

## **Is Secretin Magnetic Resonance Cholangio-Pancreatography an Effective Guide for a Diagnostic and/or Therapeutic Flow-Chart in Acute Recurrent Pancreatitis?**

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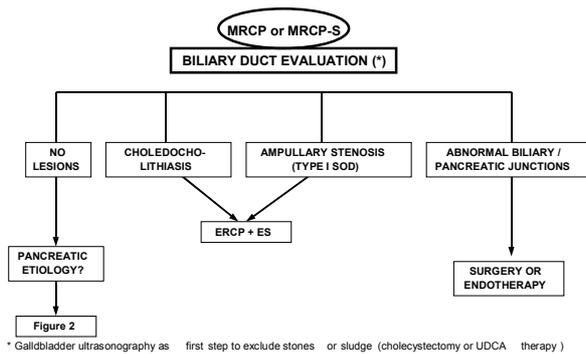
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There is increasing interest in magnetic resonance cholangio-pancreatography (MRCP) - especially when performed with i.v. secretin administration (MRCP-S) - as a procedure of first choice in the diagnostic evaluation of bilio-pancreatic diseases. The high-resolution projectional images of the bilio-pancreatic ductal system obtained by MRCP are not achievable with other non-invasive techniques such as ultrasound (US) and computed tomography (CT). Moreover, MRCP performed in conjunction with abdominal magnetic resonance (MR) imaging can be also useful in identifying pancreatic parenchyma lesions. In particular, the evaluation of the outcome of acute pancreatitis using non-enhanced MRCP can be as much accurate as by contrast-enhanced MRCP and CT [1]. The diagnostic role of MRCP-S can be an alternative to endoscopic retrograde cholangio-pancreatography (ERCP) which is limited to therapeutic purposes. The routine use of a non-invasive procedure such as MRCP-S is crucial especially in patients with recurrent acute pancreatitis (RAP) who are at high risk for developing post-ERCP pancreatitis.

MRCP-S has both morphological and functional properties. Secretin, in patients with a normal exocrine function, rapidly increases the volume of the juice within the pancreatic ducts, reaching approximately 5 mL/min [2] and giving improved ductal

images. In the 10-15 minutes following secretin administration, it is possible to measure the change in the caliber of the main pancreatic duct (MPD) in order to dynamically evaluate the outflow of pancreatic juice in the duodenal lumen across the sphincter of Oddi and to grade [3] or measure [4, 5] the consequent filling of the duodenum. In the evaluation of the caliber of the MPD, age is an important variable. As already shown by ERCP [6] and also by conventional MRCP, the caliber of the duct significantly increases with age in patients without biliopancreatic disease [7]. Thus, the age of the subject must be considered when interpreting RM pancreatography images; the basal caliber of the MPD can be considered normal when not larger than 3.5 mm in the body of the gland in subjects under 60 years of age [3, 7].

The physiopathological mechanisms of MRCP-S are the same as those already described for secretin-ultrasonography (US-S) [8]. The variables potentially affecting the evaluation of the dynamics of the pancreatic duct are the same for both procedures: secretory response, duct compliance and sphincter of Oddi resistance to juice outflow. Our data demonstrate that there are no significant differences in the secretin MRCP-S and US-S kinetics obtained by measuring the caliber of the MPD over time in patients with idiopathic recurrent pancreatitis [9].



**Figure 1.** Secretin MRCP guides the diagnostic and/or therapeutic algorithm in the case of biliary etiology of recurrent acute pancreatitis.

Nevertheless, MRCP-S is more advisable than US-S for a diagnostic algorithm since it permits a more accurate fine pancreatic duct morphology and an accurate biliary duct evaluation, including the distal portion of the common bile duct frequently not detected by US. MRCP-S is also preferable to US because it is not operator dependent as is US. The disadvantages of MRCP-S are the higher costs and the long acquisition time of the images which depends on the quality of instrumentation and software.

No data are present in the literature regarding the role of MRCP-S or that of conventional MRCP as a guide for a diagnostic and/or therapeutic flow-chart in RAP. Nevertheless, some evidence can help in the evaluation of the potential role of MRCP-S as a procedure of first choice in the diagnostic algorithm of RAP since MRCP-S can identify the bilio-pancreatic lesions which cause RAP (etiological diagnosis).

