

# S3 Guideline for Chronic Pancreatitis – Diagnosis, Classification and Therapy for the Radiologist

## S3-Leitlinie Chronische Pankreatitis: Diagnostik, Klassifikation und Therapie für die Radiologie

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### Abstract

▼  
 Chronic pancreatitis shows an increasing prevalence and incidence mainly in the Western Hemisphere. Early diagnosis and therapy are frequently delayed because of non-specific symptoms as well as non-specific blood values. The German Society of Digestive and Metabolic Diseases (DGVS) organized the preparation and publication of an interdisciplinary S3 level guideline with the support of the German Radiological Society (DRG) as 1 of 11 contributing societies. In this article we present and discuss the main topics of the guideline regarding the diagnosis, differential diagnosis and therapy of complications of this complex chronic disease with a focus on clinical and scientific radiologists.

### Key Points:

- ▶ Ultrasound represents the perfect first line imaging modality
- ▶ For further diagnostic work up MRI with MRCP are recommended for the differential diagnosis of pancreatic cancer
- ▶ For clinical studies the modified (CT, MRI) Cambridge classification is recommended

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### Zusammenfassung

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 Die chronische Pankreatitis hat vor allem in der westlichen Welt in ihrer Inzidenz und Prävalenz stark zugenommen. Durch die unspezifischen Symptome zu Beginn dieser chronischen Erkrankung bei fehlenden spezifischen Laborparametern ist die Diagnose und Therapie häufig verzögert. Über mehrere Jahre wurde die aktuelle neue deutsche S3-Leitlinie „Chronische Pankreatitis“

unter der organisatorischen Leitung der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS) mit Beteiligung der Deutschen Röntgengesellschaft (DRG) als eine von 11 kollaborierenden Gesellschaften interdisziplinär erarbeitet und veröffentlicht. Im vorliegenden Artikel möchten wir alle für den klinisch und wissenschaftlich arbeitenden Radiologen wichtigen Punkte für die Diagnose, Differentialdiagnose sowie Therapie von Komplikationen dieses komplexen chronischen Krankheitsbildes basierend auf der neuen Leitlinie zusammenstellen und diskutieren.

### Introduction

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 The prevalence and incidence of chronic pancreatitis are increasing in the Western world. The worldwide incidence is between 1.6 and 23 per 100 000 with increasing prevalence [1]. Despite the fact that the disease is typically treated on an outpatient basis, over 10 000 inpatient cases per year have been seen in Germany not including the over 50 000 cases per year of acute episodes of chronic pancreatitis, which are classified as acute pancreatitis. The overall mortality rate of the disease is specified as approximately 28–35% with the death rate of the disease being 3.6 times higher compared to the normal population [2–4]. Continued alcohol consumption significantly shortens the survival time for the disease. In the case of alcohol abstinence, the 10-year survival rate is approximately 70% and the 20-year survival rate is 45% [5]. Alcohol is the most important risk factor among adults. However, the relationship to alcohol consumption does not appear to be linear [6]. There is no clear indication that chronic pancreatitis is triggered by cholelithiasis or choledocholithiasis [7]. Anato-

mical variants, such as pancreas divisum, do not appear to be etiological [8].

Despite broad epidemiological distribution and important socioeconomic factors, the diagnosis and treatment of chronic pancreatitis are still delayed and difficult in some cases even in the 21st century. A problem for early diagnosis is the lack of specific laboratory parameters in the case of frequently non-specific clinical symptoms.

An interdisciplinary evidence-based S3 guideline for the diagnosis, staging, and treatment of chronic pancreatitis was created after many years of preparation and organization by the German Society of Digestive and Metabolic Diseases. Representatives of the Gastrointestinal and Abdominal Diagnostics Workgroup ([www.ag-gastro.drg.de](http://www.ag-gastro.drg.de)) of the German Radiological Society were significantly involved in creating the guideline for imaging diagnostics and treatment.

