2015

Asian EUS Group (AEG) Study on EUS Diagnosis of Chronic Pancreatitis (Phase II)

Training and further evaluation of the use of 6 selected diagnostic EUS features of chronic pancreatitis at individual study centres in Asia

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Background

In a recent study by the Asian EUS Group (AEG) where 30 endosonographers from across Asia rated 17 EUS imaging videos of the pancreas for 11 internationally used diagnostic EUS features of chronic pancreatitis, it was found that the overall inter-observer agreement on presence/absence of 11 commonly used diagnostic EUS features of chronic pancreatitis in the images presented is below expectation (mean agreement coefficient = 0.54 (range, 0.14 – 0.90). However, of the 11 EUS features included in the study, they were several diagnostic EUS features that were more consistently recognized by the participating endosonographers (Table I).

Table I Agreement on Present/Absent of Individual EUS Features

	Agreement Coefficient	S. E.	95% C.I.	p-Value
Feature 1	0.644	0.076	0.483 to 0.804	2.510E-07
Feature 2	0.228	0.074	0.072 to 0.385	6.892E-03
Feature 3	0.444	0.127	0.176 to 0.713	2.919E-03
Feature 4	0.340	0.090	0.150 to 0.530	1.596E-03
Feature 5	0.597	0.125	0.331 to 0.863	2.109E-04
Feature 6	0.904	0.041	0.816 to 0.991	2.438E-13
Feature 7	0.631	0.093	0.434 to 0.828	4.365E-06
Feature 8	0.595	0.083	0.418 to 0.772	2.382E-06
Feature 9	0.135	0.071	-0.014 to 0.285	7.357E-02
Feature 10	0.714	0.072	0.561 to 0.866	3.192E-08
Feature 11	0.816	0.047	0.716 to 0.915	7.7958E-12

After much consideration, we decided to choose the top 6 EUS features (mean chance-corrected inter-observer agreement coefficient = 0.73 (range, 0.6 – 0.9) to form a preliminary set of diagnostic criteria for use in training and further validation in live cases at participating centres across Asia.

Objective of this Study

The present study aims to train EUS endosonograpers at participating centres across Asia in the use and further evaluation of a preliminary set of criteria comprising 6 selected diagnostic EUS features of chronic pancreatitis as listed in Table II below in real-live cases.

Table II Selected diagnostic EUS features

1. Hyper-echoic foci with shadowing
2. Lobularity with honeycombing
3. Cysts
4. Dilated ducts
5. Dilated side branches
6. Calculi in main pancreatic duct

Table III List of Research Questions

1. In Asians, can we reliably differentiate normal pancreas from that of chronic pancreatitis based on the 6 selected diagnostic features of chronic pancreatitis?
2. What are the specificity, sensitivity and accuracy of the preliminary set of criteria, compared to existing non-EUS standard of diagnosis – CT/MRI/ERCP and histopathologic diagnoses?

The immediate aim of conducting Phase II of study is to evaluate the use of the preliminary set of criteria comprising 6 selected diagnostic EUS features in the diagnosis of chronic pancreatitis in Asians. It will seek to find out answers to the questions listed in Table III. The ultimate aim of this whole study is to develop a set of highly reliable EUS diagnostic criteria more suitable than currently used international criteria for diagnosis of chronic pancreatitis in Asian populations.

Study Procedure

Study Materials and Participants

The training and evaluation exercise will be conducted at all participating study centres across Asia. Firstly, based on Phase I results, 8 EUS videos (6 of chronic pancreatitis and 2 of normal pancreas) used in Phase I will be selected for use as training videos in Phase II of study. Each video of chronic pancreatitis cases selected will have at least 2 of the top 6 diagnostic EUS features identified in Phase I of study. Each local centre trainer (leader) will nominate 2-3 experienced endosonographers and submit the list of nominees to the AEG Secretariat.

Local Training

The area leaders will go through the 8 selected videos with their respective nominees. They will be to independently identify the presence of any of the 6 diagnostic features on their own. Following that, the same 8 videos (with diagnostic features identified and labeled) will be presented to the nominees. Each nominee must show sufficient competency in recognizing all the 6 diagnostic EUS features presented before they can participate in the AEG study.

Real-live Cases

Together with the local leader, participating endosonographers will then identify the same features in at least 10 real-live cases of normal pancreas and 5 real-live cases of chronic pancreatitis (see reference diagnosis of definitive chronic pancreatitis in next section). Centres are encouraged to study more cases if circumstances at their centre permit. They will evaluate if and how often each of the 6 diagnostic EUS features is being found in cases of chronic pancreatitis. They will also evaluate if and how often each of the 6 diagnostic EUS features is being found in cases of normal pancreas, as well as if and how often chronic pancreatitis cases do not display one or more of the 6 diagnostic EUS features. All diagnostic EUS evaluations will be entered onto the provided AEG Excel Study Template for compilation. All procedures will be recorded on

DVDs for further post-procedure assessments. A de-identified set of all the EUS videos collected will be compiled by AEG for further assessment and validation by an independent committee, comprising experts in EUS.

