Endoscopic Ultrasound Imaging for Diagnosing and Treating Pancreatic Cysts

Wiriyporn Ridtitid, MD, Mohammad A. Al-Haddad, MD, MSC

KEYWORDS
- Pancreatic cysts
- Intraductal papillary mucinous neoplasm
- Mucinous cystic neoplasm
- Serous cystic neoplasm
- Endosonographic characteristics of pancreatic cysts
- Fine needle aspiration
- Endosonographic-guided pancreas cyst ablation

KEY POINTS
- Pancreatic cysts are increasingly detected owing to widespread use of cross-sectional imaging.
- Imaging alone is inadequate to appropriately classify pancreatic cysts from a pathologic perspective.
- Endoscopic ultrasound-guided fine needle aspiration provides valuable information including cytology, tumor and molecular markers that help to classify pancreatic cysts appropriately.
- Mucinous pancreatic cysts with high-risk features for malignancy should be resected in surgically fit patients.
- Low-risk mucinous pancreatic cysts can be managed conservatively with periodic imaging surveillance.

Video content accompanies this article at http://www.giendo.theclinics.com.

INTRODUCTION

In recent years, the diagnosis of cystic lesions of the pancreas (CLPs) has significantly increased owing to the widespread use of cross-sectional radiologic imaging technologies. In the radiologic literature, the prevalence of CLPs on computed tomography (CT) and MRI examination is estimated to range between 2.4% to 14%. One population-based study demonstrated that the overall frequency of detecting...
malignant in CLPs at 2.9% in patient surveyed for known pancreatic cysts, with an annual incidence of 0.4% per year. Based on the presence of epithelial tissue, the World Health Organization classifies CLPs into epithelial and nonepithelial lesions. Inflammatory pancreatic fluid collections (pancreatitis-associated pseudocysts) are not considered true cysts owing to the absence of epithelial component.

A combination of clinical and imaging findings in addition to cyst fluid markers can help to classify CLPs appropriately and guide management. Although some lesions require surgical resection, the majority of CLPs can be surveyed safely by imaging over the long term. In this review, we expand on each of the main types of epithelial CLPs and discuss the role of endoscopic ultrasound (EUS) examination in the diagnosis and management of the commonly encountered types in clinical practice.

**DIAGNOSIS OF CYSTIC LESIONS OF THE PANCREAS**

**Mucinous Cystic Pancreatic Tumors**

Mucinous CLPs are mucin-producing neoplasms, which are composed of 2 distinct groups: intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Although mucinous CLPs are considered “premalignant,” many of them remain indolent and do not exhibit an aggressive biological behavior when observed over time. Because of this malignant potential, however, mucinous CLPs require baseline investigation to assess risk of malignant transformation and interval follow-up. Therefore, it is necessary to distinguish between mucinous and nonmucinous CLPs before making final management recommendations.

**Intraductal Papillary Mucinous Neoplasms**

**Histopathologic features**

IPMNs are mucinous tumors that arise in the main pancreatic duct or its major branches. Based on the World Health Organization classification, IPMNs are classified histologically into benign, borderline, and malignant; the malignant ones encompass noninvasive and invasive lesions. According to the consensus on the pathologic classification, IPMNs are categorized based on the presence or absence of invasive adenocarcinoma in the resected specimen owing to the negative impact of any invasive component on local recurrence and overall patient survival. In addition, the consensus suggested classifying noninvasive IPMN into low-grade dysplasia (adenomas in previous classification), moderate dysplasia (borderline tumors in previous classification), or high-grade dysplasia (carcinoma in situ), based on the maximal degree of dysplasia in the lining epithelium. From a pathologic and morphologic perspective, IPMNs can be classified as main duct (MD-IPMN), branched duct (BD-IPMN), or mixed IPMN.

**Clinical characteristics**

MD-IPMN and mixed-type IPMN are slightly more prevalent in men, with a peak age of incidence in the 6th to 7th decades (Table 1). The majority of patients are asymptomatic and most BD-IPMNs are diagnosed incidentally on imaging studies. However, IPMNs can present with symptoms such as abdominal pain, jaundice, weight loss, diabetes, steatorrhea, and pancreatitis. The overall malignancy risk in MD-IPMN has been reported to be between 40% and 50%, although in BD-IPMN, this risk varied significantly in surgical literature but is believed to be 20% or less. Nevertheless, many experts believe that these reported risks are inflated, citing selection bias in these mostly surgical series.

It is believed that IPMN lesions grow slowly and follow an adenoma to carcinoma sequence. Clinical factors associated with invasive cancer in IPMN include jaundice,
### Table 1
Endoscopic ultrasound examination morphology and pathologic features of the various types of cystic pancreatic neoplasms

<table>
<thead>
<tr>
<th></th>
<th>IPMNs</th>
<th>MCNs</th>
<th>Serous Cystic Neoplasms</th>
<th>cPNETs</th>
<th>SPTPs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range</strong></td>
<td>60s–70s</td>
<td>50s–70s</td>
<td>60s–70s</td>
<td>50s–60s</td>
<td>30s</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male &gt; female</td>
<td>Female &gt; male</td>
<td>Female &gt; male</td>
<td>Male = female</td>
<td>Female &gt; male</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Mostly asymptomatic on BD-IPMNs</td>
<td>Asymptomatic if small</td>
<td>Frequently asymptomatic</td>
<td>Nonfunctioning lesions and often asymptomatic</td>
<td>Asymptomatic or abdominal pain</td>
</tr>
<tr>
<td><strong>Macroscopic findings</strong></td>
<td>Various degrees of ductal dilatation in MD-IPMNs; mucin-filled cystic cavity in BD-IPMNs</td>
<td>A smooth surface and a fibrous pseudocapsule with variable thickness septations</td>
<td>A few or numerous small cysts filled with serous fluid around a central fibronodular core</td>
<td>A single locule, surrounded by a rim of neoplastic parenchyma, filled with clear to straw-colored fluid</td>
<td>Cystic areas of hemorrhage and necrosis with a well-defined fibrous pseudocapsule</td>
</tr>
<tr>
<td><strong>Microscopic findings</strong></td>
<td>Intraductal proliferation of columnar mucin-producing cells</td>
<td>Benign: no mitosis</td>
<td>Malignant: changes of high-grade intraepithelial neoplasia or invasive adenocarcinoma</td>
<td>A single layer of cuboidal or flattened epithelial cells with clear cytoplasm; positive PAS staining</td>
<td>Monotonous cells with granular chromatin and plasmacytoid morphology, positive synaptophysin and chromogranin A stains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pseudopapillary structures composed of tumor cells surrounding small central vessels</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Head &gt; body, tail</td>
<td>Body, tail &gt; head</td>
<td>Body, tail ≥ head</td>
<td>Body, tail &gt; head</td>
<td>Throughout the pancreas</td>
</tr>
</tbody>
</table>