## Method

The guideline recommendations are specified according to the particular level of evidence corresponding to the Oxford scheme (<http://www.cebm.net>). The recommendations are formulated to reflect the strength of the recommendation. The level of consensus is determined by the percentage agreement of the consensus conference participants as follows: strong consensus >95%, consensus 65% to 95%, and majority agreement 50% to 75%. The guidelines were created according to the regulations of the AWMF for S3 guidelines after the creation of workgroups via systematic and documented literature research and critical evaluation of the literature with consecutive consensus building via Delphi rounds with online questionnaires and a subsequent 2-day consensus conference. The following discusses the relevant topics of the guidelines for radiological diagnostics as well as the possible treatment of chronic pancreatitis and its complications. Statements from the guidelines are cited and are then discussed and commented on with a focus on radiological issues regarding diagnostics and treatment.

## Definition of chronic pancreatitis

Chronic pancreatitis is defined as a disease of the pancreas in which the pancreatic parenchyma is replaced by fibrotic connective tissue as a result of recurring inflammatory episodes. This results in a loss of exocrine and endocrine pancreatic function and typical complications such as pseudocysts, pancreatic duct stenoses, duodenal stenoses, or vascular or biliary tract complications. The main clinical complications and symptoms are malnutrition and pain syndromes [9]. In addition, the risk of a pancreatic carcinoma is increased by a factor of 16 in chronic pancreatitis [5]. Diagnosis is made based on clinical, morphological, and functional parameters of the disease. Since these three points correlate only insufficiently with the clinical symptoms, which primarily consist of non-specific abdominal pain, clinical as well as morphological and functional diagnostic methods are to be used in a complementary manner.

## Diagnosis of the disease

The guidelines recommend transabdominal sonographic examination of the pancreas as the primary imaging method following careful recording of the anamnesis and clinical examination. In the case of an unclear finding in sonography which should typically show an inhomogeneous organ and changes to the pancreatic duct, endosonographic (EUS) clarification can be performed as a further method and can be followed by histological or cytological diagnosis with EUS-supported fine-needle puncture. Computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are defined as supplementary diagnostic methods in the case of unclear pancreatic changes on ultrasound and endosonography. These recommendations are specified with evidence level IIA and recommendation level B. According to the literature, endosonography achieves similar results to endoscopic retrograde pancreatography (ERP) with respect to disease diagnosis but does not involve the complications and side effects of ERP [10–13]. Therefore, the relatively stressful and invasive ER(C)P method is no longer viewed as the gold standard in the current guideline. MRI with MRCP has also shown high sensitivities in prospective studies in the diagnosis of a malignancy and with a sensitivity of 84% and a specificity of 94% even appears superior to ERCP [14]. Among diagnostic methods, EUS is the leading method with regard to sensitivity and specificity. However, there are only a limited number of studies and no adequate meta-analyses (Table 1). Unfortunately, there are no large prospective randomized studies comparing computed tomography with EUS and ultrasound in chronic pancreatitis. There are only comparative prospective studies for ERCP with EUS and MRCP with EUS [15, 16] as well as ultrasound with ERCP [17].

With respect to the possible administration of secretin for better visualization of the pancreatic ducts in MRCP, there are no definitive statements and recommendations in the guidelines due to a lack of comparative prospective literature in adults [18–21]. The administration of secretin is only recommended in the diagnosis of pediatric patients to increase the diagnostic relevance of MRCP on the basis of two publications [21, 22].

Based on the currently available studies and socioeconomic aspects, sonography should therefore be performed first in the case of suspicion of chronic pancreatitis. In the case of a normal imaging finding, EUS possibly with puncture for histology or with cytology can then be additionally performed [23–25]. CT and especially MRI with MRCP are important for further diagnostics and for possible treatment planning

**Table 1** Sensitivity and specificity of imaging methods for diagnosing chronic pancreatitis according to the current literature.

examination	sensitivity	specificity	evidence	references
CT	n/a	n/a	2b	[15]
ERCP	70–80%	80–100%	2a	[14, 15, 47–50]
MRCP	88%	98%	2b	[16, 28]
US	60–81%	70–97%	2a	[14, 26, 51]
EUS	80–100%	80–100%	2a	[23, 24, 48, 52, 53]

in terms of surgical planning or the differential diagnosis of tumors [15, 26].

