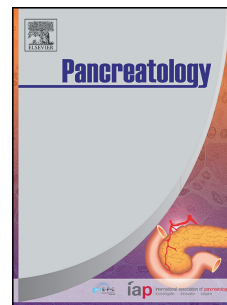


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Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis*

*: Recommendations from the Working Group for the International Consensus Guidelines for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club (IAP – APA – JPS – EPC)

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Abbreviations: ADC: apparent diffusion coefficient, CP: chronic pancreatitis, CT: computed tomography, DWI: diffusion weighted imaging, ERCP: endoscopic retrograde cholangiopancreatography, EUS: endoscopic ultrasound, FNA: fine needle aspiration, MRCP: magnetic resonance cholangiopancreatography, MRI: magnetic resonance imaging, s-MRCP: secretin-stimulated MRCP.

Abstract

The paper presents the international guidelines for imaging evaluation of chronic pancreatitis. The following consensus was obtained: Computed tomography (CT) is often the most appropriate initial imaging modality for evaluation of patients with suspected chronic pancreatitis (CP) depicting most changes in pancreatic morphology. CT is also indicated to exclude other potential intraabdominal pathologies presenting with symptoms similar to CP. However, CT cannot exclude a diagnosis of CP nor can it be used to exclusively diagnose early or mild disease. Here magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP) is superior and is indicated especially in patients where no specific pathological changes are seen on CT. Secretin-stimulated MRCP is more accurate than standard MRCP in the depiction of subtle ductal changes. It should be performed after a negative MRCP, when there is still clinical suspicion of CP. Endoscopic ultrasound (EUS) can also be used to diagnose parenchymal and ductal changes mainly during the early stage of the disease.

No validated radiological severity scoring systems for CP are available, although a modified Cambridge Classification has been used for MRCP. There is an unmet need for development of a new and validated radiological CP severity scoring system based on imaging criteria including glandular volume loss, ductal changes, parenchymal calcifications and parenchymal fibrosis based on CT and/or MRI. Secretin-stimulated MRCP in addition, can provide assessment of exocrine function and ductal compliance. An algorithm is presented, where these imaging parameters can be incorporated together with clinical findings in the classification and severity grading of CP.

Introduction

Aiming to produce the first truly International Guidelines on chronic pancreatitis (CP), John P Neoptolemos, David C Whitcomb and Tooru Shimosegawa in 2016 embarked on a joint venture with endorsement from the four International Societies (International Association of Pancreatology (IAP), American Pancreatic Association (APA), Japan Pancreas Society (JPS) and European Pancreatic Club (EPC)). The core committee identified international experts to ensure multidisciplinary representation within subgroups focusing on the different key topics of CP, and calls for volunteers to participate in the process were also circulated across the societies. Although different guidelines exist, such as the recent European consensus[1], the aim was to create a consensus that was mechanism based, truly international and multidisciplinary. The first major step was to agree the definition of CP which after several meetings agreed to adopt the mechanistic definition of CP[2]. For further description of this definition of CP and the process behind the international consensus guideline work, please see Appendix A and references[2,3]. Although imaging provides outstanding morphological and some functional information about the pancreas, many of the early features are non-specific. Thus, the diagnosis of CP, and especially early CP, requires assessment of risk factors, clinical features, *different biomarkers including imaging* and exclusion of diseases with overlapping features of CP[2,4–6].

The members of the imaging working group were appointed to represent worldwide specialists in pancreatic imaging with representatives from radiology, gastroenterology and surgery. It was also decided to focus on imaging in adults, and on cross sectional imaging (computed tomography (CT) and magnetic resonance imaging (MRI)) since this is the primary diagnostic approach at most institutions. Since a separate guideline work is planned about ultrasound, transabdominal ultrasound was not included in this guideline and the usefulness of endoscopic ultrasound (EUS) is addressed in one question for detailed diagnosing and grading of CP as supplement to cross sectional imaging. JBF was appointed as chairman of the group. Thirteen questions deemed to be the most urgent and clinically relevant in CP were identified.

Methods

The imaging working group provided a structured format for a narrative review of each question, and included instructions how to evaluate the level of evidence according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach (see <http://www.uptodate.com/home/grading-tutorial>). The strengths of the recommendations were graded as strong (1) or weak (2), and the levels of quality of evidence as high (A), moderate (B) or low (C). Finally, the working group members voted using a nine-point Likert scale on their level of agreement with the recommendations and their GRADE score. For agreement the voting results were classified using the percentage of votes that were 7 or above (the alpha-score) as either strong (alpha-score \geq 80%), conditional (alpha-score \geq 65%), or weak (alpha-score $<$ 65%). Typically, two authors wrote the statements and comments to each question and afterwards all statements were reviewed by all authors to ensure the general relevance and applicability of the conclusions. Some of the answers were not strict guidelines, but rather recommendations or consensus. However, to ensure a uniform nomenclature for the working group, the term guideline was used in the title. It should be noted as a limitation that this work has not been subject to a Delphi process (or other external review).

