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ORIGINAL ARTICLE

Assessing the value of endoscopic ultrasound in predicting symptom severity and long-term clinical course in chronic pancreatitis

Neal Bhutiani[1], John S. Richey[1], Amber N. Brown[1], Joshua Tierney[1], Stephen A. McClave[2], Michael H. Bahr[1] & Gary C. Vitale[1]

[1]Department of Surgery, University of Louisville, 550 S. Jackson Street, and [2]Department of Medicine, Division of Gastoenterology, University of Louisville, Louisville, KY, United States

Abstract

Background: To date, no studies have evaluated the correlation between number of endoscopic ultrasound (EUS) criteria met for chronic pancreatitis (CP) and symptom severity over the course of the disease. This study assessed the relationship between number of EUS-based diagnostic criteria for CP and CP severity over time.

Methods: A University of Louisville database was queried for patients undergoing EUS due to concern for chronic pancreatitis between 2005 and 2016. Patients were grouped based on EUS criteria met for CP and groups were compared along outcome and procedural variables.

Results: Of a total of 243 patients, 24, 129, and 90 patients met 1–3, 4–5, and ≥6 EUS diagnostic criteria, respectively. Median follow-up time was 33 months. Along all follow-up parameters, number of diagnostic criteria was positively correlated with an increased percentage of patients requiring operative intervention for chronic pancreatitis on univariate and multivariate analysis.

Conclusions: In addition to the role of EUS criteria in establishing the diagnostic severity of patients with symptomatic chronic pancreatitis, the number of EUS-based criteria may help predict patients who will eventually require operative intervention and thus prompt referral to a pancreatobiliary surgeon earlier in the course of a patient's disease.

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Correspondence

Gary C. Vitale, University of Louisville, Department of Surgery, 550 S. Jackson Street, Louisville, KY 40202, United States. E-mail: garyvitale@gmail.com

Introduction

Chronic pancreatitis (CP) represents a complex disease with a very heterogeneous natural history. As a result, its management continues to present a challenge to clinicians. CP involves progressive inflammatory changes in the pancreatic tissue, which lead to permanent structural changes in the gland. In approximately 90–95% of patients, this inflammation results in significant epigastric abdominal pain and, eventually, exocrine and endocrine insufficiency. These in turn cause inadequate oral intake, fat and nutrient malabsorption, and weight loss.[1] Thus, management of CP largely involves control of these symptoms and physiologic perturbations. Of these, chronic pain remains the most difficult to control, often leading to narcotic dependence, multiple hospitalizations, and decreased quality of life.

In general, pain and symptom management in patients with chronic pancreatitis comprises endoscopic and, in certain cases, operative interventions. Identifying those patients who will suffer from a more aggressive disease process and require more intensive and invasive interventions unfortunately remains quite difficult. Endoscopic ultrasound (EUS) currently represents an effective diagnostic tool that allows for well-validated assessment of the severity of pancreatitis at diagnosis.[2–9] Diagnosis of CP by

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way of EUS involves evaluating the parenchyma and ductal system of the pancreas for changes consistent with CP. These include ductal changes such as bright duct walls, visible side branches, prominence of main pancreatic duct, duct irregularity, as well as parenchymal changes included stranding, lobularity, calcification (with acoustic shadowing) cystic changes, and bright central foci.[10] However, whether the number of EUS criteria corresponds to a disease process with a more aggressive natural history (i.e. one more likely to be refractory to medical and endoscopic management, to result in more pain-related hospitalizations, etc.) remains unknown. To our knowledge, there has not been a study evaluating the correlation of number of EUS criteria for CP with the natural history of this disease process.

Ultimately, having a predictive tool for long-term disease prognosis in patients with chronic pancreatitis would prove invaluable in guiding progression along the medical to endoscopic to surgical treatment algorithm. Given the use of EUS in diagnosing and classifying chronic pancreatitis, it warrants investigation as a possible predictor of the natural history of the disease. This study sought to identify how EUS criteria correlate with disease-related outcomes as well as the need for endoscopic and operative intervention and thus better guide clinicians in managing patients with chronic pancreatitis.

