysis limited to the five studies that used endoscopy-based CLE found a sensitivity of 94.8% (95% CI 90.6% to 98.92%) and a specificity of 94.4% (95% CI 90.7% to 99.2%). When findings of the six studies on probe-based CLE were pooled, the sensitivity was 91.5% (86.0% to 97.0%) and the specificity was 80.9 (95% CI 69.4% to 92.4%).

Nonrandomized Studies

Ohmiya (2017) evaluated the ability of CLE to differentiate among ulcerative colitis (UC)-associated neoplasia (differentiated type or undifferentiated type), sporadic adenoma, and circumscribed regenerative lesions.[8] The authors examined 12 patients with suspected UC-associated neoplasia with probe-based CLE and compared findings with pathological diagnoses determined by magnifying chromoendoscopy with crystal violet and narrow band imaging. Sensitivity, specificity, and accuracy of CLE were 100%, 83%, and 92%, respectively. The authors stated that CLE was helpful in evaluating suspected UC-associated neoplasia, but it is limited by the small sample size.

In 2017, Kim evaluated probe-based CLE for feasibility and safety in evaluating colorectal submucosa following removal of colorectal neoplasms.[9] Colorectal submucosa were classified as negative or indicative of carcinoma infiltration. The results were compared to pathological findings. The sensitivity, specificity, and accuracy of the classifications were 91.7, 86.8, and 88.0 %, respectively. The authors concluded that CLE is useful but that large-scale prospective studies are needed.

In a 2012 study by Shadid two methods of analyzing CLE images, real-time diagnosis and blinded review of video images after endoscopy (known as “offline” diagnosis), were compared.[10] The study included 74 patients with a total of 154 colorectal lesions. Eligibility criteria were similar to the Buchner study (see above); the included patients undergoing surveillance or screening colonoscopy. Patients underwent white-light colonoscopy and identified polyps were also evaluated with virtual chromoendoscopy and probe-based CLE. Intravenous fluorescein sodium was administered after the first polyp was identified. At the time of examination, an endoscopist made a real-time diagnosis based on CLE images. Based on that diagnosis, the patient underwent polypectomy, biopsy or endoscopic mucosal resection, and histopathologic analysis was done on the specimens. The CLE images were then de-identified and then reviewed offline by the same endoscopist at least one month later. At the second review, the endoscopist was blinded to the endoscopic and histopathologic diagnosis. Of the 154 polyps, 74 were found by histopathologic analysis to be non-neoplastic and 80 were neoplastic (63 tubular adenomas, 12 tubulovillous adenomas, three mixed hyperplastic-adenoma polyps and two adenocarcinomas). Overall, there was not a statistically significant difference in the diagnostic accuracy of real-time CLE diagnosis and blinded offline CLE diagnosis (i.e., confidence intervals overlapped). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for real-time CLE diagnosis was 81%, 76%, 87%, and 79%, respectively. For offline diagnosis, these numbers were 88%, 77%, 81% and 85%, respectively. However, in the subgroup of 107 smaller polyps, less than 10 mm in size, the accuracy of real-time CLE was significantly lower than offline CLE. For the smaller polyps, sensitivity, specificity, PPV and NPV of real-time CLE was 71%, 83%, 78%, and 78% and for offline CLE was 86%, 78%, 76%, and 87%, all respectively. For larger polyps, in

contrast, there was a nonsignificant trend in favor of better diagnostic accuracy with real-time compared to offline CLE.

A 2011 study by Hlavaty included patients with ulcerative colitis or Crohn disease.[11] Thirty patients were examined with standard white-light colonoscopy, chromoendoscopy and an endoscopy-based CLE system. An additional 15 patients were examined only with standard colonoscopy. All lesions identified by white-light colonoscopy or chromoendoscopy were examined using CLE to identify neoplasia using the Mainz classification system. Suspicious lesions underwent biopsy and, additionally, random biopsies were taken from four quadrants every 10 cm per the standard surveillance colonoscopy protocol. All specimens underwent histologic analysis by a gastrointestinal pathologist who was blinded to the CLE diagnosis. Diagnostic accuracy of CLE was calculated for examinable lesions only. Compared to histologic diagnosis, the sensitivity of CLE for diagnosing low-grade and high-grade intraepithelial neoplasia was 100%, the specificity was 98.4%, the PPV was 66.7%, and the NPV was 100%. However, whereas CLE was able to examine 28 of 30 (93%) flat lesions, it could examine only 40 of 70 (57%) protruding polyps. Moreover, 6 of 10 (60%) dysplastic lesions, including three of five low-grade and high-grade intraepithelial neoplasms were not evaluable by CLE. It is also worth noting that the diagnostic accuracy of chromoendoscopy was similar to that of CLE. The sensitivity, specificity, PPV and NPV of chromoendoscopy was 100%, 97.9%, 75%, and 100%, respectively.