In the present document, we listed a summary of the most relevant information and references. It should be noted that this guideline was developed by experts from advanced care centers of pancreatic diseases, and that some advanced imaging options may not be available at smaller care centers and to general practitioners. In general, there is a lack of literature dealing with recommendations for imaging protocol settings for chronic pancreatitis, which to great extent is dependent on scanners types, local practice and preference, etc. A recent review has a proposal for advanced MRI protocol settings based on literature review[7]. Furthermore, some centers will also rely on transabdominal ultrasound and EUS as the primary imaging approach, which is not within the focus of the present guidelines. Adjustments should be considered according to local traditions and resources, and taking the characteristics of patients into

account (a-priori probability of severe CP, mild CP or normal pancreas). The guidelines are meant to guide practitioners and radiologists in the clinical handling and diagnostic work-up of patients at different levels of healthcare.

Figure 1 illustrates the overall concept of “Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis” with reference to the 13 questions.

Question 1: What are the indications for CT in the investigation of CP?

CT is indicated as part of a diagnostic algorithm when there is clinical suspicion of CP, in the presence of typical symptoms and recognized risk factors. CT is also indicated to exclude other potential intraabdominal pathologies presenting with symptoms similar to CP. In patients with established CP, CT is indicated to assess complications and the need for further interventions.

(Quality assessment: High; Strength of recommendation: Strong; Grade 1A; Agreement: Strong (alpha-score 100%))

Comment:

Abdominal CT is widely accepted as the first-line cross sectional imaging modality of choice when investigating an individual with clinical suspicion of CP[8], for instance presenting with symptoms such as abdominal pain, weight loss, history of acute recurrent pancreatitis and the presence of risk factors. Since the initial CT studies evaluating CP features[9,10], it remains a key imaging modality as it is non-invasive, relatively inexpensive and readily available. Not only can CT confirm a diagnosis of CP, it also offers the ability to rule out other intraabdominal pathologies that may have similar symptom profiles (such as upper abdominal pain and weight loss) including pancreatic and upper gastrointestinal cancers[11].

Ease of access to CT, and its non-invasive nature, makes CT ideal for: diagnosing of CP, evaluating the relapsing phase of acute recurrent pancreatitis, monitoring disease progression and development of

complications due to CP (including pseudocysts, biliary obstruction, gastric outlet obstruction, fistulae formation and vascular compromise[12]), and facilitating operative planning in those who require surgical or interventional procedures. There is a paucity of studies describing the best imaging modality to assess the varying types of CP related complications, and recommendations are based on low grade evidence[13]. Furthermore, the risk of a pancreatic ductal adenocarcinoma is increased by a factor of 16 in CP[14], and CT is also particularly useful in the differential diagnosis of pancreatic tumors[15,16].

Question 2: Is CT the best initial test when investigating CP, and should CT be performed as a baseline investigation in all CP patients?

CT is the best initial imaging modality for the evaluation of patients with suspected CP, because it is widely available and can depict most changes in pancreatic morphology (parenchymal atrophy, parenchymal or ductal calcifications, ductal changes and complications). CT is also useful to detect incidental lesions and pathology of the pancreas, e.g. malignancy or autoimmune etiology.

(Quality assessment: Moderate; Strength of recommendation: Strong; Grade 1B; Agreement: Strong (alpha-score 100%))

Comment:

According to the widely used M-ANNHEIM diagnostic criteria of CP, a patient with typical clinical history of CP has “definite CP” when pancreatic calcifications and/or moderate or marked ductal changes are present on CT[17]. “Probable CP” is present when mild ductal alterations (Cambridge classification: normal main duct with 3 or more abnormal side branches) and/or recurrent or persistent pseudocysts are seen on CT[17]. However, the M-ANNHEIM criteria has never been tested for reliability or validity. Pancreatic calcifications, moderate or marked ductal changes and pseudocysts are typically well depicted on CT, while mild ductal alterations often cannot be ruled out. Hence, the diagnosis of “probable CP” cannot be completely established using CT (see Question 3), and in these circumstances an additional MRI is needed

(see Question 4). However, CT is recommended as the baseline investigation in all new patients with suspected CP, since the symptoms of CP may mimic other pathologies of the pancreas such as malignancy or autoimmune pancreatitis, as well as other abdominal diseases, where an detection can aid in providing curative procedures[18–20]. Furthermore, first CT examination also represents a baseline in these often complex CP patients who require consecutive CT scans for assessment of the progressive changes, and subsequently multimodality imaging (MR/EUS). CT can be performed in non-tertiary set-up with no access to EUS/MRI, and is less time consuming and a cheaper alternative than most secondary investigations.

