INTRODUCTION

Pancreas divisum (literally, “divided pancreas”) is the most common anatomic variant of the pancreas and is thought to exist in 5-10% of the population. Pancreas divisum is the result of the failed fusion of the dorsal and ventral pancreatic buds early in development, resulting in the majority of the pancreas being drained through the minor papilla. (Figure 1) In patients with normal anatomy, the majority of the pancreas drains through the major papilla. More formally stated, in patients with pancreas divisum, the variant pancreatic ductal anatomy leads to the relatively large dorsal pancreas segment being drained through the minor papilla while the smaller ventral bud drains through the major papilla. There is no known etiology for pancreas divisum however, some genetic abnormalities including mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and Serine Protease Inhibitor Kazal-type 1 (SPINK1) genes have been associated with the condition. CFTR mutations may be present in up to 22% of patients with pancreas divisum who develop pancreatitis.

The majority of patients with pancreas divisum will remain clinically asymptomatic and may only be diagnosed incidentally in the context of an imaging study ordered for another indication. However, some patients may be found to have pancreas divisum in the setting of a history of, or investigation into, episodes of pancreatitis. It has been proposed that a relatively stenotic minor papilla may predispose patients with pancreas divisum to recurrent episodes of pancreatitis. As such, in some cases patients are recommended to undergo therapy for pancreas divisum, usually in the form of endoscopic minor papilla sphincterotomy and/or endoscopic pancreatic duct stenting and, rarely, via surgical intervention. (Figure 2) This approach can be technically challenging, remains controversial, and is still being debated in the literature. This review article will focus on the literature regarding endoscopic intervention for symptomatic pancreas divisum and briefly touch upon the role of surgical intervention for definitive management.
Treatment: Endoscopic Intervention

Endoscopic therapy for symptomatic pancreas divisum has been well documented since the early 1980’s. However, given the relative rarity of the condition, there has been a paucity of high quality and well-defined studies that evaluate the efficacy of endoscopic intervention in this complex and somewhat difficult-to-study group of patients. Furthermore, the modality of intervention has evolved over this time period as well and has included minor and major papilla cannulation with balloon dilation, minor papilla stenting and a combination of minor papilla sphincterotomy and stenting.4,5,6,7,8,9,10,11,12,13

As a clinical entity, patients with symptomatic pancreas divisum often manifest in three groups, which include recurrent acute pancreatitis, chronic pancreatitis, and pancreatic-type pain. It should be stressed that the majority of patients with pancreas divisum will be asymptomatic. The particular manifestation of pancreas divisum encountered clinically is important as it may predict long term response to both endoscopic and surgical interventions.14

The definition of recurrent acute pancreatitis varies depending on the study but is optimally defined as pancreas divisum with two or more episodes of pancreatitis, a serum amylase or lipase level greater than three times the upper limit of normal, abdominal pain, and imaging that is suggestive of pancreatic inflammation without chronic changes. If abdominal imaging demonstrates morphological changes to the pancreatic duct or parenchyma then chronic pancreatitis is more likely to be present. If none of these criteria are present but the patient continues to experience abdominal pain that is characteristically similar to that of pancreatitis then pancreatic-type pain can be considered.

Recurrent Acute Pancreatitis

It has been hypothesized that recurrent acute pancreatitis can develop secondary to the reflux of pancreatic secretions across the dorsal pancreatic duct due to a relatively stenotic minor papilla and, although manometric data has demonstrated mixed results, endoscopic intervention has been of some benefit in select patients with recurrent acute pancreatitis.15,4,16 In perhaps the most well described study in the literature, Lans et al. (1992) conducted a prospective randomized controlled trial of 19 patients with symptomatic pancreas divisum thought to be due to recurrent acute pancreatitis. In this study the authors found that patients who underwent endoscopic dorsal duct dilation followed by stent placement for one year had nearly a 100% response rate with only one episode of recurrent pancreatitis (due to stent occlusion), no hospitalizations, and significantly fewer emergency room visits for abdominal pain compared to controls. In addition, the patients who underwent endoscopic intervention reported subjective improvements in symptoms and general overall well being. Unfortunately, these results have not entirely been reflected elsewhere in the literature although most studies are difficult to interpret given less well-defined patient populations, varying definitions of successful endoscopic treatment, and a lack of long-term follow-up. Furthermore, this study also did not include minor papilla sphincterotomy, thus limiting its generalizability.