A 2011 study by Xie included 116 consecutive patients who had polyps found during CLE; one patient was excluded from the analysis. All patients had an indication for colonoscopy (19 were undergoing surveillance postpolypectomy, two had a family history of colorectal cancer, three had IBD and 91 were seeking a diagnosis). All patients first underwent white-light colonoscopy. Endoscopy-based CLE was used on the first polyp identified during withdrawal of the endoscope (i.e., one polyp per patient was analyzed). Intravenous fluorescein sodium was used. Real-time diagnosis of the polyp was performed based on criteria used at the study center (which is adapted from the Mainz classification system). The polyps were biopsied or were removed and histopathologic diagnosis was determined. Real-time CLE diagnosis correctly identified 109 of 115 (95%) adenomas or hyperplastic polyps. Four adenomas were misdiagnosed by CLE as hyperplastic polyps (two were tubulous adenomas and two were tubulovillous adenomas) and two hyperplastic polyps were misdiagnosed as adenomas. The overall sensitivity, specificity, PPV, and NPV of CLE diagnosis was 93.9% (95% CI 85.4% to 97.6%), 95.9% (95% CI 86.2% to 98.9%), 96.9% (95% CI 89% to 99%), and 94.8% (95% CI 89.1% to 97.6%), respectively. For polyps less than 10 mm, the CLE diagnosis had a sensitivity of 90.3% and specificity of 95.7%, and for polyps 10 mm and larger, sensitivity was 97.1% and specificity was 100%.[12]

In 2010, Buchner published findings on 75 patients who had a total of 119 polyps.[13] Patients were eligible for study participation if they were undergoing surveillance or screening colonoscopy or undergoing evaluation of known or suspected polyps identified by other imaging modalities or endoscopic resection of larger flat colorectal neoplasia. White-light colonoscopy was used as the primary screening method. When a suspicious lesion was identified, it was evaluated by virtual chromoendoscopy system and a probe-based CLE system. Intravenous fluorescein sodium was administered after the first polyp was identified. Following the imaging techniques, the appropriate intervention, i.e., polypectomy, biopsy, or endoscopic mucosal resection, of lesions were performed and all resected specimens underwent histopathologic analysis by a pathologist blinded to CLE information. Confocal images of the 199 polyps were evaluated after all procedures were completed; the evaluator

was blinded to histology diagnosis and endoscopic appearance of the lesion. Diagnosis of confocal images used modified Mainz criteria; polyps were classified as benign or neoplastic. According to histopathologic analysis, there were 38 hyperplastic polyps and 81 neoplastic lesions (58 tubular adenomas, 15 tubulovillous adenomas and 4 adenocarcinomas). CLE correctly identified 74 of 81 neoplastic polyps (sensitivity, 91%; 95% CI 83% to 96%). In addition, CLE correctly identified 29 of 38 hyperplastic polyps (specificity, 76%; 95% CI, 60% to 89%). In contrast, virtual chromoendoscopy correctly identified 62 neoplastic polyps (sensitivity, 77%; 95% CI 66% to 85%) and 27 hyperplastic polyps (specificity, 71%; 95% CI 54% to 85%).

Section Summary

Multiple studies have evaluated the accuracy of confocal laser endoscopy compared with histopathology for diagnosing colorectal lesions. In three published systematic reviews, pooled estimates of overall sensitivity of CLE ranged from 81% to 94% and pooled estimates of specificity ranged from 88% to 95%. Although the reported diagnostic accuracy tended to be relatively high, it is not clear whether the accuracy is high enough to replace biopsy/polypectomy and histologic analysis.

BARRETT ESOPHAGUS

The ideal study would determine whether CLE with targeted biopsy can distinguish Barrett's Esophagus (BE) without dysplasia from BE with low- and high-grade dysplasia. In addition, study results would need to determine if CLE with target biopsy led to fewer biopsies of benign tissue compared to surveillance with random biopsies. The ideal study to address the above questions would include an unselected clinical population of patients with BE presenting for surveillance and would randomly assign patients to CLE with targeted biopsy or a standard biopsy protocol without CLE. Relevant outcomes include diagnostic accuracy for detecting dysplasia, the detection rate for dysplasia, and the number of biopsies. Several studies with most or all of these elements of study design were identified, including randomized controlled trials (RCTs).