**Abbreviations:** cPNETs, cystic neuroendocrine tumors of the pancreas; MD-IPMN, main duct intraductal papillary mucinous neoplasm; PAS, periodic acid Schiff; SB-IPMN, side branch intraductal papillary mucinous neoplasm; SPTPs, solid pseudopapillary tumors of the pancreas.
weight loss, intramural nodules, progressive dilation of the main duct, and malignant cytology on fine needle aspiration (FNA).\textsuperscript{20,21} Although BD-IPMN is associated with a lower risk of malignancy, pancreatic ductal adenocarcinoma has been reported concomitantly in patients with BD-IPMN\textsuperscript{22–24} in a location distant from the IPMN lesion. During follow-up, the 3- and 5-year rates of IPMN-concomitant pancreatic ductal adenocarcinoma occurrence were 4.0% and 8.8%, respectively, according to 1 report\textsuperscript{22}; therefore, surveillance is recommended for all lesions.\textsuperscript{25–27}

\textbf{Radiologic and endoscopic ultrasound-guided fine needle aspiration features}

On CT imaging, MD-IPMN demonstrates diffuse or focal dilatation of the main pancreatic duct with possible intraductal heterogeneous densities, representing mucin or intraductal tumor growth (Table 2).\textsuperscript{28} BD-IPMN can be either unifocal or multifocal.\textsuperscript{11,29} MRI technology is better suited to outline the morphology of the main duct and its side branches, as well as determine the presence of septations, mural nodules, or mass.\textsuperscript{28,30} MCNs and BD-IPMNs may be difficult to differentiate on imaging alone because both can appear as simple unilocular cystic lesions, with variable cystic wall thickness. Intramural filling defects seen on imaging of BD-IPMNs can be either mucin or mural nodules. Based on earlier studies,\textsuperscript{30–34} CT or MRI features associated with malignancy in IPMNs include lesion size of greater than 3 cm, main duct dilation of greater than 6 mm, irregularly thickened wall, mural nodule larger than 5 mm, ductal wall enhancement, and common bile duct dilation. A metaanalysis evaluating imaging features to distinguish malignant from benign BD-IPMNs\textsuperscript{35} found that the presence of mural nodules was the most suggestive finding for malignancy (odds ratio [OR], 6.0), followed by main pancreatic duct dilatation (OR, 3.4), thick septum or cyst wall (OR, 2.3), and cyst size greater than 3 cm (OR, 2.3).

The classic endoscopic finding of fish-mouth appearance of the papilla, which is characterized by the presence of mucin exuding from a patulous major or minor papilla with or without papillary tissue protrusion (fish egg appearance) is diagnostic of MD-IPMN (Fig. 1). EUS characteristics include a macrocystic morphology of the cyst, with or without septations, which could communicate with a dilated main pancreatic duct (Video 1) or a side branch (Fig. 2).\textsuperscript{36} However, in the absence of duct communication, BD-IPMN may be morphologically indistinguishable from MCNs. A mucin nodule may be seen with a hypoechoic core and a hyperechoic rim (Fig. 3) and should be differentiated from real tissue nodules (Fig. 4). The differential diagnosis of a unilocular pancreatic cyst on EUS imaging includes commonly macrocystic serous cystic neoplasm, MCN, and inflammatory cyst.\textsuperscript{37} Previous studies reported a strong association between the presence of mural nodule (height >10 mm, lateral spread >15 mm) and malignancy in BD-IPMN.\textsuperscript{38,39} FNA is generally recommended for cyst fluid acquisition, mainly owing to the limitations of relying on EUS morphology alone to classify the lesion appropriately. A large, prospective, multicenter US study found that the accuracy of EUS imaging features alone for the diagnosis of mucinous lesions was only 51\%.\textsuperscript{40}

