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# Current trends in the diagnosis of pancreatic cancer

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Pancreatic ductal adenocarcinoma (PDAC) is a dreaded malignancy with a dismal 5-year survival rate despite maximal efforts on optimizing treatment strategies. Currently, early detection is considered to be the most effective way to improve survival as radical resection is the only potential cure. PDAC is often divided into four categories based on the extent of disease: resectable, borderline resectable, locally advanced, and metastatic. Unfortunately, the majority of patients are diagnosed with locally advanced or metastatic disease, which renders them ineligible for curative resection. This is mainly due to the lack of or vague symptoms while the disease is still localized, although appropriate utilization and prompt availability of adequate diagnostic tools is also critical given the aggressive nature of the disease. A cost-effective biomarker with high specificity and sensitivity allowing early detection of PDAC without the need for advanced or invasive methods is still not available. This leaves the diagnosis dependent on radiodiagnostic methods or endoscopic ultrasound. Here we summarize the latest epidemiological data, risk factors, clinical manifestation, and current diagnostic trends and implications of PDAC focusing on serum biomarkers and imaging modalities. Additionally, up-to-date management and therapeutic algorithms are outlined.

**Key words:** pancreas, pancreatic cancer, pancreatic ductal adenocarcinoma, pancreatic cancer diagnosis, pancreatic cancer management, pancreatic cancer therapy.

## Současné trendy v diagnostice karcinomu pankreatu

Duktální adenokarcinom pankreatu (pancreatic ductal adenocarcinoma – PDAC) je obávanou malignitou s velice nízkým 5letým přežíváním i přes veškeré snahy o zdokonalení léčebných strategií. V současnosti je včasná detekce považována za nejúčinnější způsob, jak zlepšit přežití, jelikož pouze radikální resekce představuje kurativní potenciál. PDAC se dělí do čtyř kategorií podle rozsahu onemocnění: resekabilní, hraničně resekabilní, lokálně pokročilý a metastatický. Většina pacientů je bohužel diagnostikována s lokálně pokročilým nebo metastatickým onemocněním, a tím pádem není způsobilá pro kurativní resekci. To je dáno především absencí průvodních příznaků či jejich nevýrazností v době, kdy ještě onemocnění není lokálně pokročilé. Vhodná indikace a rychlá dostupnost adekvátních diagnostických nástrojů je nicméně rovněž kritickým bodem vzhledem k agresivní povaze onemocnění. Nákladově efektivní biomarker s vysokou specificitou a senzitivitou umožňující

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včasnou detekci PDAC bez potřeby pokročilých a invazivních metod stále chybí. Diagnostika tak zůstává závislá na radiologických metodách a endoskopické ultrasonografii. V naší přehledové práci shrnujeme nejnovější epidemiologická data, rizikové faktory, klinickou manifestaci a současné diagnostické trendy se zaměřením na sérové biomarkery a zobrazovací modality. Kromě toho popisujeme aktuální terapeutické postupy.

**Klíčová slova:** pankreas, karcinom pankreatu, duktální adenokarcinom pankreatu, diagnostika karcinomu pankreatu, management karcinomu pankreatu, léčba karcinomu pankreatu.