### Biliary Duct Evaluation

The use of secretin with MRCP can be superfluous when the bile ducts are explored because the hormone has a limited effect on biliary secretion. When biliary etiology is suspected, the goals of MRCP are to exclude or identify choledocholithiasis, the most frequent cause of RAP, and/or ampullary stenosis. The sensitivity and specificity of MRCP in detecting such biliary lesions is so

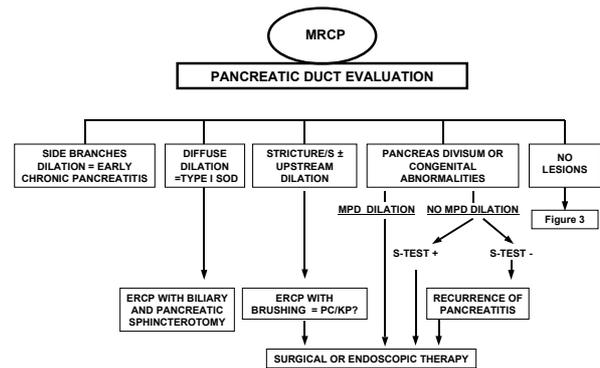
high [10, 11, 12, 13, 14, 15, 16, 17, 18, 19] which would seem to justify its routine use at the beginning of the diagnostic algorithm of RAP. Nevertheless, the capability of MRCP to detect stone less than 2 mm in size, such as microlithiasis or sludge, is doubtful. Frequently, in fact, the size of the stones detected in the common bile duct is not mentioned in the different MRCP studies and some false positive results are reported because of the difficulty in differentiating small stones from air bubbles [18, 19, 20]. The high frequency of sludge or microlithiasis as causative factors of RAP makes it mandatory to have as a first choice procedure one with a high accuracy in the etiological diagnosis of biliary RAP. Biliary ultrasound has the best accuracy in the detection of sludge in the gallbladder [21, 22, 23] especially when this is made up of calcium bilirubinate [22] while the diagnostic accuracy of MRCP is generally higher in the distal portion of the common bile duct. For this reason, when a biliary RAP is suspected, MRCP or MRCP-S can be placed at the beginning of the diagnostic algorithm but as a complementary procedure of biliary ultrasonography (Figure 1). The usefulness of MRCP when the biliary etiology of RAP is suspected may depend on by some associated clinical, ultrasonographic and biochemical criteria. When the suspicion of choledocholithiasis is high, as in the case of patients who presented with jaundice, cholangitis, severe gallstone pancreatitis and ultrasonographic common bile duct dilation, the patients can be directly referred for ERCP avoiding MRCP [24]. On the other hand, when predictive criteria for choledocholithiasis are lacking (common bile duct diameter less than 10 mm, abnormal serum liver tests persisting for no more than three days, no jaundice or cholangitis and no history of gallstone pancreatitis) [25], ERCP is not mandatory and MRCP could be proposed as a screening procedure using subsequent therapeutic ERCP only if MRCP evidences choledocholithiasis.

In addition to gallstones, an abnormal pancreatobiliary junction or choledochal cysts are morphological lesions which are less frequently encountered. They are associated with RAP and are well evidenced by both MRCP and ERCP. In the presence of these anatomical variations pancreatitis is induced by a facilitated reflux of bile into the pancreatic duct. The use of MRCP in identifying such lesions is particularly crucial in children with pancreatitis so a needless diagnostic ERCP can be avoided and the type of intervention can be directly chosen [26, 27]. Secretin MRCP can facilitate the detection of a common channel and, when performed after the oral intake of a fatty meal as a further stimulating factor, can also depict the range of contraction of the sphincter of Oddi [28].

### Pancreatic Duct Evaluation

Even if the most frequent cause of recurrent pancreatitis is biliary in nature, the first crucial step in the evaluation of this disease is the exclusion of chronic pancreatitis and pancreatic cancer. MRCP/MRCP-S can fulfil this double goal [29] (Figure 2).

In the diagnosis of pancreatic cancer, conventional MRCP can have a sensitivity similar to ERCP, as shown in a recent prospective controlled study [30] (no data about MRCP-S). The additional use of secretin with MRCP permits us to obtain more accurate images of the strictures, dilations or small cysts of the pancreatic ducts, as described in patients with chronic pancreatitis without exocrine function impairment [31, 32] (Figure 2). Compared with ERCP, MRCP-S can reduce the false negative rate of MRCP when strictures are localized at the tail portion of the MPD or when an initial dilation is present in the side branches. It has been shown that MRCP-S, in patients with recurrent attacks of acute non-biliary pancreatitis and in the absence of pancreatic ductal alterations at US or CT, identified almost the totality of the main pancreatic duct segments (97% vs. 65% of