Systematic Reviews

In 2017, Xiong published a systematic review and meta-analysis to assess the accuracy of within-patient comparisons of narrow band imaging and CLE for the diagnosis of high-grade dysplasia and esophageal adenocarcinoma in BE patients.[14] The quality of studies was assessed using the QUADAS-2 tool. A total of five studies with 251 patients were included in the meta-analysis. The pooled sensitivities were not significantly different, with values of 62.8% (95% CI 0.56 to 0.69, I2=94.6%) for narrow band imaging and 72.3% (95% CI 0.66 to 0.78, I2=89.3%) for CLE. Pooled specificities were also not significantly different (narrow band imaging 85.3% [95% CI 0.84 to 0.87, I2=92.1%] vs CLE 83.8% [95% CI 0.82 to 0.85, I2=96.8%]). The pooled additional detection rate of CLE compared to narrow band imaging for per-lesion detection of neoplasia was 19.3% (95% CI 0.05 to 0.33, I2=74.6%).

In 2016, Xiong published a meta-analysis of prospective studies evaluating the diagnostic accuracy of CLE in patients with BE and using histopathologic analysis as the criterion standard.[15] Studies were not required to compare CLE to standard four-quadrant biopsy. Fourteen studies were included. Three were reported to have a high risk of bias and the rest a low risk of bias. There was no statistically significant publication bias. In a pooled analysis of seven studies (n=473 patients) reporting a per-patient analysis, the sensitivity of CLE for

detecting neoplasia was 89% (95% CI, 82% to 94%) and the specificity was 83% (95% CI 78% to 86%). The pooled positive and negative likelihood ratios were 6.53 (95% CI, 3.12 to 13.4) and 0.17 (95% CI 0.11 to 0.29, respectively). Reviewers did not report PPV or NPV. Sensitivity and specificity were similar to those reported below in the 2014 meta-analysis by Gupta. Limitations to this analysis include heterogeneity of the results and a lack of relationship between the diagnostic odds ratio and the characteristics of the studies.

Gupta (2014) conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of the CLE-based targeted biopsies in detecting high grade dysplasia (HGD)/adenocarcinoma compared with four-quadrant random biopsies.[16] All the studies that compared the diagnostic yield from CLE-based targeted biopsies to detect HGD/adenocarcinoma with a gold standard of histopathology were included and a meta-analysis was carried out to estimate the pooled sensitivity, specificity, and positive and negative likelihood. Seven studies with 345 patients and 3080 lesions were included in the meta-analysis. All the studies had reported per-lesion analyses; however, only four of the seven studies had data reported on per-patient analyses. 'Per-lesion' analysis for the diagnosis of HGD/adenocarcinoma yielded a pooled sensitivity and specificity of 68% (95% CI of 64-73%) and 88% (95% CI 87 to 89%), respectively. The pooled positive and negative likelihood ratios were 6.56 (95% CI 3.61 to 11.90) and 0.24 (95% CI 0.09 to 0.63), respectively. Similar numbers were calculated on the basis of 'per-patient' basis, which showed a pooled sensitivity and specificity of 86% (95% CI 74 to 96%) and 83% (95% CI 77 to 88%), respectively. The pooled positive and negative likelihood ratios were 5.61 (95% CI 2.00 to 15.69) and 0.21 (95% CI 0.08 to 0.59), respectively. Authors noted that CLE, by providing targeted biopsies, has a good diagnostic accuracy in identifying HGD/EAC; however, the overall prevalence of HGD/EAC in the studies included was much higher than what would be seen in clinical practice and these results should be interpreted with caution. Due to its relatively low sensitivity and negative predictive value, CLE may currently not replace standard biopsy techniques for the diagnosis of HGD/EAC in Barrett's esophagus.

In 2013, a meta-analysis by Wu of observational studies and RCTs focused on the diagnostic accuracy of CLE for detecting neoplasia in BE patients.[17] In a pooled analysis of data from four studies that reported per-patient accuracy of CLE, the pooled sensitivity for detection of neoplasia was 89% (95% CI 0.80% to 0.95%), and the pooled specificity was 75% (95% CI 69% to 81%). Seven studies reported per-location accuracy of CLE. The pooled sensitivity for CLE was 70% (95% CI 65% to 74%) and the pooled specificity was 91% (95% CI 90% to 92%). This study did not address other outcomes such as number of biopsies and did not compare CLE for detection of neoplasia in patients with BE with white-light endoscopy.