Inclusion & Exclusion Criteria for Real-Live Cases

Chronic Pancreatitis Cases

To be included as chronic pancreatitis cases for this study, subject must have had a definitive diagnosis of chronic pancreatitis, satisfying criteria (i) or (ii) listed below:

(i) Definitive imaging findings characteristic of chronic pancreatitis on CT/MRCP (see Table IV) or ERCP (see Table V).

(ii) Definitive histological findings characteristic of chronic pancreatitis (see Table VI)

Table IV Characteristic CT/MRI findings in chronic pancreatitis

	Mild (II)	Moderate (III)	Marked (IV)
CT/MRI scan	≥2 of the following: enlarged main duct (2–4 mm), gland enlargement, heterogenous parenchyma, small cavities (<10 mm), irregular ducts, focal AP, increased echogenicity of main duct wall, irregular head/body contour	Cannot distinguish from mild	Moderate changes plus ≥1 of the following: large cavities (>10 mm), gland enlargement, intraductal filling defects/calculi, duct obstruction, stricture or gross irregularity

Adapted from the practice guidelines of the American Pancreatic Association

Table V Characteristic ERCP findings in chronic pancreatitis

a) Stones in pancreatic ducts

b) Multiple or numerous calcifications distributed in the entire pancreas

c) Irregular dilatation of the MPD and irregular dilatation of pancreatic duct branches of variable intensity with scattered distribution throughout the entire pancreas on the ERCP

d) Irregular dilatation of the MPD and branches proximal to complete or incomplete obstruction of the MPD (with pancreatic stones or protein plugs) on the ERCP

Adapted from the JPS revised clinical diagnostic criteria for chronic pancreatitis

Table VI Definitive Histological Findings

Loss of exocrine parenchyma with irregular fibrosis. The fibrosis is distributed chiefly in the interlobular spaces showing nodular pattern of lobules called ''cirrhosis''

Adapted from the JPS revised clinical diagnostic criteria for chronic pancreatitis

Normal Pancreas Controls

Subjects diagnosed with having normal pancreas will be used as controls. These subjects should not have been diagnosed with any hepatobiliary diseases including pancreatitis. They also should not have diabetes mellitus, a history of heavy alcohol use, family history of pancreatic disease, history of gallstone & renal stone disease.

Table VII Checklist for inclusion/exclusion of prospective subjects

	Chronic Pancreatitis	
	Include	Exclude
Definite Diagnosis of chronic pancreatitis based on CT/MRCP (see Table IV)	✓	
Definite Diagnosis of chronic pancreatitis based on ERCP (see Table V)	✓	
Definitive histological findings characteristic of chronic pancreatitis (see Table VI)	✓	

	Normal Pancreas	
	Include	Exclude
Negative for chronic pancreatitis in imaging/histology findings	✓	
(i) any hepatobiliary & pancreatic diseases (ii) diabetes mellitus (iii) history of heavy alcohol use, (iv) family history of pancreatic disease (v) history of gallstone & renal stone disease		✓

To facilitate recruitment of the appropriate subjects, participating centres are encouraged to use the following checklist for inclusion/exclusion of prospective subjects (see Table VII).

Outcome Measures

The study outcome measures include the sensitivity, specificity and accuracy of the use of the preliminary set of 6 diagnostic EUS criteria for diagnosis of chronic pancreatitis in Asian population(s). Both positive predictive value and negative predictive value will also be computed. These outcome indices will be calculated with respect to reference diagnosis made by established non-EUS diagnostic methods, as listed above.

Data Handling and Statistics

The AEG Secretariat will collect and compile the study data from each study centre. The compiled data will be analyzed for relevance of the 6 diagnostic EUS features for use as criteria for diagnosis of chronic pancreatitis in Asians. Results will be validated against reference diagnoses based on two currently used non-EUS diagnostic methods – CT/MRI/ERCP and histopathologic diagnoses. We will determine the sensitivity, specificity of using the 6 diagnostic EUS criteria for diagnosis of chronic pancreatitis, as well as the accuracy or how well the criteria of 6 diagnostic EUS features correctly identifies or rules out chronic pancreatitis. The accuracy level of the criteria of 6 diagnostic EUS features correctly identifying or ruling out chronic pancreatitis will also be computed. Both positive predictive value and negative predictive value will also be computed.

Sample Size

For this pilot evaluation exercise, we have not set a sample size, but will try to gather as many participants as we can at various participating study centres across Asia to study at least a total of 100 live cases of normal pancreas and 50 live cases of chronic pancreatitis (expected more if some centres can study more cases than the minimum number required from each centre). Further

expansion of sample size will be recommended as deemed fit from results obtain from an interim data analysis expected midway through study.

