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Title Needle-based confocal endomicroscopy for the characterisation of pancreatic cystic tumours

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Aim

The purpose of this review is to assess the benefit of adding confocal endomicroscopy to the diagnostic strategy in two different scenarios. Two assessment questions were thus selected during the definition phase:

- Question No. 1: What is the diagnostic added value of needle-based confocal endomicroscopy for the characterisation of pancreatic cystic lesions (diameter ≥ 2 cm) of undetermined malignant potential before the result of the needle biopsy analysis?
- Question No. 2: What is the diagnostic added value of needle-based confocal endomicroscopy for the characterisation of pancreatic cystic lesions (diameter ≥ 2 cm) of undetermined malignant potential after the result of the cytological and biochemical analysis and tumour marker assay?

Results

❖ **Literature review**

The literature selection process identified 20 publications including five meta-analyses, 11 clinical studies, three best practice guidelines, and one health technology assessment report.

It was not possible to process the findings of the meta-analyses within the scope of this assessment. Indeed, the detailed review of the clinical trials included in these meta-analyses gives rise to limitations associated with the variety of lesion classification methods, and with the inclusion of several publications and/or papers relating to the same cohorts, resulting in analysis of duplicate data. It was thus decided to review all of the studies meeting the selection criteria.

➢ *Clinical utility of endomicroscopy*

The literature search did not identify any studies of clinical utility, the primary outcome measure validated during the definition phase of this review.

➢ *Decision impact and diagnostic performances of endomicroscopy*

One decision impact study and ten diagnostic performance assessment studies were reviewed (the findings of the diagnostic performance studies were compiled as part of a meta-analysis).

The review of the decision impact study indicates that adding endomicroscopy has an impact on the monitoring rate and the rate of abstention from care. On the other hand, no evidence of an impact of endomicroscopy in respect of the surgery rate was demonstrated within the scope of this study.

The meta-analysis conducted as part of this assessment included ten diagnostic performance trials (of which six were monocentric trials). The sample sizes for these studies were between 20 and 90 patients. The assessment of the methodological quality of these trials using the QUADAS 2 grid indicates that most have uncertain to high risk levels. Three clinical trials had a low risk of bias.

The estimated sensitivity within the scope of the meta-analysis is 85% [76-90], the estimated specificity is 87% [76-93].

➢ *Safety of endomicroscopy*

The review of the safety-related aspect indicates that the main adverse effect of endomicroscopy is acute pancreatitis; cases were reported in five clinical trials with a rate varying between 1.3% and 7%.

A single case of allergy to fluorescein was reported out of all of the trials. In addition, cases of cystic bleeding were also reported in a single trial.

❖ **Expert opinion**

The ten members of the working group (WG) met on 23 March 2022. They approved the methodology, and had no comments to make about the literature search and review.

Regarding the validation of endomicroscopy for the characterisation of pancreatic cystic lesions (diameter ≥ 2 cm) of undetermined malignant potential before the result of the needle biopsy sample analysis (during the first ultrasound-guided endoscopy), the majority of the members of the working group were not in favour of validating the indication.

The majority of the members of the working group validated the indication of endomicroscopy for the characterisation of pancreatic cystic lesions (diameter ≥ 2 cm) of undetermined malignant potential after the result of the needle biopsy sample analysis (during a second ultrasound-guided endoscopy).

The French National Professional Council of Pathologists, National Professional Council of Vascular and Digestive

Surgery, National Professional Council of Hepato-Gastroenterology, and National Professional Council of Radiology and Medical Imaging were consulted as stakeholders within the scope of this assessment. The National Professional Councils expressed their support for the assessment methodology (bibliographic search and literature review) They also expressed their agreement with the conclusions of the report.

➢ *Conditions for performing endomicroscopy*

According to the experts, endomicroscopy must be performed by a gastroenterologist performing endoscopy procedures and trained in the use of endomicroscopy. The estimated learning curve is around 30 procedures. The medical team is the same as for performing ultrasound-guided endoscopy. The presence of an anatomical pathologist during the investigation to compile or interpret endomicroscopy images is not necessary. Endomicroscopy is a highly technical procedure which must only be performed in high-volume expert centres for pancreatic disease care, with the necessary expertise and material and human resources.

Conclusions

In view of the literature review and expert opinions, needle-based confocal endomicroscopy of pancreatic cystic lesions (diameter ≥ 2 cm):

- is of acceptable safety when performed in under ten minutes in order to limit the risk of onset of acute pancreatitis;
- is of no clinical utility for the characterisation of cystic lesions of undetermined malignant potential before the result of the needle biopsy sample analysis (assessment question No. 1) failing clinical utility data, despite satisfactory diagnostic performances;
- would be likely, in the experts' view, to be of clinical benefit as a last resort, for the characterisation of cystic lesions remaining of undetermined status after performing all existing routine investigations (imaging and ultrasound-guided investigations and needle biopsy fluid analysis) (assessment question No. 2).

However, in the absence of diagnostic performance and clinical utility data in the latter scenario, this clinical benefit remains presumed and must be confirmed. As a minimum, this confirmation could be obtained by assessing diagnostic performances in patients for whom all the routine investigations have not enabled the characterisation of the cystic lesion, and for whom a decision to conduct surgery has been made, with the histological analysis of the surgical specimen then acting as the standard. This assessment must be conducted within the framework of comparative prospective clinical studies.

Finally, in view of its technical nature which requires specific expertise, this investigation must be performed in high-volume expert centres for pancreatic disease care, which have the necessary expertise and material and human resources.

Methods

The standard diagnostic and therapeutic procedure assessment method was adopted to process this request; it consists of:

- a critical review of the scientific literature identified after a systematic search and selected based on explicit criteria, defined in PICOTS grids;
- consultation of professionals via:
  - meetings of external experts within a working group,
  - and the review of the final version of the report by representatives of relevant professional bodies, consulted as stakeholders;
- the compilation of these various items in a health technology assessment report, examined by the Committee for guidelines, suitability, pathways, and indicators, and ultimately validated by the HAS Board.

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