Validity of endoscopic ultrasound findings of chronic pancreatitis: Evaluation from the viewpoint of disease risk factors

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Short Title: Evaluation for endoscopic ultrasound findings of chronic pancreatitis

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Abstract

Background: The diagnosis of chronic pancreatitis (CP) using endoscopic ultrasound (EUS) criteria, referred to as the Rosemont classification (RC), has been widely performed. However, the validity of the RC, which was based on expert opinion, is still controversial. If EUS findings are associated with chronic pancreatitis, then they should be associated with risk factors for chronic pancreatitis. In this study, to verify the appropriateness of the RC and each EUS finding, we performed a retrospective analysis from the viewpoint of risk factors for CP.

Summary: Three hundred forty-four patients were enrolled in this study. Clinical background characteristics that associate with CP were alcohol intake, smoking, history of acute pancreatitis (AP), and age. The correlation between EUS criteria for CP and clinical background was investigated. All EUS findings except the presence of cysts showed significant correlations with one or two of the three following factors: ethanol (EtOH) intake, smoking status, and history of AP. Results of the univariate and multivariate analyses showed that three factors (EtOH intake, smoking, and history of AP) other than age were positively correlated with the RC. Moreover, the risk of progression from normal to consistent CP to indeterminate and suggestive CP was found to increase with increasing EtOH intake.

Key messages: The RC and each EUS finding was validated from the viewpoint of risk factors for CP.

Introduction

Chronic pancreatitis (CP) is defined as irreversible pancreatic parenchymal damage and the development of inflammation and fibrosis that may lead to varying degrees of exocrine and endocrine dysfunction [1]. Currently, endoscopic ultrasound (EUS) is the most sensitive imaging test for screening symptomatic CP; it has the ability to visualize subtle alterations in the pancreatic structure before traditional imaging and functional tests are able to reveal any abnormalities [2-5]. In 2007, the Rosemont classification (RC), which specifies the criteria for diagnoses determined using EUS, was developed [6]. This classification categorized various EUS findings into major and minor features according to the consensus of attendees (based on weighting of the importance of each EUS finding). Using the RC, standardized EUS criteria for diagnosing CP (consistent, suggestive, or indeterminate) were proposed. However, the criteria were based on expert opinion alone and have not been prospectively validated. Additionally, the histological interpretation of each EUS finding is unclear because it is difficult to perform one-to-one comparisons of EUS findings and histological findings. Therefore, the clinical interpretation of EUS findings for CP has been controversial.

CP can be caused by genetic, environmental, and/or other risk factors in those who develop persistent pathological responses to parenchymal injury or stress [7]. Until now, various known risk factors for CP were alcohol consumption, smoking, history of acute pancreatitis (AP), metabolic abnormalities, sex, and some genetic factors [8-14]. In addition, past literatures have indicated that it appears undeniable that aging is associated with the development of CP [15]. Therefore, if EUS findings according to the RC are definitely associated with chronic pancreatitis, then they should be correlated with the risk factors for chronic pancreatitis. In this study, to verify the appropriateness of the RC and each EUS finding, we retrospectively analyzed the RC and each EUS finding from the viewpoint of risk factors for CP.

Materials and Methods

Study design and patients

We performed a retrospective clinical study with a target population of 344 consecutive individuals who underwent EUS for the evaluation of pancreatic hepatobiliary disease (including

suspicion) at the Aizu Medical Center Hospital of Fukushima Medical University between January 2012 and August 2014. Patients who were younger than 20 years old, abstained from alcohol use, had definite pancreatobiliary tumors, or had undergone surgical procedures for pancreatobiliary disease were excluded from this study. The reasons for EUS in the object patients (n=344) were follows; elevated/decreased serum pancreatic enzyme level in 86 (25%), abdominal pain of unknown origin in 76 (22.1%), elevated serum bile enzyme level in 44 (12.8%), follow-up for chronic pancreatitis including early stage defined by the "the revised Japanese clinical diagnostic criteria for chronic pancreatitis" [16]) in 42 (12.2%), polyps/wall thickess of gall bladder in 32 (9.3%), suspicion of biliary stones in 24 (7%), elevated tumor maker in 23 (6.7%), exacerbation of diabetes mellitus in 6 (1.7%), and others in 11 (3.2%). There is no disease bias in the target patients.

