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REVIEW

Endoscopic Ultrasound and Pancreas Divisum

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Summary

Pancreas divisum is the most common congenital anatomic variation of the pancreatic ductal anatomy and in most of the individuals it is asymptomatic. However, in minority of individuals it is presumed to cause recurrent acute pancreatitis and chronic pancreatitis. Endoscopic retrograde cholangiopancreatography is the gold standard for its diagnosis, but is invasive and associated with significant adverse effects. Endoscopic ultrasound (EUS) allows the detailed evaluation of the pancreaticobiliary ductal system without injecting contrast in these ducts. Moreover, it provides detailed images of the parenchyma also. Therefore EUS, both radial and linear, has potential for being a minimally invasive diagnostic modality for pancreas divisum. A number of EUS criteria have been suggested for the diagnosis of pancreas divisum. These criteria have varying sensitivity and specificity and hence there is a need for objective and uniform criteria that have the best diagnostic accuracy. Secretin EUS has a potential for diagnosing minor papilla stenosis and thus help in planning appropriate therapy. EUS guided pancreatic duct interventions can help in draining dorsal duct in symptomatic patients with failed minor papilla cannulation. But these techniques are technically demanding and associated with potential severe complications.

Introduction

Pancreas divisum, the most common congenital anatomic variation of the pancreatic ductal anatomy, occurs in approximately 10% of the population [1, 2]. The normal pancreas develops from the fusion of dorsal and ventral pancreatic buds during the fetal development. In up to 90% of individuals the ducts of both the dorsal and ventral buds fuse along with the parenchymal fusion resulting in the main pancreatic duct draining whole of the pancreas via the major papilla. In pancreas divisum this ductal fusion does not occur and the dorsal duct drains majority of the pancreas via the minor papilla and the ventral duct drains only a small proportion of the pancreas (inferior portion of the head) via the major papilla [2].

Most of the individuals with pancreas divisum remain asymptomatic. It has been estimated that less than 5% individuals will develop symptoms attributable to the altered ductal anatomy [3]. The most likely mechanism for this is the presence of small and stenotic minor papilla orifice in some individuals. This leads onto high dorsal ductal pressure during active secretion resulting in inadequate drainage and ductal distension. This presumably causes acute recurrent pancreatitis, chronic pancreatitis and pancreatic type abdominal pain without biochemical or radiological evidence of pancreatitis [1, 2, 3].

Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard for diagnosis of pancreas divisum. The pancreatogram is obtained after cannulating both the major and minor papilla in order to delineate ventral as well as dorsal ducts, respectively [1, 2, 3]. But ERCP is seldom used for its diagnosis as minor papilla cannulation is difficult and ERCP is associated with a significant risk of pancreatitis. Magnetic resonance cholangiopancreatography (MRCP), non-invasively, evaluates the pancreaticobiliary ductal system and has good sensitivity and specificity for the diagnosis of pancreas divisum [4]. Secretin enhancement further improves the diagnostic accuracy of MRCP [5]. Endoscopic ultrasound (EUS), allows the detailed evaluation of the pancreaticobiliary ductal system without injecting contrast into these ducts. Moreover, by providing detailed imaging of the pancreatic parenchyma it can help in diagnosing early chronic pancreatitis as well as detect small pancreatic tumors. This review focuses on the current as well as potential role of EUS in diagnosing and treating patients with pancreas divisum.

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Abbreviations S-EUS: stimulated endoscopic ultrasound

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EUS and Diagnosis of Pancreas Divisum

The published data on the accuracy of detection of pancreas divisum by endoscopic ultrasound is scanty. Several EUS criteria for the diagnosis of pancreas divisum, both on radial as well as linear endosonography, have been proposed. However, very few studies have evaluated the accuracy of these criteria.

Radial Endosonography

On radial endosonography, absence of the "stack sign" has been suggested as a useful criterion for diagnosing pancreas divisum (Figure 1) [6]. To obtain the stack sign, the echo endoscope is positioned in the duodenal bulb in the long position and the balloon is inflated after positioning the tip of the endoscope in the apex of the bulb. From this position, the distal common bile duct, ventral pancreatic duct and the portal vein can be seen to run in parallel being stacked together. The bile duct will be closest to the transducer.

Bhutani *et al.* [6] evaluated 6 patients with pancreas divisum and attempted to obtain a stack sign in them. The results were compared with the EUS findings in 30 patients without pancreas divisum. A stack sign was obtained in 2/6 (33.3%) patients with pancreas divisum and this was significantly lower than the frequency of it in patients without pancreas divisum (83.3%; P=0.04). The presence of a markedly dilated ventral duct in one patient, and an unusually large ventral pancreas in the other, led onto a false positive stack sign. The authors concluded that the absence of stack sign during EUS may suggest the diagnosis of pancreas divisum.

