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# Significance of normal appearance on endoscopic ultrasonography in the diagnosis of early chronic pancreatitis

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## ABSTRACT

**Background and Objectives:** The Rosemont classification (RC) was developed as a consensus-based standard for the diagnosis of chronic pancreatitis (CP) by endoscopic ultrasonography (EUS), however, it is more complicated than the conventional scoring system. We have noticed that in the early stages of CP, it is not unusual to observe pancreas with abnormal appearance coexisting with the areas of normal parenchyma. The aim of this study was to investigate the validity of a "normal" pancreas appearance and to evaluate the usefulness of modified diagnostic criteria in comparison to the traditional EUS criteria and the RC. **Patients and Methods:** One hundred and seventy-seven patients who had undergone both EUS and endoscopic retrograde pancreatography (ERP) within 2 months were enrolled in the study, and patients with pancreatic cancer were excluded from the study. ERP findings were used as the gold standard for the diagnosis of CP. The EUS images obtained were classified according to both the RC and our new modified criteria. The latter includes an additional criterion to the modified traditional criteria: fine-reticular pattern (F-RP) was defined as a normal pancreatic parenchyma. We compared the accuracy between the new modified EUS criteria and the RC. **Results:** (1) Normal or equivocal findings on ERP were obtained for 132 patients; 113 patients had F-RP on EUS. In contrast, F-RP was found in only 6 out of 45 CP cases on ERP ($P < 0.0001$). (2) We investigated the diagnostic capability of our new criteria for endoscopic retrograde cholangiopancreatography normal/equivocal pancreas compared to the traditional criteria. In cases where fewer than two points were defined as normal, the incidence of normal pancreas was significantly higher based on the new criteria than on the traditional criteria ($P = 0.002$). (3) No significant differences were found between the new criteria and the RC across all ERP grades. **Conclusion:** Our new proposed "normal-added EUS criteria" for diagnosing CP was equivalent to the RC.

**Key words**: Chronic pancreatitis, early stage, endoscopic ultrasonography

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## INTRODUCTION

Chronic pancreatitis (CP) is an inflammatory disease of the pancreas characterized by irreversible morphological changes and compromised endocrine/exocrine function. Its progression may be prevented and the pathophysiology may be improved if there is therapeutic intervention at the early disease stage. To achieve this, it is essential to diagnose CP prior to complications by diseases such as main pancreatic duct stenosis, diabetes mellitus, and pancreatic cancer. Diagnostic imaging such as computed tomography (CT), magnetic resonance imaging, and endoscopic retrograde cholangiopancreatography (ERCP) can diagnose advanced CP, but the diagnosis of early CP is difficult with these methods because both functional and morphological changes associated with the disease are minimal. Thus, there is currently no established method for diagnosing early CP.[1]

To date, the Cambridge classification is universally acknowledged as a CP diagnostic tool and enables disease severity evaluation through the scoring of the pancreatic duct findings obtained from ERCP.[2] However, ERCP can evaluate the pancreatic duct but not the pancreatic parenchyma, which limits its utility in early CP diagnosis[3,4] as early changes associated with CP often arise from the pancreatic parenchyma. The diagnosis of early CP is therefore difficult with ERCP alone.[5]

In contrast, endoscopic ultrasonography (EUS), in which the probe can approach the pancreas, is capable of yielding high-resolution visualization of abnormal pancreatic parenchyma and duct that is not possible with other modalities. In practice, EUS has been used for observation of both early and advanced CP as it is a method that is less likely to cause complications. Bhutani reported EUS could detect changes suggestive of alcohol-induced chronic pancreatic damage in up to 58% of asymptomatic alcoholic cases and in 89% of alcoholic cases with pancreatic type pain.[6] EUS is now viewed as the most sensitive diagnostic imaging device[7-11] and is regarded as a promising modality for the diagnosis of early CP.

