

Pancreatic cancer in 2021: What you need to know to win

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Abstract

Pancreatic cancer is one of the solid tumors with the worst prognosis. Five-year survival rate is less than 10%. Surgical resection is the only potentially curative treatment, but the tumor is often diagnosed at an advanced stage of the disease and surgery could be performed in a very limited number of patients. Moreover, surgery is still associated with high post-operative morbidity, while other therapies still offer very disappointing results. This article reviews every aspect of pancreatic cancer, focusing on the elements that can improve prognosis. It was written with the aim of describing everything you need to know in 2021 in order to face this difficult challenge.

Key Words: Pancreatic cancer treatment; Advanced pancreatic cancer; Metastatic pancreatic cancer; Pancreatic cancer surgery; Pancreatic cancer chemotherapy; Pancreatic cancer screening

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Core Tip: Pancreatic cancer is a very dangerous enemy and the results are still very unsatisfactory. But we have not given up. Research is running fast on many paths, without losing its enthusiasm. The number of articles published on this subject in the last two years is impressive. I have tried to summarize all the most significant data from the different lines of research, ranging from screening and early diagnosis to new developments in surgery and associated therapies. I hope I have succeeded in the task of describing as comprehensively as possible the most promising fields of research available to us today, in order to achieve the improved results we desire.

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INTRODUCTION

Pancreatic cancer is currently the seventh leading cause of cancer death worldwide and the fourth following lung, colorectal and breast cancers in the United States and Europe. It will become the third by 2030. It is an age-related neoplasm and this trend is similar between males and females. In particular the number of both deaths and incident cases peaked at the ages of 65-69 years in males, whereas the peak in females was observed at the ages of 75-79 years[1-4]. The commonly used term "pancreatic cancer" usually refers to ductal adenocarcinoma (PDAC), which represents 85% of all pancreatic tumor[4]. Complete surgical resection significantly prolongs survival, but the tumor is often diagnosed at an advanced stage and only a small percentage of patients are therefore candidates for surgery. Moreover, surgery is still associated with high post-operative morbidity. Despite ongoing developments, PDAC remains one of the most difficult tumors to treat, and the five-year survival rate is less than 10%[5]. There are four fundamental challenges that underlie the high mortality. First, the retroperitoneal location of the pancreas, deep in the abdomen, protects growing tumors from detection. The symptoms are late and therefore the diagnosis is made when the tumor is already in an advanced stage. Second, PDAC has an aggressive biology characterized by early metastasis and 50% of patients has metastatic disease at presentation. In addition, a large number of patients undergoing surgery develop metastases within 4 years. This suggests the presence of micrometastasis in apparently localized cases[6]. Third, pancreatic cancer dramatically weakens patients, limiting their ability to withstand aggressive treatments. Finally, it shows resistance to many antineoplastic therapies[7,8]. Advances in prevention, screening, early detection, and therapy, particularly on new frontiers, are essential to improve outcomes. This article has been written with the aim of describing everything you need to know in 2021 in order to face this difficult challenge.

NON-FAMILIAL RISK FACTORS AND PREVENTION

Identification of risk factors, high-risk populations and early detection markers is the first and crucial step to change the pancreatic cancer horizon[9]. PDAC incidence rates are nearly four times higher in high-income countries such as the United States and Western European countries than in middle- and low-income countries[3]. The different incidence seems to be related with different lifestyles.

Obesity, smoking, alcohol consumption and type 2 diabetes are considered non-familial risk factors for pancreatic cancer. Chronic pancreatitis, cystic fibrosis and intraductal papillary mucinous neoplasm (IPMN) should also be considered. An increased risk of pancreatic cancer has been observed following gastrectomy[10-17].