Randomized Controlled Trials

In 2013, Canto published findings from a single-blind multicenter RCT conducted at academic centers with experienced endoscopists.[18] The trial included consecutive patients undergoing endoscopy for routine surveillance of BE or for suspected or known neoplasia. Patients were randomized to high-definition white-light endoscopy with random biopsy (n=98) or white-light endoscopy with endoscopy-based CLE and targeted biopsy (n=94). In the white-light endoscopy-only group, four-quadrant random biopsies were taken every one to two cm of the entire length of the BE for patients undergoing surveillance and every one cm in patients with suspected neoplasia. In the CLE group, biopsy specimens were obtained only when there was CLE evidence of neoplasia. The final pathology diagnosis was the reference standard. A per-patient analysis of diagnostic accuracy for diagnosing BE-related neoplasia found a sensitivity

of 40% with white-light endoscopy alone and 95% with white-light endoscopy plus CLE. Specificity was 98% with white-light endoscopy alone and 92% with white-light endoscopy plus CLE. When the analysis was done on a per-biopsy specimen basis, when CLE was added, the sensitivity was substantially higher and the specificity was slightly lower. The median number of biopsies per patient was significantly higher in the white-light endoscopy group compared with the group that also received CLE (4 vs 2, p<0.001). The investigators conducted an analysis of the number of cases in which CLE resulted in a different diagnosis. Thirty-two of 94 (34%) patients in the white-light plus CLE group had a correct change in dysplasia grade after CLE compared to the initial endoscopic findings. Six of the 32 (19%) patients had lesions and the remaining 26 did not. In 21 of the 26 patients without lesions, CLE changed the plan from biopsy to no biopsy. The remaining 62 of 94 (65%) patients in the white-light endoscopy plus CLE group had concordant diagnoses with the two techniques. The study was conducted at academic centers and used endoscopy-based CLE. Findings may not be generalizable to other clinical settings or to probe-based CLE.

In 2011, Sharma published an international, multicenter RCT that included 122 consecutive patients presenting for surveillance of BE or endoscopic treatment of high-grade dysplasia or early carcinoma.[19] This study was described in the systematic review and meta-analysis described by Gupta in the previous section. Patients were randomly assigned to receive, in random order, both standard white-light endoscopy and narrow-band imaging. Following these two examinations, which were done in a blinded fashion, the location of lesions was unblinded and, subsequently, all patients underwent probe-based CLE. All examinations involved presumptive diagnosis of suspicious lesions. Also, in both groups, after all evaluations were performed, there were biopsies of all suspicious lesions, as well as biopsies of random locations (four quadrants every two cm). Histopathologic analysis was the reference standard. Twenty-one patients were excluded from the analysis. Of the remaining 101 patients, 66 (65%) were found on histopathologic analysis to have no dysplasia, four (4%) had low-grade dysplasia, six (6%) had high-grade dysplasia and 25 (25%) had early carcinoma. The sensitivity of CLE with white-light endoscopy for detecting high-grade dysplasia or early carcinoma was 68.3% (95% CI, 60.0% to 76.7%), which was significantly higher than white-light endoscopy alone; 34.2% (95% CI 25.7% to 42.7%, p=0.002). However, the specificity of CLE and white-light endoscopy was significantly lower than white-light endoscopy alone: 92.7% (95% CI 90.8% to 94.6%) versus 87.8% (95% CI 85.5% to 90.1%; p<0.001). For white-light endoscopy alone, the PPV was 42.7% (32.8% to 52.6%) and the NPV was 89.8% (95% CI 87.7% to 92.0%). For white-light endoscopy with probe-based CLE, the PPV was 47.1% (95% CI 39.7% to 54.5%) and the NPV was 94.6% (95% CI 92.9% to 96.2%). White-light endoscopy alone missed 79 of 120 (66%) areas with high-grade dysplasia or early carcinoma and white-light endoscopy with CLE missed 38 (32%) areas. On a per-patient basis, 31 patients were diagnosed with high-grade dysplasia or early carcinoma. White-light endoscopy alone failed to identify four of these patients (sensitivity, 87%), whereas white-light endoscopy and CLE failed to identify two patients (sensitivity, 93.5%).

