Is Cambridge scoring in chronic pancreatitis the same using ERCP and MRCP? – A need for revision of standards

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Abstract

Purpose

Grading of chronic pancreatitis (CP) is a clinical and radiologic challenge. Retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) use a version of the Cambridge criteria for ductal evaluation and CP staging, but interchangeability between the modalities lacks validation. This work compares ERCP and MRCP Cambridge scores and evaluates diagnostic performance of MRCP in a large cohort of patients with CP.

Methods

A large radiology database was searched for CP patients who underwent MRCP between 2003 and 2013. Next, patients who also had an ERCP within 90 days of their MRCP were selected. These were categorized into mild, moderate, and severe CP using the standardized Cambridge classification for ERCP. Radiologists blinded to ERCP findings then rated MRCP with modified Cambridge scores.

Results

The cohort comprised of 325 patients (mean age 51 years; 56% female). By ERCP Cambridge classification, 122 had mild CP, 109 moderate CP, and 94 severe CP. MRCP and ERCP showed total agreement of Cambridge score in only 43% of cases. With ERCP as reference, the

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sensitivity and specificity of MRCP in detecting Cambridge scores 4+5 (main-duct predominant) was 75.9% and 64.3%, and for Cambridge score 3 (side-branch predominant) it was 60.0% and 76.9%, respectively.

Conclusions

There is a lack of strong concordance between ERCP and MRCP based grading of CP using the Cambridge criteria. MRCP had moderate to good performance in diagnosing side-branch predominant versus main-duct predominant CP. This suggests an inherent challenge in comparing literature and calls for a revision of the standards.

Keywords: Chronic pancreatitis; Magnetic resonance cholangiopancreatography; ERCP; Diagnosis

Declarations:

The authors have no relevant disclosures or other declarations.

Introduction

The approach for diagnosis and staging of chronic pancreatitis (CP) continues to evolve. Although cases of severe CP may be readily apparent by clinical presentation and imaging, mild and moderate cases continue to pose diagnostic challenges [1-3]. This is an important area of active investigations, as diagnosing CP accurately and early provides the possibility for intervention (lifestyle modification, possible medical/endoscopic therapies) for patients whose quality of life suffers as a result of the disease [4].

Historically, a common approach to diagnosis and staging of CP has been the use of the Cambridge criteria, originally created for use with endoscopic retrograde cholangiopancreatography (ERCP) [5,6]. These criteria focus on the morphology of the main-duct and the appearance of prominent side-branches, and categorize CP ranging from equivocal through severe.

It has been demonstrated that magnetic resonance imaging (MRI) and especially magnetic resonance cholangiopancreatography (MRCP) can be used to evaluate the pancreas in a noninvasive way that allows for excellent visualization of the pancreatic ductal system [7-11]. In addition, the use of pancreatic secretagogues such as secretin has been shown to increase visualization of the main pancreatic duct and side branches to improve diagnostic utility [12-16]. Because of this, and due to the risk of post-ERCP pancreatitis [17], MRCP is widely used as part of the diagnostic workup for CP, and modified Cambridge criteria for MRCP were developed to assist in CP staging [18].

Despite this, surprisingly little information is available comparing the results of the ERCP based Cambridge score with the modified MRCP Cambridge score. This is of note, especially as international efforts continue to search for a unifying clinical and imaging diagnostic framework for assessment of CP [19-21]. Additionally, recent publications suggest that focusing solely on the pancreatic ducts at the expense of pancreatic parenchymal changes may limit our ability to stage disease severity in CP [21-23].

It is also significant to note that the ongoing Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) trial, Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translational Studies (PROCEED), uses the Cambridge classification for its patient cohorts. Specifically, patients with CP changes seen in side-branches (Cambridge scores 2 and 3) are grouped separately compared to patients with changes seen in the main pancreatic duct (Cambridge scores 4 and 5) [24].

We hypothesized that the Cambridge scoring for patients with CP would be comparable using ERCP and MRCP, and that the diagnostic performance of MRCP (as compared to ERCP) would be acceptable for detecting the clinically relevant subgroups of patients with main-duct and side-branch CP. Our study aims were: 1) To compare the ERCP and MRCP based Cambridge scores in a large number of patients with CP; 2) To assess the level of agreement between the two modalities, and 3) to assess the diagnostic performance of MRCP for detection of main-duct CP (Cambridge scores 4+5) and side-branch CP (Cambridge score 3), using ERCP as the reference.