One-third of all cancers could have been prevented through lifestyle correction[18]. A 2020 European prospective study (EPIC) evaluated the association between the healthy lifestyle index score and PDAC[19-22]. Healthy lifestyle habits were inversely related to the risk of PDAC. Adherence to healthy behaviors, corresponding to a three-point increase in the score, was associated with a 16%-23% lower risk. The result summarizes many previous studies[23-29] and support the adoption of healthy lifestyles in PDAC prevention.

A recent nutrigenomic study has highlighted nutrients capable of preventing cancer through epigenetic modifications. An optimal diet should include omega 3 fatty acids, polyphenols, folic acid, selenium and zinc. Particularly important for PDAC prevention could be the epigallocatechin, a polyphenol from tea and green tea[30,31].

Data linking type 2 diabetes with pancreatic cancer suggest that the new onset of diabetes in a lean older adult should prompt consideration of PDAC. This is even more valid if new-onset diabetes is associated with unintentional weight loss[32-34]. A Mayo Clinic study evaluated the use of computed tomography (CT) at the time of diabetes diagnosis in otherwise asymptomatic patients. A higher likelihood of showing potentially resectable tumors was observed compared with scans performed six months later[32]. However, CT screening of all elderly subjects with new-onset

diabetes is not feasible[33]. With the identification of these characteristics that differentiate pancreatic cancer-associated diabetes from other cases of new-onset diabetes, perhaps the guidelines will update[35].

HEREDITARY RISKS FACTORS

PDAC can be hereditary. There are two categories of inherited risk for PDAC: Genetic syndromes (20% of cases) and familial pancreatic cancer (80%). Familial pancreatic cancer is defined as a predisposition that is based on familial clustering in families in which there is at least one pair of first-degree relative (FDR) relatives with PDAC in the absence of a known genetic syndrome. Genetic syndromes that predispose to pancreatic cancer are listed in Table 1. Table 1 also shows in parentheses the frequencies of mutated genes in PDAC patients[36-42].

Knowledge of inherited risk factors is important because it allows us an effective stratification and management of patients. According to American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines, all patients diagnosed with PDAC should be evaluated to understand if there is a risk of familial predisposition to cancer. All patients should undergo risk assessment for syndromes associated with an increased risk of PDAC. Germline genetic testing is recommended for patients with PDAC and an unremarkable family history[43,44].

SCREENING

Screening aims to detect preinvasive lesions (IPMNs and pancreatic intraepithelial neoplasias) with high-grade neoplastic changes and early invasive tumors that are more amenable to potentially curative resection[45-49].

Candidates for screening

(1) Patients with Peutz-Jeghers syndrome or CDKN2A mutation, regardless of family history; (2) BRCA2 mutation with at least one affected FDR or at least two affected relatives of any degree; (3) BRCA1, partner and localizer of BRCA2 (PALB2), ataxia-telangiectasia mutated (ATM), and Lynch syndrome mutation carriers with one or more affected FDRs; (4) Hereditary pancreatitis with a PRSS1 mutation; and (5) Regardless of gene mutation status: (a) At least three affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance; (b) At least two affected relatives who are FDRs of each other, of whom at least one is an FDR of the individual being considered for surveillance; and (c) At least two affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance.

General population-based screening for average-risk patients is not recommended [33] because the average lifetime risk for developing PDAC is too low[49].

Screening modality

The current recommendation provides for the execution of endoscopic ultrasonography (EUS) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP). It has been demonstrated that they detect more lesion as compared with CT scan[50]. Screening is recommended at age 50 years or 10 years younger than the youngest relative with PDAC in familial pancreatic cancer relatives. In other cases, screening is carried out between 35 and 45 years. For patients with a normal pancreas on imaging, repeat the procedure every year alternating EUS and MRCP. The age for stopping screening should be individualized based on each patient's medical status, life expectancy, and preferences.