Question 3: Can a normal CT exclude CP, and can early or mild CP be diagnosed on CT?

Despite CT being the imaging modality of choice for initial investigation of CP, it cannot exclude a diagnosis of CP nor can it be used to exclusively diagnose early or mild CP.

(Quality assessment: High; Strength of recommendation: Strong; Grade 1A; Agreement: Strong (alpha-score 100%))

Comment:

When investigating chronic pancreatitis, CT of the pancreas is the initial imaging modality of choice [8]. In the event of a CT leading to suspicion of “possible” or “mild” CP, or indeed equivocal findings, other imaging modalities, pancreatic function tests, etc., may be required to further complement the diagnostic work-up. The diagnostic process in a clinical setting will typically adopt a “step-up” approach with regard to relative complexity of the imaging modality of choice balanced against the clinical needs. Timing of the scanning shall be individualized depending on the symptoms, but shall not be unnecessary delayed.

In patients with “probable CP” (according to the M-ANNHEIM diagnostic criteria[17]) and early or mild CP, the use of CT is significantly limited since the parenchymal and ductal changes are often very subtle and not readily detectable on CT[21]. In cases of a CT scan depicting a normal pancreas in a patient with clinical

suspicion of CP, it is recommended to perform further imaging with MRI (and/or EUS) to visualize mild ductal changes (see Question 4). MRI/MRCP is superior to CT in detecting significant pancreatic ductal changes such as pancreatic duct dilatation and strictures, and picking up more subtle ductal changes including atrophy and dilated side branches that may be signs of “early CP”[22], see Question 4.

However, no criteria or scoring systems so far exist to define the cross-sectional imaging findings needed for establishing a diagnosis of early CP (see Question 9). For detection of early or mild CP there is a lack of published data defining a normal from a slightly abnormal pancreas. An important obstacle is that the morphologic changes of early/mild CP are discrete, and even experienced radiologists may not be able to distinguish diseased from normal tissue[9,23].

Question 4: What are the indications of MRI/MRCP in the investigation of CP?

MRI/MRCP is indicated in the investigation of CP, especially in patients where no specific pathological changes are seen on CT, but the clinical suspicion of a diagnosis remains high. MRI/MRCP is superior to CT in identifying early CP changes or mild degrees of CP.

(Quality assessment: Moderate; Strength of recommendation: Strong; Grade 1B; Agreement: Strong (alpha-score 100%))

Comment:

MRI/MRCP provides valuable information on CP related changes of the main pancreatic duct such as diffuse or focal strictures, ductal irregularities, abnormal side branches and cystic lesions. MRCP provides information in both suspected CP to characterize ductal abnormalities and in established CP to evaluate disease progression[24,25]. Although MRI and CT reportedly have comparably high diagnostic accuracy in the diagnosis of CP[26], a normal pancreas at CT is reported in up to 7% of patients with established CP[10]. MRI/MRCP reported a sensitivity and specificity in the diagnosis of CP of 78% and 96%, while CT had 75%

and 91%, respectively[26]. Although these numbers are not significantly different, MRI/MRCP seems indicated for better visualization of subtle pancreatic changes (such as in “probable CP” according to the M-ANNHEIM diagnostic criteria[17]). Also, MRCP can be relevant to monitor disease progression in patients with previously diagnosed CP. MRI/MRCP not only provides better morphologic information than CT considering ductal changes[27,28], but MRI/MRCP can also be used to differentiate CP from pancreatic adenocarcinomas or intraductal papillary mucinous neoplasms, etc.[28–33].

Question 5: Can the ERCP Cambridge criteria (1984) for CP be extrapolated to MRCP findings?

Although the Cambridge Classification system cannot be directly translated to MRCP findings and ERCP tends to overestimate of the caliber of the MPD, a very good correlation has been described between ERCP and MRCP findings. However, standard MRCP (without secretin administration) has low sensitivity in diagnosing mild CP since very subtle ductal changes cannot be clearly identified.

(Quality assessment: moderate; Strength of recommendation: strong; Grade: 1B; Agreement: Strong (alpha-score 83%))

Comment:

A modified MRCP based classification has been proposed[34], based on the ERCP Cambridge Classification of pancreatic ductal changes[35,36]. The most important fundamental difference is that the main pancreatic duct is filled with contrast media in a retrograde manner at ERCP, and in some cases forceful administration of contrast media may exaggerate ductal abnormalities. In a comparative study in CP patients, the mean diameter of the MPD at ERCP was on average 50% larger than that at MRCP[37]. Also, ERCP poorly visualizes the very upstream portion of the pancreatic duct so that focal pancreatitis mainly affecting the tail part of the pancreatic duct and the duct beyond a strictures cannot be seen. MRCP visualizes the entire main pancreatic duct without exaggeration of ductal abnormalities, and without the risk of procedure induced acute pancreatitis[37].