The use of EUS for diagnosis of CP was first reported by Jones *et al.*, followed by a report by Wiersema *et al.*, and proposals based on several criteria were made thereafter.[4,12] These criteria for EUS are designed to diagnose CP and its severity based on the total score of observed features. Specifically, the scoring covers: (1) features of pancreatic parenchyma, including hyperechoic foci, hyperechoic strands, lobularity, and cyst and (2) features of the pancreatic duct, including duct irregularity, and stones. Although the view varies among investigators, CP severity rated by EUS is usually classified as follows based on findings from endoscopic retrograde pancreatography (ERP; the existing gold standard for CP diagnosis): mild (two to four positive items), moderate (five to six positive items), and severe (seven or more positive items). This method is simple but is limited by the similar emphasis on both the "stone" (a feature of advanced CP) and "hyperechoic foci and strands" (less specific features of the pancreatic parenchyma), and the lack of consideration of stage-specific CP characteristics. Furthermore, although EUS can detect subtle changes that cannot be detected by other diagnostic imaging modalities, interpretation of the results can be difficult. Particularly in cases of early CP, interpretation is dependent on examiners and may be potentially "overdiagnosed."[13] In view of such circumstances, opinion leaders have recently proposed the Rosemont classification (RC).[14] This classification attempts to standardize EUS-based CP diagnosis and better define the significance of individual findings by classifying each finding as major or minor. The RC is indeed reasonable but has not been validated or proven to have a better interobserver agreement (IOA) compared to the previous criteria.[15] Furthermore, it is quite complex for clinical use.

We have noticed that in the early stages of CP, it is not unusual to observe pancreas with abnormal appearance coexisting with the areas of normal parenchyma. We, therefore, attempted to add the "normal appearance of pancreatic parenchyma" to the existing criteria for EUS-based diagnosis to enable a simple and accurate distinction between a "normal" pancreas and early CP while avoiding overdiagnosis. The present study was undertaken to investigate the validity of a "normal" pancreas appearance as assessment criteria, and to evaluate the usefulness of a modified diagnostic criteria that includes this as criteria for early CP diagnosis compared to the existing EUS criteria and the RC.

## PATIENTS AND METHODS

### *Patients*

From December 2000 to December 2011, 177 consecutive patients (106 men and 71 women;

mean age 61.2 years, range: 20–84) were enrolled in the study. They had undergone both EUS and ERP within 2 months at Fukushima Medical University Hospital for suspicion of pancreatic, bile duct, or gallbladder-related abnormal lesion on CT/ultrasonography or because of suggestive symptoms. Patients were excluded if they had a pancreatic tumor or lower biliary ductal cancer. Clinical symptoms included patients with and without abdominal pain or back pain. In all cases, the endoscopists who prospectively performed the EUS and ERP were aware of the patient's history and other findings, including CT. These findings were analyzed retrospectively.

## *Methods*

### Endoscopic ultrasonography

EUS was performed before or after ERCPs using a radial or curved linear arrayed scope (UM 2000, UCT240-AL5, UCP240-AL5, UCT260, or UE260 System; Olympus Corp., Tokyo, Japan) with 6–7.5 MHz frequencies. All patients were placed in the left lateral position. Sedation was accomplished using either intravenous diazepam (5 mg) or midazolam (5 mg). Using radial arrayed EUS, the head of the pancreas was examined through the duodenum. The body to tail was scanned through the stomach. Using curved linear arrayed EUS, the head of the pancreas was scanned through the duodenum and stomach. The body to tail of the pancreas was observed through the stomach, according to the previous reports.[4,16]

All EUS images obtained during the procedure were stored on a computer as electronic images. We confirmed and analyzed these images retrospectively through discussion by two experienced endosonographers (Atsushi Irisawa and Ai Sato).

The obtained EUS images were classified according to the RC [Tables 1 and 2] and our modified criteria based on the traditional criteria [Tables 3 and 4]. The latter is a modification of the traditional criteria by including an additional criterion: Fine-reticular pattern (F-RP) as a normal pancreatic parenchyma [Figure 1]. Using these new proposed criteria (normal-added criteria), CP consisted of EUS images according to the traditional criteria such as hyperechoic foci [Figure 2a], hyperechoic strands [Figure 2b], lobularity [Figure 2c], cysts as parenchymal features, hyperechoic ductal margin, dilated main pancreatic duct, duct irregularity, dilated side branches, and stones in the duct as ductal features. For these new proposed criteria, we defined lobularity as findings with honeycombing.

**Table 1. Consensus-based features of chronic pancreatitis (Rosemont classification)**

| Feature | RC | |
|---|---|---|
| | Major/minor criteria | Histologic correlation |
| Parenchyma | | |
| Hyperechoic foci with shadowing | Major A | Parenchymal-based calcifications |
| Lobularity | | |
| With honeycombing | Major B | Unknown |
| Without honeycombing | Minor | |
| Hyperechoic foci without shadowing | Minor | Unknown |
| Cysts | Minor | Pseudocyst |
| Stranding | Minor | Unknown |
| MPD calculi | Major A | Stones |
| Irregular MPD contour | Minor | Unknown |
| Dilated side branches | Minor | Side-branch ectasia |
| MPD dilation | Minor | MPD dilation |
| Hyperechoic MPD margin | Minor | Ductal fibrosis |