SURGICAL RESECTION FOR IPMNS AND OTHER CYSTIC LESIONS

Surgical resection is indicated in patients with any of the following[45]: (1) Solid pancreatic lesion ≥ 5 mm of indeterminate pathology or if additional evaluation does not yield a definitive preoperative diagnosis; (2) Any positive fine-needle aspiration (FNA) result, except for a pancreatic neuroendocrine tumor; (3) Main-duct IPMNs with any one of the following: (a) Main pancreatic duct dilation of ≥ 10 mm; (b) Main pancreatic duct stricture; or (c) Mural nodules; (4) Branch duct IPMNs (BD-IPMNs)

Table 1 Genetic syndromes predisposing to pancreatic cancer (the frequency of mutated genes among patients with pancreatic ductal adenocarcinoma is indicated in brackets)

Genetic syndrome	Mutated genes
Hereditary breast/ovarian cancer syndrome[36,37]	<i>BRCA1</i> (0.7%), <i>BRCA2</i> (1.4%), <i>PALB2</i> (1%)
Familial atypical multiple mole melanoma syndrome[38]	<i>CDKN2A</i> (0.7%)
Peutz-Jeghers syndrome[39]	<i>STK11</i>
Familial adenomatous polyposis	<i>APC</i> (0.4%)
Lynch syndrome[40]	<i>MLH1</i> , <i>MSH2</i> (0.4%), <i>PMS2</i> (0.3%)
Hereditary pancreatitis[41]	<i>PRSS1</i> , <i>SPINK1</i>
Ataxia telangiectasia[42]	<i>ATM</i> (1.4%)
Li-Fraumeni syndrome[42]	<i>P53</i> (0.4%)

with any one of the following: (a) Rapid growth (> 5 mm over six months); (b) Mural nodules or an enhancing solid component; (c) Abrupt main pancreatic duct caliber change with distal atrophy (even if no mass is visible); (d) Main pancreatic duct dilation of ≥ 10 mm; (e) Positive cytology; or (f) Associated symptoms of pancreatitis, jaundice, or pancreatic-type pain; or (5) Asymptomatic main pancreatic duct stricture with an associated suspicious mass.

For patients who do not meet these criteria for surgery, repeat imaging in three months if worrisome features are present[47,51]. Worrisome features include the following: (1) Solid lesion with main pancreatic duct size of 5 mm to 9 mm in diameter; (2) Main pancreatic duct stricture and/or dilation ≥ 6 mm of unknown etiology without an associated mass; and (3) Solid lesion < 5 mm of uncertain significance.

Repeat imaging in six months is recommended for patients who have the following imaging abnormalities: (1) Cystic lesion (presumed BD-IPMN) ≥ 3 cm in size; (2) Cystic lesion with associated main pancreatic duct 5 mm to 9 mm; (3) Cystic lesion associated with lymphadenopathy; (4) Cyst growth rate of ≥ 5 mm in two years; and (5) Increased serum carbohydrate antigen 19-9 (CA 19-9).

Individuals without worrisome features of malignancy should undergo repeat imaging in 12 mo[47,51].

Screening/surveillance should be continued until the patient is no longer a surgical candidate.

A 2020 paper analyzed the benefits of screening. Nine out of 10 screen-detected PDAC were resectable, with a three-year survival of 85%, compared with 25% in PDAC detected outside surveillance. With continued follow-up of patients with resectable PDAC, the five-year overall survival (OS) rate was 60%[49].

BIOMARKERS AND EARLY DETECTION

Different biomarkers are being evaluated to improve early diagnosis of tumor not detectable by imaging and to differentiate cancer and high-grade dysplasia from benign disease[52].