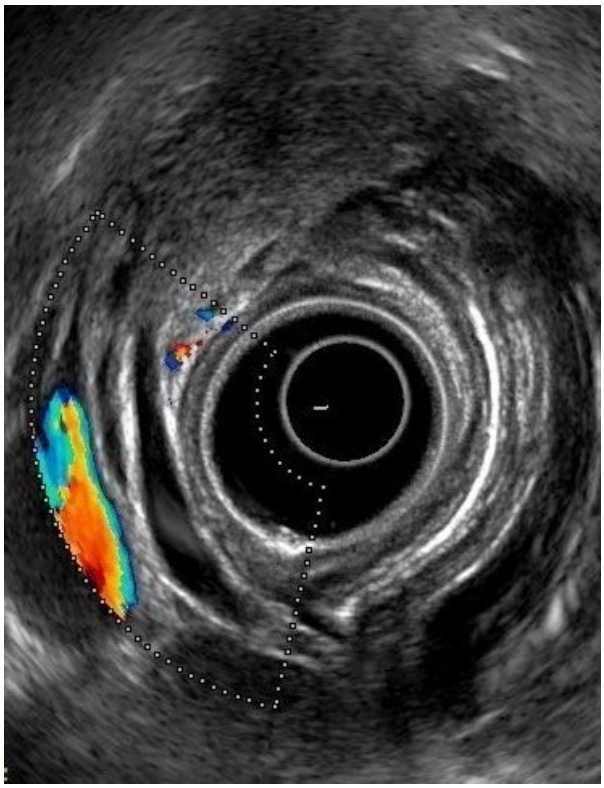

Figure 1. Radial EUS: stack sign showing common bile duct, pancreatic duct and portal vein.

Tandon *et al.* [7] felt that absence of stack sign may not be specific for diagnosis of pancreas divisum and therefore they evaluated more exhaustive criteria for its diagnosis. They diagnosed pancreas divisum when on EUS they could find the bile duct and pancreatic duct entering the second part of duodenum in separate locations with pancreatic duct traversing to the duodenal wall proximal and anterior to the bile duct. Pancreas divisum was not diagnosed when the pancreatic duct converged with the bile duct at the duodenal wall, crossed from ventral to dorsal pancreas, or could not be identified. Using these criteria, the authors correctly identified two of the three cases of pancreas divisum prospectively and there were no false positive diagnosis. The authors felt that these criteria may not be highly sensitive but are more specific than the mere absence of a "stack sign".

Vaughan *et al.* [8] retrospectively evaluated the accuracy of EUS in the diagnosis of pancreas divisum in a busy clinical setting. In this study, published in an abstract form, the authors calculated the sensitivity and specificity of blinded EUS compared to ERCP in consecutive patients with and without pancreas divisum (77 patients each). The criteria used for diagnosis of pancreas divisum were not mentioned in the abstract but majority (73%) of the patients underwent radial endosonography. The sensitivity of EUS for the detection of pancreas divisum was 50.6% (95% confidence interval (CI): 39.0% to 62.2%) and the specificity was 94.8% (95% CI: 87.2-98.6%). The authors concluded that, in routine practice, the sensitivity of EUS in the diagnosis of pancreas divisum appears to be poor, but has high specificity.

Tessier and Sahai [9] prospectively evaluated multiple EUS criteria for the diagnosis of pancreas divisum in 24 patients who underwent both EUS and ERCP. The presence or absence of the following criteria were studied: 1) diminutive or absent ventral pancreatic duct; 2) ''crossed duct sign'' (bulb view showing Santorini duct crossing the common bile duct; 3)''V sign'' (second part of duodenum view of Santorini duct and ventral/dorsal demarcation of the head of pancreas making a ''V''); 4) dominant Santorini duct (Santorini duct diameter more than the ventral pancreatic duct diameter); 5) ''VD transition'' (ability to follow main pancreatic duct from main papilla from ventral to dorsal pancreas and/or well around the genu); 6) ''trace back'' (bulb view following pancreatic duct from the main papilla back around genu). The pancreas divisum was diagnosed on ERCP in 8/24 patients. EUS diagnosed it in all 8 patients but had also 3 false positive diagnoses. EUS had a sensitivity of 100%, specificity of 81.3%, positive predictive value of 72.7% and negative predictive value of 100% for the diagnosis of pancreas divisum. The frequency of chronic pancreatitis was more frequent when EUS was incorrect in the diagnosis of pancreas divisum (100% *vs*. 33.3%; P=0.05). They concluded that EUS reliably excludes pancreas divisum and architectural distortion due to chronic pancreatitis may lead onto false positive diagnosis.