Methods

Study design

A University of Louisville IRB approved single-institution database consisting of was evaluated from January 2005 to August 2016 for patients undergoing endoscopic ultrasound (EUS) for evaluation of the pancreas in the setting of a clinical diagnosis of chronic pancreatitis. Clinical diagnosis of CP was based on a history of episodes of acute pancreatitis with subsequent attacks and chronic pain in conjunction with CT and MRI evaluations noting pancreatic ductal abnormalities (e.g. dilation or strictures) and parenchymal abnormalities (e.g. calcifications and atrophy). The study was conducted in compliance with the principles and protocol established in the Declaration of Helsinki in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP).

Endoscopic ultrasound evaluation

Endoscopic ultrasound was performed by a single gastroenterologist, Dr. Stephen A. McClave, at the University of Louisville. For each patient, the pancreas was evaluated with respect to traditional markers for changes associated with scar tissue from chronic pancreatitis.[10] Ductal changes included bright duct walls, visible side branches, prominence of main pancreatic duct

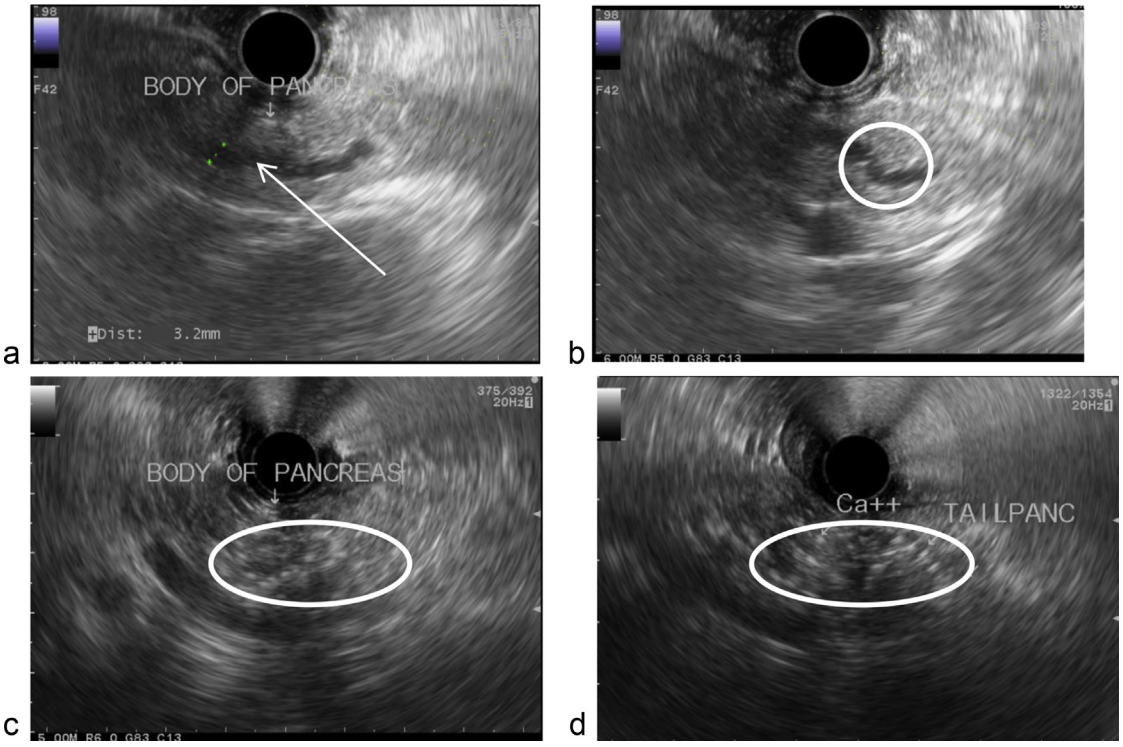

Figure 1 Endoscopic ultrasound findings suggestive of chronic pancreatitis. (A) Main pancreatic duct dilation (arrow). (B) Main pancreatic duct irregularity (circle). (C, D) Hyperechoic foci (calcifications) in the parenchyma of the pancreatic body (C) and tail (D) (circles)

(Fig. 1a), and duct irregularity (Fig. 1b). Parenchymal changes included stranding, lobularity, calcification (with acoustic shadowing) (Fig. 1c–d), cyst, and bright central foci. Interpretation of findings were as follows: 0–3 findings = Normal pancreatic EUS, 4–5 findings = Suggestive of diagnosis of chronic pancreatitis, and ≥6 criteria = EUS diagnosis of chronic pancreatitis (Table 1). Common bile duct abnormalities, including dilation and stenosis, were also noted.