Another RCT was published in 2012 by Bertani in Italy; this was a single-center study.[20] The study compared the dysplasia detection rate of biopsies obtained by standard white-light endoscopy only to the detection rate with standard endoscopy followed by probe-based CLE in patients with BE who were enrolled in a surveillance program. One hundred consecutive patients were included, and 50 were randomly assigned to each group. In both groups, targeted biopsies of suspicious lesions and random four-quadrant biopsies (one biopsy every one cm) were taken. The authors described the criteria they used for classifying CLE images as dysplastic or neoplastic. According to histopathologic analysis, the reference standard,

high-grade dysplasia, was diagnosed in three patients and low-grade dysplasia was diagnosed in 16 patients, for an overall detection rate of 19 in 100 (19%) cases. Five cases were in the standard endoscopy group (one case of high-grade dysplasia and four cases of low-grade dysplasia) and 14 were in the CLE group (two cases of high-grade dysplasia and 12 cases of low-grade dysplasia). No suspicious lesions were identified in the standard endoscopy group and thus, only random biopsies were performed. In the CLE group, no suspicious lesions were identified when patients were initially evaluated with standard endoscopy but CLE detected areas suspicious for neoplasia in 21 of 50 (42%) of patients. All the cases of dysplasia were in patients with areas suspicious for neoplasia at CLE but not standard endoscopy. The sensitivity, specificity, PPV and NPV of probe-based CLE for detecting dysplasia were 100%, 83%, 67%, and 100%, respectively. Overall, the mean number of biopsies did not differ between groups (mean of 6.6 per patient in the standard endoscopy group and 6.1 in the CLE group, p=0.77), so the increased detection rate in the CLE group cannot be explained by a larger number of biopsies.

A single-center crossover RCT was published in 2009 by Dunbar.[21] This study was able to evaluate whether CLE can reduce the biopsy rate. This study was described in the systematic review and meta-analysis described by Gupta (2014) in the previous section. Forty-six patients with BE were enrolled, and 39 (95%) completed the study protocol. Of these, 23 were undergoing BE surveillance and 16 had BE with suspected neoplasia. All patients received endoscopy-based CLE and standard endoscopy, in random order. One endoscopist performed all CLE procedures and another endoscopist performed all standard endoscopy procedures; endoscopists were blinded to the finding of the other procedure. During the standard endoscopy procedure, biopsies were taken of any discrete lesions followed by four-quadrant random biopsy (every one cm for suspected neoplasia and every two cm for BE surveillance). During the CLE procedure, only lesions suspicious of neoplasia were biopsied. Endoscopists interpreted CLE images using the Confocal Barrett's Classification system, developed in a previous research study. Histopathologic analysis was the reference standard. Among the 16 study completers with suspected high-risk dysplasia, there were significantly fewer biopsies per patient with CLE compared to standard endoscopy (mean of 9.8 biopsies vs 23.9 biopsies per patient, p=0.002). Although there were fewer biopsies, the mean number of biopsy specimens showing high-grade dysplasia or cancer was similar in the two groups: 3.1 during CLE and 3.7 during standard endoscopy, respectively. The diagnostic yield for neoplasia was 33.7% with CLE and 17.2% with standard endoscopy. None of the 23 patients undergoing BE for surveillance were found to have high-grade dysplasia or cancer. The mean number of mucosal specimens obtained for patients in this group was 12.6 with white-light endoscopy and 1.7 with CLE (p<0.001).

Nonrandomized Studies

Richardson (2019) conducted a prospective study at eight centers to compare probe-based CLE to conventional histology using the Seattle Protocol (random 4-quadrant biopsy) to identify intestinal metaplasia among 172 patients undergoing screening or surveillance endoscopy for BE.[22] Endoscopists recruited for the study were early users of CLE with less than two years of experience and no formal pathology training. All patients underwent a standardized endoscopy with white light and narrow band imaging evaluation, identification of landmarks, and recording of columnar lined esophagus visualized according to the Prague classification. Patients then received fluorescein followed by optical biopsy; images were interpreted both in real time and immediately following the procedure. After CLE images were acquired, esophageal biopsies were taken via the Seattle Protocol. Endoscopists were able to

identify intestinal metaplasia among 99 patients (57.6%) using CLE compared to 46 patients (27%) using the Seattle Protocol (p<0.0001). Dysplasia was identified in 6 patients using CLE compared to 2 patients using the Seattle Protocol (both of which were also identified via CLE). Confocal laser endomicroscopy also identified significantly more patients with intestinal metaplasia compared to the Seattle Protocol among those with visible columnar lined esophagus (75 vs. 31 patients, respectively; p<0.0001), but not among those without columnar lined esophagus (24 vs. 15 patients; p=0.067). Identification of intestinal metaplasia was not found to be significantly different when comparing CLE to expert review.

Section Summary

Several RCTs and a meta-analysis of RCTs and non-randomized, observational studies suggest that CLE has high accuracy for identifying dysplasia in patients with BE. A 2014 meta-analysis found that the pooled sensitivity, specificity, and negative predictive value in available studies is not sufficiently high to replace the standard Seattle protocol, according to criteria adopted by the American Society for Gastrointestinal Endoscopy (ASGE).