## Introduction

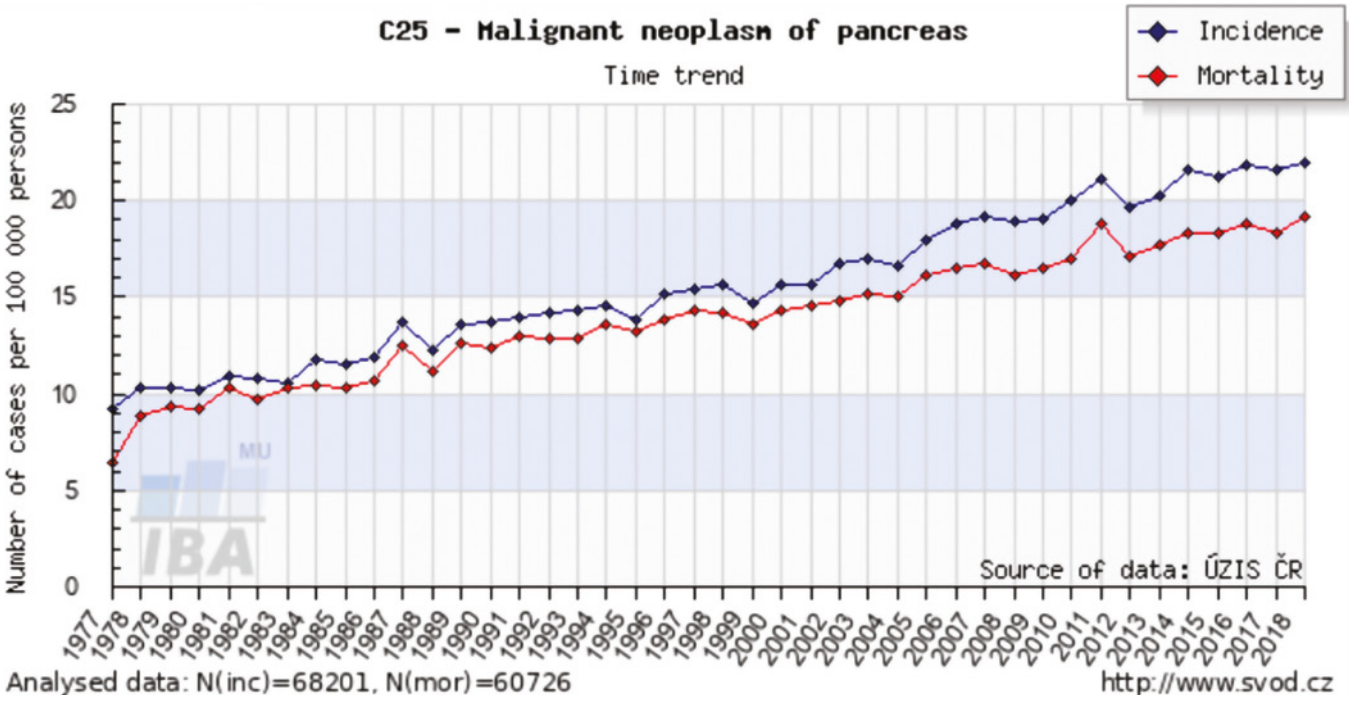
Pancreatic cancer commonly refers to pancreatic ductal adenocarcinoma (PDAC), which represents the majority of malignant pancreatic neoplasms and has one of the worst prognosis among solid malignancies. Based on the GLOBOCAN 2020 estimates, it is the seventh leading cause of cancer-related death in both men and women worldwide with 496,000 new cases and mortality rate almost identical when accounting for 466,000 deaths (1). Incidence and mortality rates have been steadily rising in many countries, likely reflecting the increasing prevalence of obesity, diabetes, and alcohol consumption, although improvements in diagnostic and cancer registration practices may also be in play in some countries (1, 2). Rates are 4-fold to 5-fold higher in countries with high social-demographic indices, with the highest incidence rates in Europe, Northern America, and Australia/New Zealand (1). The time trend of malignant pancreatic neoplasms in the Czech Republic is demonstrated in Fig. 1 (3); in 2018 it was the seventh most frequently diagnosed malignancy with 2,332 new cases and the third most common cause of cancer mortality with 2,159 deaths, which ranked third in Europe (4). In the United States PDAC is currently the third leading cause of cancer death after lung cancer and colorectal cancer, and it is predicted to be the second deadliest cancer by 2030 (5, 6).