Follow-up

Patients were followed clinically with regular office visits by a single surgical endoscopist, Dr. Gary Vitale. Body mass index and daily narcotic utilization was noted at each follow-up visit. Patients with recurrent abdominal pain and concern for a pancreatic ductal or ampullary abnormality were taken for endoscopic retrograde cholangiopancreatography (ERCP) with or without stent placement or, in the setting of worsening symptoms despite endoscopic interventions, for parenchymal resection. For patients with intractable abdominal pain and no evidence of pancreatic anatomic abnormality, bilateral thoracoscopic splanchnicectomy was performed at the surgeon's discretion.

Data analysis

Patients were grouped according to the number of EUS criteria met for a diagnosis of chronic pancreatitis (1–3, 4–5, 6+). Patients in each group were then compared along demographic variables, including age and gender, as well as outcome variables. Outcome variables included number of hospital admissions since initial evaluation for chronic pancreatitis, change in body mass index (BMI), number of ERCPs, and daily narcotic usage in milligrams (mg) of morphine equivalents from the time of their first EUS evaluation to the date of last follow-up. Operative complications, as well as the number of pancreatic duct stents placed over that time, whether patients underwent operative intervention (pancreatic drainage, pancreatic resection, or bypass procedure (e.g. gastrojejunostomy, choledochojejunostomy, hepaticojejunostomy)) for symptom relief, and whether patients underwent splanchnicectomy were followed as well. Univariate analysis was performed using ANOVA with Tukey's Honest Difference Test (HSD). Multivariate logistic regression analysis was then performed to assess the association between diagnostic EUS criteria and outcome variables significant on univariate analysis when accounting for patient demographic and anatomic differences. Statistical significance was defined as a p-value <0.05. Statistics were calculated using JMP software (JMP, SAS institute, Inc., Cary, NC).

Table 1 Endoscopic ultrasound criteria for chronic pancreatitis

Ductal criteria	**Parenchymal criteria**
Duct irregularity	Bright central foci
Bright duct walls	Calcification with acoustic shadowing
Visible side branches	Stranding (including honeycombing)
Prominence (>3 mm diameter in head, 2 mm in body, 1 mm in tail)	Lobularity Cyst
Number of criteria met	**Interpretation**
0–3 Criteria	Normal pancreatic EUS
4–5 Criteria	Suggestive of CP
6–9 Criteria	Confirms EUS diagnosis of CP

Results

Of a total of 243 patients included in the analysis, 24 had 1–3 EUS criteria, 129 had 4–5, and 90 had 6 or more. In general, EUS findings correlated reasonably well with Imaging modalities tended to correlate well regarding diagnosis of CP. Median time from EUS to last follow up was 33 months (range 1–269 months). Groups did not differ significantly with respect to average age (Table 2). There was a significantly greater proportion of males for patients meeting ≥6 EUS criteria. With respect to specific findings on EUS, patients with a greater number of sonographic criteria for chronic pancreatitis were more likely to have parenchymal calcifications and a pancreatic duct abnormality (Table 2).

Regarding outcomes, there were no significant differences in total number of hospital admissions, daily narcotic use in mg morphine equivalents at last follow-up, or change in BMI among the groups (Table 3). Similarly, patients in the three groups underwent approximately the same average number of ERCPs over the documented course of their disease. They also had similar

Table 2 Demographic and endoscopic ultrasound findings comparison among groups

	Endoscopic ultrasound diagnostic criteria for chronic pancreatitis			**p-value**
	1–3 (n = 24)	**4–5 (n = 129)**	**≥6 (n = 90)**	
Age (years)	52.6	54.5	56.9	0.33
Male Gender	10 (41.7%)	53 (41.1%)	54 (60%)	**0.02**
Calcifications	4 (16.7%)	13 (10.1%)	26 (28.9%)	**0.001**
Pancreatic Duct Abnormality	8 (33.3%)	100 (78.5%)	87 (96.7%)	**<0.001**
Common Bile Duct Abnormality	5 (20.8%)	25 (19.4%)	27 (30%)	0.18

*Continuous variables expressed as median, range. Categorical variables expressed as n, %.
The bold typeface was used to highlight significant p-values (p < 0.05).