Materials and Methods

Enrolment of patients into the study is illustrated in Figure 1. Initially, patients who underwent MRCP between 2003-2013 were included from a database of more than 15000 secretin enhanced MRCPs performed between 2003 and 2013 (Indiana University Health University Hospital, Department of Radiology and Imaging Sciences, Indianapolis, Indiana, USA). From this list, patients who had at least one ERCP within 90 days following their MRCP were selected. Exclusion criteria for these patients were previous sphincterotomy, presence of pancreatic duct stent, presence of pancreatic mass, and prior pancreatic surgery. Initial approval from the IRB was obtained (#1902679588).

Endoscopy reports prepared by the performing gastroenterologist for the included patients were then reviewed for the presence or absence of CP by ERCP Cambridge criteria. Gastroenterologists at our institution performed over 22,000 ERCPs in the study time frame, and have extensive experience grading CP. The patients were then further classified as having mild, moderate, or severe CP, corresponding to ERCP Cambridge scores of 3, 4, or 5, respectively. ERCP reports at the performing institution did not routinely grade studies as equivocal for CP, and Cambridge scores of 2 were not included [5,6]. Patients where ERCP reported a normal ductal system (Cambridge 1) were not included, as the scope of this study was focused on patients with known CP. This lead to a cohort of 325 CP patients with both ERCP and MRCP.

Given the time span which was analyzed, MRCP technique was not uniform; however, each scan did include both radial slab and 3D MRCP acquisitions (Table 1). Following this, the MRCP evaluations were divided among three abdominal radiologists, each with over 5 years of

experience, who were blinded to the ERCP Cambridge score and other clinical imaging of each patient. The main pancreatic duct and associated side branches were evaluated using 2D and 3D MRCP sequences without secretin stimulation, and modified Cambridge scores were given for each exam according to Schreyer et al. [18]. The maximum diameter of the main duct was measured at its widest segment on either 2D or 3D MRCP sequences depending on image quality, with a measurement > 3 mm considered to be dilated. 15 patients were unable to be scored by MRCP due to suboptimal imaging, and were excluded.

Statistical analysis:

A Pearson's chi^2-test of independence was performed to examine the relation between the modified MRCP Cambridge scores to the ERCP Cambridge scores. For assessing the diagnostic performance of MRCP in detecting both main-duct and side-branch CP, chi^2-tests of independence were performed including calculation of sensitivity, specificity, positive and negative predictive values. MRCP based Cambridge score 4 and 5 was defined as main-duct CP and grade 2 and 3 as side-branch CP, and with ERCP as reference (Cambridge scores 4 and 5 as main-duct CP and Cambridge score 3 as side-branch CP). P-values less than 0.05 were considered statistically significant. The software package STATA version 15.1 (StataCorp LP, College Station, Texas, USA) was used.

Results

After exclusion of 15 patients with non-diagnostic MRCP image quality, the studied cohort of 310 patients included 115 with mild CP, 106 with moderate CP, and 89 with severe CP based on ERCP. Mean age of the patients was 51 years, and there was a slight female predominance of 57% (177/310).

Agreement between modified MRCP Cambridge scores and ERCP Cambridge scores

Comparisons of modified MRCP Cambridge scores to ERCP Cambridge scores are listed in Table 2. There was a strong association between the MRCP and ERCP based Cambridge scores (χ^2=93.7, P<0.001). However, only 43% of cases (135/310) demonstrated absolute agreement between the two scores. Illustrative examples of discordant and concordant results between MRCP and ERCP are given in Figures 2-4. Concordance was best in patients categorized as severe CP by ERCP, but still demonstrated only 68% (61/89) agreement between MRCP and ERCP. Complete agreement between MRCP and ERCP was 30% (35/115) and 36% (39/106) of cases categorized as mild and moderate CP by ERCP, respectively.