Because of the absence of specific symptoms, the majority of PDAC are diagnosed late with poor prognosis, as most patients have advanced and incurable disease at detection (7). The 5-year survival rate for metastatic disease is 3.0%, rising to 14.4% for regional and 41.6% for localized disease (8). The dismal prognosis is also due to the aggressive nature of the tumor and its resistance to chemotherapy and radiotherapy (9–11). Compared to other malignancies, there has been little improvement in the survival rate of patients with PDAC in recent decades, and radical surgical resection of localized disease remains the only curative approach (12–14).

Screening with detection of asymptomatic stages of PDAC and its precursors has been proposed to improve results. At present, however, guidelines recommend against unselected screening for PDAC in asymptomatic adults, concluding that the potential benefits do not outweigh the potential harms, and such approach is reserved for high-risk individuals (15, 16). Given the lack of highly sensitive and specific diagnostic biomarkers, the diagnosis is currently dependent on advanced imaging modalities; sometimes it requires preoperative tissue acquisition.

The purpose of this review is to summarize the current diagnostic approach to PDAC in the general population, reviewing clinical presentation, relevant conventional and investigational biomarkers, and

**Fig. 1.** *Incidence and mortality trends of malignant pancreatic neoplasms in the Czech Republic (3)*



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).

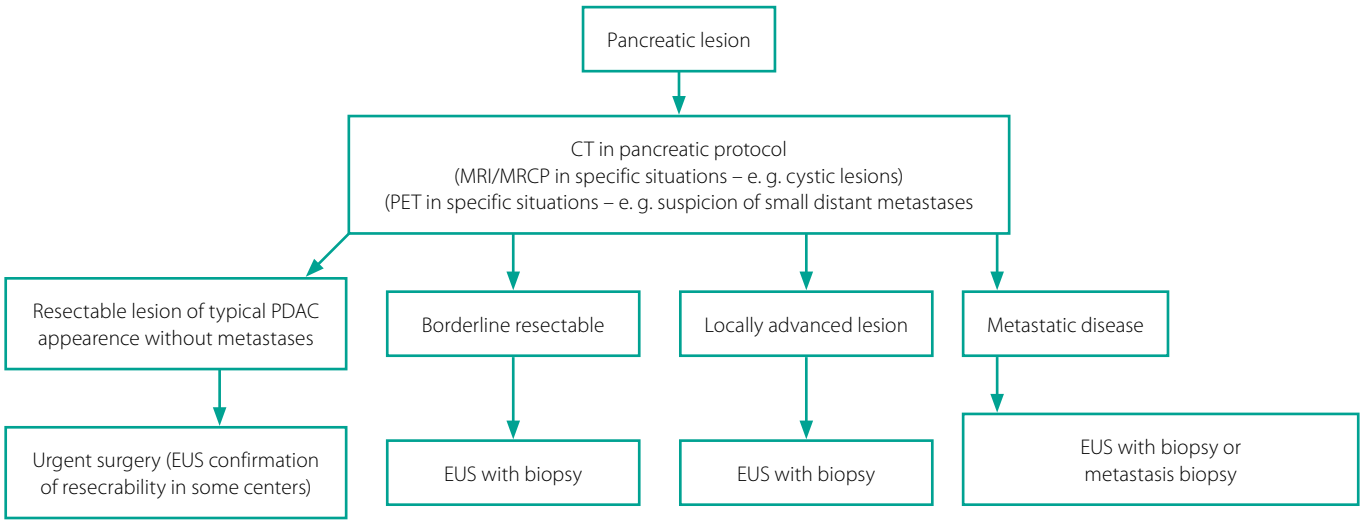
## Diagnostic approach

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-

**Fig. 2.** *Diagnostic work-up of a suspected pancreatic tumor (according to Ducreux et al. and Lang et al. (37, 38)).*




*CT – computed tomography; MRI – magnetic resonance imaging; MRCP – magnetic resonance cholangiopancreatography; PET – positron emission tomography; PDAC – pancreatic ductal adenocarcinoma; EUS – endoscopic ultrasound.*

ring disease response to systemic treatment in the neoadjuvant or metastatic setting (50–53). Elevated preoperative CA 19-9 may also help identify patients whose surgeries are less likely to result in an R0 (margin-negative) resection and can predict long-term survival after resection (19, 39, 54).