\section*{CYST FLUID EVALUATION

\textbf{Cytology and Tumor Markers}}

Cytologic aspirates from IPMNs are typically viscous and cytology may reveal columnar epithelial cells and thick extracellular mucin although often are hypocellular.\textsuperscript{41–43} Columnar mucinous cells from IPMNs may be arranged in a papillary configuration. The sensitivity of EUS-FNA for invasive malignancy in IPMNs is reportedly as low as 44\%, but can be enhanced with cytology brushings and recent microforceps.\textsuperscript{41,44–46}
<table>
<thead>
<tr>
<th></th>
<th>IPMNs</th>
<th>MCNs</th>
<th>SCN</th>
<th>cPNETs</th>
<th>SPTPs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical features</strong></td>
<td>Fish mouth appearance on endoscopy. Macrocystic, septated cyst with dilated PD (main or side branch)</td>
<td>Macrocystic cyst with a visible wall</td>
<td>A well-demarcated lesion with multiple small fluid filled cavities, with or without central calcified scar</td>
<td>Unilocular or multicellular lesion with a visible wall</td>
<td>Well-defined, mixed echogenicity lesion, with or without internal or peripheral calcifications</td>
</tr>
<tr>
<td><strong>Echogenicity</strong></td>
<td>Anechoic</td>
<td>Anechoic</td>
<td>Usually anechoic Hypoechoic if solid variant</td>
<td>Anechoic, hypoechoic, or mixed</td>
<td>Anechoic, hypoechoic, or mixed</td>
</tr>
<tr>
<td><strong>Wall thickness</strong></td>
<td>Thin</td>
<td>Mostly thick</td>
<td>Thin</td>
<td>Mostly thick</td>
<td>Mostly thick</td>
</tr>
<tr>
<td><strong>Septation</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Nodule</strong></td>
<td>Mucin aggregation; with or without true soft tissue mural nodule</td>
<td>With or without mural nodule</td>
<td>Rare</td>
<td>With or without mural nodule</td>
<td>With or without mural nodule</td>
</tr>
<tr>
<td><strong>Communication with the pancreatic duct</strong></td>
<td>Usually seen</td>
<td>Rarely seen</td>
<td>Not seen</td>
<td>Not seen</td>
<td>Not seen</td>
</tr>
<tr>
<td><strong>Cyst fluid viscosity</strong></td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Cyst fluid cytology</strong></td>
<td>Acellular with background of mucin. Mucinous epithelial cells with papillary projections and variable atypia may be seen</td>
<td>Hypocellular with background mucin. Occasional mucinous epithelium and variable atypia</td>
<td>Mostly bloody and acellular aspirate. Rarely shows glycogen staining cuboidal cells</td>
<td>Small homogenous population of cells with round nuclei that stain positive for chromogranin and synaptophysin</td>
<td>Branching papillae with myxoid stroma that reacts to Vimentin on cell block</td>
</tr>
<tr>
<td><strong>Cyst fluid CEA</strong></td>
<td>Moderate elevation</td>
<td>Usually high</td>
<td>Undetectable to low</td>
<td>Undetectable to low</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Cyst fluid amylase</strong></td>
<td>Usually high</td>
<td>Variable</td>
<td>Low</td>
<td>Low</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Molecular Markers</strong></td>
<td>K-ras mutation; GNAS mutation</td>
<td>K-ras mutation; p53 mutation; SMAD4 mutation</td>
<td>Von Hippel-Lindau gene mutation</td>
<td>CTNNB1 mutation</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CEA, carcinoembryonic antigen; cPNETs, Cystic neuroendocrine tumors of the pancreas; MD-IPMN, main duct intraductal papillary mucinous neoplasm; NA, not applicable; PAS, periodic acid Schiff; PD, pancreatic duct; SB-IPMN, side branch intraductal papillary mucinous neoplasm; SCN, serous cystic neoplasm; SPTPs, solid pseudopapillary tumors of the pancreas.
Multiple tumor markers present in IPMNs such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA 72-4, and CA 125 have been evaluated to improve diagnostic yield. CEA, the most commonly used marker, is generally higher in mucinous lesions and lower in pseudocysts and nonmucinous tumors (see Table 2). Early studies using percutaneous FNA reported that a CEA of less than 5 ng/mL provided 100% sensitivity and 86% specificity for distinguishing mucinous neoplasms from other cystic lesions.47 A large, prospective study40 using EUS-FNA determined that a cyst fluid CEA cutoff of 192 ng/mL provided a sensitivity of 73% and specificity of 84% for differentiating mucinous from nonmucinous CLPs. Furthermore, no other combination of factors, including cytology, morphology, and CEA levels, was found

Fig. 1. Fish mouth deformity of the major papilla in a patient with main duct intraductal papillary mucinous neoplasm with polypoid, fish egg–appearing epithelium protruding through the gaping papilla.

Fig. 2. A small side branch intraductal papillary mucinous neoplasm incidentally detected on endoscopic ultrasound examination performed for an unrelated reason. The communication with the undilated main pancreatic duct is clear.
to be more accurate than CEA levels alone in diagnosing mucinous cysts according to this study. Cyst fluid amylase is usually elevated in IPMN owing to communication with the main pancreatic duct.

Recent advances in the diagnosis of CLPs include the identification of specific genetic changes associated with various tumors and premalignant potential (Table 3). The increasing knowledge about common genetic alterations leading to pancreatic adenocarcinoma, like p53 and K-ras mutations, increased interest in the evaluation of similar changes in CLPs. In malignant transformation of CLPs, K-ras mutations seem to occur early in the malignant transformation process. In IPMN, this occurrence is reported to be a result of tumor suppressor gene inactivation, which is represented by loss of heterozygosity at 9p12(p16) and 17p13(p53). The use of these markers has been evaluated in pancreatic juice and cyst fluid. K-ras mutation is a very specific for mucinous cysts and specific mutation acquisition sequences we found to be associated with malignancy. CEA alone had the highest sensitivity (82%) compared with 11% for K-ras mutation and 70% for allelic imbalance. Al-Haddad and colleagues demonstrated in a prospective study including mainly IPMNs that molecular markers had a sensitivity of 50% and a specificity of 80% in identifying cystic mucinous lesions with an overall accuracy of 56%. The combination of molecular analysis with cyst fluid CEA and cytology resulted in higher diagnostic

Fig. 3. A mucin nodule attached to the wall of a side branch intraductal papillary mucinous neoplasm with a hyperechoic rim and hypoechoic core.

