J. Mössner

Guidelines, Clinical Evaluation, Short Track

History may reveal known gallbladder stones or alcohol abuse as potential causes of acute pancreatitis. Physical findings are dependent upon the severity of the disease. However, serum laboratory parameters and imaging procedures are mandatory not only for diagnosis, but also for decision making for further therapeutic options. Contrast-enhanced computed tomography (CT) is the most accurate, noninvasive, single method for evaluating the severity of acute pancreatitis. Detection of bacterial infection of necrosis is mandatory to decide between the continuation of conservative treatment or indication for either surgery or endoscopically transgastral or transcutaneous CT-guided drainages. In chronic pancreatitis, leading symptoms are upper relapsing abdominal pain and weight loss. There are numerous imaging procedures that can be used to diagnose chronic pancreatitis and its complications. Due to rapid technical improvements, comparative trials between CT, magnetic resonance (MR) cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endosonography are mostly outdated at the time of publishing. Endosonography has probably the highest sensitivity in diagnosing early changes in chronic pancreatitis. Pancreatic function tests are usually not necessary for further therapeutic decisions. Up to now there are no reliable and cost-effective screening methods for detecting early pancreatic cancer. Diagnosis of pancreatic cancer at a stage where the disease can be cured is a rather rare event. Transabdominal sonography may already diagnose metastatic disease. However, most patients with suspicion of pancreatic cancer will have an abdominal CT to detect the tumor. MR imaging (MRI) in combination with MR-angiography and MRCP ("one-stop shopping") is probably the most reliable method for the decision as to whether the patient can still be operated with R0 resection as a main goal. Despite the use of all imaging procedures, in up to 25% irresectability is only seen during operation. Another unresolved problem is the early diagnosis of pancreatic cancer in patients with chronic pancreatitis. Positron emission tomography (PET) does not help very much in the differentiation between chronic inflammation and pancreatic cancer. The following chapter presents some recent comparative trials of various imaging procedures regarding their sensitivity and specificity in the diagnosis of the three leading diseases of the exocrine pancreas (i.e., acute and chronic pancreatitis, and pancreatic cancer). However, due to the lack of comparative trials stratified to the various stages of each disease, the diagnostic recommendations (i.e., "short track") cannot completely avoid the subjective recommendations of the author.

Acute Pancreatitis

History

Gallstones and excessive alcohol abuse are the most important risk factors for acute pancreatitis. Sometimes acute pancreatitis is initiated by large fatty meals and/or acute alcohol excess. Thus, history may reveal known gallbladder stones or alcohol abuse. Amongst numerous rare causes, such as drugs (e.g., angiotensin converting enzyme inhibitors, L-asparaginase, azathioprine, 6-mercaptopurine, estrogens, sulfasalazine, 5-aminosalicylic acid, thiazides, valproic acid), hyperlipidemia, hypercalcemia, trauma, and viral infection (mumps), one has to mention diagnostic and therapeutic ERCP. According to a prospective multicenter study, when endosonography was performed to confirm or exclude a biliary origin of acute pancreatitis, age, gender, and alanine transaminase levels at admission were the only factors predictive of a biliary cause [32].

The typical symptoms of acute pancreatitis are severe, knifelike pain located in the upper and midepigastric abdomen combined with nausea, vomiting, and anorexia [54]. Pain may radiate to the back like a belt. The onset of pain is rather rapid, but not as rapid as in perforated duodenal or gastric ulcer. At the beginning, pain may be colic-like, and later more dif-

fuse and felt deep in the abdomen. Pain may gradually increase; mostly it is steady and very severe. In mild pancreatitis, pain resolves after a few days but may return after the patient starts to eat. In severe attacks, pain progresses.

Physical Findings

The physical findings are dependent upon the severity of the disease. Abdominal tenderness varies from mild to severe. In severe pancreatitis, the patient looks severely ill, lies still, and often has abdominal distention. One will find tenderness in the upper abdomen. In necrotizing pancreatitis, a progression to peritonitis is possible. Due to the inflammation of an organ located retroperitoneally, signs of peritonism are usually absent at the beginning. In metabolic or hereditary cases and in cases associated with alcohol abuse, the onset may be less abrupt [54].