Carcinoembryonic antigen (CEA) and CA 125 are nonspecific markers that might be elevated in patients with PDAC as well. According to reports in the literature, the combination of serum CA 19-9 with CA 125 increased sensitivity, and the combination of CA 19-9 with CEA increased specificity compared to CA 19-9 alone (55, 56).

In recent years, novel blood-based biomarkers for early diagnosis and prognostic stratification have made progress. Studies have confirmed that abnormally expressed serum non-coding microRNAs (miRNAs) have certain significance in the diagnosis of early-stage PDAC, or even in precancerous pancreatic lesions (44, 57). The diagnostic value of microRNAs was shown to be higher than that of conventional serum markers (58), and there is evidence that the combination of miRNAs and CA 19-9 is more accurate (59, 60). Moreover, miRNA expression profiles may distinguish between malignant and benign lesions of the pancreas (61), and they may be used for the prediction of chemoresistance and facilitate personalized treatment planning (44, 62). Another emerging strategy are so-called "liquid biopsies" that can capture tumor-associated components, such as circulating tumor DNA, extracellular vesicles, and circulating tumor cells. It has been reported that circulating tumor cells can be detected in the peripheral blood of 40%–100% of pancreatic cancer patients, which may be used for the diagnosis of early PDAC (63). These novel methods seem very promising, although further studies are needed to verify the results and validity of these strategies in clinical practice.

## Imaging methods

Abdominal ultrasound (US) is a non-invasive, broadly available, and easily feasible technique that is usually the first imaging method used in suspected pathology of the pancreatobiliary tract (64). The disadvantage of abdominal US is its low specificity, expert dependence, and also the dependence on the patient's body habitus (64). According to various authors, the sensitivity of US in PDAC detection ranges from 48%–98% (64, 65). In a Japanese multicenter study involving early-stage pancreatic cancers, dilatation of the MPD was the most common abnormality on US in up to 75% patients (66).

Computed tomography (CT) has a crucial role in diagnosis, staging, and planning or monitoring the treatment of patients with PDAC (64, 67). Currently, a biphasic pancreatic protocol with submillimeter section thickness and standard use of multiplanar reconstructions are recommended (64, 67). It involves both intravenous contrast with a high iodine content (at a rate of 3–5 ml/s) and ingestion of water as a neutral oral contrast (64). The pancreatic phase should be performed after 40–50 seconds and the portal phase after 65–70 seconds following intravenous contrast application. Three-dimensional (3D) images are convenient for assessing tumor-vessel relationships, especially before planned surgery (64).

Based on the extent of disease, PDAC is divided into one of four categories: resectable (Fig. 3), borderline resectable, locally advanced (Fig. 4), and metastatic (Fig. 5). Due to the gradual improvement of CT imaging technology, the sensitivity of CT for detection and evaluation of PDAC resectability has increased from 76% to 95% and 73% to 83%, respectively (67). CT is accurate for determination of unresectable disease with sensitivity of up to 91% and specificity of 100% (64).

To assess resectability of the lesion, it is necessary to assess potential infiltration of the superior mesenteric artery, coeliac axis and its branches, portal vein, and superior mesenteric vein. Three degrees of vascular contact with the tumor are evaluated, i.e., no contact, abutment (≤180°), or encasement (>180°), on the basis of which it is possible to predict resectability (64, 68). The disadvantage of CT in determining local resectability of PDAC is the existence of interobserver variability among evaluators, even among experienced radiologists (69). In additi-

