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Title Assessment of real-time optical endomicroscopy performed during mapping of Barrett's esophagus (BE) (for diagnosis of BE-associated early neoplasia)

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Aim

To assess the clinical utility (impact on healthcare), the diagnostic accuracy and safety of endomicroscopy-based biopsy method in comparison to the standard of care during an endoscopic evaluation of patients with Barrett's esophagus (BE) using white light endoscopy (WLE) +/- high-definition (HD) view. The standard of care is currently the Seattle protocol which correspond to biopsy any visible lesion and practice complementary random four-quadrant biopsy of the remaining metaplastic mucosa. The aim of this heath technology assessment (HTA) is to decide on the coverage by French National Health Insurance of medical procedure using esophagus's endomicroscopy in two different clinical situations: surveillance of patients with non-dysplastic BE (for diagnosis of BE early neoplasia) or pre-therapeutic mapping with dysplastic BE (for diagnosis of synchronous early neoplasia). The target lesion in this assessment was early oesophageal adenocarcinoma[1].

Conclusions and results

Concerning this domain, confocal laser endomicroscopy (CLE) was the only one technology evaluable with CE approval requirement[2].

No professional guideline concerning the role of CLE in oesophageal mapping has clearly been identified despite relatively long-dated clinical development of this technology[3]. Meta-analyses did not provide any additional information to the primary studies because the eligible studies were too heterogeneous and based on others criteria than those adopted by HAS. No primary study has reported CLE's accuracy in identification of low-grade dysplasia. Five CLE's accuracy studies (out of 21 pre-selected studies) involved analysis of 4 930 biopsies. The attrition rate of patients was 11 %. No study collected longitudinal follow-up clinical data

In the case of non-dysplastic BE, regarding the diagnostic imaging of BE, the PIVI (Preservation and Incorporation of Valuable endoscopic Innovations) guideline published by the American Society for Gastrointestinal Endoscopy (ASGE) recommends the following minimum "per patient" thresholds for diagnostic performance: sensitivity > 90 % and NPV[4] > 98% in comparison to the Seattle protocol to be able to replace the reference method by a set of single CLE-based targeted biopsies. In this target population, despite a 7-fold reduction observed in the number of biopsies performed, the sensitivity per patient was 73 % CI [39-94 %][5] and NPV 93% CI [85-99 %] in a good quality study. These values were below the recommended thresholds. In one study, the per biopsy performance of CLE was as poor as 14 % CI [6-25 %] for sensitivity, and varied between 0 and 18 % for PPV[6] in two others. In one study, the head-to-head comparison revealed no identification of BE neoplasia in both methods due to a poor diagnostic yield in this population at low risk of cancerous degeneration.

In pre-therapeutic situation (dysplastic BE identified), only a per-biopsy analysis was relevant. Despite a 2.5- to 6.5-fold observed reduction in biopsies observed, sensitivity fluctuated, depending on the study, between 62 % CI [54-71 %] and 76 % CI [63-85 %] with CLE resulting in a risk of missed early neoplasia of 15 to 44 % in comparison to performing systematic biopsies with the standard Seattle protocol. This risk was confirmed by head-to-head comparisons in regard to the number of early neoplasias diagnosed by the two methods: missed lesions' diagnoses, depending on the studies and the technical environment of the endoscopic examination, ranged from 15 % to a maximum of 35 % for one study using HD + NBI[7] (i.e. in one study 75 neoplasias were identified with the CLE-guided biopsy method versus 116 neoplasias with standard systematic biopsies).
In a CLE-based immediate endoscopic mucosal resection (EMR) strategy, similarly, the PPV (which is the main indirect diagnostic value to analyse in this circumstance) fluctuated between 19 % CI [15-25 %] and 58 % CI [49-66 %] according to three studies. Although its indirectness, the risk of overtreatment with unnecessary EMR (resection without pathological findings) could be real in the case of the CLE-guided therapeutic choice and could be motivate endoscopists to perform it. It was confirmed in at least one