CP: Chronic pancreatitis, MPD: Main pancreatic duct, RC: Rosemont classification

**Table 2. Endoscopic ultrasonography diagnosis of chronic pancreatitis on the basis of consensus criteria (Rosemont classification)**

| | RC |
|---|---|
| Consistent with CP | |
| 1 major A feature (+) ≧3 minor features | |
| 1 major A feature (+) major B feature | |
| 2 major A features | |
| Suggestive of CP | |
| 1 major A feature (+) 3 minor features | |
| 1 major B feature (+) ≧3 minor features | |
| ≧5 minor features (any) | |
| Indeterminate for CP | |
| 3-4 minor features, no major features | |
| Major B feature alone or with<3 minor features | |
| Normal | |
| ≦2 minor features*, no major features | |

*Excludes cysts, dilated MPD, hyperechoic foci without shadowing, dilated side branch. CP: Chronic pancreatitis, MPD: Main pancreatic duct, RC: Rosemont classification

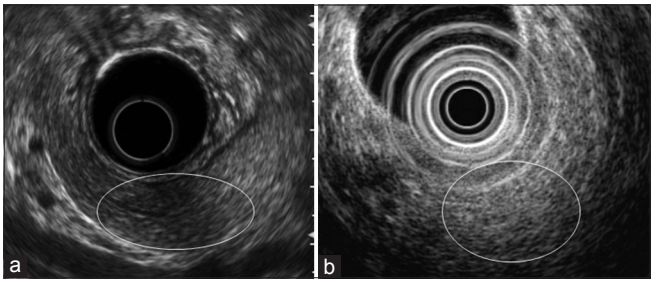


**Figure 1.** Normal pancreatic parenchyma on endoscopic ultrasonography. Homogeneous and fine-reticular pattern is visible in both images (a and b, circle) of parenchyma without dilated ducts (a, circle)

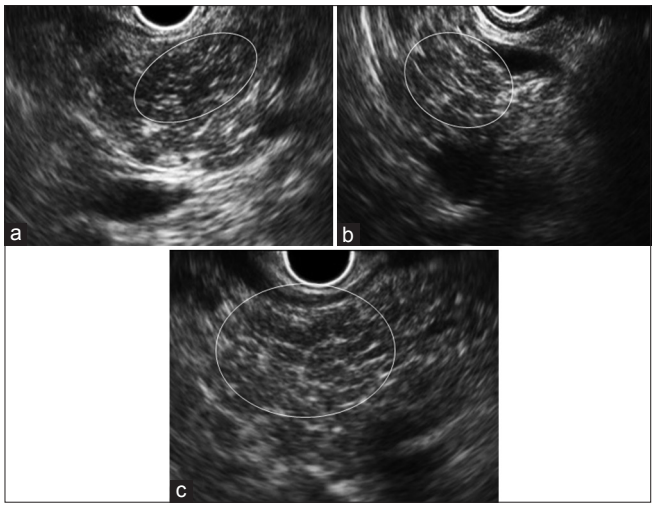


**Figure 2.** (a) Hyperechoic foci in the pancreatic parenchyma. Many hyperechoic small dots are identified (circle). (b) Hyperechoic strands. Many linear hyperechoes are visible (circle). (c) Lobularity. Pancreatic parenchyma is lobulated by linear hyperechoes (circle)

Lobularity without honeycombing excluded the finding of lobularity. Each item was weighted as one point. If F-RP was identified in the pancreatic parenchyma, or in all the areas; head, body, and tail, then one point was deducted from the total points. We defined the diagnostic criteria as follows [Table 5]: suggestive/consistent CP with more than four points, indeterminate CP with two to three points, unlikely with one point, and normal with −1 (minus one) or 0 point

### Endoscopic retrograde pancreatography

ERP was performed using oblique duodenoscopes (JF240, TJF240, TJF260V: Olympus Corp., Tokyo, Japan) and a triple lumen ERP catheter (Tandem XL; Boston Scientific Japan, Tokyo, Japan). After cannulation into the pancreatic duct, contrast medium (60% meglumine sodium amidotrizoate) was injected slowly until the first side branches were contrasted. All patients were placed in the abdominal position, with sedation accomplished using either intravenous diazepam (5 mg) or midazolam (5 mg). Pentazocine (15 mg) was administered as needed.

