

# Novel investigative modalities for evaluation of pancreatic cystic lesions: Does increased diagnostic accuracy justify the high costs?



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## Bibliography

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Pancreatic cystic lesions (PCLs) are increasingly detected on imaging studies, resulting in undue anxiety to the patient and the treating physician. Diagnostic differentiation of PCLs continues to be challenging. There have been multiple guidelines for management of PCLs, mostly due to lack of tests with high diagnostic accuracy. Cost-effectiveness studies for managing PCLs have been mostly retrospective and have demonstrated that improvement in diagnostic accuracy effectively prevents unwarranted surgery, thereby reducing healthcare resource utilization. In the last 5 years, molecular analysis of PCL fluid and needle-based confocal laser endomicroscopy (nCLE) have demonstrated promising results with potential to improve diagnostic accuracy of PCLs and thereby impact patient management and outcomes. In a study published in this issue of *Endoscopy International Open*, Claude Le Pen et al. have performed a cost-effectiveness analysis to evaluate the economic benefit of diagnosing serous cystadenomas (SCA) by augmenting endoscopic ultrasound-guided fine-needle aspiration with nCLE. Despite the increased overall cost of diagnostic evaluation of PCLs, the improved accuracy of diagnosing SCAs and prevention of unwarranted pancreatic surgeries can potentially reduce healthcare resource utilization.

Pancreatic cystic lesions are incidentally diagnosed in 13% to 45% of patients undergoing magnetic resonance imaging and 2% of computed tomography scans [1, 2]. Despite judicious utilization of current standard of care including endoscopic ultrasound (EUS), fine-needle aspiration (FNA), cyst fluid analysis (CEA), and cytology, it is challenging to accurately classify PCLs into mucinous or non-mucinous (serous cystadenomas or

pseudocysts) PCLs. In fact, preoperative diagnosis of mucinous PCLs is incorrect in up to 30% of cases and these benign cysts are often surgically resected, exposing patients to an operative morbidity of 30% to 40% [3, 4]. Therefore, accurate characterization of PCLs would minimize healthcare costs and resource utilization associated with unwarranted surgical resections.

In a previous cost-effectiveness analysis of the 2006 International Consensus Guidelines (ICG) [5, 6], a Markov model was utilized and the authors created 3 scenarios. In Scenario 1, patients with suspected SCAs were followed as a benign disease. In Scenario 2, patients, if deemed fit, underwent surgical resection with no further follow-up. In Scenario 3, patients underwent preoperative EUS-FNA and cyst fluid (CEA and cytology) analysis, and surgery was performed based on the differentiation of PCL [6]. In this analysis, Scenario 2 was the cheapest (US \$ 13,200 per patient) but with lowest quality-adjusted life years (QALY) and Scenario 3 accounted for the highest costs (\$ 23,337 per patient) and highest QALY. The cost increment to reach Scenario 3 was \$ 11,394, indicating that additional costs were within acceptable range for satisfactory return on investment.

In a more recent cost-effectiveness analysis [7], 4 scenarios were tested in a hypothetical cohort of 1,000 asymptomatic patients with incidental PCLs (size  $\geq 3$  cm). In Scenario 1, wait and watch with cross-sectional imaging, and surgery was recommended for symptoms or high-risk features based on ICG 2012 guidelines [8]. In Scenario 2, patients were considered for resection without initial EUS. In Scenario 3, patients underwent EUS-FNA and cyst fluid analysis (CEA and cytology) and mucin-

nous cysts (CEA >192 ng/mL) were referred for resection. Scenario 4 was similar to Scenario 3 with added cyst fluid integrated molecular pathology (IMP) and surgery was considered for mucinous-aggressive PCLs (other 3 classifications based on IMP, including non-mucinous, mucinous-benign, and mucinous-indolent PCLs, were followed conservatively). Scenario 4 with EUS-FNA and cyst fluid CEA/cytology with IMP provided the greatest increase in QALY with cost nearly identical to Scenario 1 (\$18,966 vs. \$18,766 per patient). The authors concluded that adding IMP was the most cost-effective strategy.