The primary endpoint of this study was to verify the appropriateness of each EUS finding based on the RC according to an analysis of correlations between individual EUS findings and each CP risk factor. The secondary endpoint was to assess the relationship between the severity of CP based on the RC and each risk factor of CP.

This study was reviewed and approved by the institutional review board of Fukushima Medical University. It was conducted in accordance with the human and ethical principles of research set forth in the Declaration of Helsinki. We provided a means to opt out instead of omitting informed consent, which is a method of guaranteeing the opportunity to publish research information on our website.

EUS diagnosis of CP using the RC

CP was diagnosed by EUS using the RC. The major criteria of the RC included hyperechoic foci with shadowing, main pancreatic duct calculi, and lobularity with honeycombing. The minor criteria included cysts, strands, non-shadowing hyperechoic foci, lobularity without honeycombing, dilated main pancreatic duct (MPD) >3.5 mm, irregular MPD contour, dilated side branches >1 mm, and a hyperechoic MPD margin (Table 1). Representative EUS images of CP were shown in Figure. A classification scheme based on combinations of these criteria for the diagnosis of CP as consistent, suggestive, or indeterminate was proposed.

Consistent CP was defined as follows: one major feature plus three or more minor features; one major feature plus one major feature; or two major features. Suggestive CP was defined as follows: one major feature plus fewer than three minor features; one major feature plus three or more minor features; or five or more minor features. Indeterminate CP was defined as follows: three or four minor features and no major features; one major feature alone; or fewer than three minor features. In addition, normal was defined as two or fewer minor features and no major features [17]. Therefore, 344 patients were divided into four categories according to the RC as follows: normal patients (n = 251); patients with indeterminate CP (n = 70); patients with suggestive CP (n = 14); and patients with consistent CP (n = 9) (Table 2).

Risk factors for CP

According to previous reports [17-20], the risk factors of CP are as follows: quantity of current or previous alcohol intake over the course of 10 years (ethanol [EtOH]: <20 g/day; 20–40 g/day; 40–60 g/day; 60–80 g/day; >80 g/day); smoking habit (Brinkman Index [BI] >400); history of AP at least once; and age (Table 3). The conversion factor for EtOH (1 mL of EtOH contains 0.8 g of pure EtOH) was also considered when measuring the quantity of alcohol contained in a standard drink. For example, one bottle of beer (500 mL) with 5% alcohol content contains 20 g of EtOH (500 × 5% × 0.8), one glass of wine (140 mL) with 14% alcohol content contains 15.7 g of EtOH (140 × 14% × 0.8), one glass of rice wine (180 mL) with 15% alcohol content contains 21.6 g of EtOH (180 × 15% × 0.8), one glass of a distilled spirit (180 mL) with 25% alcohol content contains 36 g of EtOH (180 × 25% × 0.8), and one shot of whiskey (40 mL) with 40% alcohol content contains 12.8 g of EtOH (40 × 40% × 0.8).

EUS equipment and evaluation of EUS images

EUS was performed by seven experienced endosonographers (each with experience performing EUS more than 100 times per year) who were trained regarding the EUS procedures for chronic pancreatitis and the RC. The entire pancreas was examined with a radial-array echoendoscope (GF-UE260-AL5; Olympus, Tokyo, Japan) and curved linear-array echoendoscope (GF-UCT260 or GF-UCT240; Olympus) at 6 MHz with unified sensitivity and

time control (the level of the gain/contrast was manipulated depending on the condition of the individual). All records and findings of the EUS procedures were written according to the RC. EUS data were obtained from medical records, and the archived images (pictures and/or video) were re-evaluated by two endosonographers (AY and AI) who were in complete agreement regarding whether the description of the record was insufficient or unclear. Interrater agreement was calculated using multi-rater kappa statistics for eleven EUS features in the RC.