Table 3 Association between number of endoscopic ultrasound diagnostic criteria for chronic pancreatitis and outcome variables

	Endoscopic ultrasound diagnostic criteria for chronic pancreatitis			p-value
	1–3 (n = 24)	4–5 (n = 129)	≥6 (n = 90)	
Number of Hospitalizations since Diagnosis	0 (0–10)	0 (0–32)	1 (0–16)	0.37
Daily Narcotic Use (mg morphine equivalents)	42 (20–90)	23 (10–360)	105 (30–180)	0.90
Change in BMI	0.05 (–2.90–1.76)	–0.04 (–6.60–6.20)	0.50 (–11.30–5.40)	0.21
Operative Intervention	1 (4.2%)	7 (5.4%)	13 (14.4%)	**0.049**
Thoracoscopic Splanchicectomy	0 (0%)	8 (6.2%)	4 (4.4%)	0.44
# ERCP since Diagnosis	0 (0–7)	0 (0–23)	1 (0–11)	0.37
PD Stent Placement	7 (29.2%)	31 (24.0%)	32 (35.6%)	0.18
PD Stent Number	0 (0–6)	0 (0–17)	1 (0–8)	0.25

*Continuous variables expressed as median, range. Categorical variables expressed as n, %.
The bold typeface was used to highlight significant p-values ($p < 0.05$).

rates of pancreatic duct stent placement and average number of pancreatic duct stents placed over the course of their disease.

Rates of splanchnicectomy did not differ significantly among the three groups. However, a larger percentage of patients with a greater number of endoscopic criteria for chronic pancreatitis required operative intervention for symptom control at some point during the course of their disease (Table 3). Operative details are listed in Table 4. At a median time from operative intervention to last follow-up of 42 months (range 1–269 months), approximately 48% of patients undergoing operative intervention experienced symptom relief and had no further episodes of pancreatitis in the time between their procedure and last recorded follow-up. On multivariate analysis, greater number of EUS criteria for chronic pancreatitis was associated with an increased rate of operative intervention (OR = 2.80, 95% confidence interval (CI) = 1.10–7.13, p = 0.03).

Discussion

The results of this study demonstrate that diagnostic findings on endoscopic ultrasound in patients with chronic pancreatitis may predict therapeutic requirements during the course of the disease. Specifically, more severe disease as assessed by EUS criteria is associated with a greater likelihood of requiring operative intervention for symptom relief. EUS criteria do not, however, predict elements such as narcotic requirements and number and frequency of endoscopic interventions.

As mentioned previously, the natural history of chronic pancreatitis varies not only with etiology, but also from patient to patient.[11] While some may develop steadily worsening abdominal pain over several years, others experience acute attacks with interspersed periods of symptom remission. Regardless of symptomatology, however, the cumulative damage to the pancreatic parenchyma and ductal system, as well as surrounding neural tissue, leads to exocrine and endocrine insufficiency and chronic pain.

In addition to patient history, imaging, and serologic evaluation, EUS represents a widely utilized and effective tool for diagnosis of chronic pancreatitis. Our findings indicate that patients with a greater number of endoscopic criteria at the time of initial EUS are more likely to have an unfavorable disease course as evidenced by requirement of surgical intervention for

Table 4 Operative interventions for chronic pancreatitis and patient outcomes

	1–3 Criteria (n = 1)	4–5 Criteria (n = 7)	6 + Criteria (n = 13)	Total (n = 21)
Subtotal Pancreatectomy	0 (0%)	4 (57%)	4 (31%)	8 (38%)
Pancreaticoduodenectomy	0 (0%)	1 (14%)	2 (15%)	3 (14%)
Distal Pancreatectomy	0 (0%)	0 (0%)	2 (15%)	2 (10%)
Pancreaticojejunostomy	0 (0%)	2 (28%)	2 (15%)	4 (20%)
Bypass Procedure				
Gastrojejunostomy	0 (0%)	0 (0%)	1 (8%)	1 (5%)
Hepaticojejunostomy	0 (0%)	0 (0%)	2 (15%)	2 (10%)
Choledochojejunostomy	1 (100%)	0 (0%)	0 (0%)	1 (5%)
Outcomes				
Symptom Improvement	0 (0%)	3 (43%)	7 (54%)	10 (48%)
Pancreatitis since Procedure	1 (100%)	4 (57%)	6 (46%)	11 (52%)

*Continuous variables expressed as median, range. Categorical variables expressed as n, %.

management and relief of symptoms resulting from their disease process.