Rarely seen, but typical for a severe course, is a brownish discoloration of the skin (i.e., ecchymosis) due to the spread of the inflammation to flanks (Grey-Turner-sign) and the periumbilical region (Cullen-sign). When these signs are present, the prognosis is usually worse. On auscultation, bowel sounds are reduced or absent as signs of paralytic ileus. Tachycardia and fall in blood pressure are already symptoms of the beginning shock syndrome. Shock and fall in hemoglobin may be caused by gastrointestinal bleeding (peptic ulcer, Mallory-Weiss-syndrome), or intra-abdominal or retroperitoneal bleeding, splenic lesions, or vessel arrosions. Flushing of the face is the consequence of the release of vasoactive substances. Fever may be present initially due to aseptic inflammation, and later as a sign of sepsis due to infected necrosis. Fever over 38.5°C, chills, shock, leukocytosis above 16,000/µl, thrombocytopenia, and metabolic acidosis are signs of a septic course, the most severe complication. Further clinical signs of a severe course are hypotension, shock, oligo-, anuria, dyspnea, bleedings, precoma, and coma. Shallow respiration and tachypnea can be caused by subdiaphragmatic exudates, leading to painful breathing.

Severe vomiting may be due to duodenal compression caused by the inflammatory mass of the head of the pancreas or due to paralytic ileus. Jaundice may be seen when the distal bile duct is compressed. Ascites and ileus lead to an increase in the abdominal circumference. In alcoholic pancreatitis, when liver damage is also present, one may see typical liver skin signs, such as, for example, spider angiomas and thickening of the palmar sheaths.

Necrosis, Abscess, Sepsis

Necrosis of the pancreas is a potentially very harmful complication. Primarily there are no bacteria in the pancreas. Paralytic ileus favors the penetration of bacteria from the gut into the pancreas. Infected necrosis is the source for sepsis causing an increase in mortality. Leukocytosis is seen even in uncomplicated pancreatitis. However, leukocytosis is especially prominent in sepsis. The presence of fever is an indication for contrast-enhanced CT to detect necrosis and perform fine-needle aspiration (FNA) microbiology. Contrast-enhanced CT remains the most accurate noninvasive single method for evaluating the severity of acute pancreatitis [20, 24, 30].

Shock

Due to fluid and blood losses into the retroperitoneum and fluid losses caused by paralytic ileus, blood circulation is endangered. Measurement of blood pressure, pulse rate, and central venous pressure is mandatory for the early detection of shock syndrome. In necrotizing pancreatitis, blood penetrates not only the retroperitoneum, but may also penetrate the intestine. This may cause severe blood loss. Furthermore, bleeding may be caused by stress ulcerations of the stomach and duodenum. Disturbances in serum electrolytes can be marked due to enormous fluid losses. Hypocalcemia may also result from fat necrosis.

Acute Kidney Failure

Severe volume losses and toxic damage of the renal tubuli are responsible for kidney failure. Measurement of 24-h urinary excretion is obligatory. Values below 40 ml/h are critical. Elevation of serum creatinine may be seen after a delay. Serum levels of creatinine and urea have to be determined to detect renal failure.

Acute Respiratory Distress Syndrome, Shock Lung

Analysis of blood oxygen and carbon dioxide and acid–base status are mandatory to detect respiratory insufficiency and determine indications for artificial ventilation (decrease of oxygen partial pressure of <65 mmHg). Auscultation of the lungs and chest x-ray are not very helpful in this regard.

Obstruction of the Common Bile Duct

In obstruction of the bile outlet due to impacted bile stones or an inflammatory mass of the pancreatic head, one will see cholestasis in serum parameters such as elevation of gamma-glutamyl transferase, alkaline phosphatase, and bilirubin. Jaundice is only seen in marked obstruction.

Disseminated Intravascular Coagulation

In disseminated intravascular coagulation one will find hematomas of the skin. It is very important to establish patients at risk of having a severe, potentially lethal course of the disease. Numerous various scoring systems, such as the Atlanta criteria, Ransons's score, CT severity index, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Glasgow score, Multi Organ System Score, and urinary trypsinogen activation peptide are available (for further literature see [13, 14, 31, 37, 41, 49, 54, 55]). Besides the CT severity index, these all include the combination of clinical parameters and various laboratory values, which will be discussed in another chapter. None of these scoring systems is simple, really easy to perform, or absolutely reliable to early detect those patients at risk.