Fig. 4. A “true” mural nodule with homogenous echotexture and irregular contour seen in a side branch lesion.
<table>
<thead>
<tr>
<th>Study (Year) (Ref)</th>
<th>Study Design</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Malignant Cysts (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khalid et al&lt;sup&gt;155&lt;/sup&gt;, 2005</td>
<td>Prospective</td>
<td>36</td>
<td>31</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Schoedel et al&lt;sup&gt;156&lt;/sup&gt;, 2006</td>
<td>Retrospective</td>
<td>16</td>
<td>25</td>
<td>25</td>
<td>44</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Khalid et al&lt;sup&gt;157&lt;/sup&gt;, 2009</td>
<td>Prospective</td>
<td>113</td>
<td>35</td>
<td>45</td>
<td>67</td>
<td>96</td>
<td>66</td>
<td>53</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Sawhney et al&lt;sup&gt;54&lt;/sup&gt;, 2009</td>
<td>Retrospective</td>
<td>100</td>
<td>26</td>
<td>11</td>
<td>70</td>
<td>100</td>
<td>29</td>
<td>93</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Shen et al&lt;sup&gt;158&lt;/sup&gt;, 2009</td>
<td>Retrospective</td>
<td>35</td>
<td>17</td>
<td>57</td>
<td>93</td>
<td>100</td>
<td>43</td>
<td>83</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Sreenarasimhaiah et al&lt;sup&gt;159&lt;/sup&gt;, 2009</td>
<td>Retrospective</td>
<td>20</td>
<td>45</td>
<td>33</td>
<td>50</td>
<td>93</td>
<td>71</td>
<td>33</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Nikiforova et al&lt;sup&gt;160&lt;/sup&gt;, 2013</td>
<td>Retrospective</td>
<td>142</td>
<td>8</td>
<td>54</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Al-Haddad et al&lt;sup&gt;55&lt;/sup&gt;, 2014</td>
<td>Prospective</td>
<td>48</td>
<td>16</td>
<td>42</td>
<td>11</td>
<td>90</td>
<td>100</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Winner et al&lt;sup&gt;161&lt;/sup&gt;, 2015</td>
<td>Retrospective</td>
<td>40</td>
<td>20</td>
<td>48</td>
<td>31</td>
<td>89</td>
<td>67</td>
<td>44</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>

Using surgical pathology reference standard whenever available.

*Abbreviation: LOH, loss of heterozygosity.

<sup>a</sup> Number of patients included with confirmed diagnosis; retrospective.
performance than either one of its individual components. GNAS is another oncogene mutation that is almost exclusively found in IPMNs and has not been observed in MCNs or in solid pancreatic adenocarcinoma of a non-IPMN origin.\textsuperscript{56,57} The combination of KRAS and GNAS mutation testing are highly sensitive and specific for IPMNs.

Despite the expanding role of genetic markers, they are best reserved for pancreatic cysts in which cytology and CEA testing is inconclusive for classifying the lesion as mucinous or nonmucinous, or in cases when the volume of fluid obtained is insufficient for CEA. Additional studies are needed to further elucidate the role of molecular markers in the diagnostic and management algorithms of IPMN.

**MUCINOUS CYSTIC NEOPLASMS**

*Histopathologic Features*

MCNs are defined as cystic epithelial neoplasms with no communication with the pancreatic ductal system and is composed of columnar, mucin-producing epithelium, supported by ovarian-type stroma, which is the pathologic hallmark and is required to differentiate this tumor from IPMN.\textsuperscript{5} Similar to IPMNs, MCNs are classified as noninvasive (low-grade dysplasia, moderate dysplasia, and high-grade dysplasia) and invasive lesions. Histologically, MCNs exhibit columnar epithelium with basally located nuclei and the absent or minimal mitosis, whereas mucinous cystadenocarcinomas show changes of high-grade intraepithelial neoplasia (nuclear stratification, severe nuclear atypia, and frequent mitoses), which are usually focal.\textsuperscript{6}

*Clinical Characteristics*

Females are more frequently affected with MCNs, particularly in their 5th to 7th decades (see Table 1).\textsuperscript{58–60} The tumors occur most frequently in the pancreatic body and tail.\textsuperscript{10} MCNs can be found incidentally,\textsuperscript{61} however, and can present with abdominal pain, palpable mass, and weight loss, particularly in association with large lesions.\textsuperscript{8,10} Pancreatitis is infrequent with MCNs but can be seen in up to 10% to 20% of cases.\textsuperscript{58,62,63} A recent study demonstrated factors predictive of high-grade dysplasia and invasive carcinoma in MCNs, which included the presence of symptoms, obstructive jaundice, and elevated serum CEA and CA 19-9.\textsuperscript{54} Although MCNs have malignant potential, they carry a lower overall risk of malignancy in comparison with MD-IPMNs.\textsuperscript{61} In a study of 163 patients undergoing surgery, the prevalence of malignancy in such tumors was found to be 17.5% (5.5% with carcinoma in situ and 12% with invasive cancer).\textsuperscript{62} Nevertheless, surgical resection is recommended for all surgically fit patients with MCNs owing to the long-term risk of cancer in this predominantly younger cohort of patients.\textsuperscript{21}

**Radiologic and Endoscopic Ultrasound-Guided Fine Needle Aspiration Findings**

CT typically shows a unilocular cystic lesion in pancreatic body or tail, with or without septations and a thick enhancing wall (see Table 2). Peripheral calcifications can be present in 15% to 23% of cases, and occasionally can be linear taking the shape of an egg shell.\textsuperscript{58,63} MCNs appear as round and homogenous, with high signal intensity on T2-weighted MRI, with regular rim enhancement on delayed T1-weighted images.\textsuperscript{28,65} On EUS, MCNs present as macrocystic lesions with a visible wall and septations of variable thickness (Fig. 5).\textsuperscript{38} Solid component or mural nodule may be seen. Peripheral calcifications can be present focally or as a rim but is only seen in up to 15% of lesions.\textsuperscript{58} Mucinous cystadenocarcinoma are more likely to appear as a hypoechoic cystic or solid mass, or a complex cyst, and are frequently associated with a dilated main pancreatic duct upstream from the lesion and regional adenopathy.\textsuperscript{66} Cyst fluid
Amylase is usually low in MCN (see Table 2). In a pooled analysis from 12 studies, a cyst fluid amylase of less than 250 U/L supported a diagnosis of serous cysts or MCNs (sensitivity 44%, specificity 98%) and thus virtually excluded pseudocysts. In the same analysis, cyst fluid CEA of less than 5 ng/mL suggested a serous cyst or pseudocyst (sensitivity 50%, specificity 95%) and a CEA of greater than 800 ng/mL strongly suggested MCN (sensitivity 48%, specificity 98%). Cytologic analysis from FNA of MCNs could reveal mucinous epithelium, but this can be difficult to differentiate IPMN based on cytology alone because ovarian stroma is rarely present on FNA specimens. Molecular analysis can assist in the diagnosis of MCNs with similar findings to IPMN lesions (see Table 3). Kim and colleagues found that one-third of MCN were associated with K-ras mutations and further changes in tumor suppressor genes like p16 and p53, but were not observed in any serous cystic lesions.