[1] It includes high-grade dysplasia (HGD) and intramucosal carcinoma (IMC).
[2] This assessment showed that first and second generation of optical coherence tomography (OCT) used for BE's assessment are always in early phase of clinical development
[3] The first study on CLE in BE was published in 2005.
[4] Negative predictive value
[5] CI: 95% confidence interval according to the Clopper-Pearson exact method
[6] Positive predictive value
[7] Narrow band imaging (virtual chromoendoscopy)

study by a 4 -fold increase in the number of EMR performed by endoscopists using CLE. When this was clearly reported by the authors (one study), the rate of unnecessary EMR remained around 35 % despite using CLE tool. Significantly, EMR remains a challenging technical procedure at risk, possibly associate with iatrogenic consequences.

Reliability

Assessment of inter-observer reliability with CLE was systematically done in "offline"[8] design and revealed that the agreement on images (or videos) between observers was moderate to good (kappa 0.5 to 0.7). The learning curve was short but rapidly reached a plateau despite the constant acquisition of expertise.

General considerations

The CLE-based procedure was usually performed under general anaesthesia with spontaneous ventilation (deep sedation) particularly to increase the quality of the images (or videos). Taking into account long-term observed safety data, fluorescein was injected intravenously with equivalent method to retinal angiography. The use of CLE tool resulted in at least a 2-fold increase in the time taken to evaluate BE compared to conventional endoscopy (20' versus 10'). The quality of images (or videos) was good in less than 20 to 30 % of cases, making real time interpretation of images (or videos) series difficult for the endoscopists . These issues seemed to have a negative impact on the confidence level of endoscopists[9] to actually change their medical decision making.

Stakeholders

According to the French Society for Gastrointestinal Endoscopy (Société Française d'Endoscopie Digestive, SFED)[10], CLE should be exclusively reserved for pre-therapeutic evaluation (dysplastic BE at risk of synchronous cancer and recurrence) in tertiary centres with expertise in the conservative treatment of early oesophageal carcinoma. In this situation, the main goal of CLE should be to reduce the number of biopsies (targeted-biopsies) performed on the remaining flat metaplastic mucosa. According to the SFED and the French Society of Pathology (SFP), any visible lesion should always have histopathological confirmation of malignancy before any endoscopic treatment (particularly with regard to EMR).

Recommendations

The HAS final appraisal was that CLE-guided biopsy method cannot replace the standard method (oesophageal mapping with systematic biopsies according to the Seattle protocol). However, it can be integrated exclusively at the level of the pre-therapeutic management for dysplastic-confirmed BE at high risk of synchronous cancer and recurrence, after first identification usually managed in primary care centres. A biopsy providing histopathological confirmation of early neoplasia remains a prerequisite for any treatment decision (resection or ablation). CLE must be used exclusively in the population at high risk of cancer and in centres of excellence (specialised in interventional oesophageal endoscopy). These guidelines could be based on article 1151-1 of the French Public Health Code.

Methods

The assessment method used in this report includes:

- critical analysis of clinical guidelines, meta-analyses and primary diagnostic studies identified by a systematic review in French and English (Medline, Embase, Cochrane Library, Center for Reviews and Dissemination databases, websites of medical caregiver societies and HTA agencies) focusing on a period from January 2004 to August 2014;
- a compendium of the substantiated position concerning this analysis by three caregiver stakeholders (gastrointestinal endoscopists, pathologists and anaesthetists).

17 guidelines, 2 meta-analyses, 5 primary diagnostic studies and 3 primary reliability studies were analysed for CLE. No study was at the end analysed for "OCT"[11]. An additional systematic research on guidelines and synthetic documents to evaluate the use and safety of fluorescein was also performed.

Conclusions have been reviewed by the Commission (CNEDiMTS), the HAS specialised appraisal committee (then validated by the HAS Collège [board]).

Further research/reviews required

None

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[8] Not in "real time" pragmatic clinical assessment
[9] In two specific studies identified
[10] According to their representative questioned as part of the report.
[11] Cf. Previous considerations