Systemic inflammatory response syndrome (SIRS) is rather easy to detect and monitor. SIRS is characterized by two or more of the following signs: temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20/min; arterial carbon dioxide partial pressure <32 mmHg; leukocytosis >12,000/µl; leukopenia <4000/µl. The course of SIRS is highly predictive of further prognosis [40].

A differential diagnosis of chronic pancreatitis is described in Table 13.1.

Short Track

Diagnosis and Clarification of Etiology

Pancreatitis is mostly proven when abdominal pain and elevation of serum lipase more than three times above normal are present [27]. In fulminant pancreatitis and delayed diagnostic work up, serum lipase can already be normal due to loss of pancreatic acini [56]. Patient history may already help to discriminate between biliary and alcohol-induced pancreatitis or rare causes such as drugs. MRCP can be used to detect bile duct stones, with high sensitivity [46]. However, endosonography is probably the most sensitive method to detect bile duct stones and has replaced diagnostic ERCP. In contrast to ERCP, endosonography imposes only a minor risk of inducing or aggravating pancreatitis. Endosonography is also the most sensitive method for detecting early pancreatic changes characteristic of chronic pancreatitis [45]. In a recent study using endosonography to confirm or exclude a biliary origin of acute pancreatitis, it was reported that age, gender, and alanine transaminase level at admission were the only factors predictive of a biliary cause [32]. Acute pancreatitis should not be declared as idiopathic as long endosonography has not excluded abnormalities such as bile duct stones [42].

Evaluation of Severity of the Disease

Serum levels of lipase or other pancreatic enzymes do not correlate with the severity of the disease. Other parameters such as trypsinogen activation peptide, polymorphonuclear-elastase, and hematocrit are either not evaluated in larger trials or are not routinely available, such as determination of interleukin-6.

Table 13.1. Differential diagnosis of acute pancreatitis. *CT* Computed tomography, *ECG* electrocardiogram, *CK* cholecystokinin

Diagnosis	Diagnostic procedures
Perforation of gastric or duodenal ulcer	Free air: abdominal plain x-ray: upright or left-sided position
Acute cholecystitis	History of colic possible, pain in right upper abdomen, sonography
Occlusion of mesenteric artery	History of postprandial pain, angiography
Aneurysma dissecans of abdominal aorta	Sonography, CT
Ileus	Abdominal plain x-ray
Acute appendicitis	History, physical examination, laboratory, sonography
Left-sided ureter colic	Sonography, urography
Heart infarction	History, ECG, troponin, CK, CK-MB
Lung embolus with pleuritis	Physical examination, D-dimer, chest x-ray, echocardiography, chest CT, perfusion scintigraphy

Obesity is certainly a risk factor of both the severity and mortality of the disease [36]. Serum C-reactive protein and contrast-enhanced CT are the most reliable methods of detecting pancreatic necrosis [5, 6, 9]. MRI may be as sensitive and has not the risk to deteriorate renal function. However, severely ill patients are more difficult to handle in MRI as compared to CT. To evaluate the development and extension of pancreatic necrosis, CT is better performed not earlier than 2 days after the clinical onset of pancreatitis. However, CT is often indicated in patients with acute abdomen of unknown origin. A normal pancreas in CT excludes pancreatitis as a cause of acute abdomen. Up to now there are no simple screening techniques and laboratory parameters for predicting the further course of the disease. Ranson's score, the Imrie-Glasgow score, APACHE II score, and Atlanta criteria have been offered to characterize the severity of the disease and to predict prognosis [10, 13, 22, 43, 48]. These criteria, however, are not routinely used by all experts treating patients with acute pancreatitis. A recent study reported that the interobserver agreement of the Atlanta classification for categorizing peripancreatic collections in acute pancreatitis on CT was rather poor [8]. The Marshall score is used to monitor organ failure. Rapid resolution of organ failure (i.e., within 48 h) is suggestive of a good prognosis, in contrast to persistent organ failure [23].

Detection of bacterial infection of necrosis is mandatory to decide between continuation of conservative treatment or indication for either surgery or endoscopically transgastral or transcutaneous CT-guided drainages. CT- or ultrasonographically guided FNA are standard [7, 18, 44]. Further signs of infected necrosis or sepsis are provided by measurements of rectal temperature (>38.5°C), hematocrit (<35%), and oxygen partial pressure (<60 mmHg) [9].