These studies suggest that radial EUS may be a useful modality for the diagnosis of pancreas divisum but further studies are required to determine which specific EUS criteria are most reliable.

Linear Endosonography

As gastroenterologists are more trained for cross sectional imaging, they find radial anatomy easier to understand than the linear anatomy. But, pancreas divisum can be diagnosed with high sensitivity and specificity with linear EUS also. Lai *et al*. [10] evaluated linear endosonography for diagnosing pancreas divisum in 162 patients who underwent ERCP also. They reported that in normal individuals, the pancreatic duct can be easily followed form the major papilla to the mid body of the pancreas using a linear array echo endoscope. Also, a discrete endo-sonographic border between the hypoechoic ventral anlage and a brighter dorsal anlage can be seen in up to 75% of the patients, although this may be less apparent on a linear EUS [10, 11, 12]. The authors used these two features to diagnose or exclude pancreas divisum. Using a linear array echoendoscope in short scope position with inflated balloon, the major papilla was first identified sonographically and thereafter an attempt was made to follow the pancreatic duct from the major papilla to the pancreatic body by gently withdrawing the scope with a clockwise rotation. While doing this, the presence or absence of a distinct border between the dorsal and ventral pancreas was also observed. The diagnosis of pancreas divisum was excluded if the pancreatic duct could be followed continuously from the major papilla into the pancreatic body or crossed the endosonographic border between the ventral and dorsal pancreatic anlage. The lack of either of these findings was considered suggestive of pancreas divisum. Twenty two of 162 patients had pancreas divisum on ERCP. The pancreatic duct could not be adequately visualized by EUS in 35 patients because of poor duct visualization presumably due to small diameter, large obstructing pancreatic masses or cysts, shadowing calculi and duodenal obstruction and three of these patients had having pancreas divisum. These 35 patients were excluded and in the remaining 127 patients EUS correctly identified pancreas divisum in 18 patients with one false negative and three false positives. The overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy rates of EUS was 95%, 97%, 86%, 99% and 97%, respectively. MRCP was also performed in 43 patients and 5 of them had pancreas divisum. MRCP correctly identified 3 of these 5 patients with two false negative and four false positive diagnoses. The authors concluded that linear EUS is a promising test for the diagnosis of pancreas divisum. In our experience also, the diagnosis of pancreas divisum can be excluded if the pancreatic duct can be followed from the major papilla to the pancreatic body or crosses the endosonographic border between the ventral and dorsal pancreas (Figures 2 and 3).

Apart from diagnosing pancreas divisum, EUS has an added advantage of detecting small pancreatic tumors that separate the dorsal and ventral ducts by obstructing their junction causing pseudo divisum [10]. Using linear EUS, a fine needle aspiration of the pancreatic tumors can also be performed. EUS can also detect small common bile duct stones, microlithiasis, as well as early chronic pancreatitis, often missed by other imaging modalities and thus help in evaluating patients with idiopathic pancreatitis [13]. The potential limitations of EUS include inability to pass the echoendoscope because of duodenal obstruction and inability to visualize the pancreatic duct because of shadowing calcifications, its small diameter and obstructing upstream tumors and cysts. Also, false positive results may be obtained by EUS in chronic pancreatitis, obstructing pancreatic duct strictures in the head or ductal variations such as ansa pancreatica [10].

Which Patients with Pancreas Divisum Need Treatment: Can EUS Help?

The clinical conditions associated with pancreas divisum include acute recurrent pancreatitis, chronic

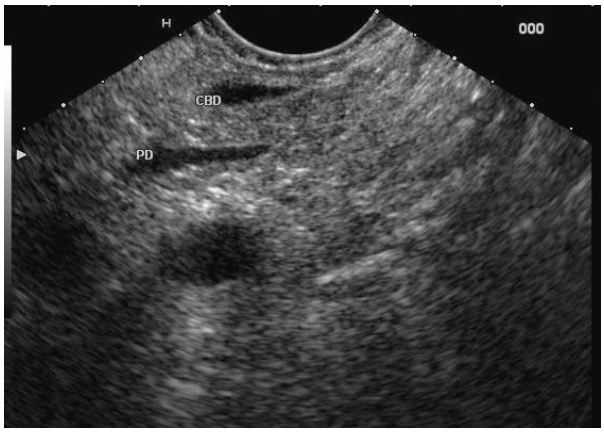

Figure 2. Linear EUS: pancreatic duct (PD) and common bile duct (CBD) identified at the papilla resembling the stack sign obtained in radial EUS.