**Fig. 3.** *CT scan of resectable pancreatic ductal adenocarcinoma (PDAC) within the pancreatic head*

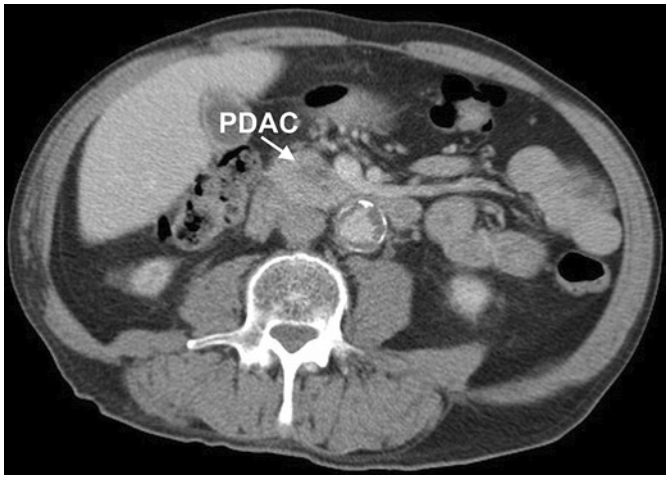



**Fig. 4.** *CT scan of locally advanced pancreatic ductal adenocarcinoma (PDAC) of the pancreatic body with infiltration of the celiac trunk*

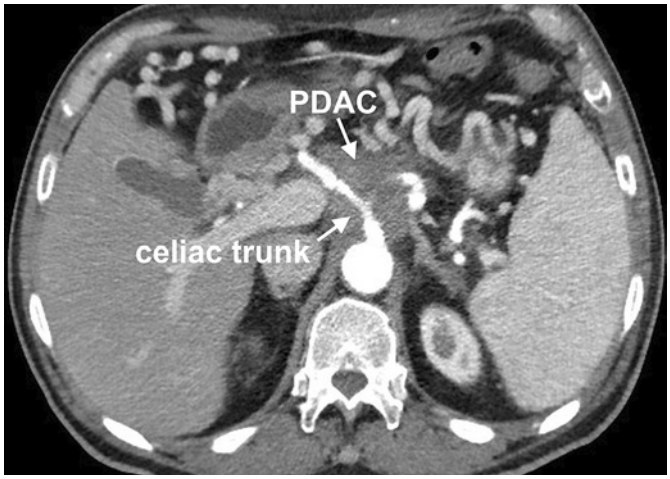
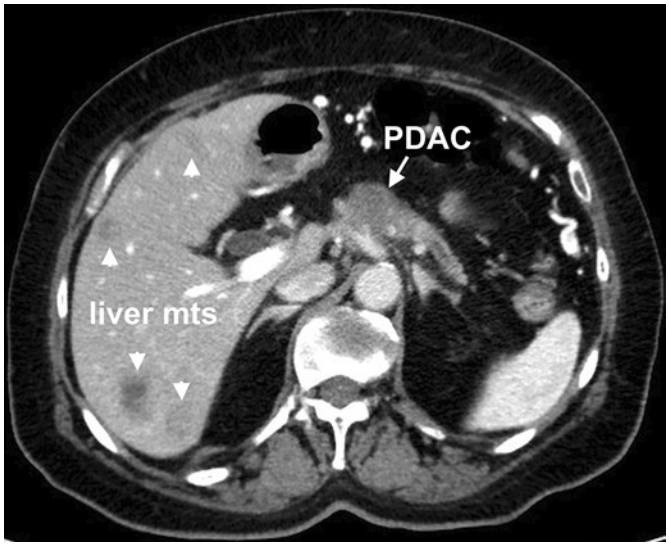



**Fig. 5.** *CT scan of generalized pancreatic ductal adenocarcinoma (PDAC) of the pancreatic body with liver metastases (arrowheads)*




on to the tumor-vessel contact, the size of the tumor itself also predicts resectability. Significantly more positive resection margins are described in tumors measuring >4 cm than in tumors measuring <2 cm on CT (70). Thrombosis, vascular deformation, and collateral vessel development are other features increasing the likelihood of vascular invasion (68, 71).