Due to these fundamental differences between ERCP and MRCP, the Cambridge Classification system cannot be directly translated to MRCP findings. Despite lack of an independent scoring system of CP using the MRCP technique, a very good correlation has been described between ERCP and MRCP findings in CP patients[38,39]. In a recent meta-analysis, the sensitivity and specificity for ERCP and MRCP were comparable[26]. One of the important limitations of MRCP, as compared to ERCP, is that CP related subtle changes in early or mild CP not always are visualized with MRCP, such as tiny abnormal side branches, mild strictures and subtle ductal irregularities. Secretin-stimulated MRCP (s-MRCP) can improve the diagnostic performance of detecting these subtle ductal changes[40,41], see Question 6.

Question 6: Should secretin-stimulated MRCP be used in the investigation and diagnosis of CP?

In the depiction of subtle ductal changes, secretin-stimulated MRCP is more accurate than standard MRCP, and should after a negative MRCP be considered when there is clinical suspicion of CP.

(Quality assessment: Moderate; Strength of recommendation: Weak; Grade: 2B; Agreement: Conditional (alpha-score 75%))

Comment:

S-MRCP can be particularly relevant in the diagnosis of “probable CP” according to the M-ANNHEIM diagnostic criteria (normal main duct with 3 or more abnormal side branches)[17], as well as in the description of early/mild CP. Hence, s-MRCP should be considered in cases where there is still a clinical suspicion of CP, but where CT and standard MRCP depicts an apparently normal pancreas. S-MRCP has shown a better performance in detecting early changes in CP, but comparative studies with ERCP are needed[42,43]. The number of abnormal MRI/s-MRCP features are reported to correlate with the histopathology of non-calcifying CP[44]. S-MRCP has also been shown to aid in the differentiation between pancreatitis and small size malignancies as underlying causes of pancreatic duct stenosis[33]. Accessibility to specialist services for s-MRCP is, however, limited at many institutions, and if not available, EUS

(preferable with secretin stimulation) may provide a feasible alternative. Many institutions all over the world, which are specialized in advanced pancreatic MRI/MRCP are currently using secretin stimulation to improve duct visualization[40]. S-MRCP also allows semi-quantitative or quantitative assessment of secretin induced pancreatic exocrine secretion, with potential relevance for the clinical phenotype in CP[7,45–48].

New emerging MRI techniques (e.g. using spin labeling or inverse recovery pulse) may also allow visualization and quantification of pancreatic juice flow within the duct without secretion stimulation[49–51]. These techniques seem promising and should be evaluated for the detection of early/mild CP.

Question 7: Can a normal MRCP exclude a diagnosis of CP, and can early or mild CP be diagnosed on MRI?

A normal MRI/MRCP without secretin-stimulation cannot exclude the diagnosis of early/mild CP where the ductal changes are very subtle. In these cases, s-MRCP (or EUS) should be considered although early changes still cannot be excluded.

(Quality assessment: Moderate; Strength of recommendation: Strong; Grade: 1B; Agreement: Strong (alpha-score 92%))

Comment:

In most cases, standard MRCP is diagnostic for CP. However, according to the M-ANNHEIM diagnostic criteria of CP, a patient with a typical clinical history of CP can have “definite CP” without any ductal changes but only with pancreatic calcifications, which are best visualized at CT[17]. Hence, CT is needed in all patients with clinical suspicion of CP, see Question 2. With a high quality MRCP, mild ductal alterations can usually be identified. Hence, the diagnosis of both “definitive CP” and “probable CP”, according to the M-ANNHEIM diagnostic criteria, can normally be made based on a standard MRCP. The diagnosis of early/mild CP is, however, challenging based on all imaging modalities, including ERCP which has been considered the gold standard. Furthermore, the diagnosis of mild CP can be made if three abnormal side

branches are seen; however, endoscopists usually do not fill the entire main pancreatic duct in order to reduce the risk of ERCP-related acute pancreatitis[52,53].

No uniform imaging definition for early/mild CP incorporating novel non-invasive imaging techniques currently exists[3]. It seems reasonable that identification of more subtle imaging findings revealed by s-MRCP in mild CP may aid in understanding the course of the disease and in defining the best treatment and follow-up in CP (see Questions 9, 12 and 13).

Question 8: When is EUS needed (in addition to cross sectional imaging) in the diagnosis and grading of CP?