Statistical analysis

To evaluate the inter-rater agreement using kappa value, A scale proposed by Landis and Koch [18] was used to interpret the magnitude of agreement for a range of kappa values as follows:Fair: K=0.21–0.40, Moderate: K=0.41–0.60, Substantial: K=0.61–0.80, Almost perfect: K=0.81–1.00.

To analyze the relationship between 11 individual findings of EUS according to the RC and the four risk factors for CP (alcohol intake, smoking habit, history of AP, and age), the chi-squared test for alcohol intake, smoking, and history of AP and Student's t test for age were used in the univariate analysis. For the multivariate analysis, a binomial logistic regression model was used. In this model, 11 EUS findings were set as individual objective variables; however, alcohol intake, smoking, history of AP, and age were set as explanatory variables. In addition, the fitness of the model was confirmed using the Hosmer-Lemeshow test.

To analyze the relationship between the RC (consistent with CP, suggestive of CP, indeterminate for CP, normal) and the four risk factors for CP, a chi-squared test was performed for alcohol intake, smoking, and history of AP, and a one-way analysis of variance was performed for age; these were used for the univariate analyses. Furthermore, an ordered logistic regression model was used for the multivariate analysis. In this model, the four classes of the RC were set as objective variables using progressive ordinal data in the following order: normal, indeterminate, suggestive, and consistent; alcohol intake, smoking, history of AP, and age were set as explanatory variables. In addition, the fitness of the model was confirmed using Pearson's goodness-of-fit test.

For the statistical test, the significance level of the two-tailed test was set as $\alpha = 0.05$, and $p < 0.05$ was considered significantly different. SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Inter-rater agreement of EUS findings between 2 endosonographers who reevaluated in this study

We evaluated the inter-rater agreement between 2 endosonographers for eleven EUS features of the RC as seen in Table 4. Each kappa (K) value was as follows; hyperechoic foci with shadowing was 1.00 (95% confidence interval [CI]: 1.00–1.00), MPD calculi was 1.00 (1.00–1.00), lobularity with honeycombing was 0.87 (0.75–0.99), cysts was 1.00 (1.00–1.00), strands was 0.83 (0.77–0.89), non-shadowing hyperechoic foci was 0.86 (0.80–0.91), lobularity without honeycombing was 0.87 (0.80–0.95), dilated MPD was 0.95 (0.90–0.99), irregular MPD contour was 1.00 (1.00–1.00), dilated side branches was 0.81 (0.63–0.99), and a hyperechoic MPD margin was 1.00 (1.00–1.00), respectively. The inter-rater agreement was evaluated "almost perfect" in all EUS findings.

Correlation between individual EUS findings based on the RC and each CP risk factor

The following individual EUS findings based on the RC were investigated to determine their association with the risk factors for CP by means of univariate and multivariate analyses: hyperechoic foci with shadowing; main pancreatic duct calculi; lobularity with honeycombing; cysts; strands; non-shadowing hyperechoic foci; lobularity without honeycombing; dilated main pancreatic duct (MPD); irregular MPD contour; dilated side branches larger than 1 mm; and hyperechoic MPD margin (Table 5).

Regarding hyperechoic foci with shadowing, the binominal logistic regression model showed no convergence in the calculations; however, the univariate analysis showed strong correlations with EtOH intake and history of AP. Regarding the main pancreatic duct calculi, the binominal logistic regression model showed no convergence in the calculations; however, the univariate analysis showed strong correlations with EtOH intake and history of AP. For lobularity with honeycombing, the multivariate analysis showed strong correlations with smoking status and history of AP. Cysts were only found to be correlated with age. The multivariate analysis found that strands were strongly correlated with EtOH intake and smoking status. Regarding non-shadowing hyperechoic foci, the multivariate analysis showed strong correlations with EtOH intake and smoking status. Regarding lobularity without honeycombing, the multivariate analysis showed strong correlations with EtOH intake and history of AP. The

multivariate analysis showed that MPD dilation was strongly correlated with EtOH intake and history of AP. The binominal logistic regression model showed no convergence in the calculations for the MPD contour; however, the univariate analysis showed strong correlations with EtOH intake and history of AP. Dilated side branches primarily showed a strong correlation with history of AP. The MPD margin was primarily correlated with smoking status. In summary, all these findings, other than the presence of cysts, showed correlations with EtOH intake, smoking status, and/or history of AP.

