Endosonographic Diagnosis of Chronic Pancreatitis

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Abstract

Chronic pancreatitis (CP) is characterized by irreversible damage that engenders fibrosis and necrosis of the pancreatic tissue [1], with the loss of endocrine and exocrine function of the pancreas [2]. Alcohol is the most common etiology of CP in 64.8% and idiopathy (unidentified) in 18.2%. Sarles et al. reported that 60-70% of patients with CP have a 6-12 year history of alcohol abuse [3]. In addition, regarding the relation between smoking and CP, smoking rates of CP patients are high (74.7% in men, 26.0% in women). Furthermore, lifestyles that include drinking and smoking are strongly associated with the onset and progress of CP. The clinical course of CP engenders a high rate of morbidity and mortality over a 20-25 year period. Moreover, CP is recognized as a risk factor of pancreatic cancer; patients with CP are 16 times more likely to develop pancreatic cancer than normal individuals are [4]. In view of these facts, current efforts emphasize establishment of early diagnosis to commence intervention that can positively affect the natural history of the disease: follow-up of CP in a rigorous manner is necessary using various modalities.

Endoscopic ultrasonography (EUS) is a well-established and less-invasive modality for CP diagnosis [5-10]. Although endoscopic retrograde pancreatography (ERP) has been regarded as the gold standard for CP diagnosis, ERP cannot investigate the parenchymal changes. In that respect, the higher imaging resolution provided by EUS enables detection of subtle pancreatic abnormalities, not only parenchymal, but also ductal changes that are undetectable using other modalities. This review presents an overview of the endosonographic diagnosis of chronic pancreatitis.

Keywords: Chronic pancreatitis; EUS; Early chronic pancreatitis; ERP

Introduction

Chronic pancreatitis (CP) is characterized by irreversible damage that engenders fibrosis and necrosis of the pancreatic tissue [1], with the loss of endocrine and exocrine function of the pancreas [2]. Alcohol is the most common etiology of CP in 64.8% and idiopathy (unidentified) in 18.2%. Sarles et al. reported that 60-70% of patients with CP have a 6-12 year history of alcohol abuse [3]. In addition, regarding the relation between smoking and CP, smoking rates of CP patients are high (74.7% in men, 26.0% in women). Furthermore, lifestyles that include drinking and smoking are strongly associated with the onset and progress of CP. The clinical course of CP engenders a high rate of morbidity and mortality over a 20-25 year period. Moreover, CP is recognized as a risk factor of pancreatic cancer; patients with CP are 16 times more likely to develop pancreatic cancer than normal individuals are [4]. In view of these facts, current efforts emphasize establishment of early diagnosis to commence intervention that can positively affect the natural history of the disease: follow-up of CP in a rigorous manner is necessary using various modalities.

Endoscopic ultrasonography (EUS) is a well-established and less-invasive modality for CP diagnosis [5-10]. Although endoscopic retrograde pancreatography (ERP) has been regarded as the gold standard for CP diagnosis, ERP cannot investigate the parenchymal changes. In that respect, the higher imaging resolution provided by EUS enables detection of subtle pancreatic abnormalities, not only parenchymal, but also ductal changes that are undetectable using other modalities. In this review, the authors describe the role of EUS in CP diagnosis, especially in the early stage.

Normal Pancreas on EUS

An understanding of normal pancreas on EUS is extremely important for making EUS diagnosis of CP. The normal pancreatic parenchyma is uniformly depicted in equal or a slightly less hyperecho to the liver; it presents a so-called fine reticular pattern. The main duct dilation, duct irregularity and side branch ectasia are not visualized within the parenchyma [8]. Furthermore, the main duct wall is observed as a uniform and slightly hyperlinear echo: 2.4 mm diameter in the head, 1.8 mm in the body, and 1.2 in the tail [6]. The EUS image of CP is defined based on these views. The EUS image of a normal pancreas is presented in figure 1.

EUS Features of Chronic Pancreatitis

CP is characterized by fibrosis of parenchyma along with ductal changes in the pancreas. These changes of fibrosis have been characterized as hyperechoic using ultrasound [11-13]. The superiority of EUS is not so high in the case of advanced CP because typical CP findings such as atrophy, calcification, main duct dilation, duct irregularity, cyst are readily observed even using other modalities. However, it is difficult to observe minute changes of pancreatic parenchyma using means other than EUS. Among patients with chronic pancreatitis, EUS will reveal all pancreatic abnormalities. Typical EUS findings are shown in figures 2-6.

Diagnosis of CP using EUS

Traditional EUS criteria for diagnosis of CP

Several studies have compared EUS findings with ERP (Cambridge classification) for CP evaluation [14]. Results of these studies suggest that ductal and parenchymal abnormalities detected using EUS correlate with the presence of CP. From these studies, the traditional EUS criteria...
for CP are recognized as follows: hyperechoic foci, hyperechoic strands, parenchymal lobularity, irregular pancreatic duct margins, hyperechoic pancreatic duct margins, visible pancreatic side branches, pancreatic duct dilation, shadowing calcifications and cysts. Opinions vary among researchers, but the presence of CP was diagnosed when EUS revealed at least 2-3 of the features described above. Our investigation also showed the over 80% patient who showed changes over ‘equivocal’ in Cambridge classification had more than three EUS findings [12]. In addition, the EUS is able to evaluate the severity of CP depending on the number of criteria present with high sensitivity and specificity. The disease severity was classified as mild (2 or 3-4 features), moderate (5-6 features), and severe (more than 7 features), based on ERP findings as a gold standard [8-10].