Blood tests

The most useful serum tumor marker for PDAC is CA 19-9. It is recommended adding this test when there are worrisome features on abdominal imaging. The sensitivity and the specificity of elevated CA 19-9 to detect PDAC are 79% and 82%, respectively[53-55]. It becomes more precise when used in combination with CA 125[56,57]. Other carbohydrate markers, such as CA 50, CA 72.4 and CA 242, were extensively analyzed in PDAC patients. Although they exhibited less sensitivity than CA 19-9 for the diagnosis, they improved specificity[58-61]. Satake and Takeuchi[62] also studied SPan-1 and DUPAN-2. SPan-1 has a high sensitivity for PDAC (81.4%), but the specificity (67.5%) and diagnostic accuracy (71%) are lower than those of CA19-9. SPan-1 may be considered as an additional useful serum marker, but it does not significantly improve the diagnostic accuracy obtained with CA 19-9. In contrast, DUPAN-2 has a high specificity (85.3%) and low sensitivity (47.7%). Furthermore, it seems that serum levels of DUPAN-2 are influenced by liver function. SPan-1 and DUPAN-2 unfortunately have not yet shown the sensitivity and specificity needed to

be used for early detection[62,63].

A huge step forward in the early detection of pancreatic cancer could come from studying cell-free DNA (cfDNA), which consists of circulating double-stranded DNA molecules that can be found in plasma or blood serum. From the analysis of these molecules, it is possible to understand if we are in the presence of a tumor DNA and to go back to the tissue of origin. By analyzing the methylation status of two genes in cfDNA, ADAMTS1 and BNC1, early stage cancer can be identified with a sensitivity of 94.8% and a specificity of 91.6%[64].

Innovative discoveries have also been made in the field of RNA. Abnormal microRNA expressions are potential diagnostic markers for several cancers, including PDAC. Multiple microRNA tests performed in combination with CA 19-9 can improve diagnostic accuracy, particularly miR-216[65-69]. Permutth *et al*[70] demonstrated that a combination of eight lncRNAs helps in the differential diagnosis between malignant and non-malignant IPMNs. Furthermore, three lncRNAs (HAND2-AS1, CTD-2033D15.2, and lncRNA-TGF) could be exploited as early diagnostic biomarkers of IPMN[71,72].

Pancreatic juice and pancreatic cyst fluid

Pancreatic juice collected at the time of ERCP and cyst fluid obtained by EUS-guided FNA can be analyzed for molecular markers. These procedures also have broad potential in terms of early diagnosis of PDAC. Next-generation sequencing can be performed at low cost to detect low-frequency mutations. Potential markers include mutant GNAS (specific for IPMNs) and mutant KRAS. TP53, SMAD4, PIK3CA, PTEN, and AKT1 mutants are also useful as they correlate with IPMN-associated tumors[73-75]. According to Suenaga *et al*[76], a pancreatic juice collection, to ensure optimal yield of mutations for pancreatic screening assays, should be performed 10 min after secretin administration. The authors detected 40 patients with KRAS mutations in pancreatic juice out of 45 undergoing surveillance with EUS, reconfirming the usefulness of these analysis[76].

There are many other biomarkers that are currently being validated for clinical use, such as mucins (MUC). Normal pancreatic ductal epithelium expresses low levels of MUC, while an upregulation of MUC occurs in BD-IPMNs and more pronounced changes in expression in PDAC. Normal pancreatic ductal epithelium expresses low levels of MUC, while upregulation of MUC occurs in BD-IPMN and PDAC[77-83]. The analysis of mucin changes in the fluid of pancreatic cysts allows us to differentiate mucinous from non-mucinous pancreatic cysts with high sensitivity and specificity and to diagnose PDACs associated with IPMN at an early stage[84]. MUC4 and MUC16 have been reported to be 100% specific for PDAC, while associated with sensitivities of 63% and 67%, respectively[85].

Interesting data were reported about interleukins (IL). Higher concentrations of IL-1b, IL-5, and IL-8 have been identified in cystic lesions with high grade dysplasia or malignancy[86]. IL-1b is a potentially useful factor in differentiating high-risk from low-risk pancreatic cysts.

The Das-1 monoclonal antibody is also capable of detecting pancreatic cysts at risk of malignancy with high levels of sensitivity (88%) and specificity (98%)[87,88]. Das-1, IL and MUC could be used in conjunction with clinical guidelines to identify patients at risk for malignancy.