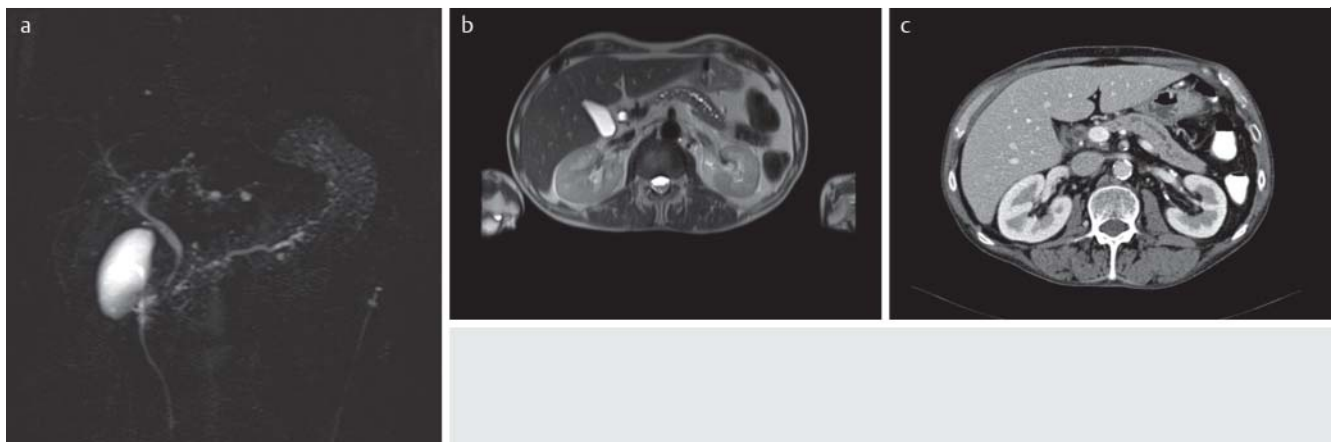
### Imaging classification

Modifications of the Cambridge classification, which was primarily created for ERC, CT, and ultrasound, should be used to classify chronic pancreatitis with imaging methods (Table 2) [27]. In the case of ERC, a classification of Cambridge 0 indicates absolutely no pathological change of the pancreatic duct, Cambridge I indicates less than 3 pathological side branches with a normal main duct, Cambridge II indicates more than 3 pathological side branches with a normal main duct, and Cambridge III indicates more than 3 pathological side branches with a pathological main duct. Cambridge IV additionally includes cystic changes and duct stones and strictures. As mentioned above, the original Cambridge classification was limited to duct visualization via ERP with an expansion to include CT and ultrasound.

Therefore, adaptations and standardizations of the nomenclature for sonography, CT and primarily MRCP are being undertaken and will be important for future multimodal clinical studies [12, 18, 28–30]. In the radiological adaptation of the Cambridge classification (Fig. 1–3) for CT and MRI, the modification of Cambridge 0 entails absolutely no changes. Changes cannot be defined in Cambridge 1 with current CT and MRI techniques. In the CT/MRCP modification, Cambridge 2 means 2 or more of the following changes (Fig. 1): Pancreatic duct between 2 mm and 4 mm in the body of the pancreas, discrete enlargement of the pancreas, heterogeneous parenchymal structures, cystic changes < 10 mm, duct irregularities, pathological side ducts. In the case of Cambridge 3 (Fig. 2), all of the changes mentioned for II must be present with a pathological main duct, while in Cambridge 4 (Fig. 3) cystic structures > 10 mm with parenchymal calcifications (Fig. 4), interductal defects, duct obstructions, and severe duct irregularities must additionally be present. In contrast to the ERP-based Cambridge classification, changes in the pancreatic parenchyma are