EUS is considered to be the most appropriate and sensitive imaging technique to diagnose parenchymal and ductal changes, mainly during the early stage of the disease. Hence EUS is indicated when CT (and MRI) are negative or doubtful in patients with clinical suspicion of CP.

(Quality assessment: high; Strength of recommendation: strong; Grade 1A; Agreement: Conditional (alpha-score 75%))

Comment:

In case of a CT depicting a normal pancreas in a patient with a clinical suspicion of CP, further imaging is recommended. EUS is often used as supplement to cross sectional imaging to diagnose CP, because of its ability to detect subtle changes in the pancreatic structure even before traditional imaging and functional testing detect any abnormalities, but which can be confirmed by histology[54–57]. EUS can assist the diagnosis of CP based on identification of standard ductal and parenchymal criteria[58]. The ideal threshold number of EUS criteria needed for the diagnosis of CP still remains unclear. It has been suggested that the presence of 1-2 EUS features should be considered as a normal gland, and that the presence of 3-4 criteria may indicate early CP. However, the predictive value of individual EUS criteria remains controversial. EUS

features of CP are not necessarily pathologic as a normal aging, smoking, alcohol consumption, obesity and diabetes may cause parenchymal and or ductal changes without symptoms, defined by the term pancreatopathy[59,60]. Hence, CP cannot be diagnosed based solely on minimal EUS criteria. In order to address these controversies, and to standardize endosonographic features that is more clinically relevant and reproducible, the Rosemont criteria was established[61]. This consensus-based diagnostic system is divided into major and minor features according to perceived predictive accuracy for diagnosing CP. However, this classification does not improve the diagnostic value and it has been shown that a “normal” Rosemont classification has a poor correlation with histopathology, meaning that it does not rule out early CP[62]. When compared with histology as the gold standard, the sensitivity of EUS for the diagnosis of CP exceeds 80%, with a specificity of 100%[57] within a defined cohort. It is possible that EUS with fine needle aspiration (FNA) can be supporting the diagnosis and staging of CP. It must be emphasized that EUS technique requires high operator experience and is very operator dependent in its diagnostic accuracy; variability is only low in the hands of experienced endosonographers[63].

Some of the features of CP depicted by EUS can also be obtained by transabdominal US. However, pancreas may often be poorly visualized by transabdominal US and the image quality is dependent on the anatomy, and may be reduced by air in the gastrointestinal tract, etc. Hence, there is a great demand for skilled operators able to perform high quality ultrasonography, and access to transabdominal US may thus be limited at many institutions worldwide. However, it should be acknowledged that transabdominal US reportedly has acceptable performance at some institution with relevant expertise, and transabdominal US can at these institutions play an important role in the diagnosis and assessment of complications to CP.

Question 9: Are there any validated radiological severity scoring systems for CP?

No validated radiological severity scoring systems for CP are available, although a modified Cambridge Classification as used for ERCP has been used for MRCP.

(Quality assessment: High; Strength of recommendation: Strong; Grade 1A; Agreement: Strong (alpha-score 100%))

Comment:

Whilst radiological imaging techniques (plain radiography, CT, MRI and ultrasound) have never been systematically evaluated to establish an independent radiological severity scoring system of CP, previous attempts to produce radiological classifications of CP and severity scoring systems have been made. ERCP has been used to establish “the Cambridge Classification system” which scores the degree of ductal changes[35,36]. However, ERCP does not provide any information about the pancreatic parenchymal changes related to CP except for the presence of calcifications. Based on the Cambridge Classification scoring system, a modified MRCP based classification has been proposed[34], but as mentioned (see Question 5) the classification cannot be directly translated to MRCP findings and has never been systematically evaluated.

Several other clinical classifications of CP exist in which imaging findings are taken into account including the Manchester classification which combines imaging findings of CP with clinical findings[64], the ABC criteria which requires positive imaging for all stages whilst the presence of exocrine or endocrine insufficiency and/or complications alone determines the severity of CP[65,66], and the complex M-ANNHEIM criteria which characterizes patients according to etiology, clinical stage and severity[17]. In the M-ANNHEIM diagnostic criteria, both the presence of parenchymal calcifications (based on CT) and ductal changes (based on ERCP, MRCP, CT or ultrasound) are used[17]. The M-ANNHEIM criteria are widely used but has never been tested for reliability or validity. Several of the clinical classification systems include diagnostic criteria that are only taking the presence (present or not present) of certain parenchymal and ductal imaging findings into account to confirm the diagnosis of CP.

Question 10: Is there a need for CT/MRI based criteria to assess the severity of CP?

There is an unmet need for development of a new and validated radiological scoring system based on imaging criteria for the assessment of CP severity.