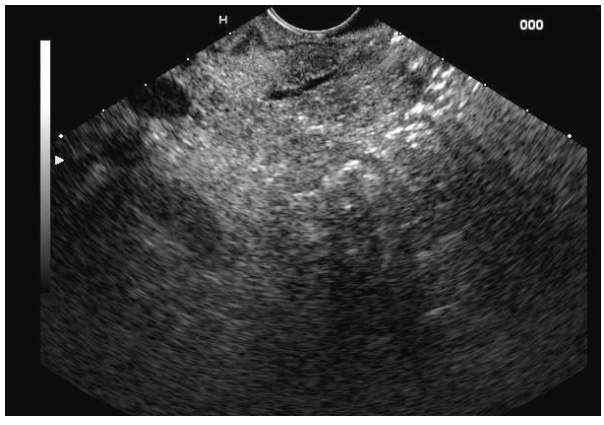

Figure 3. Linear EUS: pancreatic duct seen crossing the endosonographic border between hypoechoic ventral anlage and brighter dorsal anlage.

pancreatitis and pancreatic type abdominal pain [1, 2, 3]. Most of the studies evaluating the efficacy of endoscopic treatment in pancreas divisum have demonstrated best results in patients with recurrent pancreatitis. The lowest response rates have been obtained in patients with only abdominal pain [3, 14, 15, 16]. The mechanism responsible for pancreatic symptoms in patients with pancreas divisum is probably the stenosis at the minor papilla [1, 2, 3]. Despite relative obstruction, most patients with pancreas divisum do not develop dilation of the dorsal duct, possibly because of intermittent blockage of the pancreatic duct. Hence, it becomes difficult to identify the patients who would benefit from the endoscopic therapy. Various strategies to identify the best responders to therapy have been tested. These include treating patients with demonstrable acute recurrent pancreatitis only, or treating patients with minor papilla stenosis identified by investigations like secretin MRCP, minor papilla manometry or resistance to passage of a 3 Fr, 4 Fr or 5 Fr catheters across the minor papilla during ERCP [17].

EUS, by diagnosing chronic pancreatitis and determining the extent of ductal and parenchymal damage, may be of help in determining prognosis and planning appropriate therapy. EUS has also been evaluated for the detection of minor papilla stenosis in order to select the appropriate therapy. Catalano *et al*. [18] studied 61 symptomatic patients with pancreas divisum by secretin stimulated endoscopic ultrasound (S-EUS) prior to an ERCP. On S-EUS, an abnormal response was defined as sustained (more than 10 minutes) 1 mm, or more, dilation of the dorsal duct following intravenous secretin (1 U/kg). Of these 61 patients, 37 patients were subsequently treated by stenting or sphincterotomy based on clinical presentation, drainage, and/or ductal dilation at the time of ERCP. Twenty one of 37 patients responded to pancreatic therapy and S-EUS predicted response to therapy in 20 (95%). S-EUS also predicted the absence of response to therapy in 13 of 16 patients (81%) who did not respond to endoscopic therapy. In the subgroup analysis, S-EUS predicted response to therapy in 100%, 100% and 80% of patients with acute recurrent pancreatitis, chronic pancreatitis and symptomatic abdominal pain, respectively. The authors concluded that secretin EUS is a sensitive and specific test for the diagnosis of minor papilla stenosis and can help in planning appropriate therapy. These results are encouraging but further studies are needed to evaluate this method.

EUS-Guided Pancreatic Endotherapy for Pancreas Divisum

Since its inception, EUS has undergone a tremendous technological advancement and now it is not only a diagnostic technique but has also been shown to have immense therapeutic potentials. A large number of interventional procedures both in the routine clinical setting, as well as experimental setting, are being performed worldwide [19]. EUS guided transmural drainage of pancreatic fluid collections has been shown to be safe and effective and the same would be true of the pancreatic fluid collections occurring in the setting of pancreas divisum [20].