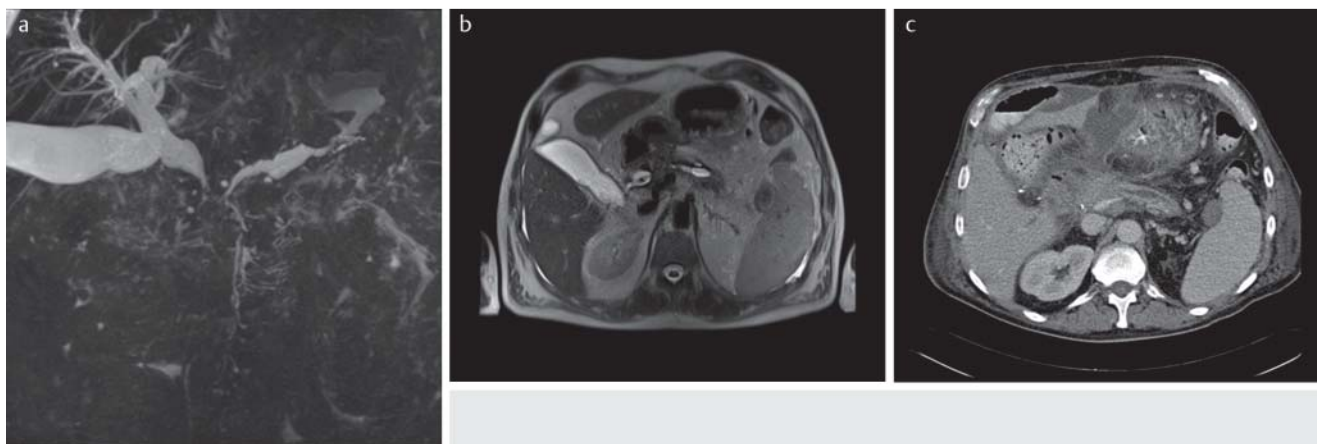
**Table 2** Summary of the Cambridge classification with modification for CT and MRCP.

Cambridge	ERCP	CT/MRCP
0	no pathological changes with complete visualization of the pancreatic duct	none
1	fewer than 3 pathological side branches, normal main duct	cannot be delimited in CT/MRCP with current methods
2	3 or more pathological side branches, normal main duct	2 or more of the following changes: – pancreatic duct between 2 and 4 mm in the body of the pancreas – slight enlargement of the pancreas – heterogeneous parenchymal structure – small cystic changes (< 10 mm) – duct irregularities – 3 or more pathological side ducts
3	3 or more pathological side branches plus pathological main duct	all changes specified in 2 plus pathological main duct (> 4 mm)
4	as in 3 plus cysts, duct stones, strictures, involvement of neighboring organs	one of the changes specified in 2 and 3 plus one or more of the following: – cystic structures > 10 mm – parenchymal calcifications intraductal filling defects (chalk stones) – duct obstruction (strictures), severe duct irregularities



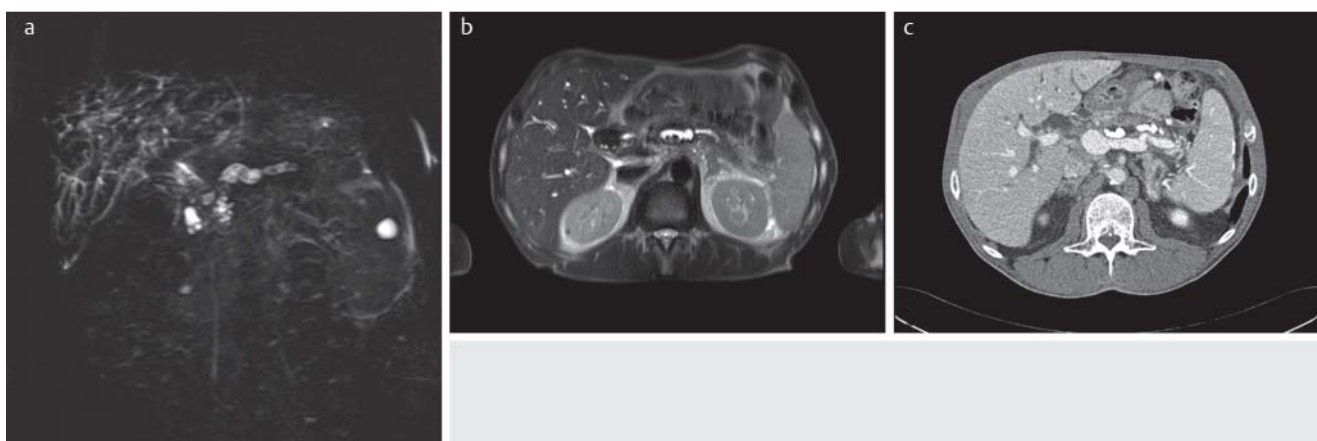
**Fig. 1** 56-year-old patient with chronic pancreatitis (Cambridge 2): **a** Coronal 3D-MIP-MRCP with discretely dilated pancreatic duct (to 3 mm) with duct irregularities and small, cystic changes. **b** Corresponding axial T2 se-