Regardless of severity of chronic pancreatitis upon diagnosis, the algorithm for management of CP focuses on symptom relief and usually begins with endoscopic intervention. ERCP with stenting of the pancreatic duct increases drainage of the gland, which, for early stage disease, effectively decreases abdominal pain.[12–15] For more advanced disease, robust data for the immediate and long-term role of endoscopic stenting is lacking.[12,16] The subset of patients in whom endoscopic interventions provide adequate pain relief over the course of their disease remains unclear, though our findings suggest it may be limited to those patients meeting fewer EUS criteria for chronic pancreatitis.

Surgical management of chronic pancreatitis, meanwhile, generally involves drainage of the pancreatic duct with or without removal of diseased parenchyma or a bypass procedure for symptom relief. Multiple studies have demonstrated that surgery (specifically pancreatic drainage and/or resection) represents a safe, effective, and durable intervention in patients with chronic pancreatitis that provides better long-term symptom relief than endoscopic interventions.[12,13,17–19] This is reflected by our data, which demonstrates a nearly 50% long-term symptom relief rate even among patients who have failed endoscopic management. However, despite its safety, the risks of a surgical procedure exceed that of endoscopic interventions. Thus, the question becomes "when is the ideal time for surgery?"

Recent data suggest that earlier surgical intervention, specifically with respect to resection may be important to consider. A Cochrane systemic review evaluating endoscopic versus surgical interventions for chronic pancreatitics with pancreatic ductal dilatation revealed that surgery effectively relieved pain and preserved pancreatic function when utilized in the setting of early stage disease.[17] These findings are supported by a single-institution study demonstrating that early surgery (within 26.5 months of diagnosis) was associated with high rates of complete relief of abdominal pain and decreased of opioid analgesics among chronic pancreatitics.[20] Indeed, one of the major problems with a "step up" approach – namely, narcotic analgesics followed by endoscopic therapy followed by surgery as salvage therapy – is a failure to address the chronic inflammatory process with either narcotics or endoscopy.[12] Patients additionally develop opioid dependence, which often persists despite addressing the underlying cause of their pain with a surgical procedure. Furthermore, they would have a lesser volume of functional exocrine and endocrine pancreatic tissue at the time of surgery and thus are at greater risk for post-operative pancreatic exocrine and/or endocrine insufficiency. Particularly in patients with severe disease at time of diagnosis who would be more likely to ultimately require surgical intervention, early operative parenchymal resection and/or duct decompression may enable them to avoid the above complications. This may, as a result, afford them improved quality of life not only by decreasing abdominal pain but also by decreasing complications associated with pancreatic endo/exocrine insufficiency. Hopefully, the results of the early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE) trial, conducted by the Dutch Pancreatitis Study Group, will help provide insight into the optimal management of these patients.[21]

This study's results should be viewed in light of several limitations. The retrospective nature of this study prevented systematically assessing subjective pain scores, presence of associated symptoms (e.g. nausea), and changes in quality of life throughout the course of each patient's disease. Additionally, some patients included in this dataset were initially diagnosed with chronic pancreatitis and had their disease managed by a gastroenterologist for a period of time before being referred to our practice for endoscopic intervention. While the date of the initial EUS evaluation was accurately captured, the treatment algorithm may have been different had those patients been managed within our practice from the time of initial diagnosis. Regarding hospital admissions, the data used for analysis does not account for the possibility that patients may have presented to and received treatment for abdominal pain at hospitals outside the University of Louisville/Norton Healthcare network. However, in our experience, most patients undergoing treatment for chronic pancreatitis within this network present to in-network hospitals when they develop worsening abdominal pain.

Conclusion

The number of EUS-based ultrasonographic criteria for diagnosis of chronic pancreatitis may help identify patients with potentially more severe disease and predict patients who will eventually require operative intervention. The care of patients meeting multiple diagnostic criteria, namely those having 6 or more, should be undertaken in close collaboration with a pancreatobiliary surgeon to allow for optimal timing of operative intervention.