Saliva

Saliva is a suitable substance for screening because it is obtained in a simple and noninvasive manner. In addition, salivary mRNA is relatively stable and informative for disease diagnosis, including cancer. Zhang *et al*[89] identified 7 up-regulated genes (MBD3L2, KRAS, STIM2, DMXL2, ACRV1, DMD, and CABLES1) and 5 down-regulated genes (TK2, GLTSCR2, CDKL3, TPT1, and DPM1) in subjects with PDAC compared with healthy controls or those with chronic pancreatitis. A combination of 4 mRNAs (MBD3L2, KRAS, ACRV1, and DPM1) can discriminate diseased patients from healthy ones with sensitivity and specificity over 90%[89]. Xie *et al*[90] worked on miR-3679-5p and miR-940. The former is down-regulated, while the latter is up-regulated in PDAC patients compared to controls. The combination of the two miRNAs identifies diseased subjects with sensitivity and specificity of 70%. The same group evaluated the expression of salivary long non-coding RNAs (lincRNAs). They identified HOTAIR and PV1T as significantly up-regulated lincRNAs in the PDAC group compared with controls and benign pancreatic tumors. The combination of salivary HOTAIR and PVT1 differentiated PDAC from healthy controls with a sensitivity of 78.2% and specificity of 90.9% and PDAC from benign tumors with a sensitivity of 81.8% and specificity of 95%[90,91]. Another important mRNA studied in

serum, urine, and saliva is MIR1246. Salivary expression of miR-1246 is related to serum CA19-9 levels[92]. Significantly higher expression of MIR1246 in serum and urine was observed in patients with cancer compared with healthy controls. Ishige *et al* [93] observed an AUC for MIR1246 in serum of 0.87 (sensitivity, 92.3%; specificity, 73.3%), for MIR1246 in urine of 0.90 (sensitivity, 90.2%; specificity, 83.3%). Combining the expression of MIR1246 in serum and urine resulted in a sensitivity of 85%. These results indicate that MIR246 may be a useful diagnostic biomarker for pancreatic cancer. The accuracy further increases if we consider miR-1246 and miR-4644 simultaneously[92].

Urine

Several biomarkers have also been evaluated in urine. Radon *et al*[94] used three protein biomarkers (REG1A, TFF1 and LYVE1) to form a powerful urinary panel that can detect patients with stages I-II PDAC, with over 90% accuracy. Brezgyte *et al*[95] found four miRNAs (miR-143, miR-204 and miR-223) in significantly higher amounts and one miRNA (miR-30e) in lower amounts in the urine of PDAC Stage I patients compared to the healthy population. These miRNAs (except for miR-204) also showed a decreased expression in Stage II-IV compared to Stage I[95]. However, more studies are needed to validate the clinical utility of these biomarkers.

CLINICAL FEATURES

The presenting symptoms in patients with PDAC varies according to location. Tumors in the body and tail present with pain and weight loss, while tumor of the head cause jaundice and steatorrhea[96]. Pain associated with PDAC is usually insidious, visceral, generally epigastric, radiating to the sides or straight through to the back. It is worse by eating or lying supine at night. Rarely, it develops acutely on account of acute pancreatitis due to tumoral occlusion of the main pancreatic duct[97]. Pancreatic cancer may result in an onset of diabetes mellitus[98,99]. The hypercoagulable state that accompanies PDAC can result in Trousseau syndrome, which consists of superficial, sometimes migratory thrombophlebitis[100]. Thromboembolic complications occur more commonly in patients with tumors arising in the tail or body of the pancreas[101]. Skin manifestations could occur as paraneoplastic phenomena[102]. Rarely, erythematous subcutaneous areas of nodular fat necrosis (pancreatic panniculitis), typically located on the legs, may be evident. It is more frequent in patients with the acinar cell variant of PDAC. It is not pathognomonic for an PDAC, because it has also been described in associated with pancreatic neuroendocrine tumors, IPMNs and chronic pancreatitis[103].