**NONMUCINOUS CYSTIC LESIONS OF THE PANCREAS**

Nonmucinous CLPs vary greatly in their clinical, radiologic, and EUS characteristics owing to variable underlying pathology. Serous cystadenomas (SCAs) are the most commonly encountered nonmucinous true cystic tumors of the pancreas. Other nonmucinous pure cystic or mixed solid cystic tumors such as pancreatic neuroendocrine tumors (PNETs) and solid pseudopapillary tumors of the pancreas (SPTPs) are discussed elsewhere in this article.

**SEROUS CYSTADENOMAS**

**Histopathologic Features**

SCAs are defined as cystic epithelial neoplasms composed of glycogen-rich, ductular-type epithelial cells that produce a watery fluid similar to serum. Gross pathology often demonstrates a few or numerous small cysts filled with serous fluid around a central fibrous core with fine septations (central scars). By histology, the cysts are lined by a single layer of cuboidal or flattened epithelial cells with clear cytoplasm. The periodic acid-Schiff stain is positive owing to their intracytoplasmic glycogen. Morphologically, microcystic SCAs (typically with individual cysts measuring <5 mm in size) are more common, whereas the macrocystic variant (>2 cm in size) is relatively
infrequent. Microcystic tumors are usually well-delineated with multiple small fluid-filled cavities that are separated by thin septae and lined by cuboidal epithelial cells.11 Macrocytic SCAs may be difficult to differentiate from MCNs or BD-IPMNs based on morphology alone. The presence of any intramural nodules, cyst wall thickening, floating debris, mucin, or associated pancreatic duct dilation or communication often indicates a mucinous lesion.66,69

Clinical Characteristics

SCAs frequently occur in females around the 6th to 7th decades of life,8,10,70 and are believed to be predominantly located in the pancreatic body and tail6,8 (see Table 1). However, a multicenter study from Japan reported similar distribution in the pancreas head (39%), body (35%), and tail (22%).70 Patients are usually asymptomatic, with SCAs being an incidental finding on imaging studies.10,70 Among symptomatic patients, abdominal pain is the most common presentation (12%),70 but other symptoms include back pain, jaundice, or pancreatitis.8,9,70 Malignant SCAs of the pancreas are extremely rare; therefore, these tumors are considered to have a negligible malignant potential.71,72 An observational study showed a steady rate of growth of pancreatic SCA over time, with an estimated doubling in size time of 12 years.73

Radiologic and Endoscopic Ultrasound-Guided Fine Needle Aspiration Characteristics

SCAs can appear as polycystic (70%), honeycomb (20%), or oligocystic (<10%) on imaging (see Table 2),74 with a central scar in some cases.75 The honeycomb appearance is described as numerous subcentimeter cysts, separated by fibrous septa28,74; however, this may appear as a well-delineated mass with mixed attenuation and a sharp interface with vascular structures on CT scan.74 The oligocystic pattern is recognized by fewer large cysts measuring greater than 2 cm, which may appear like MCNs or BD-IPMNs.74 Magnetic resonance cholangiopancreatography usually shows no communication with the pancreatic duct.

The typical SCA is a well-demarcated lesion on EUS studies with multiple small, fluid-filled cavities separated by thin septations (Fig. 6, Video 2).10,37 The honeycomb

![Fig. 6. A serous cystic neoplasm (SCN) in a patient referred for suspicion of a solid mass on a computed tomography scan. Microcystic variants of SCN can be mistaken for solid tumors in imaging.](image-url)
pattern is noted in most of the microcystic lesions by EUS. A central calcified scar may exhibit a “sunburst” appearance. The solid variant of SCAs has been rarely reported, but can lead to misdiagnosis as a solid tumor. Nevertheless, the presence of mural nodule, wall thickening, ductal dilatation, or a mucin-filled cavity is an atypical manifestation for SCAs and should raise the suspicion of a mucinous lesion.

Owing to the distinctive endosonographic appearance of microcystic SCA, cyst sampling is generally not needed. Furthermore, the diagnostic yield of EUS-FNA for SCA is usually poor owing to the small size of the cystic compartments and the relatively vascular intercystic septa, leading to typically very bloody aspirates. Cyst fluid from SCA is usually thin, nonviscous, and colorless if no blood contamination occurred. Cellularity from cyst fluid is usually very low, but when present may contain cuboidal epithelial cells that stain positive for glycogen but not mucin (see Table 2).

The macrocystic variant of SCA should be sampled for cytology and tumor markers because morphology alone cannot differentiate these from mucinous lesions. In a pooled analysis from 12 studies, a cyst fluid amylase of less than 250 U/L supported the diagnosis of SCA (sensitivity 44%, specificity 98%) and virtually excluded pseudocysts. In the same analysis, cyst fluid CEA of less than 5 ng/mL suggested an SCA or pseudocyst (sensitivity 50%, specificity 95%). Molecular analysis in SCAs is less studied compared with mucinous lesions. Moore and colleagues described allelic losses on chromosome 10q in 50% and on chromosome 3p in 40% of cases, in addition to von Hippel-Lindau (VHL) gene mutations in 22% of patients. The same study reported the complete absence of K-ras or p53 mutations in these tumors. In 1 small study, 4 of 8 lesions included contained mutations of the VHL gene.

Cystic pancreatic neuroendocrine tumors

Histopathologic Features

PNETs pathology typically shows small or medium-sized monotonous cells with granular chromatin and plasmacytoid morphology. Tumor cells may be difficult to detect in the cystic fluid. However, the diagnosis can be confirmed by synaptophysin and chromogranin A staining, which are practically diagnostic of these lesions. In comparison with ductal adenocarcinomas, tumor necrosis, perineural invasion, vascular invasion, and regional lymph node metastasis are less likely to be seen in cystic PNETs.