Conflict of interest

The authors have nothing to disclose.

References

1. Cameron JL, Cameron AM. (2014) *Current surgical therapy*, 11th ed. xxxviii, 1493.
2. Trikudanathan G, Munigala S, Barlass U, Malli A, Han Y, Sekulic M *et al*. (2017) Evaluation of Rosemont criteria for non-calcific chronic pancreatitis (NCCP) based on histopathology - a retrospective study. *Pancreatol Off J Int Assoc Pancreatol (IAP)* 17:63–69. [et al].
3. Irisawa A, Katakura K, Ohira H, Sato A, Bhutani MS, Hernandez LV *et al*. (2007) Usefulness of endoscopic ultrasound to diagnose the severity of chronic pancreatitis. *J Gastroenterol* 42(Suppl 17):90–94.
4. Raimondo M, Wallace MB. (2004) Diagnosis of early chronic pancreatitis by endoscopic ultrasound. Are we there yet? *JOP J Pancreas* 5:1–7.
5. Stevens T. (2013) Role of endoscopic ultrasonography in the diagnosis of acute and chronic pancreatitis. *Gastrointest Endosc Clin N Am* 23: 735–747.

6. Seicean A. (2010) Endoscopic ultrasound in chronic pancreatitis: where are we now? *World J Gastroenterol* 16:4253–4263.
7. Chong AK, Hawes RH, Hoffman BJ, Adams DB, Lewin DN, Romagnuolo J. (2007) Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointest Endosc* 65:808–814.
8. Albashir S, Bronner MP, Parsi MA, Walsh RM, Stevens T. (2010) Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. *Am J Gastroenterol* 105:2498–2503.
9. Badea R, Diaconu B. (2005) Contribution of ultrasound to the diagnosis of chronic pancreatitis and to evaluating its main complications. *Rom J Gastroenterol* 14:183–189.
10. Sahai AV. (2002) EUS and chronic pancreatitis. *Gastrointest Endosc* 56: S76–S81.
11. Majumder S, Chari ST. (2016) Chronic pancreatitis. *Lancet (London, England)* 387:1957–1966.
12. Windsor JA, Reddy ND. (2017) Endoscopic vs. Surgical interventions for painful chronic pancreatitis: what is needed for future clinical trials. *Clin Transl Gastroenterol* 8:e213.
13. Dite P, Ruzicka M, Zboril V, Novotny I. (2003) A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy* 35:553–558.
14. Bartoli E, Delcenserie R, Yzet T, Brazier F, Geslin G, Regimbeau JM *et al*. (2005) Endoscopic treatment of chronic pancreatitis. *Gastroenterol Clin Biol* 29:515–521.
15. Topazian M, Aslanian H, Andersen D. (2005) Outcome following endoscopic stenting of pancreatic duct strictures in chronic pancreatitis. *J Clin Gastroenterol* 39:908–911.
16. Weber A, Schneider J, Neu B, Meining A, Born P, von Delius S *et al*. (2013) Endoscopic stent therapy in patients with chronic pancreatitis: a 5-year follow-up study. *World J Gastroenterol* 19:715–720.
17. Ahmed Ali U, Pahlplatz JM, Nealon WH, van Goor H, Gooszen HG, Boermeester MA. (2015) Endoscopic or surgical intervention for painful obstructive chronic pancreatitis. *Cochrane database Syst Rev*, Cd007884.
18. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR *et al*. (2007) Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N. Engl J Med* 356:676–684.
19. Jawad ZA, Kyriakides C, Pai M, Wadsworth C, Westaby D, Vlavianos P *et al*. (2017) Surgery remains the best option for the management of pain in patients with chronic pancreatitis: a systematic review and meta-analysis. *Asian J Surg* 40(3):179–185.
20. Yang CJ, Bliss LA, Freedman SD, Sheth S, Vollmer CM, Ng SC *et al*. (2015) Surgery for chronic pancreatitis: the role of early surgery in pain management. *Pancreas* 44:819–823.
21. Ahmed Ali U, Issa Y, Bruno MJ, van Goor H, van Santvoort H, Busch OR *et al*. (2013) Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial. *BMC Gastroenterol* 13:49.