Several retrospective studies that utilized sphincterotomy in combination with or without pancreatic duct stenting have described clinical success rates ranging from 53-84% after a single ERCP session in patients with recurrent acute pancreatitis that was felt to be due to pancreas divisum.12,17,18,19,20 There is an additional study that suggests that this initial success rate may be increased with subsequent ERCP sessions, but this approach is uncommonly undertaken in the absence of recurrent stricturing at the site of the minor papilla.21 A recent meta-analysis demonstrated a pooled response rate of 76% in patients with recurrent acute pancreatitis who underwent minor papilla sphincterotomy, minor papilla sphincteroplasty, dorsal duct stenting, or a combination procedure. In this study, the rate of improvement following endoscopic intervention relied upon the individual study definition of success, which may limit the applicability of the results. A subgroup of patients in this meta-analysis who underwent dorsal duct stenting alone without sphincterotomy experienced higher rates of success when compared to those who underwent combined sphincterotomy with stenting.22

Although few in number, studies evaluating
the long-term efficacy of endoscopic intervention in patients with pancreas divisum suggest that improvement in symptoms may be sustained in those who initially respond to therapy with long-term response rates ranging from 50-85%.\textsuperscript{12,23}

**Chronic Pancreatitis**

Evidence for endoscopic therapy in patients with chronic pancreatitis and pancreas divisum is sparse. Some studies have reported no improvement in symptoms following endoscopic therapy while others have demonstrated long-term response rates between 30-50% at five years.\textsuperscript{4,24,21} It is somewhat difficult to reconcile these diverse success rates. Typically, response rates are defined as a reduction in subjective pain level, reduced narcotic use, or a reduction in hospital admissions. It should be noted that up to 45% of patients may require surgical management within 5 years of the initial endoscopic intervention.\textsuperscript{10} Dorsal duct dilation on imaging may reflect more severe pancreatic disease. Distal intrapancreatic bile duct strictures have been reported in advanced calcific pancreatic disease and may be resistant to endoscopic intervention.\textsuperscript{25,26} One study found that patients with dorsal duct dilation required 3 or more ERCP sessions over the course of their disease and progressed to surgical intervention at a higher rate.\textsuperscript{14} A recent study that utilized stricture dilation and stent exchange based on symptoms was able to avoid subsequent surgical intervention in 95% of patients. However, extracorporeal shock wave lithotripsy was performed in this study for patients with dorsal duct caliculi, which may have influenced the overall response rate.\textsuperscript{27}

**Pancreatic Type-Pain**

The evidence for endoscopic intervention in patients with only pancreatic type-pain in the setting of pancreas divisum suggests that the vast majority of patients undergoing endoscopic intervention will not experience a change in symptoms. Individual studies have reported that between 20-40% of patients may subjectively report improvements in pain. However, no statistically significant effect has been demonstrated.\textsuperscript{18,28,29} A meta-analysis of 10 studies with 131 patients estimated a pooled response rate of 48% although the effect of endoscopic intervention was considered to be equivocal and no long-term data are available.\textsuperscript{22} Furthermore, there has been no difference demonstrated between patients who undergo sphincterotomy and stenting versus stenting alone in patients with pancreatic type-pain.\textsuperscript{21}

Taken as a whole, endoscopic intervention for symptomatic pancreas divisum appears to be of most benefit in those with well-defined recurrent acute pancreatitis without another clear etiology. There is some evidence that patients with chronic pancreatitis may benefit from endoscopic therapy; however, a large portion may still progress to surgical intervention or require multiple ERCP sessions. In patients with pancreatic type-pain endoscopic therapy is unlikely to yield any benefit and long-term data are lacking.