quence with irregularities of the pancreatic duct and cystic lesions of the pancreas. **c** Axial CT on corresponding slice plane in the portal venous phase with emphasis of the pancreatic duct without evidence of calcifications.



**Fig. 2** 63-year-old patient with chronic pancreatitis (Cambridge 3): **a** Coronal 3D-MIP-MRCP with greatly dilated pancreatic duct (> 4 mm) with significant duct irregularities and cystic changes, pathological pancreatic side branches and intra- and extrahepatic cholestasis. **b** Corresponding axial

T2 sequence with significantly dilated pancreatic duct and cystic lesions of the pancreas. **c** Axial CT on corresponding slice plane in portal venous phase with dilated pancreatic duct and start of calcification in the head of the pancreas.



**Fig. 3** 58-year-old patient with chronic pancreatitis (Cambridge 4): **a** Coronal 3D-MIP-MRCP with massively dilated pancreatic duct (> 4 mm) with strictures and evidence of intraductal filling defects. **b** Corresponding axial

T2 sequence with dilation of the pancreatic duct, duct stricture, and intraductal filling defects. **c** Axial CT on corresponding slice plane in portal venous phase with dilated pancreatic ducts and intraductal chalk stones.

also taken into consideration in the imaging methods. In principle, this classification should be primarily used for study classification since it provides a uniform classification even for different imaging methods.

### Imaging of typical complications of chronic pancreatitis

In the case of necrosis, contrast-enhanced ultrasound examination (CEUS) is put on par with contrast-enhanced CT even though an evaluation of severity as in CT is not possible [31]. Moreover, this statement is based on a single publication and has not yet been confirmed by further studies [32]. In the clinical routine contrast-enhanced CT continues to be the method of choice due to its high availability and objectivity especially since CEUS currently still requires a high degree of specialization on the part of the examiner. Contrast-enhanced MRI can also be used with the same

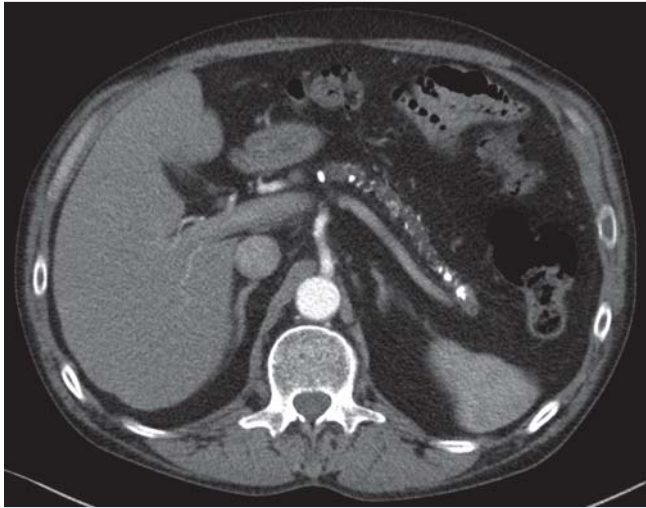
sensitivity and specificity. However, this still plays a secondary role in practice [32, 33].