The anatomical (radiological) definition of borderline PDAC is not fully uniform. It is generally described as a locally advanced tumor without distant metastases that affects the mesentericoportal veins or potentially resectable arteries (68, 72, 73). In addition to the anatomical definition, it is necessary to evaluate the risk of distant metastases, CA 19-9 levels, and the patient's performance status or comorbidities (68, 73).

PDAC typically becomes hypodense on postcontrast CT. However, in 5–14% it can be directly indistinguishable, i.e, isodense compared to the surrounding parenchyma (74). EUS with fine-needle tissue acquisition can confirm these isodense tumors with a sensitivity of 90.5% (75). As an early predictor of a malignant tumor before development of a focal pancreatic lesion on CT, a novel feature may be suggestive – the "K sign". It is a localized narrowing of the pancreatic parenchyma on an axial CT scan resembling the shape of the letter K (76). Advances in the use of artificial intelligence also represent a great potential, offering new opportunities not only for the detection but also for the classification of pancreatic lesions (67).

Magnetic resonance (MR) imaging of the pancreas along with MR cholangiopancreatography (MRCP) allow for accurate detection of early PDAC by facilitating morphological analysis of pancreatic ductal changes (64). A recent study found that incipient MPD stenosis on pre-diagnostic MRCP can be detected 26–49 months prior to pancreatic tumor detection on any of the imaging methods (CT, MR, or EUS) (77). The advantages of MR include the ability to identify isodense tumors or tumors within a hypertrophic pancreatic head, distinguish neoplasm from mass-forming pancreatitis, and also to detect small liver metastases unrecognized on CT (64, 73). Its sensitivity and specificity in assessing vascular invasion is comparable to CT (73). Nonetheless, MR imaging might not be routinely done in some centers due to its lower availability and higher costs compared to CT. Therefore, MR is not currently used as the primary imaging method in PDAC (64).

Positron emission tomography (PET)/CT is not routinely indicated in the diagnostic evaluation of PDAC, but it should be considered in patients with a high risk for occult metastatic disease, such as those with CA 19-9 concentrations out of proportion to their suspected stage (19).

## Endoscopy

The role of endoscopic retrograde cholangiopancreatography (ERCP) in patients with suspected PDAC has evolved into a mainly therapeutic modality for patients with biliary obstruction requiring placement of a biliary stent. However, routine preoperative decompression for obstructive malignant jaundice should not be performed in patients who are eligible for resection; it has not been proven to be beneficial in regard to patient outcome, and there is evidence for increased postoperative complications (78). Strict indication criteria should thus apply, e.g., concurrent acute cholangitis.

EUS is considered the most sensitive method for detecting early pancreatic neoplasms (79). The median sensitivity of EUS for the detec-

tion of pancreatic tumors across 22 studies was 94% (80). Importantly, it has a very high negative predictive value (81, 82). This is valuable for clinicians as it indicates that EUS can also exclude pancreatic cancer. In patients with PDAC it is frequently used as a complementary staging tool to evaluate regional lymph nodes, define the degree of tumor-vascular involvement, or secure a definitive cytologic or histologic diagnosis (77, 83).

EUS-guided fine-needle biopsy (preferred over fine-needle aspiration) is the most favorable modality for obtaining tissue specimens from the pancreas (Fig. 6). However, preoperative tissue diagnosis may not be needed in surgical candidates with potentially resectable pancreatic lesions that are highly suspected of malignancy. While a positive sample can confirm the diagnosis, benign findings don't exclude the presence of malignancy. Once PDAC is suspected on initial imaging, the next step is generally a staging evaluation to establish disease extent and resectability rather than biopsy. A preoperative biopsy may be recommended if a diagnosis of chronic or autoimmune pancreatitis is suspected and differential diagnosis yields difficulties.