Diagnostic performance of MRCP in detecting main-duct CP (ERCP as reference)

The comparison of MRCP and ERCP in detecting main-duct CP is given in Table 3. There was a strong association between the classification based on MRCP and ERCP (χ^2=49.2, P<0.001). The sensitivity and specificity for MRCP in detecting main-duct CP was 75.9% (95% CI: 69.3-81.7%) and 64.3% (95% CI: 54.9-73.1%), respectively. The positive predictive value was 78.3% (95% CI: 71.7-84.0%) and negative predictive value was 61.2% (95% CI: 51.9-69.9%).

Diagnostic performance of MRCP in detecting side-branch CP (ERCP as reference)

The comparison of MRCP and ERCP in detecting side-branch CP is given in Table 4. There was a strong association between the classification based on MRCP and ERCP (χ^2=42.4, P<0.001). The sensitivity and specificity for MRCP in detecting side-branch CP was 60.0% (95% CI: 50.4-69.0%) and 76.9% (95% CI: 70.4-82.6%), respectively. The positive predictive value was 60.5% (95% CI: 50.9-69.6%) and negative predictive value was 76.5% (95% CI: 70.0-82.3%).

Discussion

We found that MRCP and ERCP based Cambridge scores in patients with established CP are not directly comparable, indicating that the MRCP and ERCP methods are fundamentally not the same. However, seen from a more clinically relevant point of view, MRCP had acceptable diagnostic performance at detecting main-duct predominant and side-branch predominant CP, with ERCP as reference. The sensitivity to detect main-duct CP with MRCP was moderate to good, but with lower specificity as compared to detection of side-branch CP. However, specificity was higher for assessment of main-duct CP.

Direct comparison of MRCP and ERCP based Cambridge scores

This work adds to the limited available literature directly comparing MRCP and endoscopy for ductal changes. Segmental analysis of main pancreatic duct dilation severity by Sica et al. [25] showed good agreement between MRCP and ERCP, but did not evaluate Cambridge scores. Further work by Pungpapong et al. [26] showed that MRCP and endoscopic ultrasound (EUS) agreed on the presence or absence of ductal changes, but again did not compare Cambridge scores.

There is ample available evidence in the literature that MRI and MRCP are useful tools for diagnosing CP, as they have been shown to correlate with patient symptoms [27], fecal elastase [28,29], histopathology [30] and a variety of other disease markers [31,32]. However, even high quality MRCP scans with good spatial resolution do not always depict dilated side branches, and MRCP findings do not always correlate well with exocrine function of the gland [33,34]. On the other hand, ERCP as a standard for grading of CP also carries limitations, chief among which is

that ERCP does not mimic physiologic conditions. Hence, direct contrast injection into the main pancreatic duct can lead to overestimation of pancreatic duct dilation [35], which can be at least 50% larger than that seen on MRCP [19]. In addition, ERCP is an invasive procedure with associated risk of complications, and may also have difficulty filling the upstream pancreatic duct.

These methodological differences between MRCP and ERCP are well described, and in this context it is not surprising that our work demonstrated only moderate total agreement between Cambridge scores based on MRCP and ERCP. Our work should also be evaluated in the context of our evolving understanding of CP as a progressive disease process (from early to severe end-stage CP) [23]. Specifically, the conventional focus on changes of the main-duct and side-branches alone is likely not sufficient to identify and grade the disease [19]. The inability of these two useful diagnostic modalities for Cambridge scoring to strongly agree on the severity of CP adds further support for ongoing interdisciplinary work to standardize CP grading [19,21], likely incorporating new imaging parameters (such as DWI, T1 mapping, MR elastography, etc.) and/or clinical techniques [36-38]. Our study also addresses the challenges of using ERCP Cambridge or modified MRCP Cambridge alone as a reference standard for disease severity.

Clinical usefulness of MRCP in detecting main-duct and side-branch involvement in CP

The M-ANNHEIM diagnostic criteria, widely used in clinical settings, differentiate between definitive CP (moderate/marked Cambridge grades, with main duct changes) and probable CP (mild Cambridge grade, with only side branch ductal changes). The ongoing PROCEED and MiniMap trials also support this idea of division of CP patients into those with main duct

changes and those with non-main duct changes. Distinguishing between CP that predominately involves pancreatic duct side-branches (i.e. Cambridge score 3) and CP that predominately involves the main pancreatic duct (i.e. Cambridge scores 4+5) therefore has clinical relevance. This is supported by our study, as MRCP demonstrated moderate to good diagnostic performance in identifying and differentiating main-duct CP cases from side-branch CP cases. While our study demonstrated that MRCP can help distinguish between these clinically relevant groups, the lack of excellent performance supports ongoing the efforts to broaden the diagnostic criteria of CP beyond just ductal changes.