The results for each patient were analyzed and evaluated in agreement by two investigators (Atsushi Irisawa and Ai Sato). The Cambridge classification was used to assess CP severity as follows: normal, no abnormal features; equivocal, fewer than three abnormal side branches; mild, more than three abnormal side branches with normal main duct; moderate, abnormal main duct and branches; and severe, same as moderate disease except with one or more additional abnormalities (large cavity, ductal stone/filling defect, duct obstruction/stricture, gross irregularity).

**Table 3. Traditional endoscopic ultrasonography criteria for chronic pancreatitis**

| |
|---|
| Parenchymal features |
| Hyperechoic foci |
| Hyperechoic strands |
| Lobularity |
| Cysts |
| Ductal features |
| Hyperechoic ductal margin |
| Dilated MPD |
| Duct irregularity |
| Dilated side-branches |
| Stones |

MPD: Main pancreatic duct

**Table 4. Normal-added criteria for diagnosis of chronic pancreatitis**

| |
|---|
| Parenchymal features (+1 point) |
| Hyperechoic foci |
| Hyperechoic strands |
| Lobularity |
| Cysts |
| Ductal features (+1 point) |
| Hyperechoic ductal margin |
| Dilated MPD |
| Duct irregularity |
| Dilated side-branches |
| Stones |
| Fine-reticular pattern (−1 point) |

MPD: Main pancreatic duct

**Table 5. Endoscopic ultrasonography diagnosis of chronic pancreatitis based on normal-added criteria**

| |
|---|
| Consistent/suggestive with CP - >4 points |
| Indeterminate for CP - 2-3 points |
| Unlikely - 1 point |
| Normal - −1 or 0 point |

CP: Chronic pancreatitis

### Investigational approach

First, we evaluated F-RP to validate it as a normal pattern. The frequency of F-RP appearance was initially analyzed by each ERP grade, and subsequently investigated based on both ERP and EUS, which was added to this evaluation as it is known as the most sensitive pancreas assessment modality. F-RP would be observed more frequently in cases without EUS abnormal findings than in cases with EUS abnormal findings. The frequency of hyperechoic foci and/or hyperechoic strands was also examined as abnormal

findings because each is a finding of pancreatic parenchyma, which was not observed using other modalities.

We subsequently compared the accuracy of our new proposed criteria (normal-added criteria) with the traditional criteria. EUS findings are sometimes controversial because of potential overdiagnosis, especially in early stages. Therefore, normal ERP was needed to infer a normal pancreas. A true boundary between normal and early CP would exist between ERP normal and EUS normal or EUS subtle abnormal. Finally, we compared the accuracy between our new proposed criteria and the RC.

All patients provided informed consent to participate in this study, which included pancreatograms for the evaluation of pancreatic disease that was not detectable on CT. The study protocol was approved by the institutional review board of our hospital.

### *Statistical analysis*

The Fisher's exact test was used to measure associations among categorical data. Two-tailed $P < 0.05$ was considered statistically significant. Analyses of Tables 6-8 were performed using the R statistical package, version 3.0.2 (http://www. r-project.org/) and of Table 9 was done using SPSS version 22.0 for Windows (IBM Japan, Ltd., Tokyo, Japan).

## RESULTS

### *Clinical significance of fine-reticular patterns on endoscopic ultrasonography*

Patients were classified by ERP as normal (normal or equivocal) or having CP (mild, moderate, and severe) based on the Cambridge classification. Normal or equivocal findings on ERP were obtained for 132 patients; 113 patients (85.6%) had F-RP on EUS. In contrast, F-RP was found in only 6 (13.3%) our of 45 CP cases on ERP ($P < 0.0001$) [Table 6]. In addition, we evaluated whether F-RP as a normal finding on EUS was observed in patients with and without CP [Table 7]. In this assessment, normal was defined as both normal/equivocal ERP findings and no EUS abnormality ($n = 56$). Apparent CP was defined as having both ERP findings scoring above mild on the Cambridge classification and parenchymal hyperechoic abnormalities on EUS ($n = 45$). F-RP was identified in all patients without CP. In contrast, only five patients (11.1%) among CP patients were identified among findings of F-RP. A significant difference was found between them ($P < 0.0001$). These findings suggested that F-RP on EUS was a specific finding in normal pancreatic parenchyma.