The sensitivity of CLE in the individual studies was higher than for white-light endoscopy alone, but the specificity was not consistently higher. There are limited data comparing standard protocols using random biopsies to protocols using CLE and targeted biopsies, so data are inconclusive regarding the potential for CLE to reduce the number of biopsies in patients with BE undergoing surveillance without compromising diagnostic accuracy. Moreover, studies do not appear to use a consistent approach to classifying lesions viewed using CLE as dysplastic.

PANCREATIC DISEASES

Systematic Reviews

Saghir (2022) conducted a systematic review to evaluate the diagnostic accuracy of CLE for pancreatic lesions.[23] A total of 443 patients were included in the analysis which demonstrated a pooled diagnostic accuracy of 83%. The pooled rate of sensitivity, specificity, positive predictive value, and negative predictive value were 85.29% (95% CI = 76.9-93.68), 90.49% (95% CI = 82.24-98.74), 94.15% (95% CI = 88.55-99.76), and 73.44% (95% CI = 60.16-86.72), respectively. Additional studies are needed evaluating pancreatic lesions in order to establish diagnostic criteria and to establish the clinical utility of CLE for pancreatic lesions.

Konjetia (2020) conducted a systematic review to evaluate the diagnostic performance and safety of needle-based confocal laser endomicroscopy (nCLE) in the diagnosis of pancreatic cystic lesions.[24] Seven studies were included in the review with a total sample size of 324 patients. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ration of nCLE was 85% (95% CI, 71-93), 99% (95% CI, 90-100), 78.66 (95% CI, 7.99-774.68), and 0.15 (95% CI, 0.07-0.31) respectively. The diagnostic accuracy as measured by summary receiver operating characteristic curve was 99%. The results showed that nCLE may be effective in diagnostic evaluation of PCLs, however a large amount of heterogeneity was present in the analysis which is consistent with prior reviews.

In 2020, Facciorusso published a meta-analysis of needle-based confocal laser endomicroscopy (nCLE) in pancreatic cystic lesions.[25] Ten studies with a total of 536 patients met inclusion criteria. Three studies were rated as low-quality and the rest as high quality using the Newcastle/Ottawa scale. There was no evidence of publication bias. Diagnostic outcomes from the included studies were pooled using a random-effects mode. Overall pooled diagnostic

accuracy was 88.6% (83.7 to 93.4%; I^2=41.73%). Pooled sensitivity and specificity of nCLE were calculated from nine studies to be 82.4% and 96.6%, respectively. A direct comparison between the diagnostic sensitivity of nCLE and endoscopic ultrasound-guided fine needle aspiration (FNA) was conducted. No statistically significant difference was reported (OR=1.51, 0.34 to 6.68), although the authors cautioned that there was high heterogeneity.

Also in 2020, Chin published a systematic review on the role of needle-based confocal laser endomicroscopy in the evaluation of pancreatic cystic lesions.[26] Twelve studies were included, six retrospective and six prospective. No meta-analysis was completed. The accuracy of nCLE was between 46% and 95%, although only one study reported accuracy below 71%. The reported incidence of acute pancreatitis, the most common complication related to nCLE, was 1.3% to 12%.

Nonrandomized Studies

Hao (2020) published a study to study was to evaluate the diagnostic efficacy of EUS-guided nCLE in solid pancreatic lesions (SPLs) and pancreatic cystic lesions (PCLs).[27] A total of 172 patients were enrolled and underwent EUS-nCLE. The reported mean sensitivity, specificity, negative predictive value, positive predictive value and accuracy of the nCLE in diagnosis of pancreatic ductal adenocarcinoma were 90.3%, 89.5%, 93.3%, 85.0% and 90.0%, respectively.

Nakaoka (2020) reported a study of 30 patients who underwent endoscopic retrograde cholangiopancreatography with pCLE for the evaluation of indeterminate pancreatic diseases.[28] Compared to cytology, the diagnostic accuracy (96.7% vs. 76.7%; p=0.0227) and the sensitivity (91.7% vs. 41.7%; p=0.0094) of pCLE for pancreatic ductal adenocarcinoma was significantly higher. The diagnostic accuracy (93.3% vs. 63.3%; p=0.0048) and the specificity (90.9% vs. 50%; p=0.0029) for pancreatitis were significantly higher for pCLE than for cytology. However, the diagnostic accuracies of the two methods did not significantly differ for main duct intrapapillary mucinous neoplasms.