Limitations

Some study limitations could also have affected our results. There was a short time interval between ECRP and MRCP procedures; however, significant ductal changes would likely not occur within 90 days. Our recruitment/inclusion criteria (based on ERCP without the equivocal group, Cambridge grade 2) could limit the findings, but ERCP is the most readily available standard and thus the most logical recruitment criteria. Also, the inter-reader agreement itself between observers (for both MRCP and ERCP) could potentially contribute to our results. However, studies demonstrate that moderate inter-reader agreement for Cambridge scores can be seen with MRCP [39]. In addition, we relied on ERCP reports from gastroenterologists at our institution given their high volume of studies performed and extensive experience evaluating ERCP images for Cambridge scores.

It is also possible that using the secretin enhanced MRCP images could have changed the concordance between MRCP and ERCP, as increased fluid in the pancreatic ducts as a result of

secretin administration may result in improved visualization of the ducts with MRCP. However the modified Cambridge criteria as published do not use secretin and most institutions are not using secretin enhanced MRCP for clinical use. Hence, future studies should aim at further validating inter-reader agreement of the methods, and explore the role of secretin enhancement for better concordance with ERCP finding.

Conclusion

In this comparative study, we found lack of strong absolute concordance between Cambridge scores based on ERCP and MRCP. However, our work demonstrates that MRCP provides value in differentiating between main duct predominant and side branch duct predominant cases of CP. A fundamental consideration in the diagnosis and staging of CP is what should serve as a "true" gold standard. While ERCP has served this role for decades, a growth in understanding of the progressive CP disease process continues to emphasize the importance of factors beyond the pancreatic duct, and the need for a revision of imaging standards in CP. Future systems for diagnosing/grading CP with MRI/MRCP may benefit from a focus on main-duct vs. side-branch division, as well as on parenchymal changes of the pancreas to standardize the imaging approach to CP.

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Table 1. Representative MRI parameters for MRCP image acquisition

TE – Echo time. TR- Repetition time. FOV- Field of View. FA- flip angle.

HASTE (half-Fourier single-shot turbo spin echo)

SPACE (sampling perfection with application optimized contrast using different flip angle evaluation

Table 2. Comparison of ERCP Cambridge score to modified MRCP Cambridge score. Number of patients who received MRCP Cambridge score, sorted by CP severity using ERCP as the reference. Concordant scores are listed in bold. (1=no evidence of CP, 2=equivocal, 3=mild, 4=moderate, 5=severe)

Table 3. Comparison of ERCP Cambridge score to modified MRCP Cambridge score in patients with *main duct predominant CP*. Concordant scores are listed in bold.

Table 4. Comparison of ERCP Cambridge score to modified MRCP Cambridge score in patients with *side branch predominant CP*. Concordant scores are listed in bold.

Figure 1

Study enrollment flow diagram

Figure 2

Example of discordant results between MRCP and ERCP in a 54 year old male with chronic pancreatitis. ERCP Cambridge score was 3 with small abnormal side branches (white arrows) and a smooth caliber main duct with diameter of 2.1 cm. MRCP modified Cambridge score was 5 with diffuse dilation (4 cm) and irregularity of the main duct, as well as numerous prominent side branches (white arrows).

Figure 3

Example of discordant results between MRCP and ERCP in a 48 year old female with chronic pancreatitis. MRCP modified Cambridge score was 3 with three prominent side branches (white arrows). ERCP Cambridge score was 5 with abnormal side branches as well as a stricture of the main duct in the head (black arrow).

Figure 4

Example of concordant results between MRCP and ERCP in a 58 year old male with chronic pancreatitis. MRCP modified Cambridge score was 5 with diffuse main duct dilation and irregularity as well as a filling defect (white arrow). ERCP Cambridge score was 5 with diffuse main duct dilation and irregularity.