**Table 6. Endoscopic ultrasonography diagnosis of chronic pancreatitis based on normal-added criteria**

| ERP grade | Fine-reticular pattern on EUS | | *P* |
|---|---|---|---|
| | Positive (%) | Negative (%) | |
| Normal/equivocal (*n*=132) | 113 (85.6) | 19 (14.4) | <0.0001 |
| Mild/moderate/severe (*n*=45) | 6 (13.3) | 39 (86.7) | |

EUS: Endoscopic ultrasonography, ERP: Endoscopic retrograde pancreatography

**Table 7. Frequency of fine-reticular pattern with/without chronic pancreatitis**

| Fine-reticular pattern | Both normal/equivocal ERP and no EUS abnormalities (*n*=56) | Both CP findings on ERP and some EUS abnormalities (*n*=45) | *P* |
|---|---|---|---|
| Positive (%) | 56 (100) | 5 (11.1) | <0.0001 |
| Negative (%) | 0 | 40 (88.9) | |

CP: Chronic pancreatitis, EUS: Endoscopic ultrasonography, ERP: Endoscopic retrograde pancreatography

**Table 8. Frequency of hyperechoic foci/strands on endoscopic ultrasonography according to endoscopic retrograde pancreatography grade**

| ERP grade | Hyperechoic foci/strands on EUS | | *P* |
|---|---|---|---|
| | Positive (%) | Negative (%) | |
| Normal/equivocal (*n*=132) | 75 (56.8) | 57 (43.2) | <0.0001 |
| Mild/moderate/severe (*n*=45) | 44 (97.8) | 1 (2.3) | |

EUS: Endoscopic ultrasonography, ERP: Endoscopic retrograde pancreatography

### *Meanings of parenchymal hyperechoic abnormalities*

Next, we investigated the frequency of hyperechoic abnormalities (hyperechoic foci and/or stranding, excluding lobularity) occurrence on EUS [Table 8]. Lobularity was excluded from this inspection because it was the major finding among the RC (hyperechoic foci and strands were categorized as minor items based on the RC). Hyperechoic foci and strands were observed in 75 of 132 cases (56.8%) in patients with normal/equivocal pancreatic duct on ERP. However, they were observed in 44 (97.8%) among patients ($n = 45$) having CP on ERP. A significant difference was found between them ($P < 0.0001$). These results indicated that the findings of hyperechoic foci/strands were equivocal as a diagnostic item for CP

**Table 9. Evaluation of normal-added criteria in comparison with traditional criteria and Rosemont classification**

| | TC | | RC | | NaC | | *P* in comparison | |
|---|---|---|---|---|---|---|---|---|
| | Normal (≦1 point) | CP (≧2 points) | Normal | CP* | Normal (≦1 point) | CP (≧2 points) | NaC *vs.* TC | NaC *vs.* RC |
| ERCP findings | | | | | | | | |
| Normal/equivocal (*n*=132) | 87 | 45 | 122 | 10 | 112 | 20 | | |
| mild/moderate/severe (*n*=45) | 3 | 42 | 4 | 41 | 4 | 41 | | |
| Sensitivity (95% CI) | 65.9 (57.2, 73.9) | | 92.4 (86.5, 96.3) | | 84.9 (77.6, 90.5) | | 0.002 | 0.239 |
| Specificity (95% CI) | 93.3 (81.7, 98.6) | | 91.1 (78.8, 97.5) | | 91.1 (78.8, 97.5) | | >0.999 | >0.999 |
| PPV (95% CI) | 96.7 (90.6, 98.9) | | 96.8 (92.3, 98.7) | | 96.6 (91.6, 98.6) | | >0.999 | >0.999 |
| NPV (95% CI) | 48.3 (42.1, 54.5) | | 80.4 (69.2, 88.2) | | 67.2 (57.5, 75.6) | | 0.086 | 0.412 |

*Indeterminate/suggestive/consistent. CI: Confidence interval, TC: Traditional criteria, RC: Rosemont classification, CP: Chronic pancreatitis, PPV: Positive predictive value, NPV: Negative predictive value, NaC: Normal-added criteria, ERCP: Endoscopic retrograde cholangiopancreatography

diagnosis although these EUS findings were identified frequently in patients with obvious CP.

### *Diagnostic ability for normal findings of pancreas using our new proposed criteria*

Based on these results, F-RP was included to reduce overdiagnosis of CP, especially early/mild CP. We added F-RP as an item to the traditional criteria and our new proposed EUS criteria (normal-added criteria) for the diagnosis of CP. Subsequently, we investigated whether the normal-added criteria had a high diagnostic capability of ERCP normal/equivocal pancreas in comparison with traditional criteria. In cases where fewer than two points were defined as normal, the incidence of normal pancreas was significantly higher in the normal-added criteria than in the traditional ones (112/132 *vs.* 87/132, $P = 0.002$) [Table 9]. Results indicated that the addition of F-RP as a normal pattern was useful to avoid overdiagnosis.