Clinical Characteristics

PNETs make up as much as 1% to 2% of all pancreatic neoplasms, which typically occur in the body and tail of the pancreas and could have a cystic component less than 10% of the time. The majority of cases are detected incidentally on imaging studies. Compared with solid neuroendocrine tumors, cystic PNETs tend to be larger, are more likely to be nonfunctional, and are associated less frequently with multiple endocrine neoplasia type 1. Furthermore, cystic PNETs have been reported in 4% to 15% of patients with VHL disease. Similar to solid tumors, they occur nearly equally among males and females who are 50 to 60 years of age at diagnosis (see Table 1). Patients may present with abdominal pain, pancreatitis, or symptoms related to the functioning cystic PNETs.

Radiologic and Endoscopic Ultrasound-Guided Fine Needle Aspiration Characteristics

CT scanning usually demonstrates a cystic lesion with peripheral arterial enhancement (see Table 2). Septations or solid components are occasionally identified.
Compared with solid pancreatic neoplasms, cystic PNETs are less likely to be associated with lymph node or liver metastases. MRI shows homogenous unilocular lesion on T2-weighted imaging with thick wall enhancement. On EUS, cystic PNETs can appear as a unilocular or multilocular, anechoic, mixed solid cystic, or hypoechoic lesion. Wall thickening and nodule may be present in 60% of cases (Fig. 7). Cystic neuroendocrine tumors vary in size and morphology; therefore, FNA is recommended. Cytology shows a small, homogenous small cell population with round nuclei that should stain positive for chromogranin and synaptophysin (see Table 2). Routine cell block preparation is therefore recommended in these patients.

SOLID PSEUDOPAPILLARY TUMORS OF THE PANCREAS

SPTPs are uncommon neoplasms, composed of monomorphic cells forming solid and pseudopapillary structures, frequently undergoing hemorrhagic–cystic changes. Microscopically, SPTPs are composed of solid nests of uniform neuroendocrine-looking epithelial cells around delicate fibrovascular stalks. SPTPs predominantly affect young women in their third decade of life (see Table 1). Patients may be asymptomatic, presenting with such lesion incidentally on imaging studies. Abdominal pain is the most common presenting symptom, followed by abdominal mass, pancreatitis, and weight loss. The tumors can occur throughout the pancreas. SPTPs are usually of low-grade pathology, but high-grade carcinomas have been rarely reported.

Radiologic and Endoscopic Ultrasound-Guided Fine Needle Aspiration Characteristics

SPTPs are typically of mixed density on imaging, with a solid part in the periphery and cystic component in the center on CT scan (see Table 2). Large tumors have a well-defined capsule and often demonstrate peripheral or central calcifications. Magnetic resonance cholangiopancreatography does not show communication with pancreatic duct, and pancreatic duct dilation, vessel encasement and metastasis may be used to differentiate solid pseudopapillary carcinomas from benign SPTPs. SPTPs are endosonographically well-defined, echo-poor lesions and can be solid, mixed solid cystic, or cystic in nature (Fig. 8). Internal or peripheral calcifications may be seen with postacoustic shadowing. EUS-FNA is useful for definitive preoperative diagnosis of SPTPs. The largest series of EUS-FNA (with or without

Fig. 7. A cystic neuroendocrine tumors of the pancreas incidentally diagnosed in a 55-year-old man. The lesions exhibits a thick wall that is nodular.
immunochemistry) for the preoperative diagnosis of SPTPs demonstrated a diagnostic accuracy of 75%. FNA usually shows branching papillae with myxoid stroma, which is best seen on cell block slides (see Table 2).

OTHER CYSTIC LESIONS OF THE PANCREAS

Lymphoepithelial cysts (LECs) of the pancreas are rare lesions composed mainly of keratinous material and can occur throughout the pancreas. Histologically, the cysts are lined by stratified squamous epithelium and surrounded by dense epithelial lymphoid tissue containing lymphoid follicles. Since the first case was reported in 1985, more than 110 patients with LECs have been described in the literature. Such lesions are predominantly seen in middle-aged men. Although the most common presentation is abdominal pain, nausea, vomiting, anorexia, and back pain may occur or patients could be asymptomatic. LECs exhibit a benign behavior and are not considered a risk factor for the development of pancreatic cancer. The imaging characteristics of LECs on CT can be similar to those of a pseudocyst or an MCN. EUS typically shows a hypoechoic, uniloculated, or multiloculated lesion with fine or coarse hyperechoic debris within the cyst (Fig. 9). Thick milky, creamy, or

Fig. 8. A 28-year-old woman presents with a mixed solid-cystic mass on a computed tomography scan performed for abdominal pain. The mixed solid-cystic morphology is clear on endoscopic ultrasound examination and fine need aspiration biopsy was diagnostic for solid pseudopapillary tumors of the pancreas.

Fig. 9. Lymphoepithelial cyst lesion appears as a uniloculated lesion with coarse hyperechoic debris within the cyst cavity on endoscopic ultrasound examination.
frothy aspirate may be seen during EUS-FNA. Cyst fluid CEA and amylase levels were highly variable and therefore are not useful markers.

VHL disease is a rare autosomal-dominant hereditary disorder resulting from a germline mutation in the VHL gene. Pancreatic cysts can occur in approximately 70% of patients with VHL disease and include simple cysts (47%) and SCAs (11%), which are benign lesions. In addition, cystic PNETs have been reported in 4% to 15% of patients with VHL disease, which have malignant potential, but are believed to be of lower metastatic risk. Most pancreatic lesions in VHL disease are asymptomatic; however, abdominal pain and jaundice may be present. Pancreatic involvement in previous series of VHL detected by CT and MRI has varied from 20% to 80%. Simple cysts appear as unilocular, homogenous, fluid-attenuation or fluid signal lesions with a thin wall and no calcification or enhancement. SCAs and PNETs in this context have similar morphology to those identified without VHL and, as described elsewhere in this review, EUS can be helpful to better characterize the cystic lesions and may influence on clinical management.