Relationship between the severity of CP based on the RC and CP risk factors

Based on the tests for separate factors, the relationships between the RC and EtOH intake, smoking status, history of AP, and age were included in the univariate analysis (Table 6). In addition, using the RC as target variables for ordinal data and EtOH intake, smoking status, history of AP, and age as explanatory variables, a multivariate ordered logistic regression analysis was performed. The results of the univariate and multivariate analysis showed that EtOH intake, smoking status, and history of AP were positively correlated with the RC. Spearman's rank correlation coefficient for the relationship between EtOH intake and RC was 0.369, which indicated a significant, but not strong, correlation. Concomitantly, an ordered logistic regression analysis showed that the risk (odds ratio [OR]) for progression from normal to consistent CP to indeterminate and suggestive CP increased significantly with EtOH intake with the following increases (in comparison with 0 g/day EtOH): EtOH 20–40 g/day, 2.1-fold; EtOH 40–60 g/day, 3.5-fold; EtOH 60–80 g/day, 4.7-fold; and EtOH >80 g/day, 6.0-fold. Regarding smoking status, the risk (OR) for patients with BI >400 was 2.6-times higher than that for patients with lower BI, whereas the risk (OR) for patients with a history of AP was 11.3-times higher than that for patients with no such history. Both these differences were significant. The Pearson's goodness-of-fit test for the ordered logistic regression analysis resulted in $p = 0.992$, suggesting that conformity could not be ruled out.

Discussion/Conclusion

The RC, elaborated by an international consensus in 2007, uses parenchymal and ductal criteria divided into major and minor features [6]. Although it was an innovative and impressive proposal for a less invasive CP diagnosis using EUS, the RC was based on expert opinion alone and lacked definitive evidence. Therefore, we considered it necessary to assess the appropriateness of the RC and to clarify the meaning of each EUS finding by performing an analysis from the viewpoint of the risk factors for CP.

In the present study, and in accordance with previous studies, the risk factors were alcohol, smoking, and history of AP; in addition, we included age because some reports showed that pancreatic parenchymal changes were influenced by aging. Alcohol use has been commonly reported as a risk factor for CP. Alcohol consumption (80–150 g/day) is related to 60–80% of CP cases, and patients usually have a long history of alcohol abuse (6–12 years) [19-22]. Yadav et al. [22] reported that, compared with abstaining and light drinking, very heavy drinking was significantly associated with CP (OR, 3.10; 95% confidence interval [CI], 1.8–5.1). Regarding smoking, previous and current smoking were reported by 71.4% and 47.3%, respectively, of patients with CP. Yusoff et al. [19] also mentioned that heavy smoking was one of the strongest independent predictors of severe pancreatic abnormalities found with EUS (OR, 1.7; 95% CI, 1.2–2.4). Regarding the history of AP, an analysis of the long-term outcomes of patients with AP in Japan [23] showed a transition to CP for 14.8% of patients. Yasuda et al. [24] evaluated the outcomes of severe AP and reported that the transition to CP was noted in 22% of patients. Lankisch et al. [25] observed that 95% of the CP cases had progressed from AP due to alcohol use. They also reported that the cumulative risk for the development of CP was 13% within 10 years and 16% within 20 years; the risk of CP for those who survived a second episode of AP was 38% within 2 years. In addition, an investigation in the United States [26] showed a transition from AP to CP for 24.1% of patients after 3–5 years and for 32.3% after 3–4 years. In this report, transition from AP to CP also occurred occasionally in patients with non-alcohol-induced pancreatitis. These reports strongly indicated that history of AP is an important risk factor of CP. In addition, Nøjgaard et al. [27] reported that nicotine abuse substantially increased the risk of progression from AP to CP.