New EUS criteria for CP diagnosis

Several investigators have reported the total number of EUS criteria, which is not only useful for diagnosis of CP but also for assessing severity. However, individual EUS criteria are considered to have their own importance in each ERP grading. Consequently, to discriminate against EUS features in every stage of CP, each EUS criterion was made as a point of reference for comparison between normal and varying degrees of CP. Irisawa et al. [12] reported the important EUS features in each severity: hyperechoic foci in mild CP, hyperechoic foci/visible side-branches/duct dilatation in moderate CP, and visible side-branches/duct dilatation/duct irregularity/calcification in severe CP (p<0.05). These EUS features described above were found to be independent predictors for assessing CP severity.

In 2009, the Rosemont classification is proposed as new EUS diagnostic criteria. New directionality of CP diagnosis by EUS was provided in an attempt to improve EUS reliability for CP. This classification system was an attempt to standardize and define more explicitly the endosonographic features and thresholds for the diagnosis of chronic pancreatitis, with grouping of criteria into major and minor importance categories (Tables 1 and 2) [15].

As for the traditional EUS diagnostic criteria described above, the disease severity classification is accomplished merely from the number of CP findings. However, these diagnostic criteria are noticed as contrary when observing CP by EUS. Therefore, the value of each EUS finding differs in each level of CP severity. As an extreme example, findings having both calcification and cysts are equal to findings including both hyperechoic foci and strands in value as mild CP using the total number of findings in traditional criteria. In other words, the EUS findings observed on each practical CP stage are not considered in traditional criteria. However, in the Rosemont classification, each finding is assigned a grade (major or minor) in consideration of the value of findings.

In the Rosemont classification, the pancreas parenchyma findings are based on four typical findings: Hyperechoic foci, Lobularity, Cyst, Hyperechoic strands. In addition, Hyperechoic foci are subclassified
Several researchers have investigated whether EUS features of CP
the degree of agreement among three experienced endosonographers

EUS diagnosis of chronic pancreatitis. Wiersema et al. [26] compared

[7,9,10,12,25]. However, currently inter observer variation might affect

features (<0.0001), stranding (<0.001), and lobulations (p=0.04); ductal

features significantly associated with histopathologic NCCP were
dilated (p<0.0001) or irregular main pancreatic duct (p<0.0001),
side branches (p<0.001), and hyperechoic duct margins (p<0.03).

Varadarajulu et al. [22] reported that EUS features were significantly
associated with histologic abnormalities in a prospective study of 42
non-calcific CP (NCCP) patients. Parenchymal EUS features that were
significantly associated with histopathologic NCCP were echogenic foci
(p<0.0001), stranding (p<0.001), and lobulations (p=0.04); ductal
features significantly associated with histopathologic NCCP were
dilated (p<0.0001) or irregular main pancreatic duct (p<0.0001),
side branches (p<0.001), and hyperechoic duct margins (p<0.03).

Table 4: EUS criteria for diagnosis of chronic pancreatitis and its estimated
histological findings.

<table>
<thead>
<tr>
<th>EUS findings</th>
<th>Estimated histological findings</th>
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<tbody>
<tr>
<td>Hyperechoic foci</td>
<td>Focal fibrosis</td>
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<tr>
<td>Hyperechoic strand</td>
<td>Bridging fibrosis</td>
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<tr>
<td>Lobularity</td>
<td>Interlobular fibrosis</td>
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<tr>
<td>Cyst</td>
<td>Cyst</td>
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<tr>
<td>Stone</td>
<td>Calcified stones</td>
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<tr>
<td>Ductal dilatation</td>
<td>Dilated main pancreatic duct</td>
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<tr>
<td>Visible side branch</td>
<td>Side branch dilatation</td>
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<tr>
<td>Duct irregularity</td>
<td>Focal dilatation/narrowing</td>
</tr>
<tr>
<td>Hyperechoic ductal margins</td>
<td>Periductal fibrosis</td>
</tr>
</tbody>
</table>

are correlated with histology. Specific criteria such as hyperechoic foci,
hyperechoic strands, and lobularity, which are identified only by EUS,
were estimated as correlated respectively with histological findings as
follows: focal fibrosis, bridging fibrosis, and interlobular fibrosis (Table
4) [11].

Bhutani et al. [24] developed an animal model for studying EUS
changes of early chronic pancreatitis, and described the serial changes
of early chronic pancreatitis by EUS and correlates results with
histology. In this study, a CP model was made by indwelling a 5-Fr
pancreatic stent into pancreatic duct of dog. Animals were divided
into two survival groups: 2 weeks and 4 weeks. Sequential pancreatic
sections were taken from the head, body, and tail of the pancreas.