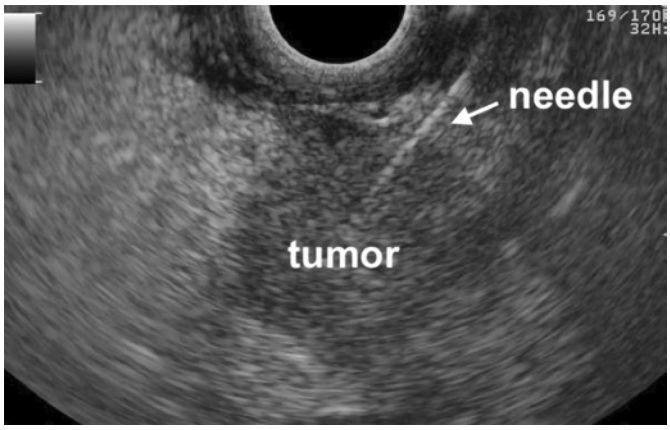
## Therapy

Radical resection is the only potential curative approach in patients with PDAC. Neoadjuvant or adjuvant chemotherapy/chemoradiotherapy may improve disease-free survival and overall survival (OS) (84, 85). However, resection with curative intent is feasible only in 10%–20% of patients. Unfortunately, in these resected patients, positive resection margins are observed in the majority of cases. Thus, neoadjuvant chemotherapy or chemoradiotherapy is the standard of care in border-line resectable and locally advanced unresectable tumors. Chemotherapeutic intensive regimen with 5-fluorouracil, oxaliplatin, and irinotecan (FOLFIRINOX) results in a significantly better secondary resection rate and OS (85, 86).

In resectable PDAC, the current standard of care is resection followed by adjuvant chemotherapy or chemoradiotherapy. However, neoadjuvant therapy can be also considered in this setting, especially if risk factors are present, e.g., large primary tumors, enlarged lymph nodes, high baseline CA 19-9 levels, significant weight loss, or severe pain. Chemotherapeutic protocols for neoadjuvant and adjuvant treatment are interchangeable and are based on FOLFIRINOX regimen or gemcitabine/nab-paclitaxel combination (87).

Metastatic disease is an indication for palliative chemotherapy. This approach can prolong survival, decrease tumor-related symptoms, and preserve quality of life. For patients with a good performance status, intensive FOLFIRINOX regimen or gemcitabine/nab-paclitaxel combination are the standard of care, whereas gemcitabine or 5-fluorouracil alone are preferred for unfit patients (88).

**Fig. 6.** *Endoscopic ultrasound-guided fine-needle biopsy of a mass at the junction of the pancreatic head and body. Histopathologic findings confirmed the diagnosis of pancreatic ductal adenocarcinoma (PDAC)*




Currently, target therapy is still limited in PDAC and is feasible in only a minority of metastatic patients. Olaparib is a specific inhibitor of Poly (ADP-ribose) polymerase. In patients with germline *BRCA1* or *BRCA2* mutations who didn't progress on chemotherapy with platinum derivatives, olaparib results in a statistically-significant prolonged median progression-free survival (89). An immune checkpoint inhibitor pembrolizumab is already approved for patients who harbor high microsatellite instability, DNA mismatch repair deficiency, or high tumor mutational burden (90). NTRK inhibitors lacotrectinib and entrectinib may be considered among patients with PDAC harbouring NTRK fusion (87).

## Conclusion

Pancreatic cancer remains one of the deadliest malignancies with dismal prognosis and limited options for effective therapy. It presents vaguely and heterogeneously, and the grim reality is that most patients have advanced or metastatic disease at diagnosis. In regards to the attempts at early detection of PDAC without the need for advanced or invasive methods, a discovery of a cost-effective biomarker with high specificity and sensitivity has currently been a goal of many researchers. Nonetheless, an effective screening tool is still not available. Contrast-enhanced CT using a dual phase pancreatic protocol remains the mainstay method for diagnosing PDAC and determining its resectability. EUS is an increasingly used adjunctive staging method that also allows for tissue diagnosis when necessary. Additionally, conscious indication of pancreatic imaging using MR may improve diagnostic rates in selected groups of patients.

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