Endoscopic ultrasound guided needle-based Confocal Laser Endomicroscopy (nCLE) is an emerging technological advance that provides in vivo, real-time, microscopic imaging of PCLs. More than 500 patients have been enrolled worldwide since 2011 in various studies involving EUS-nCLE for evaluation of PCLs. Recent major trials have established the safety profile and feasibility of diagnostic capabilities of EUS-guided nCLE in patients with PCLs [9–14]. In a recent larger, 11-year retrospective review of surgically resected SCAs at a tertiary US center, only 10% of SCAs (of 51) were diagnosed preoperatively by EUS-FNA cytology [15]. On histopathology, SCAs demonstrate a dense subepithelial capillary vascular network [11, 16]. During EUS-nCLE, a characteristic vascular network has been demonstrated and described as “superficial vascular network” or “fern pattern” of vascularity [11, 13, 17, 18]. Among external blinded EUS experts, an “almost perfect” inter- and intraobserver agreement has been demonstrated for identifying the vascular patterns of SCAs (INDEX study) [13, 19]. Further, the in vivo nCLE patterns of SCAs have been reproduced in ex vivo CLE of resected PCLs [17, 18]. While cyst fluid CEA has a pooled sensitivity of 50% and accuracy of 67% for diagnosing SCA, cytology has very low diagnostic yield; moreover there is lack of free fluid during FNA from microcystic SCAs [20]. Compared to this, EUS-nCLE has a sensitivity of 69% and specificity of 100% for diagnosing SCAs when the characteristic vascular pattern is detected [11].

In this issue of *Endoscopy International Open*, Claude Le Pen et al. have performed a cost-effectiveness analysis to evaluate the economic benefit of diagnosing SCAs with EUS-FNA and nCLE compared to EUS-FNA alone. They have theorized 2 scenarios based on published studies for patients with indeterminate non-communicating (with main pancreatic duct) PCLs (size  $\geq 2$  cm). Scenario 1 is use of EUS-FNA alone, derived from a retrospective cohort of 2622 patients with a diagnosis of SCA from 1990 to 2014 [21], and Scenario 2 is EUS-FNA with nCLE from a prospective French multicenter study (CONTACT study) [11]. Patients who underwent EUS-FNA with nCLE experienced a 23% reduction in frequency of surgical interventions, which accounted for 13% and 14% reductions in total costs in the public and private sectors, respectively. For every 1,000 patients, 4 did not experience the estimated surgery-associated mortality. In France, the total cost of EUS-FNA with anesthesia was 274.87€ (\$397.60) and that of nCLE was 600€ (\$706.80) per patient during the study period. Despite using a maximum nCLE cost estimate of 900€ (\$1060.30), application of nCLE accounted for cost reductions of approximately 9% and 7% for the public and private sectors, respectively.

While we can hypothesize that utilization of EUS-nCLE and cyst fluid molecular analysis will improve diagnostic accuracy for differentiating mucinous from non-mucinous PCLs compared to the current standard of care, there are certain limitations for these novel diagnostic modalities.

Overall, the most significant limitations of studies evaluating EUS-nCLE include: (a) fewer surgically resected lesions in mostly single-center studies; (b) lack of formal training in EUS-nCLE; and (c) requirement for high-quality nCLE imaging [12]. Limitations of studies in cyst fluid molecular analysis include: (a) lack of prospective multicenter studies; (b) suboptimal identification of specific PCL types – lower sensitivity for mucinous cystic neoplasm with molecular markers and lack of markers for cystic neuroendocrine tumor and squamous epithelium lined cysts; and (c) lower sensitivity for diagnosing SCAs due to continued dependence on Sanger sequencing for VHL gene [22]. Moreover, there are no studies combining EUS-nCLE and cyst fluid molecular markers in differentiation of PCLs and identification of advanced neoplasia (high-grade dysplasia or cancer) in mucinous-PCLs.

Patients with PCLs are a group with a high risk of operative complications and low risk of developing malignancy. Thus, accurate differentiation of a mucinous from non-mucinous or serous PCL potentially determines a cost-effective strategy. A conclusion from these cost-effectiveness studies indicates that improving diagnostic accuracy of benign non-mucinous PCLs and detecting cysts with malignant potential provides the most benefit in healthcare resource utilization. Because incidence of PCL increases with age, they are more relevant in the elderly population [23]. Despite the evidence provided, well-designed prospective studies are necessary to establish whether the proposed approach of advanced diagnostics is truly cost effective. In the meantime, these novel diagnostic modalities would theoretically result in avoiding unwarranted surgical resections of benign PCLs and promote resection of high-risk mucinous cysts with malignant potential.

## Competing interests

None

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