imaging modalities with complementary methods. Additionally, current management options are outlined.

Risk factors

The lifetime risk of developing PDAC is approximately 1.5% in the general population (8). Modifiable risk factors include dietary habits, obesity, type 2 diabetes mellitus (DM), excess alcohol consumption, and tobacco use. Among lifestyle risk factors, cigarette smoking has the strongest association with PDAC (17, 18). Estimates suggest that smokers are approximately twice as likely to develop PDAC compared with their non-smoker counterparts (19). Obesity, defined by body mass index (BMI) ≥30 kg/m2, carries an increased likelihood of developing PDAC compared to individuals with normal range BMI (hazard ratio of 1.15–1.53) (20). DM has been correlated with development of PDAC (pooled relative risk of 2.1), although PDAC itself is a risk factor for developing DM (19, 21, 22). Diets heavy on processed meat, high-fructose beverages, and saturated fat are associated with obesity, type 2 DM, and PDAC (23). Furthermore, fatty infiltration of the pancreas has been correlated with development of pancreatic intraepithelial neoplasias, precursors to PDAC (24).

Non-modifiable risk factors include age, sex, area, and genetic susceptibility. Most cases of PDAC are sporadic, but 10-15% are estimated to be attributable to inherited risk factors (16, 25, 26). Several genetic susceptibility syndromes that are associated with an increased risk of developing PDAC have been identified, particularly Peutz-Jeghers syndrome, familial atypical multiple mole and melanoma syndrome, hereditary breast and ovary cancer syndrome, Lynch syndrome, ataxia-telangiectasia, and hereditary pancreatitis (27), although a detailed overview of these is beyond the scope of this review. The risk of developing PDAC increases further with age; median is 65 years (4). However, a recent US study evaluating trends in cancer occurrence among young adults showed a disproportionate rise in the incidence of various obesity-related malignancies, including PDAC, among individuals 25–49 years old (23). This observation may be related to increasing rates of obesity and type 2 DM (28). The incidence of PDAC is overall higher in men; this gap is even more pronounced in developed countries (29).

Clinical presentation

In current practice, the diagnosis PDAC is frequently delayed, as symptoms are often few, if any, and vague. Consistent with this fact, only a minority of patients diagnosed with PDAC present with resectable disease. Most patients (85–90%) present with either locally advanced (unresectable) or metastatic disease (30). Those who do develop symptoms usually have non-specific complaints: epigastric or back pain, nausea, bloating, abdominal fullness, or change in stool consistency, all that can be often understandably attributed to alternative, benign causes, and thus can stall the diagnostic process (19, 31, 32).

The clinical features that occur with the highest frequency at the time of diagnosis include abdominal pain (40–60%), abnormal liver function tests (~50%), jaundice (~30%), new-onset DM (13–20%), dyspepsia (~20%), nausea or vomiting (~16%), back pain (~12%), and weight loss (~10%) (19, 33). Symptoms also depend on the location of the tumor within the pancreas. Most tumors (60–70%) arise from the head or neck of the pancreas and are more likely to present with biliary obstruction leading to painless jaundice. In contrast, tumors of the pancreatic body tend to invade adjacent vascular structures and are more likely to cause back pain on presentation; tail tumors can often grow unimpeded due to fewer anatomical neighbors (19). Malignant obstruction of the main pancreatic duct (MPD) can result in symptoms of pancreatic enzyme insufficiency (diarrhea, flatulence, steatorrhea, and postprandial abdominal pain) and occasionally in acute pancreatitis (19, 34).

Importantly, pancreatogenic (type 3c) DM has recently become a major topic. It refers to diabetes associated with disease of the exocrine part of the pancreas and is most often caused by chronic pancreatitis, but it can also be a paraneoplastic manifestation of PDAC. Moreover, it could fit the early diagnosis concept based on the patient's metabolic profile. Sharma et al. reported that an increase in fasting blood glucose levels may precede the diagnosis of PDAC by up to 3 years (35). Furthermore, Sah et al. described 3 distinct phases prior the diagnosis of PDAC based on metabolic and soft tissue changes: phase 1 (30–18 months; hyperglycemia) characterized by isolated hyperglycemia, phase 2 (18–6 months; pre-cachexia) with hyperglycemia and decreases in serum lipids, body weight, and subcutaneous abdominal fat, and phase 3 (6-0 months; cachexia) including loss of visceral fat with sarcopenia (36).

Diagnostic approach

It is not possible to reliably diagnose a patient with PDAC based on symptoms and signs alone. Awareness of risk factors may lead to an earlier and more aggressive evaluation in patients who present with symptoms suspicious for the disease. Traditional methods of diagnosing PDAC include serum tumor markers, imaging methods, and endoscopic ultrasound (EUS) with or without biopsy. The employment of multiple diagnostic modalities can help to detect PDAC in the early stage and thus improve survival. An overview of the diagnostic work-up of a suspected pancreatic mass is outlined in Fig. 2 (37, 38).

Laboratory testing

The only routinely used serological marker in the diagnosis of PDAC is carbohydrate antigen (CA) 19-9. Nevertheless, the sensitivity and specificity of CA 19-9 in the diagnosis of early PDAC are not high, which limits its clinical application. The marker maintains a sensitivity of 79–81% and specificity of 82–90% for the diagnosis of PDAC in symptomatic patients (19, 39), and its elevation signifies advanced disease and poor prognosis (40–42). However, as PDAC is usually asymptomatic at the early stage, the positive predictive value of CA 19-9 is only 0.9% in this setting (43, 44). Furthermore, the elevation of CA 19-9 can also be caused by other conditions, including benign diseases (pancreatitis, cirrhosis, biliary obstruction, and acute cholangitis) (45–47) and different malignancies (colorectal, gastric, and uterine cancers) (38). Moreover, CA 19-9 is not expressed in some individuals with a specific genotype, and only 65% of patients with resectable PDAC have elevated serum levels (40, 48). Due to all these reasons, CA 19-9 is not recommended for routine screening, although its value as a screening tool is being revisited (49). Serial measurements of CA 19-9 have a role in monito-