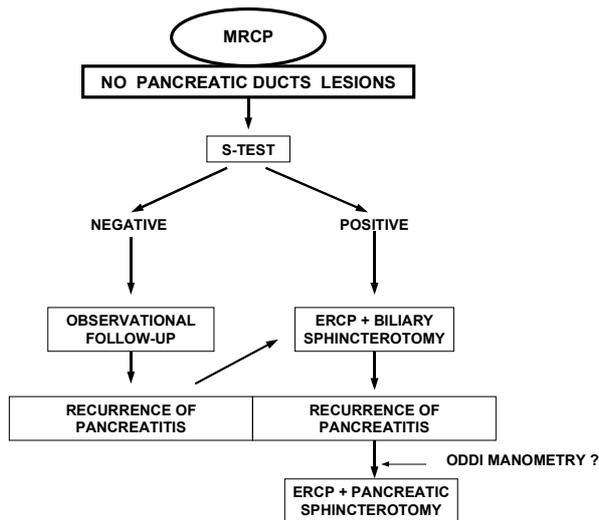
**Figure 2.** Secretin MRCP guides the diagnostic and/or therapeutic algorithm in the case of pancreatic etiology of recurrent acute pancreatitis. Abbreviations: S-test: secretin test; PC: pancreatic cancer; CP: chronic pancreatitis.

MRCP) and improved the visualization of both the dilated side branches (63% vs. 4% of MRCP) and the ductal narrowings (11% vs. 4% of MRCP) [32].

When MRCP, without the need of secretin, does not evidence segmental stenosis with upstream dilations but diffuse MPD dilation, an ampullary stenosis (pancreatic Type 1 sphincter of Oddi dysfunction) can likely be the cause of the recurrences of pancreatitis (Figure 2). ERCP with biliary and pancreatic sphincterotomy can represent the definitive treatment.

As with ERCP, MRCP-S can also evidence congenital abnormalities of the pancreatic duct anatomy, first at the pancreas divisum [31, 33] and then at the already mentioned abnormal pancreatobiliary junction [26, 27].

In diagnosing pancreas divisum, MRCP-S has the advantage over ERCP of avoiding the high cannulation failure of the accessory papilla. MRCP visualization of the dorsal dominant pancreatic duct and its different anatomical variants is significantly improved by the use of secretin [31, 32, 33, 34, 35] which can theoretically make the resistance opposed by the sphincter of the accessory papilla to an increased pancreatic secretion visible. In the case of pancreas divisum, MRCP-S can also guide in decision making in place of ERCP [29] (Figure 2). When “basal” MRCP shows a dilated dorsal duct (suspected stenosis of the accessory papilla), endoscopic therapy can be



**Figure 3.** Secretin MRCP guides the diagnostic and/or therapeutic algorithm in the case of apparent idiopathic recurrent acute pancreatitis. Abbreviations: S-test: secretin test; PC: pancreatic cancer; CP: chronic pancreatitis.

performed directly [34]. In the case of a non-dilated basal dorsal duct, only patients with delayed secretin stimulated duct emptying across the papilla (suspected dysfunction of the accessory papilla) should undergo endoscopic therapy which is indeed indicated in patients with a normal stimulated outflow in cases of persisting pancreatitis or further relapsing episodes after a temporary remission.

In most of the patients with relapsing pancreatitis, conventional MRCP or MRCP associated with secretin do not detect bilio-pancreatic lesions. In these cases, it is nevertheless important to study the kinetics of the pancreatic duct emptying across the papilla in order to verify the possible presence of Type II or III sphincter of Oddi dysfunction (SOD), the second most common cause of RAP, and to indicate possible sphincter ablation procedures.

Secretin can induce an increased pressure of the sphincter of Oddi within five minutes after its i.v. administration and a prolonged decreased pressure later on [36, 37]. This physiological action of secretin can explain potential false negative MRCP secretin tests compared with manometry which, on the contrary, may not detect a juxta-papillary stenosis, another cause of recurrent

pancreatitis which also increases the resistance to the outflow of pancreatic juice.

In patients with recurrent pancreatitis, US-S has similar behavior to that of manometry in the detection of sphincter of Oddi dysfunction [38]. According to the high concordance of results of US-S with MRCP-S in patients with recurrent pancreatitis [9], one can expect a high degree of similarity between MRCP-S and sphincter of Oddi manometry (SOM), the gold standard but, nevertheless, an invasive procedure.