Haghighi (2019) reported results of a study to determine the diagnostic utility of nCLE compared to endoscopic ultrasound-guided FNA (EUS-FNA) for PCLs.[29] A total of 32 patients diagnosed with PCL who had undergone nCLE and FNA over a 10-year period within a major urban teaching hospital were included. The diagnoses in the included patients were serous cystadenoma (n=13), intraductal papillary mucinous neoplasms (n=7), mucinous cystic neoplasms (n=2), well-differentiated neuroendocrine tumors (n=2), cysts (n=2), benign pancreatic lesions (n=2), adenocarcinoma (n=1), gastrointestinal stromal tumor (GIST; n=1), and lymphangioma (n=1). The diagnostic accuracy varied by diagnosis. The highest diagnostic accuracy was for intraductal papillary mucinous neoplasms (n=7, vs. 100% for nCLE compared to 42.8% for EUS-FNA, n=3,), while the diagnostic accuracy rate for serous cystadenoma was 69.2% (n=9; vs. 76.9% for EUS-FNA, n=10). Overall, the sensitivity, specificity, PPV, and NPV were 91.7%, 87.5%, 84.6%, and 93.3%, respectively, for nCLE and 80.0%, 92.3%, 88.9%, and 85.7%, respectively, for EUS-FNA.

ASSESSING THE ADEQUACY OF ENDOSCOPIC TREATMENT OF GASTROINTESTINAL LESIONS

Evidence is not clear regarding whether use of CLE improves the determination of residual disease compared with conventional techniques (i.e., white-light endoscopy). In 2014, Ypsilantis published a systematic review of the literature.[30] They included retrospective and

prospective studies that reported diagnostic accuracy of CLE for the detection of residual disease after endoscopic mucosal resection (EMR) of gastrointestinal lesions. After examining full-text articles, a total of three studies (one RCT and two prospective, non-randomized comparative studies) met the eligibility criteria. Studies included patients with BE, gastric neoplasia, and colorectal neoplasia. There was significant heterogeneity among studies. In a per-lesion meta-analysis, pooled sensitivity of CLE for detecting neoplasia was 91% (95% CI 83% to 96%), and pooled specificity was 69% (95% CI 61 to 76%). Based on the small number of studies and heterogeneity among studies, the authors concluded that evidence on the usefulness of CLE in assessing the adequacy of EMR is weak. The single RCT was published in 2012 by Wallace[31] This multicenter trial included patients with BE who were undergoing ablation. After an initial attempt at ablation, patients were randomized to follow-up with either with high-definition white light (HDWL) endoscopy or HDWL endoscopy plus CLE. The primary outcome was the proportion of optimally treated patients, defined as those with no evidence of disease at follow-up, and those with residual disease who were identified and treated. Enrollment in the study was halted after an interim analysis showed no difference between groups. Among the 119 patients who had enrolled by the time of the interim analysis, 15 (26%) of 57 in the HDWL group and 17 (27%) of 62 in the HDWL plus CLE group were optimally treated; the difference was not statistically significant. Moreover, other outcomes were similar in the two groups.

Section summary

There is insufficient evidence that CLE improves upon standard practice for assessing the adequacy of endoscopic treatment of gastrointestinal lesions. The single RCT on this topic was stopped early because an interim analysis reported that CLE did not improve upon high-definition white light endoscopy.

OTHER POTENTIAL APPLICATIONS OF CLE

Preliminary studies have been published evaluating CLE for diagnosing a variety of conditions including lung cancer,[32-34] bladder cancer,[35-40] head and neck cancer,[41-44] gastric cancer,[45-52] atrophic gastritis,[53, 54] esophageal cancer,[55, 56] breast surgery,[57] biliary strictures and stenosis,[58-62] gastric intestinal metaplasia,[63-65] malignant pleural mesothelioma,[66] basal and squamous cell carcinoma,[67] liver[68] and peritoneal nodules[69], gastrointestinal polypoid lesions,[70] gastroesophageal reflux disease (GERD),[71] inflammatory bowel disease,[72, 73] aganglionosis associated with Hirschsprung's disease,[74] and bile duct malignancies[75, 76]. There are insufficient studies to determine the accuracy of CLE for these applications and their potential role in clinical care.

PRACTICE GUIDELINE SUMMARY

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

In 2011 the American Gastroenterological Association (AGA) published a position statement on the management of Barrett esophagus.[77] The statement includes the following recommendations regarding endoscopic surveillance of Barrett esophagus:

> The AGA suggest that endoscopic surveillance be performed in patients with Barrett esophagus (weak recommendation, moderate-quality evidence).