Chronic Pancreatitis

History

In the industrialized nations, up to 80% of all cases of chronic pancreatitis are caused by alcohol abuse. Thus, by careful history, consumption of more than 80 g of alcohol per day can be found. Alcohol-induced chronic pancreatitis may evolve from acute pancreatitis [3]. Alcohol consumption is often associated with cigarette smoking. Smoking per se does not seem to be a risk factor for chronic pancreatitis. In less than 5%, a family history of pancreatic diseases, especially chronic pancreatitis, can be found. In hereditary chronic pancreatitis, an autosomal dominant disease with a penetrance rate of about 80%, mutations of the cationic trypsinogen are reported. In alcoholic pancreatitis these mutations are almost absent [50]. In patients with so-called idiopathic chronic pancreatitis, a serum elevation of IgG4 and detection of antibodies against carbonic anhydrase should be suspicious for autoimmune pancreatitis [4].

Leading symptoms are upper relapsing abdominal pain and weight loss later during the course of the disease [16, 47]. The disease may be classified according to different stages. In early stage I, patients are either pain free or report noncharacteristic upper abdominal discomfort. Pain may be intermittent and lasts for days and weeks. Pain is felt deep in the abdomen and sometimes like a belt with radiation into the back. Pain may improve by application of local heat (Fig. 13.1) and in a more sitting forward position. Pain is described as piercing and penetrating. In stage II,

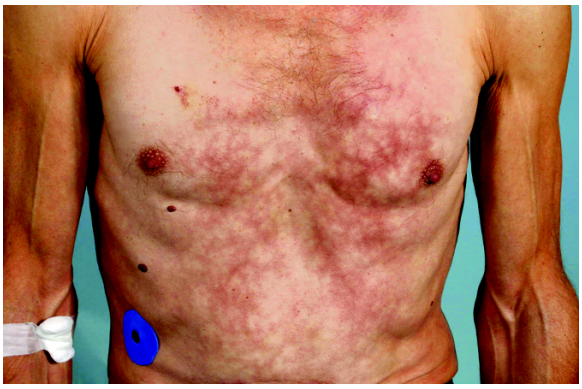

Figure 13.1

Patient with chronic pancreatitis: "erythema ab igne" due to chronic application of heat to alleviate pain

Table 13.2. Causes of pain in chronic pancreatitis

Hypertension of ducts due to obstruction
Stones, scars, pseudocysts
Inflammatory infiltration of sensory nerves
Retroperitoneal effusions
Ischemia
Compression/distension of biliary duct, duodenum, pancreatic "capsule"
Inflammatory mass, pseudocyst
Extrapancreatic causes
Ulcer, meteorism due to steatorrhea
Psychological disorders due to alcoholism

Table 13.3. Symptoms caused by pancreatic pseudocysts

Pathophysiology	Symptoms and clinical findings
Dependent on size, localization and speed of enlargement	Pain
Compression of duodenum and/or stomach	Pain, vomiting
Rupture into the abdomen	Pancreatic ascites
Infection of ascites	Peritonitis
Rupture into the gut	Spontaneous "healing"
Connection with pleura	Pleural effusion, dyspnea
Erosion of vessels	Life threatening bleeding
Thrombosis of splenic vein	Fundic varices, bleeding

patients have intermittent, often severe pain attacks or chronic pain. There is a wide variation regarding length of pain (days to weeks), interval between pain attacks, and the severity of pain. There are numerous causes of pain (Table 13.2) and these causes may vary during the course of the disease. At the clinical beginning of the disease the first acute attack can often not be differentiated from acute pancreatitis. Severe courses like necrotizing pancreatitis needing intensive care are possible. In most cases, acute relapses can be treated conservatively. During stage II, complicated courses like the formation of pseudocysts are typical. Some patients experience a decrease in severity of their relapses due to the destruction of pancreatic parenchyma, which is a substrate for inflammation [2]. Pain may "burn out." This observation by the Zürich group, however, has not been uniformly confirmed.