MANAGEMENT OF PANCREATIC CYSTS

The management of CLPs continues to evolve as our knowledge of their natural history and biological behavior increases. Nevertheless, significant variability exists among practitioners despite the multiple existing guidelines endorsed by various medical societies. Practically, the decision to resect a lesion should take into consideration surgical morbidity and mortality associated with surgery, which should be examined against the risk of malignant transformation of the lesion. Additional factors that directly impact a surgical decision should include patient age, comorbidities, and life expectancy. The next section of this review discusses available management options.

Surgery

Surgery is the only radical treatment for malignant and premalignant CLPs and is recommended for all malignant lesions or those mucinous lesions suspected to harbor minimally invasive disease or advanced dysplasia. Mortality and morbidity associated with pancreatic surgery continue to decrease in centers of expertise and are currently estimated to be less than 3% and 22%, respectively. Enucleation has emerged as a less invasive alternative to resection, with reported reduced operative times and blood loss without increasing postoperative morbidity. However, this approach remains limited to certain tertiary care centers and to a selective population of patients.

Owing to their malignant potential, published guidelines recommend surgical resection in all fit patients with MCNs. These patients are often younger than those with IPMNs and MCNs in the body or tail are often amenable to distal pancreatectomy. Patients with a unifocal MCN who have a complete resection with pathologically negative margins are not considered at risk for the development of new tumors in the remnant pancreas. Therefore, after surgical resection, postoperative surveillance for MCN recurrence or new tumor formation is not required. The 5-year survival for mucinous cystadenocarcinomas after resection exceeds 60%, which far exceeds that of standard pancreatic ductal adenocarcinoma (<10%). Similarly, the prognosis after resection of noninvasive MCN is excellent.

The International Consensus Guidelines for the Management of IPMN published in 2006 and updated in 2012 recommend resection of all MD-IMPNs and mixed variant IPMN regardless of the presence or absence of referable symptoms owing to the high risk of malignancy in this group. Resection is also recommended for
symptomatic SB-IPMN in surgically fit patients with a reasonable life expectancy. Any IPMN lesion with intracystic mural nodules, extracystic masses (indicative of possible malignancy), or cytopathology demonstrating high-grade dysplasia or malignancy should be resected when possible, regardless of the presence of symptoms.

Asymptomatic BD-IPMNs pose a particular management dilemma owing to the increase in the diagnosis of these lesions in recent years and the overall low risk of malignant transformation. It widely agreed, however, that SB-IPMNs in general have a malignancy progression rate of 5% or less over the short and intermediate terms. Studies that have reported higher rates of malignancy were surgical series that likely overestimate this risk owing to selecting patients with symptoms and those with high-risk criteria. Despite the expanding knowledge about the natural history of SB-IPMNs, controversies about the management of these patients continue to exist. The previous consensus guidelines, including the recently published American Gastroenterological Association (AGA) Guidelines, attempt to refine surgical resection criteria to avoid unnecessary operations in patients with benign disease, which according to one study of 147 patients with pure BD-IPMNs was as high as 88% of resected patients. For example, cyst size alone exceeding 3 cm has been abandoned as the sole criterion for resection in asymptomatic patients in the International Consensus Guidelines of 2012 and endorsed by the AGA guidelines. What complicates decision making in this group of patients is the conflicting data on the true incidence of malignancy in larger side branch lesions, described to be as high as 46% in some studies, including invasive cancer detected in lesions less than 3 cm in size. Most literature and experts, however, endorse that size alone is not an independent criterion for the development of malignancy and should not be the sole criterion for resection.

Resection is recommended for all symptomatic SCAs. Clinical and radiologic observation are usually sufficient for low risk, asymptomatic SCAs less than 4 cm in size because these lesions seldom undergo malignant transformation or experience rapid growth rates. Natural history studies, however, suggest that lesions greater than 4 cm may experience faster growth rates (and therefore symptoms) than small tumors and thus should be resected in fit patients. Cystic PNETs seem to exhibit less aggressive biological behavior compared with their solid counterparts, but should be considered for resection in fit patients owing to the risk of growth and metastasis. Surgery is recommended for SPTs owing to the risk of malignant transformation (up to 15%) and the relatively young age of the patients. Overall prognosis after surgical resection is excellent.

**Expectant Management and Imaging Surveillance**

Published practice guidelines and recent data take into consideration the balance between the risk of malignancy and the benefit of pancreatic resection or periodic imaging surveillance and its cost and impact on the quality of life. A cost-effective analysis for asymptomatic incidental solitary CLPs demonstrated risk stratification of malignant potential by EUS-guided FNA and cyst fluid analysis was most effective. Literature overall supports the expectant observation of small and asymptomatic mucinous CLPs lacking high-risk features like mural nodules and solid components and with benign cytology on FNA. In a study of 539 patients with various CLPs, the risk of progression to malignancy among lesions less than 3 cm in size without a solid component was found to be 3%, which is similar to the mortality associated with surgical resection of the pancreas. Other studies reported that asymptomatic BD-IPMN less than 3 cm in size can be safely surveyed by annual imaging alone. However, factors associated with progression of SB-IPMN lesions remain to be fully elucidated, resulting in significant heterogeneity in the
management styles of these lesions. This issue is further complicated by the paucity of long-term follow-up data beyond 5 years, and concerns among clinicians about adherence to the consensus guidelines or the lack of awareness of the guidelines. There are limited data on the nonoperative management of small MCNs, but recent systematic review indicates that only 0.03% of resected lesions less than 4 cm in size harbored invasive adenocarcinoma. Therefore, expectant management may be considered in unfit patients or older patients with multiple comorbidities and limited life expectancy.