The AGA suggest the following surveillance intervals (weak recommendation, low-quality evidence):

- No dysplasia: three to five years
- Low-grade dysplasia: 6 to 12 months
- High-grade dysplasia in the absence of eradication therapy: three months

For patients with Barrett esophagus who are undergoing surveillance, the AGA recommended:

- Endoscopic evaluation be performed using white light endoscopy (strong recommendation, moderate-quality evidence).
- Four-quadrant biopsy specimens be taken every 2 cm (strong recommendation, moderate-quality evidence).
- Specific biopsy specimens of any mucosal irregularities be submitted separately to the pathologist (strong recommendation, moderate-quality evidence).
- Four-quadrant biopsy specimens be obtained every 1 cm in patients with known or suspected dysplasia (strong recommendation, moderate-quality evidence).

The AGA recommend against requiring chromoendoscopy or advanced imaging techniques for the routine surveillance of patients with Barrett esophagus at this time (weak recommendation, low-quality evidence).

AMERICAN SOCIETY FOR GASTROINTESTINAL ENDOSCOPY

In 2019, the American Society for Gastrointestinal Endoscopy (ASGE) published a guideline on screening and surveillance of Barrett's esophagus.[78] The guideline includes the following recommendation regarding surveillance of dysplasia in patients with Barrett's esophagus: "In patients with BE undergoing surveillance, we suggest against routine use of CLE compared with WLE with Seattle protocol biopsy sampling (conditional recommendation, low quality of evidence)."

The ASGE published a guideline (2006; reaffirmed in 2011) on the role of endoscopy in the surveillance of premalignant conditions of the upper gastrointestinal (GI) tract.[79] Regarding the use of confocal endoscopy as an adjunct to white-light endoscopy, the guidelines stated that this technique is "still in development." The guideline also included the following statements on surveillance of patients with BE:

> The cost effectiveness of surveillance in patients without dysplasia is controversial. Surveillance endoscopy is appropriate for patients fit to undergo therapy, should endoscopic/histologic findings dictate. For patients with established Barrett's esophagus of any length and with no dysplasia, after 2 consecutive examinations within 1 year, an acceptable interval for additional surveillance is every 3 years.
>
> Patients with high-grade dysplasia are at significant risk for prevalent or incident cancer. Patients who are surgical candidates may elect to have definitive therapy. Patients who elect surveillance endoscopy should undergo follow-up every 3 months for at least 1 year, with multiple large capacity biopsy specimens obtained at 1 cm intervals. After 1 year of no cancer detection, the interval of surveillance may be lengthened if there are no dysplastic changes on 2 subsequent endoscopies performed at 3-month intervals. High-grade dysplasia should be confirmed by an expert GI pathologist.

Surveillance in patients with low-grade dysplasia is recommended. The significance of low-grade dysplasia as a risk factor for cancer remains poorly defined; therefore, the optimal interval and biopsy protocol has not been established. A follow-up EGD (screening esophagogastroduodenoscopy) (i.e., at 6 months) should be performed with concentrated biopsies in the area of dysplasia. If low-grade dysplasia is confirmed, then one possible management scheme would be surveillance at 12 months and yearly thereafter as long as dysplasia persists.

In 2012, the ASGE stated the following in their guideline on the role of endoscopy in BE and other premalignant conditions of the esophagus: "Adjuncts to white-light endoscopy used to improve the sensitivity for the detection of BE and dysplastic BE include chromoendoscopy, electrical enhanced imaging, magnification, and confocal endoscopy."[80]

The ASGE Technology Committee published a Technology Status Evaluation Report on CLE in 2014.[81] The report concluded that CLE is an emerging technology with the potential to improve patient care. However, before the technology can be widely accepted, further studies are needed in the following areas:

- Use of CLE outside of the academic setting, particularly the applicability of the technology in community settings.
- The learning curve of CLE image interpretation and any additional time needed to perform the procedure.
- The clinical efficacy of the technology compared to other available advanced imaging technologies.
- Approaches to CLE imaging and image interpretation.

In 2016, based on a systematic review of 102 studies conducted between 2004 and 2015, the ASGE concluded additional clinical trials on CLE are still necessary.[82]

SUMMARY

There is not enough research to know if or how well confocal laser endomicroscopy (CLE) works to improve health outcomes for people with any condition. This does not mean that it does not work, but more research is needed to know. Therefore, use of CLE with endoscopy is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)
	43206	Esophagoscopy, flexible, transoral; with optical endomicroscopy
	43252	Esophagogastroduodenoscopy, flexible, transoral; with optical endomicroscopy
	88375	Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session.
HCPCS	None	

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