### *Diagnostic capability of our new proposed criteria (normal-added criteria) versus Rosemont classification*

Finally, we compared results obtained using the normal-added criteria against those obtained by traditional criteria and RC [Table 9]. There was a significant difference in sensitivity between the traditional criteria and the normal-added criteria (65.9 *vs.* 84.9). No significant difference was found between the normal-added criteria and RC across all ERP grades, indicating diagnostic equivalence of normal-added criteria.

### *Adverse events in association with this study*

No patients developed severe acute pancreatitis or other adverse events as the result of the ERP or EUS procedures.

## DISCUSSION

EUS is an established modality for evaluating pancreatic disease. Past reports suggest the higher sensitivity of EUS as compared to ERCP.[4,6,8,10] However, there is no definitive evidence regarding a normal pancreas appearance as visualized by EUS. According to the conventional view, the appearance of a normal pancreas in EUS is characterized by the lack of dilation and irregularities in the main and branching pancreatic ducts and by a pancreatic parenchyma with homogeneous granular echotexture in individuals without a history of pancreatic disease. Such features have been called "finely reticular," "salt and pepper pattern," and others. The present study has succeeded in validating the conventionally viewed normal appearance as "normal findings" when such findings are compared with the ERP findings of normal cases [Table 6].

In the same study, there were 19 cases in which the ERCP finding was normal/equivocal and F-RP was absent. This suggests that EUS is superior to ERCP in detecting abnormalities, especially in pancreatic parenchyma. This fact, however, means that abnormalities visualized by EUS are difficult to endorse or that they may be "overdiagnosis."

In the course of CP, some patients develop structural changes before functional abnormalities or vice versa.[17] The border between normal pancreas and early or mild CP is ambiguous, and there is also difficulty in distinguishing between "normal" and "early CP." This seems to suggest an importance of investigating both abnormal and normal features when attempting to distinguish "early CP" from a "normal pancreas." We thought the addition of "normal appearance" of pancreatic parenchyma visualized by EUS to the

criteria for EUS-based diagnosis of CP would reduce to some extent, the uncertainty in the interpretation of findings (particularly overdiagnosis) in the diagnosis of early CP. Specifically, we added F-RP as a new criterion to the existing criteria for EUS-based diagnosis and deducted one point in cases that showed F-RP. Under this new set of criteria, cases with a total score of one or less are deemed to have a normal pancreas and cases with a total score of two or more are rated as having CP (including early CP). The greatest advantage of this set of diagnostic criteria is its simplicity. As it is based on existing techniques, there is virtually no learning curve and circumvents the complexity of using the RC. In the present study, we believe that using our new set of criteria prevent overdiagnosis, and improve the accuracy of diagnosing normal pancreas compared to the conventional technique [Table 9]. Furthermore, the precision in CP diagnosis was comparable to the more complex RC. The new set of criteria, which is simple as it only adds a normal pancreatic parenchyma appearance to the diagnostic criteria, will be useful in diagnosing early CP. In the inspection for "normal pancreas" appearance, the score deduction is not applied to cases where nonhomogeneity differing from that of a normal pancreas is seen despite the absence of a finding that precisely matches the criterion. Therefore, this set of criteria may allow a degree of ambiguity (an open issue of EUS possibly resulting in examiner-dependent evaluation) to be reflected in the evaluation.

This technique, however, has five limitations. First, ERCP-based Cambridge classification is a necessity for validating EUS-based diagnosis. If ERCP, which is unable to evaluate the pancreatic parenchyma, is adopted as a rationale, it may be useful in preventing overdiagnosis, however, interpretation of the essential findings from EUS would be debatable.

The second limitation, IOA in EUS evaluation of CP is not perfect.[18] A report by Pozo *et al.* suggests that same day back-to-back examination may result in greater IOA than evaluations from observing an EUS recording. As the recording does not show the entire exploration, some subtle focal changes may be obscured since EUS is a real-time exploration.[18] EUS was evaluated using static ultrasonographic images in this study; however, it was possible that overdiagnosis and ambiguity were avoided by the limited information, which had already been interpreted by an operator. Moreover, despite the same day examination by two experts, detection of the same images and findings is impossible. From the IOA perspective, the low IOA for hyperechoic foci without shadowing and honeycombing lobularity was pointed,[18-20] suggesting that the RC does not seem to improve the IOA of the conventional criteria.[18,20]