While awaiting a comparative study between MRCP-S and sphincter of Oddi manometry, the following MRCP-S guided algorithm could be proposed in cases of recurrent pancreatitis due to suspected Type II or III SOD (Figure 3).

Pancreatic Type II SOD may be suspected in patients having a normal MPD morphology and delayed ductal emptying time (positive secretin test) and these patients can directly undergo ERCP with biliary sphincterotomy. Biliary sphincterotomy can be effective even in the presence of suspected pancreatic SOD because the reduction of the basal pressure of the sphincter of Oddi also reduces the basal pancreatic duct pressure [39]. Type III SOD can be suspected in patients having a normal MPD and normal ductal emptying time (negative secretin test). Such patients can undergo an observational follow-up with ursodeoxycholic acid (UDCA) oral therapy [22, 40] and, thereafter, ERCP with biliary sphincterotomy only when the pancreatitis recurs and no other etiological factors are identified. In patients with relapses following biliary sphincterotomy, hypertension of the pancreatic segment of the sphincter of Oddi can be present. In such patients, at this step of the algorithm, a further MRCP-S is still likely to be normal and does not help in decision making. On the contrary, sphincter of Oddi manometry may assure a definitive diagnosis and indicate ERCP with pancreatic sphincterotomy. Nevertheless, patients with suspected pancreatic Type III SOD had abnormal SOM recordings in no more than 50% of cases [41, 42] and therefore run the

risk of post-procedural pancreatitis [42]. Microtransducer manometry of the sphincter of Oddi, a promising new less invasive endoscopic procedure comparable with traditional SOM, could substitute SOM but must be further validated [43]. Temporary (less than three months) placement of pancreatic stenting can be an alternative to SOM in patients with a short interval of time free of pain [40] because it can predict the efficacy of sphincterotomy.

MRCP-S could guide the long-term follow-up of patients with RAP since it may be repeated to locate new bilio-pancreatic ductal lesions, grade the duodenal filling, in association with the faecal elastase 1 dosage in order to exclude developing early chronic pancreatitis and dynamically evaluate the outflow of pancreatic juice in patients who have already undergone sphincterotomy, as previously observed by US-S [8, 44].

A final consideration has to be made about the cost-benefit ratio of the potential use of MRCP as a first choice procedure in the exploration of the bilio-pancreatic ducts in patients with recurrent pancreatitis. Since, no data are present in literature, we can only point out some considerations. The cost-effective ratio of MRCP-S may likely be positive due to a decreased number of ERCP and consequent saving of time and costs. Similar conclusions may be drawn in terms of cost-effective ratio. The use of MRCP-S instead of diagnostic ERCP can be assured by a similar diagnostic accuracy and clinical results other than by a higher patient compliance and absence of complications.

In conclusion, secretin MRCP has the potential of being proposed as the first choice procedure in the diagnostic algorithm of recurrent pancreatitis. Its diagnostic accuracy in detecting the various etiological lesions of RAP is similar to that of ERCP. Its advantages are the avoidance of unnecessary and time consuming ERCPs which can consequently be decreased for diagnostic tests and indicated only for therapy in selective cases and with appropriate timing. In addition,

secretin MRCP can be preferred to US-S, not only for its higher accuracy regarding bilio-pancreatic morphology, but also for its functional properties which permit us to indirectly evaluate sphincter of Oddi "resistance" and pancreatic exocrine secretion. The diagnostic power of secretin MRCP compared with manometry in patients with suspected sphincter of Oddi dysfunction is certainly lower but one hopes that secretin MRCP can be used to selectively choose only those patients having a doubtful diagnosis to undergo manometry, thereby reducing the high rate of manometry-related pancreatitis.

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**Key words** Hereditary Diseases; Magnetic Resonance Imaging; Oddi's Sphincter; Pancreas: abnormalities; Pancreatic Diseases: congenital; Pancreatic Ducts: abnormalities; Pancreatitis; Secretin: diagnostic use

**Abbreviations** CT: computed tomography; ERCP: endoscopic retrograde cholangio-pancreatography; MPD: main pancreatic duct; MR: magnetic resonance; MRCP: magnetic resonance cholangio-pancreatography; MRCP-S: magnetic resonance cholangio-pancreatography secretin test; RAP: recurrent acute pancreatitis; SOD: sphincter of Oddi dysfunction; UDCA: ursodeoxycholic acid; SOM: sphincter of Oddi manometry; US: ultrasound; US-S: ultrasonography-secretin test

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