Pseudocysts may lead to a wide variety of symptoms (Table 13.3). Jaundice may be caused by bile outlet obstruction due to the inflammatory mass of the pancreatic head, fibrosis of the distal bile duct, or by a pseudocyst. Biliary obstruction in chronic pancreatitis alone does not seem to cause pain [25].

In stage III, symptoms of exocrine and endocrine insufficiency are dominant. Diabetes is more difficult to control in alcoholics with chronic pancreatitis due to several reasons, such as lack of anti-insulin hormones (i.e., glucagon), noncompliance, and dietary faults (sometimes due to pain attacks caused by eating). Steatorrhea may lead to bacterial overgrowth, causing pain due to meteorism. Treatment with porcine pancreatic extracts may improve abdominal discomfort. However, the assumption that pancreatic enzymes inhibit pancreatic enzyme secretion via a negative-feedback mechanism and thus are beneficial in the treatment of pain is not supported by clinical studies [38].

Due to long-term cigarette smoking, patients may report symptoms of severe arteriosclerosis, such as "claudicatio intermittens," angina pectoris, and pneumonia. Symptoms due to lung cancers, and cancers of the throat and esophagus are also not uncommon.

About 5% of all patients never experienced pain attacks and may present at the first time already with symptoms of severe exocrine insufficiency, such as weight loss and steatorrhea. During the first years of the disease, with often noncharacteristic abdominal symptoms, diagnosis may be difficult.

Autoimmune pancreatitis is receiving increasing attention. Without imaging procedures such as MRI, MRCP, and endosonography, and certain serum parameters, such as the presence of antibodies against carbonic anhydrase and elevation of IgG4, it is not able to make a diagnosis just by clinical means. Sometimes these patients have additional symptoms due to other concomitant autoimmune disorders such as Sjogren's syndrome.

Physical Findings

Pain in the upper abdomen by deep palpation is a rather unspecific sign and can be seen in numerous abdominal diseases. Rarely, one can feel a large pancreatic pseudocyst. One has to pay attention to the typical signs of chronic alcohol and nicotine abuse such as yellow fingertips and liver skin signs when alcoholic liver damage is also present. In rare cases, but highly specific for chronic pancreatitis, a brownish discoloration of the skin located in the upper abdomen can be seen, so called "erythema ab igne" (Fig. 13.1). These skin changes are caused by continuous slight burning injuries due to the application of heat to improve abdominal pain.

The body mass index may be normal in the beginning of the disease. Chronic alcoholics who smoke

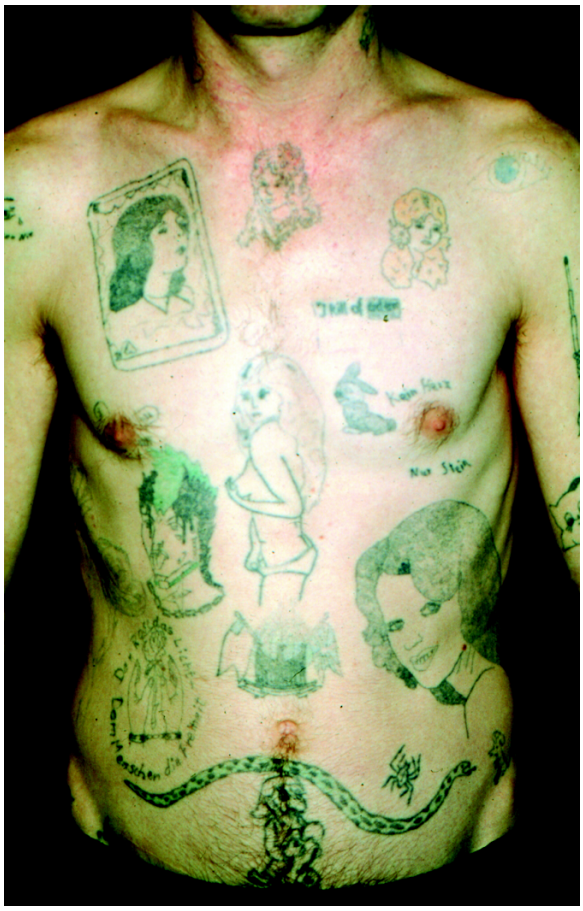

Figure 13.2

Patient with chronic pancreatitis: underweight and many tattoos

heavily are seldom overweight and are often malnourished. Decrease of body weight during the early stages of chronic pancreatitis may be caused by several factors such as fear of eating due to abdominal pain and inadequate intake of calories (i.e., alcoholic beverages instead of food). Weight loss in the later stages of the disease is caused by exocrine insufficiency or due to the development of cancers (i.e., lung, esophagus, pancreas). At least in our region, which is a formerly heavily industrialized city that currently has a high unemployment rate, many patients with chronic alcohol-induced pancreatitis belong to a lower social class. These patients very often have tattoos (Fig. 13.2).