The third limitation pertains to aging-related morphological changes of the pancreas. Like CP, aging has been considered as a factor causing changes in the parenchyma and pancreatic duct visualized by EUS. In practice, EUS reveals abnormalities in the pancreatic parenchyma and bile duct in many patients having no history or symptom of pancreatobiliary system disease.[21] Furthermore, Rajan *et al.* reported a frequent finding of abnormalities by EUS in elderly patients (≥60 years) free of pancreatic disease.[22] Bhutani *et al.* also showed that up to three EUS features were frequently present in postmortem pancreatic specimens in elderly patients dying from all causes.[23] In contrast, cases showing four or more abnormalities revealed by EUS (stones in pancreatic duct or parenchyma, pancreatic duct stenosis/dilatation, etc.,) are more likely to represent pancreatic disease than aging-related changes. In the present study, we also cannot rule out the influence of aging on the pancreatic parenchyma (hyperechoic foci and strands) changes frequently revealed by EUS despite a normal pancreas appearance by ERCP (these abnormalities are classified as minor findings according to the RC). Therefore, the above-mentioned minor abnormalities of the pancreatic parenchyma revealed by EUS are considered as having low specificity and contributing to "overdiagnosis."

The fourth limitation pertains to the relationship between findings of mild or early CP and histopathological findings. Due to difficulties in obtaining pancreatic tissue from humans, Bhutani *et al.* developed a canine model and reported the histologic correlation of EUS changes of CP.[23]

Routine pancreas biopsy is considerably risky and unrealistic. For this reason, such biopsy is not justified when dealing with asymptomatic patients. Furthermore, since the distribution of CP is often focal, random biopsy can lead to false negative judgment. In addition, the one-to-one correspondence between EUS findings and histopathological findings is not known.[24] This issue has been addressed in several studies. Bhutani *et al.* reported that EUS could accurately detect CP when compared with a histopathologic examination in human autopsies.[25] Dewitt *et al.* conducted a biopsy of the pancreatic body of 16 patients with nonfocal

CP, with the use of EUS-guided Trucut biopsy (TCB), and reported that agreement between EUS and ERCP with EUS-TCB was poor and fair, respectively.[26] They stated that EUS-TCB was not recommended at present because of possible complications and limited diagnostic capability. They also evaluated one hundred patients who underwent pancreatic resection based on fibrosis scores.[27] Severe CP was associated with lobularity with honeycombing, hyperechoic foci with shadowing, hyperechoic foci without shadowing, main pancreatic duct dilation, main pancreatic duct irregularity, and dilated side branches. Varadarajulu *et al.* analyzed EUS criteria and surgical specimens in patients with calcification-free CP.[28] In their study, a significant correlation was noted between the number of satisfied EUS criteria and the histopathological severity of calcification-free CP in 42 cases. However, as many of the study patients had undergone pancreatectomy for pancreatic cancer, it was possible that pancreatic cancer itself was a factor in the changes of the main pancreatic duct and pancreatic parenchyma that were viewed as signs of CP.[24]

The fifth limitation pertains to the definition of "early" CP. It is unclear if this term indicates the "early" stage of a progressing CP or a "mild" stable disease state that has developed and persisted. The former concept varies among investigators and it is desirable to have a more precise definition of this term through further prospective observation, including clarification of the disease stages encompassed by the term "early" CP.

Despite these unresolved issues, EUS is a definitive method that enables safe and noninvasive collection of detailed information about the pancreatic parenchyma and pancreatic duct.

## CONCLUSION

If F-RP is incorporated as a feature of normal pancreas into the diagnostic criteria through further studies, prevention of overdiagnosis will be expected without reducing the diagnostic sensitivity, therefore possibly making EUS an even more useful modality for early diagnosis of cases that are difficult to diagnose with other modalities.

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There are no conflicts of interest.