Regarding the correlation between individual EUS findings based on the RC and each CP risk factor, all EUS findings, other than the presence of cysts, showed correlations with EtOH intake, smoking status, and/or history of AP. Therefore, it is considered that almost all EUS findings are appropriate for the diagnosis of CP. However, cysts were only correlated with age in the present study. Regarding aging, Ikeda et al. [28] analyzed the incidence of subclinical morphological changes in the pancreas as detected by screening ultrasonography in relation to the background factors of 130,951 subjects, and an age-dependent increase in the incidence of MPD dilatation and cystic lesions was observed. Petrone et al. [29] demonstrated that advanced age was significantly associated with an increased risk of MPD dilatation. In fact, pancreatic changes due to aging have been pathologically demonstrated [30, 31]. These reports suggested that it is possible to recognize age-related changes as pathological changes with EUS. Therefore, it is considered that "cysts," which are associated with only aging in our study, might be excluded from the EUS criteria for diagnosing CP.

Next, regarding the relationship between the severity of CP based on the RC and each CP risk factor, the risk of progression from normal to consistent CP to indeterminate and suggestive CP was associated with increasing EtOH intake, BI >400 for smoking, and history of AP. Regarding the quantities of EtOH consumption and smoking, Yusoff et al. [19] also demonstrated that heavy alcohol use was associated with more EUS features of CP (OR, 5.1; 95% CI, 3.1–8.5). Moreover, Sahai et al. [20] indicated that the number of EUS criteria is directly proportional to the cumulative EtOH intake. However, Andriulli et al. [32] reported that smoking might increase the risk of CP development; they showed that the risk (OR) for patients with BI >400 was 2.6-times higher than that for patients with BI <400. Therefore, our data indicated the validity of each EUS criterion and the importance of weighting each EUS finding to determine the severity of CP. The RC is considered to be a reasonable and acceptable tool for diagnosing CP.

Our study had several limitations. First, it was a retrospective study; therefore, EUS findings were retrospectively evaluated using medical records. Second, EUS was performed using different types of echoendoscopes (radial, curved, or linear-array) without unified

gain/contrast. Finally, alcohol intake and smoking frequency were self-reported. Although these limitations existed, the results of the present study could firmly indicate the validity of RC.

In conclusion, the regression analysis of risk factors for CP demonstrated the validity of the RC. However, it remains uncertain whether EUS features are pathologic, normal, age-related findings, normal anatomic variants, or attributable to non-clinically significant asymptomatic fibrosis in the absence of endocrine or exocrine dysfunction. Prospective data of patients diagnosed with CP based on EUS are needed to validate the accuracy of the EUS diagnostic criteria for CP.

Disclosure Statement

The authors declare no conflicts of interest regarding this review article.

References

[1] Steer ML, Waxman I, Freedman S. Chronic pancreatitis. N Engl J Med. 1995; 332: 1482-1490.

[2] Raimondo M, Wallace MB. Diagnosis of early chronic pancreatitis by endoscopic ultrasound. Are we there yet? JOP. 2004; 5: 1-7.

[3] Sahai AV. EUS and chronic pancreatitis. Gastrointest Endosc. 2002; 56: S76-S81.

[4] Morris-Stiff G, Webster P, Frost B, Lewis WG, Puntis MC, Roberts SA. Endoscopic ultrasound reliably identifies chronic pancreatitis when other imaging modalities have been non-diagnostic. JOP. 2009; 10: 280-283.

[5] Pungpapong S, Wallace MB, Woodward TA, Noh KW, Raimondo M. Accuracy of endoscopic ultrasonography and magnetic resonance cholangiopancreatography for the diagnosis of chronic pancreatitis: a prospective comparison study. J Clin Gastroenterol. 2007; 41: 88-93.

[6] Catalano MF, Sahai A, Levy M, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009; 69: 1251-1261.

[7] Kleeff J, Whitcomb DC, Shimosegawa T, et al. Chronic pancreatitis. Nat Rev Dis Primers. 2017; 3: 17060.

[8] Law R, Parsi M, Lopez R, et al. Cigarette smoking is independently associated with chronic pancreatitis. Pancreatology. 2010; 10: 54-59.