Many patients avoid fatty meals because they cause pain. Thus, visible steatorrhea, even in severe exocrine insufficiency, is not usual. Furthermore, detection of fatty stools just by visual evaluation is not very reliable [29].

Differential and early diagnosis of pancreatic cancer remains a challenge both in patients with suspicion of autoimmune pancreatitis and in patients with known long-lasting chronic pancreatitis. One has to pay attention to symptoms of alcohol withdrawal such as hallucinations, disorientation, and agitations.

Short Track

Diagnosis and Further Therapy

There are various imaging procedures used to diagnose chronic pancreatitis and its complications. Due to rapid technical improvements, comparative trials between CT, MRI, ERCP, and endosonography are mostly outdated at the time of publishing. Figure 13.3 proposes a not-evidence-based algorithm of how to proceed when chronic pancreatitis is suspected. Endosonography probably has the highest sensitivity or diagnosing early changes in chronic pancreatitis [15, 52]. Endosonography is also used by most experts prior to endoscopic drainage of pseudocysts to avoid puncture of vessels within the wall of the pseudocysts and to check for the nearest distance of the pseudocyst to either the stomach or duodenum. To evaluate the cause of pain in chronic pancreatitis and for decision making as to whether to continue with conservative treatment or better recommend surgery, both transabdominal sonography and CT are very often "straight forward" (Fig. 13.4).