(Quality assessment: High; Strength of recommendation: Strong; Grade: 1A; Agreement: Strong (alpha-score 100%))

Comment:

The Cambridge classification system is based on ERCP classification methods and the simple presence of pancreatic calcifications. It has been adapted in most modern clinical classification systems, including M-ANNHEIM, and may still be seen by many as the ‘gold standard’ imaging based classification[17,36]. Since ERCP is no longer routinely employed for the diagnosis of CP, the Cambridge classification has been adapted to make it applicable to cross sectional imaging[13]. There have been several adaptations of the Cambridge classification although their uptake into routine use has been hampered by the lack of a standardized nomenclature and validation[37,67].

In addition to pancreatic ductal changes and the presence of calcifications, modern cross-sectional imaging techniques (CT/MRI) also provide detailed and quantitative information on parenchymal changes and pancreatic function. These include: gland atrophy, which can be quantified by two-point linear or volumetric assessment; parenchymal fibrosis, assessed by MRI and diffusion weighted imaging (DWI); subtle ductal changes and exocrine secretory function following s-MRCP. These parameters may be particularly relevant for the diagnosis of early/mild CP and provide a mean for quantitative assessment of disease severity (see Question 12). However, cross-sectional imaging techniques have never been systematically evaluated to establish an independent radiological scoring system of disease severity in CP. A generalized approach for severity grading (covering the entire range from mild to severe CP changes) should be developed based on cross-sectional imaging techniques including common features of CP (biomarkers) such as ductal changes, parenchymal atrophy and fibrosis as well as pancreatic function[68,69]. In addition, CT could be used for grading of parenchymal and ductal calcifications, and

complications. Such a radiological scoring system should be clinically and prospectively evaluated to prove its clinical relevance, see Question 13.

Question 11: How can imaging currently used in clinical practice be utilized in a scoring system of CP severity?

CT and MRI complement each other in depicting the pathological changes seen with CP including glandular volume loss, ductal changes, parenchymal calcifications and parenchymal fibrosis. Secretin stimulated MRCP in addition, can provide assessment of exocrine function and ductal compliance. These imaging parameters can then be incorporated together with clinical findings in the clinical classification and severity grading of CP.

(Quality assessment: Moderate; Strength of recommendation: weak; Grade 2B; Agreement: Strong (alpha-score 92%))

Comment:

CT aids in the diagnosis of CP by identifying pancreatic atrophy, ductal changes such as dilation, strictures and contour irregularity and presence of parenchymal/intraductal calcifications[10]. MRI/MRCP is superior to CT, and comparable to ERCP, in non-invasive depiction of abnormal side branches and main ductal changes[37]. MRI/MRCP also provides invaluable information about parenchymal changes such as focal or diffuse gland atrophy and cystic changes, which are not assessable by ERCP. Secretin-enhanced MRCP adds to diagnostic value by allowing for better visualization of the pancreatic ducts, evaluation of ductal compliance and by assessment of pancreatic exocrine function[40,70]. MRI also allows for identifying parenchymal fibrosis based on changes in parenchymal T1 signal intensity on unenhanced images and changes in parenchymal enhancement pattern on dynamic post contrast imaging. Newer MRI techniques to assess early parenchymal fibrosis include DWI, MR elastography and T1-mapping of pancreatic parenchyma[71–75].

Creating a clinically relevant and understandable scoring system of CP severity based on CT and MRI/MRCP examinations will help to use the same definitions and criteria by different specialties who are responsible for the diagnosis, medical care and treatment of the patients, see Question 12.

Question 12: What criteria should be considered as vital for inclusion in a radiological severity scoring system for CP?

Grading of gland atrophy, ductal changes, parenchymal calcifications and gland fibrosis should be included in a radiological severity scoring system. Quantification of exocrine function can be included as supplementary information.

(Quality assessment: Moderate; Strength of recommendation: Strong; Grade: 1B; Agreement: Strong (alpha-score 100%))

Comment:

Imaging of the CP severity should take into account that CP is as a fibro-inflammatory syndrome characterized by ongoing inflammation of the pancreas, including intra- and interlobular fibrosis with acinar parenchymal atrophy, duct distortion with periductal fibrosis and with intraluminal protein plugs and/or calcifications[76]. The corresponding macroscopic features of parenchymal atrophy and fibrosis, parenchymal and intraductal calcifications, ductal changes and extent of pancreatic involvement (such as focal, segmental or global) can be evaluated by CT and MRI/MRCP.