[9] Corrao G, Bagnardi V, Zambon A, et al. A meta analysis of alcohol consumption and the risk of 15 diseases. Prev Med. 2004; 38; 613-619.
[10] Pelli H, Sand J, Laippala P, et al. Long-term follow up after the first episode of acute alcoholic pancreatitis: Time course and risk factors for recurrence. Scand J Gastroenterol. 2000; 35: 552-555.
[11] Ammann RW, Muellhaupt B, Meyenberger C, et al. Alcoholic nonprogressive chronic pancreatitis: prospective long-term study of a large cohort with alcoholic acute pancreatitis (1976-1992). Pancreas. 1994; 9: 365-373.
[12] Lee JW, Kim HG, Lee DW, et al. Association between smoking and the progression of computed tomography findings in chronic pancreatitis. Gut Liver. 2016; 10: 464-469.
[13] Durbec JP, Sarles H. Multicenter survey of the etiology of pancreatic diseases. Relationship between the relative risk of developing chronic pancreatitis and alcohol, protein and lipid consumption. Digestion. 1978; 18: 337-350.
[14] Rosendahl J, Kirsten H, Hegyi E, et al. Genome-wide association study identifies inversion in the CTRB1-CTRB2 locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis. Gut. 2018; 67: 1855-1863.
[15] Yamabe A, Irisawa A, Shibukawa G, et al. Early diagnosis of chronic pancreatitis: understanding the factors associated with the development of chronic pancreatitis. Fukushima J Med Sci. 2017; 63: 1-7.
[16] Shimosegawa T, Kataoka K, Kamisawa T, et al. The revised Japanese clinical diagnostic criteria for chronic pancreatitis. J Gastroenterol. 2010;45:584-591.
[17] Rajan E, Clain JE, Levy MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. Gastrointest Endosc. 2005; 61: 401-406.
[18] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-174.
[19] Yusoff IF, Sahai AV. A prospective, quantitative assessment of the effect of ethanol and other variables on the endosonographic appearance of the pancreas. Clin Gastroenterol Hepatol. 2004; 2: 405-409.
[20] Sahai A. How much alcohol is required to produce EUS chronic pancreatitis? A prospective, blinded, quantitative assessment of the effect of alcohol intake in 1157 patients. Gastrointest Endosc. 2002; 55: AB241.
[21] Sirén J. Intraductal papillary mucinous neoplasm of the pancreas, IPMN. Duodeci. 2013; 129: 591-598.

[22] Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009; 169: 1035-1045.
[23] Ueda T, Kuroda Y, Takeyama Y, Kashima K, Kataoka K, Otsuki M. Long-term outcome of acute pancreatitis. J Jpn Pancreas Soc. 2005; 20: 455-464.
[24] Yasuda T, Ueda T, Takeyama Y, et al. Long-term outcome of severe acute pancreatitis. J Hepatobiliary Pancreat Surg. 2008; 15: 397-402.
[25] Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol. 2009; 104: 2797-2805.
[26] Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012; 107:1096-1103.
[27] Nøjgaard C, Becker U, Matzen P, Andersen JR, Holst C, Bendtsen F. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. Pancreas. 2011; 40: 1195-1200.
[28] Ikeda M, Sato T, Morozumi A et al. Morphologic changes in the pancreas detected by screening ultrasonography in a mass survey, with special reference to main duct dilatation, cyst formation, and calcification. Pancreas. 1994; 9: 508-512.
[29] Petrone MC, Arcidiacono PG, Perri F, Carrara S, Boemo C, Testoni PA. Chronic pancreatitis-like changes detected by endoscopic ultrasound in subjects without signs of pancreatic disease: do these indicate age-related changes, effects of xenobiotics, or early chronic pancreatitis? Pancreatology. 2010; 10: 597-602.
[30] Detlefsen S, Sipos B, Feyerabend B, Klöppel G. Pancreatic fibrosis associated with age and ductal papillary hyperplasia. Virchows Arch. 2005; 447: 800-805.
[31] Chantarojanasiri T, Hirooka Y, Ratanachu-Ek T, Kawashima H, Ohno E, Goto H. Evolution of pancreas in aging: degenerative variation or early changes of disease? J Med Ultrason. 2015; 42: 177-183.
[32] Andriulli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P. Smoking as a cofactor for causation of chronic pancreatitis: a meta-analysis. Pancreas. 2010; 39: 1205-1210.