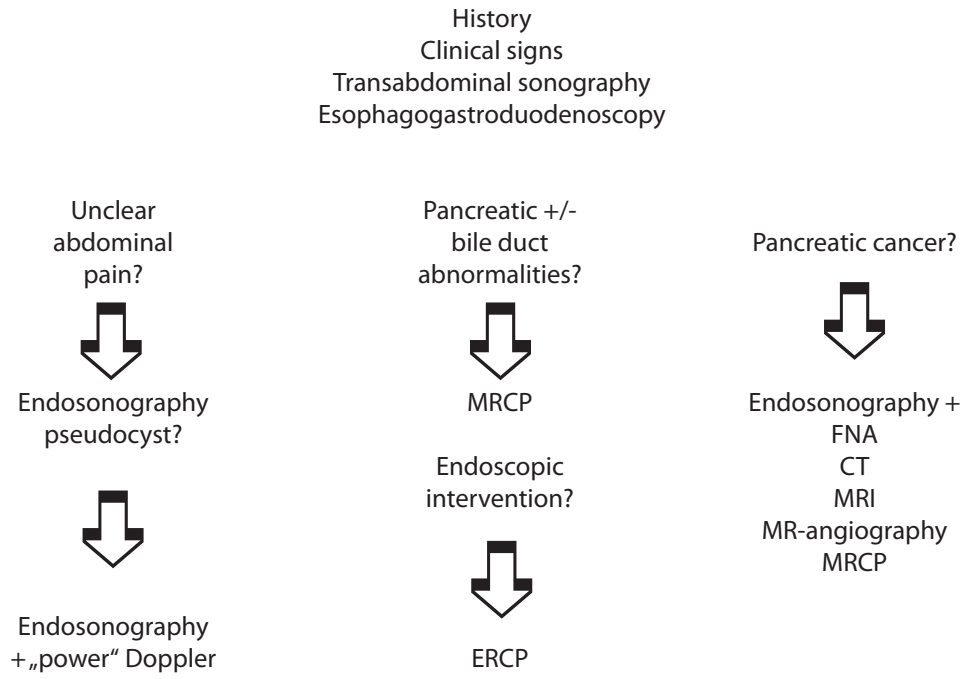

Figure 13.3

Diagnostic algorithm in suspected chronic pancreatitis

Pancreatic Cancer

History

Pancreatic cancer is one of the most devastating diseases; its associated mortality, incidence, and prevalence are almost identical. Patients rarely survive beyond 5 years; indeed most patients die within 6 months after diagnosis. Familial cancer syndromes, smoking, and to a lesser extent being overweight and having type II diabetes are known risk factors for pancreatic cancer [11, 39, 53]. There are speculations that the incidence of pancreatic cancer could be reduced by 30% if people didn't smoke. However, due to the "epidemic" of being overweight in industrialized countries, the high prevalence of smoking and the lack of reliable and cost-effective screening methods to detect early pancreatic cancer, the ability to diagnose pancreatic cancer at a stage where the disease can be really cured is still an unfulfilled dream. Even when cancer can be completely resected, most patients experience early local recurrence or metastasis.

Chronic pancreatitis is an established risk factor for pancreatic cancer [34]. However, most patients with alcoholic pancreatitis die due to their "lifestyle." Death is caused by diseases as a consequence of heavy smoking and alcohol, such as, for example, cancers, accidents, and pneumonia [35]. Patients with hereditary pancreatitis suffer from pancreatitis for decades, usually are very compliant, and do not drink or smoke. These patients have an increased risk of developing pancreatic cancer over the age of 40 or 50 years. Unfortunately, we have no reliable diagnostic procedures that will enable an early diagnosis of pancreatic cancer. There are no larger trials that demonstrate any advantage for endosonography, CT, or positron emission tomography scan when applied annually in these patients.

Usually there are no suspicious symptoms that could lead to an early diagnosis. Most patients present with obstructive jaundice caused by compression of the bile duct in the head of the pancreas. In less than one-quarter of the patients, a nontender gallbladder is palpable (i.e., Courvoisier's sign). Epigastric or back pain, vague abdominal symptoms, and weight loss are also characteristic of pancreatic cancer [17]. Pain, jaundice, or both are seen in more than 90% of all patients [26]. Other symptoms include fatigue, anorexia, and sometimes vomiting. More than one half of cases have distant metastasis at diagnosis. In cases of jaundice due to a tumor close to the papilla of Vater or due