Imaging surveillance is generally unnecessary in MCNs and SCAs after surgical resection. In contrast, IPMN are often multifocal and are thought to have a ‘field defect’ that considers all pancreatic duct epithelium at risk for neoplasia. Thus, after resection (whether or not radiographic IPMN remains present), follow-up imaging is recommended for the possible development of new lesions in the remnant pancreas. It is estimated that approximately 20% of patients will develop new IPMN lesions during surveillance imaging after surgical resection. Patients with invasive IPMNs are much more likely to develop recurrence after resection compared with those with noninvasive disease. Nevertheless, patients with invasive IPMN have a longer survival over “traditional” pancreatic adenocarcinoma after surgical resection. All guidelines endorse postresection imaging surveillance of the pancreatic remnant in patients with invasive cancer or dysplasia in a cyst that has been surgically resected every 1 to 2 years. The AGA guidelines suggest against routine postoperative surveillance of pancreatic cysts without high-grade dysplasia or malignancy at surgical resection. This is supported by recent data on postoperative recurrence of pure SB-IPMN where only benign recurrent lesions were observed up to 8 years after resection.

The question of how long IPMN lesions need to be surveyed by imaging and if there is a safe period of time after which it can be discontinued remains to be answered. The recent AGA guidelines recommend terminating surveillance when no significant change in the characteristics of the cyst has occurred after 5 years of surveillance or if the patient is no longer a surgical candidate. The remains one of the most controversial aspects of these guidelines and further data are needed to support implementing this recommendation in all patients.

**Minimally Invasive Management**

Alternative nonoperative therapies for CLPs have been described in the last decade. Since the initial pilot study of EUS-guided cyst ablation with ethanol demonstrated cyst resolution in one-third of patients, multiple other trials have demonstrated variables degrees of ablation success (Table 4). A multicenter, randomized, double-blind study reported that ethanol lavage of pancreatic cysts decreased cyst surface area greater than saline lavage alone. Overall, 33% of patients in this series had complete cyst resolution on follow-up imaging. The chemotherapeutic agent paclitaxel has been added to ethanol lavage to improve response rates. According to Oh and colleagues, this protocol of ablation resulted in 62% complete response rates. Because it is believed that the pancreatitis described after ablation can be mainly attributed to alcohol, its role in ablation was tested in a study of 10 patients randomized to alcohol or saline in addition to a chemotherapy cocktail of paclitaxel and gemcitabine. Complete ablation was achieved in 67% of patients in the alcohol-free arm compared with 75% in the alcohol arm at 12 months.

Long-term follow-up (>1 year) after successful cyst ablation seems to be associated with persistent cyst resolution by follow-up imaging according to earlier studies. However, in a recent study by Gomez and colleagues using alcohol for ablation, initial response rates at 6 months ranged from 34% to 100% reduction in cyst volume.
in 20 patients. When this cohort was followed for 12 months and then yearly, an increase in cyst volume was demonstrated in 9 patients.

Lesions suitable for ablation are typically less than 4 cm in size, ideally with 5 locules or fewer in multiseptated lesions, with no imaging evidence of communication with the main pancreatic duct. Factors associated with increased ablation response rates include smaller size of the cyst, multiple ablation sessions, and combining alcohol with chemotherapeutic agents like paclitaxel (see Table 4). Although the body of data supporting EUS-guided cyst lavage continues to grow, adoption of this technique remains limited owing to associated adverse events, and a limited ability to achieve complete ablation. A cumulative adverse events rate of 10% to 15%, including pancreatitis, peritonitis, and splenic or portal venous thrombosis, has been reported. Additionally, the persistence of neoplastic epithelium after ablation leaves a theoretic risk of progression of malignancy and therefore requires long-term surveillance.

**SUMMARY**

Practitioners are faced with the task of managing a rapidly increasing number of patients with CLPs detected by various imaging studies. Depending on the pathologic type of the cyst, clinical features, radiologic characteristics, and EUS morphology vary significantly. In combination with minimally invasive investigations like EU-SFNA, clinical and imaging findings are essential to provide an accurate diagnosis of CLPs and improving early detection of cancer in the potentially malignant ones. FNA can guide further management by providing valuable information like tumor and molecular markers to appropriately classify the lesion. Ongoing cyst fluid biomarker research can provide reliable information about biological behavior and allow risk stratification in the near future. Until then, patients with CLPs are best managed by a team of experts in a multidisciplinary approach.

### Table 4

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. of Patients</th>
<th>Ablative Agent</th>
<th>FU Period, Median, mo (Range)</th>
<th>Resolution Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan et al, 2005</td>
<td>25</td>
<td>5%–80% EtOH</td>
<td>6–12</td>
<td>35% CR (8/23) 7% PR (2/23)</td>
</tr>
<tr>
<td>Oh et al, 2008</td>
<td>14</td>
<td>80%/90% EtOH + paclitaxel</td>
<td>9 (6–23)</td>
<td>79% CR (11/14) 14% PR (2/14)</td>
</tr>
<tr>
<td>Oh et al, 2009</td>
<td>10</td>
<td>99% EtOH + paclitaxel</td>
<td>8.5 (6–18)</td>
<td>60% CR (6/10) 20% PR (2/10)</td>
</tr>
<tr>
<td>DeWitt et al, 2009</td>
<td>42</td>
<td>80% EtOH</td>
<td>3–4</td>
<td>33% CR (12/36)</td>
</tr>
<tr>
<td>Oh et al, 2011</td>
<td>47</td>
<td>99% EtOH + paclitaxel</td>
<td>20 (12–44)</td>
<td>62% CR (29/47) 13% PR (6/47)</td>
</tr>
<tr>
<td>DiMaio et al, 2011</td>
<td>13</td>
<td>80% EtOH</td>
<td>13</td>
<td>38% CR (5/13)</td>
</tr>
<tr>
<td>DeWitt et al, 2014</td>
<td>22</td>
<td>100% EtOH + paclitaxel</td>
<td>27 (17–42)</td>
<td>50% CR (10/20) 25% PR (5/20)</td>
</tr>
<tr>
<td>Gomez et al, 2016</td>
<td>23</td>
<td>80% EtOH</td>
<td>40</td>
<td>9% CR (2/23) 44% PR (10/23)</td>
</tr>
<tr>
<td>Moyer et al, 2016</td>
<td>10</td>
<td>Paclitaxel and gemcitabine +80% EtOH</td>
<td>12</td>
<td>75% (3/4) CR</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; EtOH, ethanol; FU, follow-up; PR, partial response.
SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.gie.2017.06.004.

REFERENCES