EUS findings were correlated with histologic results with respect to
degree of fibrosis, inflammation, and edema. As a result, the pancreas
appeared homogeneous with only a few echogenic septations and
echogenic margins of the main pancreatic duct at baseline EUS. At 2
and 4 weeks post-stenting, EUS images showed the following changes:
lobularity, hyper and hypochoic foci, increased echogenic septations,
visible pancreatic duct side branches, and irregular margins of the main
pancreatic duct. These EUS findings were supported by correlating
results with histology.

Issues of CP diagnosis by EUS

Table 4: EUS criteria for diagnosis of chronic pancreatitis and its estimated
histological findings.

in individual features of CP. The agreement was 88% for hyperechoic
foci, 94% for focal reduced echogenicity, 94% for lobularity, 83% for
hyperechoic duct margins, and 94% for duct irregularity. This study
showed that EUS findings of CP might have good reliability,
however, because no gold standard for diagnosis of early CP exists,
the subjective assessment of endosonographic findings might vary
among endosonographers, even among expert endosonographers,
and standardized diagnosis of CP by EUS might be difficult. In
relation to this issue, Irisawa et al. [13] conducted computer analysis to
assess quantitation of EUS changes of chronic pancreatitis, demonstrating
that, with respect to hyperechoic findings reflecting to fibrous changes,
significant differences were found between normal pancreas and mild/
moderate/severe CP, and between mild and moderate/severe CP. These
findings indicated the possibility of diagnosing CP objectively. In
addition, results of our study suggested that computer-assisted image
analysis might distinguish the appearance of early CP from that of
normal pancreas.

Aging is regarded as a factor of parenchymal/ductal changes on EUS
similar to chronic pancreatitis, in fact, many patients have pancreatic
parenchymal and ductular changes that are identifiable on EUS in
individuals without history or symptoms of pancreaticobiliary disease
[27]. Many endosonographers have the impression that aging can cause
variations in ductal and parenchymal pancreatic anatomy. Rajan et al.
[28] reported that isolated EUS abnormalities are frequent in adults >60
without pancreatic disease. They reported that the presence of more
than three EUS abnormalities, ductal or intra-pancreal parenchymal
stones, ductal narrowing or ductal dilatation is more likely to represent
disease than age-related changes. However, whether these changes represent
early pancreatic disease or simply represent normal variation remains
unknown.

In addition, several investigators have reported that not only aging
but also gender, smoking, alcohol drinking, and BMI level can influence
EUS findings. Yusoff et al. [29] demonstrated in a much larger study
(n=1157) that heavy ethanol intake (OR 5.1, 95% CI: 3.1-8.5), male
sex (OR 1.8, 95% CI: 1.3-2.6), clinical suspicion of pancreatic disease
(OR 1.7, 95% CI: 1.2-2.3), and heavy smoking (OR 1.7, 95% CI: 1.2-
2.4) are independent predictors of severe EUS changes. In another
study, Al-Haddad et al. [30] reported that a fatty pancreas causes
hyperechogenicity of the parenchyma that can imitate echogenic
changes of CP. In a logistic regression analysis, obesity, fatty liver
disease, and alcohol intake were shown to be independent predictors of
fatty infiltration of the pancreas. As described above, mild parenchymal
and ductal EUS features can have poor specificity, resulting in the ‘over
diagnosis’ of CP. All endosonographers should remain apprised of these
issues.

Role and Future Development of EUS in CP Diagnosis

A CP diagnosis produced based on EUS entails several problems,
but EUS is a useful modality that can reveal abnormalities of pancreatic
parenchyma and duct that are not detected using other diagnostic
imaging modalities. Abdominal pain is common and frequently
developing in patients with chronic pancreatitis, particularly from an
early stage. Chang et al. [31] demonstrated that EUS abnormalities are
found at high frequencies in patient with abdominal pain, and that EUS
is superior to transabdominal US for detecting CP. Consequently, they
recommended that esophagogastroduodenoscopy combined with EUS
should be considered in the first-line diagnostic evaluation of patients
with upper abdominal pain, to detect mild/early CP. In addition,
follow-up of CP for occurrence of pancreatic cancer is extremely
important. Reportedly, patients with chronic pancreatitis are 16 times

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more likely to develop pancreatic cancer than normal individuals are. Strong evidence indicates the association of hereditary pancreatitis and pancreatic cancer [4]. Therefore, the physician is frequently faced with difficult decisions about how to manage the risk. Nevertheless, the identification of pancreatic cancer in advanced CP is extremely difficult. Some reports in the literature demonstrate that EUS detectability of pancreatic cancer in patients with CP is around 60% [32], and 54-74%, even if using combined EUS-FNA [33-36]. Therefore, the follow-up of CP from early stages, which is not detected using traditional modalities (e.g., CT, ERCP), will be important to detect smaller cancer nodes.

Conclusion

EUS is a useful and safe technique for detecting pancreatic parenchymal and ductal abnormalities, which are suggestive of CP. Medical intervention for CP in the early stage, can improve the CP prognosis.

References