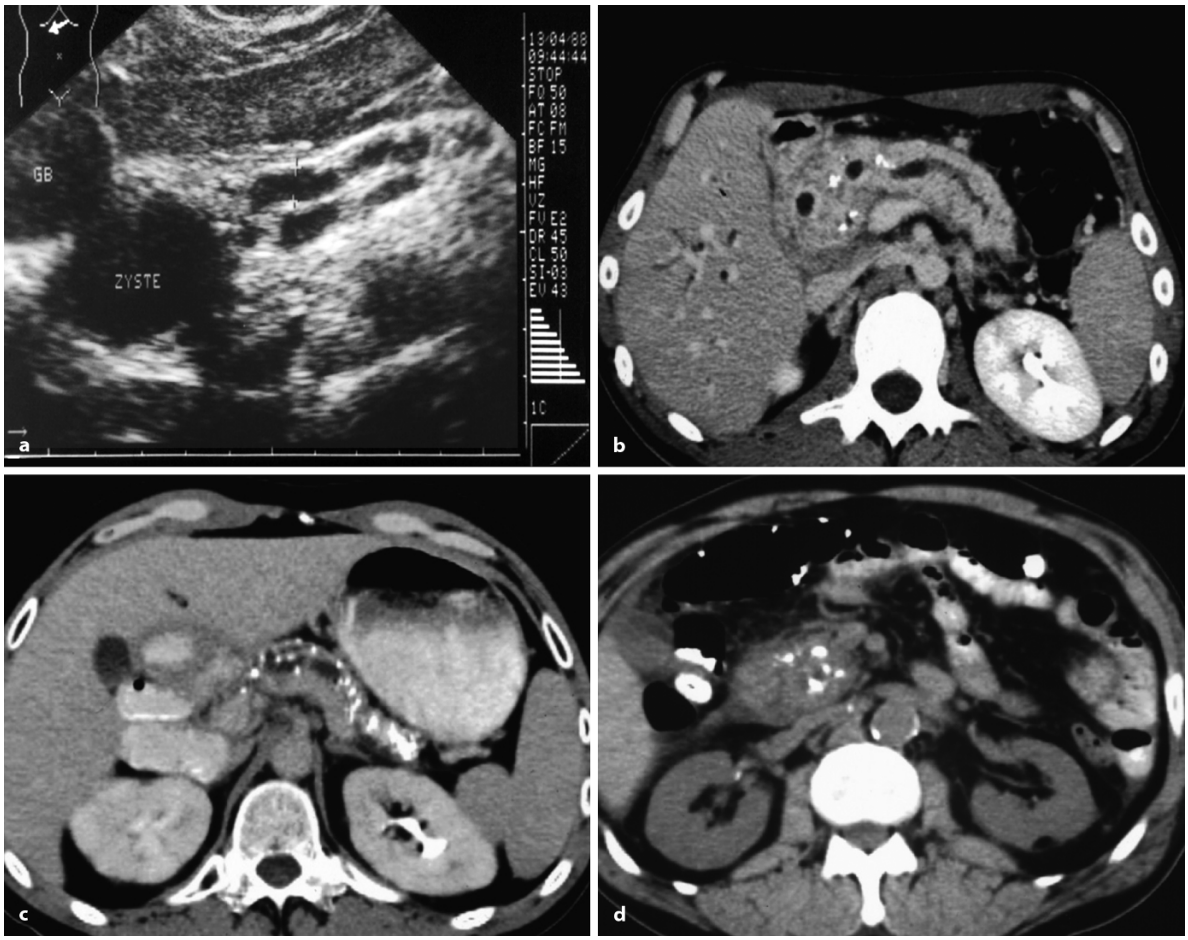

Figure 13.4

Typical complications of chronic pancreatitis. **a** Transabdominal sonography: pseudocyst leading to pancreatic duct dilatation and bile duct obstruction with gallbladder enlargement. **b** Computed tomography (CT) scan: inflammatory mass of pancreatic head leading to pancreatic duct obstruction. Numerous calcifications can be seen in the pancreatic head. **c** CT scan: pancreatic duct enlargement, pancreatic parenchymal atrophy, numerous calcifications. **d** CT scan: inflammatory mass of pancreatic head

to a tumor of the papilla itself, the tumor may still be rather small and resection with curative intention may be possible. However, very often one will find already a large tumor that can not be resected, or the patient has already liver metastases. Tumors of the distal pancreas without metastases are usually not accompanied by jaundice. They may remain painless until advanced stages [53]. However, according to an Italian study of 305 pancreatic cancer patients, there seem to be some hints with which to make an earlier diagnosis: 49.5% of these patients had some prior disturbances, 35.4% 6 months or less, before pain or jaundice, such as anorexia and/or early satiety and/or asthenia [19]; 4.6% had diabetes 7–24 months before; 1.3% had acute pancreatitis 8–26 months before. Diabetes is usually already a symptom of advanced disease.

Physical Findings

Jaundice and signs of severe weight loss are already very often seen when patients present for the first time. Rarely, the pancreatic tumor can be palpated directly.

Short Track

Diagnosis

Despite the impressive technical improvements in imaging procedures such as MRI in combination with MR-angiography and MRCP (“one stop shopping”) or multislice CT and endosonography, most cases of pancreatic cancers are diagnosed at a rather late stage.

In a study from Berlin, MR assessment of pancreatic lesions with regards to differentiation between benign and malignant had an accuracy of about 90%. The positive- and negative-predictive values for cancer nonresectability were 90% and 83%, respectively [33]. MRCP has replaced diagnostic ERCP, since it has a similar sensitivity and specificity [1]. There are no cost-effective screening procedures suitable for mass screening, or at least for screening of patients at risk, such as patients with hereditary chronic pancreatitis, patients with a family history of pancreatic cancer, and patients with Peutz-Jeghers syndrome. One recent study proposed annual endoscopic ultrasound (EUS) and CT in these patients at risk [12]. Furthermore, it is still very difficult to diagnose pancreatic cancer in patients with chronic pancreatitis. Analyses of pancreatic secretions for the existence of ki-ras mutations have been disappointing [51]. EUS-guided FNA may be slightly superior to CT/ultrasound-guided FNA for the diagnosis of pancreatic malignancy [21]. EUS-FNA samples with equivocal cytology can be tested for microsatellite loss and ki-ras point mutations. This additional analysis may improve the diagnostic accuracy and prevent unnecessary surgery [28].

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