Recently, EUS guided interventions are also being used as a rescue or a guide to failed ERCP and transpapillary drainage especially in difficult situations like altered surgical anatomy, very tight pancreatic ductal strictures, complete pancreatic duct disruptions, and pancreas divisum with stenotic minor papilla [21, 22, 23, 24, 25, 26]. The fascinating field of pancreatic interventions by puncturing the pancreatic duct under EUS guidance started with initial reports of EUS guided pancreatography [27, 28]. Subsequently, an exciting innovation of EUS in treatment of pancreas divisum was described as case report [29]. In a patient with failed ERCP, because of inability to localize the minor papilla even after intravenous secretin as well as spraying of methylene blue over the duodenum, EUS guided methylene blue injection into the pancreatic duct led onto identification and subsequent cannulation of the minor papilla. Moving a step forward, there have been recent reports of EUS guided direct pancreatic duct interventions aimed at decompressing the obstructed pancreatic ductal system. There are currently two types of direct pancreatic duct interventions described [30].

1. EUS-Guided Transpapillary Rendezvous Drainage of the Pancreatic Duct

In this technique, the pancreatic duct is punctured under EUS guidance and a guidewire is advanced antegrade through the papilla for subsequent rendezvous with ERCP. A few case reports and one case series have evaluated this technique. Mallery *et al*. [26] evaluated this technique in 4 patients and had a low success rate of 25%. One of these 4 patients had pancreas divisum and in this patient the procedure failed because of inability to puncture the dorsal duct wall even after repeated attempts.

2. EUS-Guided Transluminal Drainage of the Pancreatic Duct Via the Stomach or Duodenum

In this technique, the pancreatic duct is punctured under EUS guidance and the guide wire is advanced into the pancreatic tail region via the needle. The transmural tract is subsequently dilated followed by stent placement over the guidewire creating a pancreaticogastrostomy or pancreaticoduodenostomy. Three case series have evaluated this technique: two alone and one in combination with the rendezvous technique with technical success rates ranging from 69 to 91.6% [22, 23, 24]. Tessier *et al*. [22] attempted EUS guided transluminal drainage in 36 patients (2 with pancreas divisum) and reported a technical success of 91.6% and relief of pain in 69.4% of patients. Major complications were seen in 3 patients. Kahaleh *et al*. [23] evaluated EUS guided pancreaticogastrostomy in 13 patients. An

endoprosthesis was successfully placed in 10 patients and 2 patients had major complications. None of the patients in this series had pancreas divisum. Out of 12 patients treated by the combination method in the series by Will *et al*. [24], one patient had pancreas divisum and in this patient the procedure failed because of bleeding.

These techniques seem to be attractive and have potential in draining dorsal duct in patients with symptomatic pancreas divisum and failed ERCP. However, the techniques are technically challenging with potential severe complications and hence further innovations are desired to improve the success rates as well as minimize the complications. Until further, these methods should be used only in high volume centers in selected patients.

EUS *versus* MRCP

Magnetic resonance cholangiopancreatography (MRCP), non-invasively, evaluates the pancreatico-biliary ductal system and has been shown to have good sensitivity and specificity for the diagnosis of pancreas divisum [4]. Secretin enhancement has been shown to improve the sensitivity and specificity of MRCP in diagnosing pancreas divisum [5]. Although EUS has not been directly compared with MRCP for the diagnosis of pancreas divisum, studies have evaluated the diagnostic yield of these two modalities in patients with idiopathic acute pancreatitis [31, 32, 33]. Ortega *et al*. prospectively compared EUS and MRCP for etiological diagnosis of idiopathic acute pancreatitis in 49 patients. Four patients had pancreas divisum and MRCP could identify it in all the four patients whereas EUS could diagnose pancreas divisum in only one patient [31]. Mariani *et al*. compared secretin EUS with secretin MRCP and found that secretin EUS had higher diagnostic yield than secretin MRCP [32]. EUS has also been shown to have good diagnostic rates for diagnosis of pancreas divisum in patients with idiopathic acute pancreatitis, even in patients with non diagnostic MRCP [33]. However, EUS is an operator dependent investigative modality and it may not be possible to identify the dorsal and ventral ducts in all the patients.

Conclusion

EUS seems to be an attractive and promising investigational modality for the diagnosis of pancreas divisum as well as for planning of proper therapy. However, studies are needed to define objective EUS criteria that can optimize the sensitivity and specificity for diagnosis of pancreas divisum and test them in prospective studies. It is also important to compare the diagnostic performance of EUS with other imaging techniques like MRCP. The role of secretin EUS in improving the diagnostic capability, as well as predicting the response to therapy in patients with pancreas divisum, needs to be studied in futures studies. EUS guided pancreatic interventions are attractive but are in their infancy and improved equipments and accessories probably may improve the results and decrease risk of complications.

Conflict of interest The authors have no potential conflict of interest

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