In the case of cysts (Fig. 5), transabdominal ultrasound is initially viewed as sufficient. EUS and MRI with MRCP are specified as additional methods for differentiation with a higher transfer rate between pancreatic lesions. However, sonography should typically be sufficient [34].

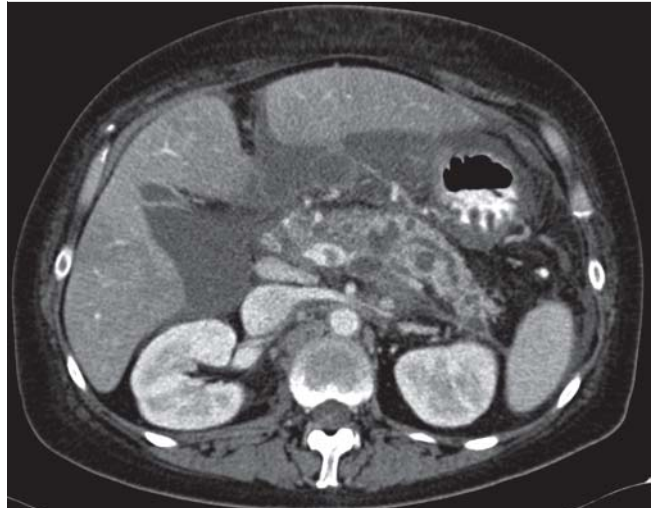
In the case of vascular changes, pseudoaneurysms in particular are a typical complication. Basic diagnosis via sonography with additional color Doppler is typically sufficient in most cases. For interventional and surgical planning, CT angiography or MR angiography should be performed. However, as in the case of sonography, there are also no adequate comparative studies here.

### Differential diagnosis in chronic pancreatitis

When diagnosing pancreatic carcinomas in patients with chronic pancreatitis, regular percutaneous ultrasound pro-



**Fig. 4** 48-year-old patient with chronic pancreatitis (Cambridge 4): Contrast-enhanced CT of the upper abdomen shows multiple calcifications in the atrophied pancreatic parenchyma.



**Fig. 5** 52-year-old patient with chronic pancreatitis (Cambridge 4): CT of the upper abdomen shows cystic changes in the pancreatic parenchyma with a dilated and irregular pancreatic duct.

vides insufficient differentiation between carcinomas and inflammatory changes. EUS with fine-needle puncture has a sensitivity of over 85% [35, 36]. For MRI with MRCP current studies specify sensitivities of approximately 84% with a specificity of 97%, while a sensitivity of 93% and a specificity of 75% were calculated for the differentiation between focal pancreatic masses in chronic pancreatitis and pancreatic carcinomas [37]. Both necrotic changes and pancreatic carcinomas have hypoperfused areas. Since EUS-based fine-needle puncture has a relatively high rate of false-negative findings, its use for ruling out surgical treatment also seems limited [38]. Histological or cytological fine-needle puncture can be helpful for the differentiation between autoimmune pancreatitis and other pancreatic diseases since up to 40% of cases of autoimmune pancreatitis present with focal lesions [39]. In principle, there is virtually no diagnostic value in performing ERP as a primary diagnostic method. Four criteria with a high sensitivity and specificity were defined only for autoimmune pancreatitis. Long stenoses > 1/3 of the pancreatic length, a lack of dilation of the downstream pancreatic duct, dilation of the side branches and multifocal strictures in the course of the pancreatic duct are described as changes indicative of autoimmune pancreatitis [34]. ERP is therefore still required for diagnosing autoimmune pancreatitis in the Japanese guidelines. ERP is explicitly not specified as the primary diagnostic method in the German S3 guideline. Instead, EUS and/or MRI with MRCP is recommended. ERP should only be performed in individual cases of unclear EUS or MRCP findings.