The potential benefits of endoscopic intervention must be weighed against the known complications associated with minor papilla interventions. A recent meta-analysis of balloon dilation, sphincterotomy with or without stenting, or stenting alone performed for symptomatic pancreas divisum reported a post-ERCP pancreatitis rate of 10%.\textsuperscript{22} This rate is above the known rate of pancreatitis following ERCP and may reflect the variant anatomy and complexity of the procedure being performed.\textsuperscript{30} Minor papilla restenosis is an established delayed complication and can occur in up to 23% of patients, with higher rates in patients who undergo minor papilla sphincterotomy without stenting.\textsuperscript{11,3,29}

**Surgical Interventions**

While most cases of symptomatic pancreas divisum are treated endoscopically there are some patients who will require surgical intervention. Surgical approaches include surgical sphincteroplasty of the minor papilla, duodenum-preserving pancreatic head resection, partial pancreaticoduodenectomy (Whipple procedure), the Frey procedure, and the Nakao procedure. The Frey procedure consists of the local resection of the pancreatic head with longitudinal drainage of the pancreatic duct while the Nakao procedure includes complete pancreatic head resection with segmental
duodenectomy, pancreaticogastrostomy and endo-
to-end duodenoduodenostomy. To date there are no
randomized controlled trials comparing endoscopic
and surgical interventions for symptomatic
pancreas divisum. A recent systematic review with
quantitative analysis of 1289 patients who were
treated endoscopically and 598 patients who were
treated surgically suggested that surgery may have
a higher success rate with lower complications
and need for re-intervention. However, the authors
cautions that selection bias may have contributed
to an unequal distribution and concluded that
existing evidence does not allow for a definitive
recommendation for clinical decision making.31

One observational study found that patients who
Pancreas Divisum: Evaluation and Treatment of a Persistently Controversial Anatomic Finding

had a partial response to endoscopic intervention but who subsequently required surgery had a better symptomatic relief following surgery than patients who did not experience symptomatic improvement with endoscopy. This has led several studies to recommend endoscopic intervention as first line therapy. Endoscopic intervention has a relatively high response rate in patients with recurrent acute pancreatitis and pancreas divisum, is minimally invasive, and has an acceptable risk profile. An individualized surgical approach should be undertaken in patients who progress to surgical intervention. Surgical sphincteroplasty has been considered a first-line therapy in patients who remain symptomatic but are without evidence of pancreatic fibrosis. Pancreatic head resection should be considered in those with fibrotic alterations of the pancreatic head.

**CONCLUSION**

Pancreas divisum is a common congenital abnormality of the pancreas and is thought to be present in 5-10% of the population. A small subset of patients with pancreas divisum have been observed to develop attacks of recurrent acute pancreatitis that can then progress to chronic pancreatitis or persistent pancreatic type pain. Endoscopic intervention with sphincterotomy and stenting or stenting alone has been shown to resolve or improve symptoms in some patients with recurrent acute pancreatitis and may be of some benefit in patients with chronic pancreatitis. This has led some studies to recommend endoscopy as the first line therapy. However, some individuals may continue to remain symptomatic despite seemingly adequate endoscopic therapy and eventually require surgical management, which itself may not be curative. An individualized surgical approach is recommended with consideration of papilla reinsertion or pancreatic head resection depending on the morphological changes seen in the pancreas.
References


Pancreas Divisum: Evaluation and Treatment of a Persistently Controversial Anatomic Finding


Answers to this month’s crossword puzzle:

<table>
<thead>
<tr>
<th>S</th>
<th>E</th>
<th>R</th>
<th>R</th>
<th>A</th>
<th>T</th>
<th>E</th>
<th>D</th>
<th>P</th>
<th>L</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>U</td>
<td>E</td>
<td>B</td>
<td>N</td>
<td>E</td>
<td>W</td>
<td>O</td>
<td>A</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>A</td>
<td>C</td>
<td>T</td>
<td>O</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>T</td>
<td>V</td>
<td>M</td>
<td>P</td>
<td>Y</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>N</td>
<td>I</td>
<td>T</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>O</td>
<td>N</td>
<td>E</td>
<td>F</td>
<td>T</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>E</td>
<td>N</td>
<td>D</td>
<td>R</td>
<td>I</td>
<td>C</td>
<td>T</td>
<td>I</td>
<td>C</td>
<td>O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>C</td>
<td>M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>H</td>
<td>A</td>
<td>I</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>P</td>
<td>V</td>
<td>I</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>H</td>
<td>U</td>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>R</td>
<td>G</td>
<td>S</td>
<td>R</td>
<td>X</td>
<td>A</td>
<td>N</td>
<td>A</td>
<td>S</td>
<td>T</td>
<td>O</td>
<td>M</td>
</tr>
</tbody>
</table>