## REFERENCES

1. Raimondo M. What is the role of EUS in screening for chronic pancreatitis? *Nat Clin Pract Gastroenterol Hepatol* 2007;4:530-1.
2. Axon AT, Classen M, Cotton PB, *et al*. Pancreatography in chronic pancreatitis: International definitions. *Gut* 1984;25:1107-12.
3. Catalano MF, Geenen JE. Diagnosis of chronic pancreatitis by endoscopic ultrasonography. *Endoscopy* 1998;30 Suppl 1:A111-5.
4. Wiersema MJ, Hawes RH, Lehman GA, *et al*. Prospective evaluation of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in patients with chronic abdominal pain of suspected pancreatic origin. *Endoscopy* 1993;25:555-64.
5. Sahai AV, Mishra G, Penman ID, *et al*. EUS to detect evidence of pancreatic disease in patients with persistent or nonspecific dyspepsia. *Gastrointest Endosc* 2000;52:153-9.
6. Bhutani MS. Endoscopic ultrasonography: Changes of chronic pancreatitis in asymptomatic and symptomatic alcoholic patients. *J Ultrasound Med* 1999;18:455-62.
7. Dancygier H. Endoscopic ultrasonography in chronic pancreatitis. *Gastrointest Endosc Clin N Am* 1995;5:795-804.
8. Bhutani MS. Endoscopic ultrasound in pancreatic diseases. Indications, limitations, and the future. *Gastroenterol Clin North Am* 1999;28:747-70, xi.
9. Sahai AV, Zimmerman M, Aabakken L, *et al*. Prospective assessment of the ability of endoscopic ultrasound to diagnose, exclude, or establish the severity of chronic pancreatitis found by endoscopic retrograde cholangiopancreatography. *Gastrointest Endosc* 1998;48:18-25.
10. Catalano MF, Lahoti S, Geenen JE, *et al*. Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. *Gastrointest Endosc* 1998;48:11-7.
11. Irisawa A, Katakura K, Ohira H, *et al*. Usefulness of endoscopic ultrasound to diagnose the severity of chronic pancreatitis. *J Gastroenterol* 2007;42 Suppl 17:90-4.
12. Jones SN, Lees WR, Frost RA. Diagnosis and grading of chronic pancreatitis by morphological criteria derived by ultrasound and pancreatography. *Clin Radiol* 1988;134:453-9.
13. Raimondo M, Wallace MB. Diagnosis of early chronic pancreatitis by endoscopic ultrasound. Are we there yet? *JOP* 2004;5:1-7.
14. Catalano MF, Sahai A, Levy M, *et al.* EUS-based criteria for the diagnosis of chronic pancreatitis: The Rosemont classification. *Gastrointest Endosc* 2009;69:1251-61.
15. Kalmin B, Hoffman B, Hawes R, *et al.* Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: Comparing interobserver reliability and intertest agreement. *Can J Gastroenterol* 2011;25:261-4.
16. Kahl S, Glasbrenner B, Leodolter A, *et al.* EUS in the diagnosis of early chronic pancreatitis: A prospective follow-up study. *Gastrointest Endosc* 2002;55:507-11.
17. Albashir S, Bronner MP, Parsi MA, *et al*. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: Correlation in chronic pancreatitis. *Am J Gastroenterol* 2010;105:2498-503.
18. Pozo DD, Poves E, Tabernero S, *et al*. Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: Interobserver agreement in same day back-to-back procedure. *Pancreatology* 2012;12:284-7.
19. Gardner TB, Gordon SR. Interobserver agreement for pancreatic endoscopic ultrasonography determined by same day back-to-back examinations. *J Clin Gastroenterol* 2011;45:542-5.
20. Stevens T, Lopez R, Adler DG, *et al.* Multicenter comparison of the interobserver agreement of standard EUS scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis. *Gastrointest Endosc* 2010;71:519-26.

21. Nattermann C, Goldschmidt AJ, Dancygier H. Endosonography in chronic pancreatitis – A comparison between endoscopic retrograde pancreatography and endoscopic ultrasonography. *Endoscopy* 1993;25:565-70.
22. Rajan E, Clain JE, Levy MJ, *et al.* Age-related changes in the pancreas identified by EUS: A prospective evaluation. *Gastrointest Endosc* 2005;61:401-6.
23. Bhutani MS, Ahmed I, Verma D, *et al*. An animal model for studying endoscopic ultrasound changes of early chronic pancreatitis with histologic correlation: A pilot study. *Endoscopy* 2009;41:352-6.
24. Kaul V, Catalano MF. EUS and chronic pancreatitis: Seeing is believing? *Gastrointest Endosc* 2007;66:510-2.
25. Bhutani MS, Arantes VN, Verma D, *et al.* Histopathologic correlation of endoscopic ultrasound findings of chronic pancreatitis in human autopsies. *Pancreas* 2009;38:820-4.
26. DeWitt J, McGreevy K, LeBlanc J, *et al.* EUS-guided trucut biopsy of suspected nonfocal chronic pancreatitis. *Gastrointest Endosc* 2005;62:76-84.
27. LeBlanc JK, Chen JH, Al-Haddad M, *et al.* Endoscopic ultrasound and histology in chronic pancreatitis: How are they associated? *Pancreas* 2014;43:440-4.
28. Varadarajulu S, Eltoum I, Tamhane A, *et al*. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: A prospective tissue characterization study. *Gastrointest Endosc* 2007;66:501-9.