Ethical Considerations

Training & Test Videos

The training of participating EUS operators will only use archived video imaging of past EUS procedures. There is no direct contact with human subjects. To protect the identity and privacy of the patients from whom the videos were originally derived, all EUS imaging videos used in the study will be de-identified, with all names, NRIC number, and other identifier of patients that may be on the videos removed.

Real-live Cases

For the evaluation/validation of the selected EUS diagnostic features in real-live cases, each participating centre will be responsible for obtaining approval from the respective Institutional Review Boards governing each participating centre before conducting the study. The study should only proceed after ethical approval or exemption of the same is given. Prospective subjects should only be enrolled into the studies after they have each given informed consent to participate. At no point in time should patient identifier be collected. All video recordings of the EUS procedures and data collected must be de-identified.

Registration of study

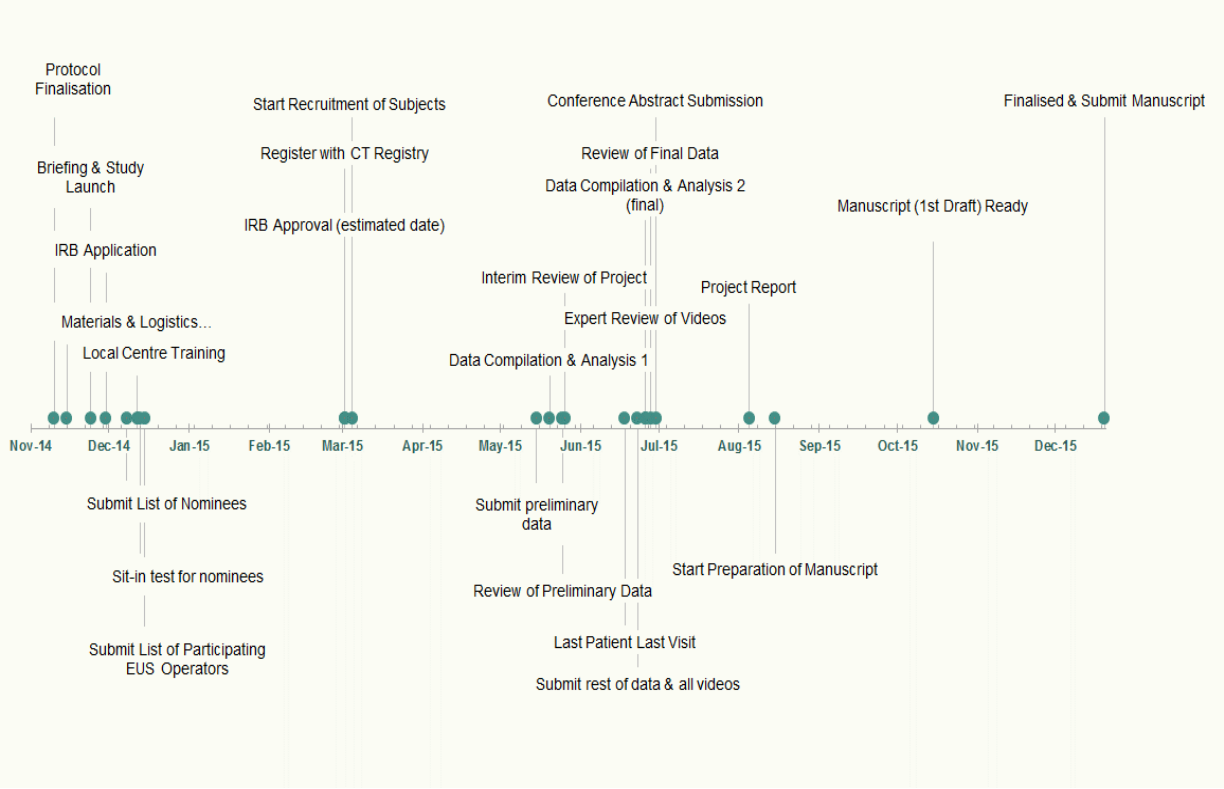
Additionally, before commencement of recruitment of patients, the AEG Secretariat will have to register the study with an approved international clinical trial registry. For this, each centre leader must provide the secretariat the names, affiliations, contact telephones and email addresses of all participating endosonographers.

Study Milestones and Timeline

The proposed timeframe for the study will be from 1 December 2014 to 1 December 2015 (see Figure 1).

Data collected from all participating centres, together with the video recordings of the real-live cases, will be sent back to the AEG Secretariat for compilation. A de-identified set of all the EUS videos collected will be compiled by AEG for further assessment and validation by an independent committee, comprising experts in EUS.

Figure 1 Proposed Study Timeline



Publication of study results

The results of this study will be summarized in an abstract for consideration of presentation at the international conferences such as the United European Gastroenterology Week (UEGW) or Digestive Disease Week (DDW, USA). Following that, we will prepare a manuscript for publication in a peer-review

journal. The sequence of authorship in the manuscript will be based on the numbers of real-cases contributed by the respective centre.

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