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Editorial
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New Trends in the Diagnosis of Cystic Pancreatic Neoplasms (CPNs): Is It the Time of Endoscopic Ultrasound (EUS) Guided Needle-Based Techniques?

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Editorial

Cystic Pancreatic Neoplasms (CPNs) have been increasingly detected over the past two decades due to the widespread use of cross-sectional abdominal imaging. CPNs are often identified in asymptomatic individuals and their incidence increases with age. CPNs can be divided into mucinous and non mucinous. Non mucinous lesions consist of serous cystic neoplasms (SNCs) which are regarded as benign and don't need any treatment, unless symptomatic and the uncommon Solid Pseudopapillary Neoplasms (SPNs), which are low malignant lesions. Mucinous lesions are considered precancerous. They are classified into Mucinous Cystic Neoplasm (MCNs) and Intraductal Papillary Mucinous Neoplasm (IPMNs) either Main Duct (MD), Branch Duct (BD) or mixed type. MD or mixed type IPMNs have a cumulative invasive malignancy rate of approximately 40% and up to 70% versus 15% of BD-IPMN [1]. Therefore, a preventive surgical resection is justified in MD IPMNs, but in case of BD-IPMNs it should be considered only for the lesions really associated with high risk of malignancy.

In order to assist the management of MCNs and BD-IPMNs over the past decade several national and international guidelines have been developed, which are based on standard clinical assessment, radiographical imaging, and ancillary fluid studies. The International Consensus Guidelines (ICG) are probably the most reliable. They were drawn up in Sendai in 2006 by the International Association of Pancreatology at. A revised version of ICG (Fukuoka 2012) [2] takes into consideration "high risk stigmata", which imply a surgical resection and "worrisome features", that necessitated a further investigation by Endoscopic Ultrasound (EUS) and EUS-FNA. Unfortunately, these worrisome features demonstrated low positive predictive values in detecting high grade dysplasia or invasive carcinoma [14 in new guidelines)]. Moreover, they cannot be adequately assessed by Magnetic Resonance Imaging (MRI), that is the most valuable noninvasive technique as well as by EUS. In addition, the ancillary evaluations on cyst fluid collected during EUS-FNA are unsatisfactory. CEA levels can be useful only to differentiate mucinous from non mucinous cysts, with a suboptimal sensitivity. Moreover the cytology has a poor sensitivity with a low diagnostic accuracy, ranging from 50 to 60%. Therefore it is evident that current diagnostic work-up should be improved. Several new tools are now emerging, which are based on EUS guided puncture of the cyst. These techniques include in particular Confocal Endomicroscopy (CLE) of the epithelial surface of the cyst and bioptic sampling of the cystic wall with microforceps. Moreover additional molecular biomarkers on cystic fluid have been recently proposed.

Confocal laser endomicroscopy is a novel technology that provides real-time laser-assisted microscopic imaging of tissue, facilitating *in vivo* histopathology. The CLE probe can be inserted through a 19-gauge FNA needle for real time microscopic examination of the pancreatic cyst epithelium during EUS (needle- based CLE). Multiple clinical trials have identified and established specific characteristic needle –based CLE (nCLE) findings of various pancreatic cystic lesions. Within of 29 pancreatic cystic lesions (16 mucinous and 13 non-mucinous cysts the overall sensitivity, specificity, and accuracy of nCLE were respectively 95%, 94%, and 95% for the diagnosis of mucinous PCLs and 99%, 98%, and 98% for the diagnosis of Serous Cystoadenoma (SCA) [3]. For IPMN and MCN, characteristic findings include finger-like papillae and a single or layers of band-like epithelium, respectively [4]. It has also been evaluated the ability of nCLE to differentiate the histologic subtypes of BD-IPMN but only the oncocytic subtype demonstrated distinct patterns [5].

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Microforceps are single-use miniature biopsy forceps, 230 cm long, with an outer diameter <1 mm, that can be passed through a standard 19-gauge EUS needle. This allows histologic sampling of PCLs by obtaining biopsies of the cyst wall and/or mural nodules before the aspiration of cystic content for fluid analysis. The largest published series includes twenty-seven cases [6]. Microforceps biopsies diagnosed mucinous cyst in 9 patients (33.3%), serous cystadenoma in 4 (14.8%), neuroendocrine tumor in 1 (3.7%), and benign and/or inflammatory cyst in 10 (37.1%). In 7 patients (26%), microforceps biopsy results drastically changed the diagnosis, providing diagnoses otherwise not suggested by cytology or cyst fluid CEA levels. Certainly the use of microforceps can improve the diagnosis of various types of PCNs and the detection of dysplasia or invasive carcinoma because the sampling can be targeted on high risk areas like mural nodules, but focal areas of dysplasia can be missed.

Over the last decade, DNA-based molecular testing of cystic fluid has emerged as a potential diagnostic modality for the assessment of pancreatic cyst lesions. However results have been controversial, due to poor sensitive detection strategies (conventional Sanger sequencing). The use of next-generation sequencing (NGS) has revealed specific molecular markers that seem to be very reliable for the diagnosis of mucinous cysts as well as detection of advanced neoplasia. In a large prospective study recently published, 626 pancreatic cystic fluid specimens from 595 patients submitted to EUS-FNA, were assessed by targeted next-generation sequencing (NGS). On 102/595 patients with surgical follow-up, KRAS/GNAS mutations were detected in 56 (100%) IPMNs and 3 (30%) MCNs, and associated with 89% sensitivity and 100% specificity for a mucinous cystic lesion. The combination of KRAS/GNAS mutations and alterations in TP53/PIK3CA/PTEN had an 89% sensitivity and 100% specificity for advanced neoplasia. [7] More biomarkers suggesting malignancy in CPNs are now being investigated. Recently, some authors reported that circulating HE4 (Human epididymis protein 4) levels were higher in subjects with pancreatic adenocarcinoma than in the controls. We found high levels of this marker on cyst fluid and low serum HE4 values with a high fluid/serum ratio in a patient with a mucinous malignant lesion [8]. Although prospective multicenter studies are needed, it is foreseeable that the integration of the novel EUS guided needle-based technologies (CLE and microforceps) with molecular analysis on the cystic fluid collected by EUS-FNA will change the management, especially of BD-IPMNs allowing for more accurate risk stratification.

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