Mandatory information that is considered needed for severity scoring of CP are: 1) Extent of pancreatic involvement (MRI, CT), 2) degree of gland atrophy (MRI, CT or EUS), pancreatic head diameter (based on MRI, CT), 3) degree of ductal changes (MRI, CT or EUS), 4) degree of parenchymal fibrosis (based on MRI), and 5) presence/quantification of parenchymal calcifications (based on CT). These descriptive morphological features of the gland can be sub-grouped as major findings. As *supplementary information s-*

MRCP can quantify exocrine function[40]. However, it remains unclear and not validated how important and vital the different imaging parameters (atrophy, ductal changes and calcifications) are and how they should be combined for severity scoring of CP, see Question 13.

Secondary clinical relevant findings must also be included in the report: 1) presence of pseudocyst formation and its relation with the main pancreatic duct (MRI, CT or EUS), 2) presence of splanchnic vein thrombosis (MRI, CT), and 3) secondary obstructive complications such as gastric outlet obstruction and biliary obstruction (based on MRI, CT).

To create a common language and understandable radiology reports, structured reporting is suggested and may simplify the effort of using a scoring system.

Question 13: How should the severity of CP be graded by CT and MRI?

Severity grading by CT and MRI/MRCP should include ductal changes, parenchymal changes (calcifications on CT and fibrosis on MRI), gland atrophy and extent of pancreatic involvement. Assessment of exocrine function based on secretin-MRCP could also be factored in to the grading.

(Quality assessment: Low; Strength of recommendation: Weak; Grade 2C; Agreement: Conditional (alpha-score 75%))

Comment:

Table 1 illustrates a proposal for MRI/MRCP (and partly CT) criteria for severity scoring of CP. The combination of these criteria of grading (extent, atrophy, ductal changes, fibrosis and calcifications) into a combined severity scoring system is challenging, and has not been done previously. The major findings can be set as numeric parameters by their severity, i.e. grade 0-1-2-3. Weighted scores (like 0-2-3-4, etc.) should be considered for findings such as ductal changes that are highly specific for CP. However, a great work remains regarding quantification of imaging biomarkers to reach consensus on validated cutoff values

for a solid grading system for CP. Indeed, a lot of work is ahead for each potential imaging feature (including the understanding of the large variation in the healthy population of both gland size, fatty infiltration, single tiny calcifications, etc.) in order to be able to propose a new imaging scoring system. In daily practice, several patients have either CT or MRI rather than both (especially in non-academic setting), and it might be meaningful to have independent and comparable/parallel scoring systems for CT and MRI, with a separate score for exocrine function based on secretin-MRCP. The concept of such an approach is illustrated in Figure 2. The secondary clinical relevant findings have to be mentioned in addition to the grading system, since they would impact on the choice of treatment management.

However, a generalized approach will have many limitations. Unresolved questions are what parameters (imaging biomarkers) are the most important in describing the severity of CP (with division into identifying mild, moderate and severe degree of CP), and whether these independent scores should be weighted equally? Also, a new radiological severity scores system for CP should be clinically meaningful and relate to symptom severity, etiology and other relevant biomarkers, and have clinical relevance in for instance predicting the progression (disease trajectory) and the outcome of treatment and interventions. Imaging should be considered as a major complementary component of an adequate evaluation of the pancreas. These aspects need to be addressed in future studies.

Summary

CT is often the most appropriate initial imaging modality for the evaluation of patients with suspected CP. All patients with a suspected diagnosis of CP should in most cases undergo a baseline CT imaging. The diagnosis of mild/early CP remains challenging. However, MRI/MRCP and especially secretin-stimulated MRCP, or alternatively EUS, is more accurate in the depiction of these subtle changes. There is a need for a validated radiological scoring system based on imaging criteria including glandular volume loss, ductal changes, parenchymal calcifications, parenchymal fibrosis and exocrine function based on CT and MRI.

Table 1:

Proposed imaging criteria for severity scoring and grading of CP (MRI/MRCP and partly CT)
<p>Extent of involvement: Graded as focal (up to 1/3 of pancreas), segmental (1/3 to 2/3 of pancreas) and diffuse (more than 2/3 of pancreas) [8]. <i>PS: Consensus should be reached as to what constitutes focal, segmental and diffuse involvement.</i></p>
<p>Atrophy: Gland size (two-point linear or volumetric assessment) corrected for age and gender should be used. This is especially relevant for patients older than 60 years, where age related atrophy becomes more pronounced[77,78]. Measurements should be avoided during an episode of acute pancreatitis. <i>PS: Consensus should be reached for providing cutoff values for mild, moderate and severe atrophy.</i></p>
<p>Ductal changes: <u>Main pancreatic duct diameter:</u> Duct diameter >3 mm is considered as abnormal using secretin stimulated MRCP [40]. Correction for age should be considered. General duct dilatation is present when >2/3 of the duct is involved, and focal duct dilatation is present when <1/3 of the duct is involved [35]. <u>Main pancreatic duct stricture:</u> Focal or diffuse strictures are important to define separately. If any ductal segment is 25-50% narrower than the adjacent duct segments it should be graded mild, 50-75% as moderate, and >75% as severe. Scoring of the ductal stricture location can be considered. <u>Main pancreatic duct contour:</u> Pancreatic duct contour should be graded as smooth, mildly irregular or moderate to markedly irregular. Contour irregularity can be graded as 'mild' if it results in abrupt changes in ductal diameter of less than 25% and 'moderate to marked' if causing abrupt ductal diameter changes of >25%. <u>Abnormal side-branches:</u> Any side-branch (except uncinata and accessory ducts) should be considered abnormal if seen on MRCP and here the modified Cambridge Classification may be used. Few abnormal side-branches should be graded as mild or moderate CP, more than three and broad-based irregular shape and large side-branches should be considered as severe CP. <i>PS: Consensus should be reached for ductal grading criteria.</i></p>
<p>Fibrosis: ADC cutoff values (or in the future T1-mapping cutoff values) for mild, moderate and severe fibrosis should be established. However, establishment of common values across hospitals will be very challenging. Also T1 parenchymal signal intensity relative to spleen, paraspinal muscles or liver[79,80] and enhancement characteristics of pancreatic parenchyma on dynamic post contrast imaging (pancreatic phase, portal phase and delayed phase)[80,81] should be considered. EUS with elastography may also be a supplementary tool in order to assess the amount of parenchymal fibrosis[82–84]. <i>PS: Consensus should be reached for criteria to grade fibrosis</i></p>
<p>Calcifications: Few and small punctate calcification (less than 3 mm) should be graded as mild, whereas irregular and large calcifications and intra-ductal calcifications should be graded as moderate or severe[85]. <i>PS: Consensus should be reached for providing cutoff values for mild, moderate and severe calcifications.</i></p>

Figure legends:Figure 1:

The overall concept of “Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis”: Diagnostic imaging algorithm to patients with clinical suspicion or risk of chronic pancreatitis (CP). References to the 13 questions (Q1-13) are provided. Adjustments should be considered according to local traditions and resources, and taking the characteristics of patients into account (a-priori probability of severe CP, mild CP or normal pancreas).

Figure 2:

Proposal for a severity scoring system for grading chronic pancreatitis based on cross-sectional imaging.

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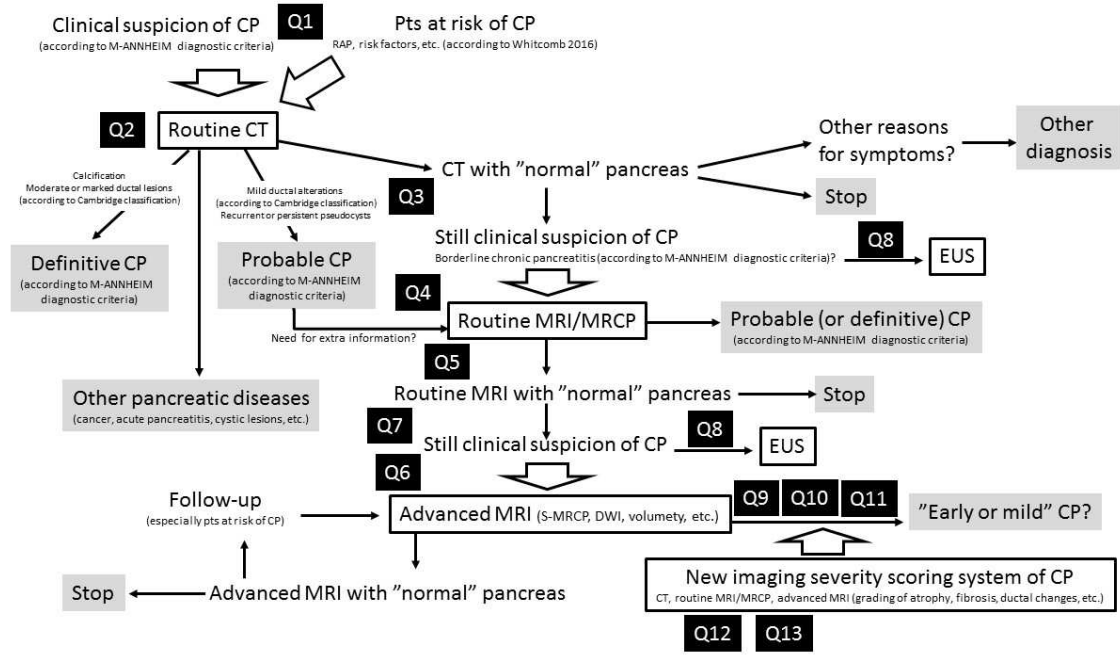
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Proposal for a cross-sectional imaging severity scoring system for grading CP