### Treatment of typical complications

Pancreatic pseudocysts are the most common complication of both acute and chronic pancreatitis with the prevalence in chronic pancreatitis being 20–40% [40]. Pancreatic pseudocysts are most common in patients with alcohol-based chronic pancreatitis [2]. Pancreatic pseudocysts spontaneously regress 6 weeks after formation in up to 40% of patients. If pseudocysts persist for more than 12

weeks, spontaneous remission is very improbable with additional complications occurring in up to 60% of cases [41]. The timing and the performing of possible therapeutic interventions in the case of pancreatic pseudocysts were partially controversial in the guideline discussion. According to the published guidelines, pseudocysts with a total size of over 5 cm and a capsule with a thickness of more than 5 mm were associated with complications. Treatment can be in the form of surgery in terms of fenestration or percutaneous and endoscopic drainage. The data regarding intervention in the case of pseudocysts is very limited. There are no suitable prospective studies. Placement of a stent in the bile duct can be sufficient in the case of cholestasis caused by a pseudocyst. In the case of compression of larger vessels or gastric outlet stenoses, the pancreatic pseudocyst should be drained. However, an endoscopic endoluminal drainage procedure that seems to have fewer complications than a surgical approach should be given preference [34, 40]. In principle, percutaneous radiological procedures are possible but are associated with a high risk of external fistula formation so that this method should not be performed if endoscopic drainage is possible. Particularly in the case of infected cysts, drains placed under radiology guidance have worse results than endoscopically placed drains. However, both minimally invasive procedures are better than the surgical approach [40].

### Vascular complications

In particular, vascular pseudoaneurysms in chronic pancreatitis must be mentioned here. These should be treated due to a risk of bleeding although there are no evidence-based prospective studies. Bleeding pseudoaneurysms should be treated due to the low morbidity of the radiological-interventional method compared to surgery with angiographic embolization. According to the literature, the success rate of angiography is approximately 66% [42].

## Follow-up

Examinations and imaging methods in intervals between 6 and 12 months after diagnosis are recommended for clinical follow-up to detect complications early. However, there are insufficient studies to support this time interval. In addition to clinical and laboratory examinations, follow-up primarily with transabdominal ultrasound examinations is recommended and with a sensitivity of approximately 60–81% is largely in the range of the sensitivity of CT or MRI examinations (Table 1). The only problem with ultrasound examination is poor specificity of approximately 35% so that the examination should be supplemented by EUS, ERCP, CT, or MRI in the case of unclear findings [43]. In the case of suspicion of a complication or the formation of a pancreatic carcinoma, the corresponding imaging (CT or MRI/MRCP) must be performed in the further course. None of the described methods has sufficient reliability to definitively rule out an operable malignancy in the case of chronic pancreatitis. According to the current literature, endosonography seems to be superior particularly due to the possibility to take biopsies. However, MRI with MRCP can be assigned a higher diagnostic value [14, 36]. Tumor markers are not very helpful with respect to pancreatic carcinomas in patients with chronic pancreatitis. The diagnostic sensitivity and specificity are not sufficient. The extent to which MRI together with diffusion-weighted sequences and dynamic MRI examinations can provide additional differential diagnostic help must be further clarified. Based on the current literature, it seems rather improbable that MRI with diffusion-weighted sequences will result in a relevant improvement in differential diagnosis [44–46].

## Summary

According to the first evidence-based German S3 guidelines regarding the diagnosis and treatment of chronic pancreatitis, transabdominal sonography is the basic examination of choice for initial diagnosis as well as in the further course for early clarification of possible complications. MRI with MRCP has a very high diagnostic value both for classification for studies and for early diagnosis and differential diagnosis of possible pancreatic carcinomas that frequently occur in patients with chronic pancreatitis. The Cambridge classification should be used in studies since it provides comparable classifications and results via modifications for the most important imaging methods. Transcutaneous methods should only be used on a limited basis in the treatment of complications, such as pancreatic pseudocysts, since fistula formation is a common complication. Angiographic embolization of vascular aneurysms in chronic pancreatitis is the method of choice for acute bleeding or for prophylaxis.

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