When assessing symptoms, it should be borne in mind that PDAC tends to infiltrate nearby organs and structures and to give distant metastases very early. Local extension typically involves adjacent structures, such as the duodenum, the portal vein (PV), or the superior mesenteric vessels. PDAC also show a striking tendency toward perineural invasion, both within and beyond the pancreas. The difficulty in achieving a wide resection margin due to the proximity to the vessels accounts for the fact that the retroperitoneal tissue behind the head of the pancreas represents the most common site of disease recurrence. Sometimes the tumor extends to the spleen, adrenal glands, vertebral column, transverse colon, and/or stomach. In these cases, tumors are not resectable. Tumor may metastasize to regional peripancreatic lymph nodes or less often to distant lymph node, peri-gastric, mesenteric, omental or porta-hepatic nodes. Distant metastasis may affect the liver, peritoneum, lungs, and less frequently, bone. Signs of advanced, incurable disease include an abdominal mass, ascites, Virchow's node, Sister Mary Joseph's node or a palpable rectal shelf. Pancreatic cancer is the origin of a cutaneous metastasis to the umbilicus in 7% to 9% of cases[104].

DIAGNOSIS

CT

CT is considered the gold standard for pancreatic cancer's diagnosis. Protocol pancreatic CT is performed for evaluation of suspected PDAC or if a routine CT scan was not sufficient for initial staging[105,106]. This protocol consists of evaluating the patient at different stages of contrast injection. The arterial phase provides excellent opacification of the celiac axis, superior mesenteric artery (SMA), and peripancreatic

arteries. An attenuation difference between tumor and normal pancreas is best achieved after peak enhancement of the aorta in the arterial phase but before the one of the liver, in the portal venous phase. This is sometimes termed the "pancreatic phase". The portal venous phase provides better enhancement of the superior mesenteric vein (SMV), splenic and PVs. In addition, peak hepatic enhancement, which optimizes the detection of hepatic metastases, also occurs in the portal venous phase[107,108].

The typical CT appearance of a PDAC is an ill-defined hypoattenuating mass within the pancreas. Smaller lesions may be iso-attenuating, making difficult their identification[109]. Secondary signs of PDAC include a dilatation of the pancreatic duct or common bile duct, parenchymal atrophy, and contour abnormalities. Dilatation of both the pancreatic duct and the common bile duct, commonly referred to as the "double duct sign" is not diagnostic for a pancreatic head malignancy[110]. Routine preoperative CT helps to identify hepatic vascular anatomy and prepares the surgeon for any potential vascular anomalies. It can detect hemodynamically significant arterial stenosis[111]. The contrast-enhanced CT scan is the best technique for PDAC staging [112] and it is essential to detect vascular invasion. CT criteria for vascular invasion include arterial embedment in the tumor mass or venous obliteration, tumor involvement exceeding one-half the circumference of the vessel, vessel wall irregularity, vessel caliber stenosis, or a "teardrop" sign of the SMV[113]. Classic CT criteria for vascular involvement are not reliable in patients who have undergone neoadjuvant therapy with a highly active chemotherapy combination such as mFOLFIRINOX (mFFX). In such cases, surgical exploration may be the only method to assess resectability[114].

MRI

Contrast-enhanced MRI of the pancreas may be useful in staging patients at initial presentation. MRI is the best technique for detection of small liver metastases[115]. The importance of MRI also lies in the ability to diagnose pancreatic cancer by identifying changes in the body that indicate systemic effects of PDAC. It has been well recognized that anorexia, sarcopenia, and weight loss are hallmarks of PDAC. Consequently, it can be used to measure adipose and muscle mass in high-risk populations to identify early disease[116-118].

EUS

EUS is considered the most sensitive method to detect early neoplasia in the pancreas. PDAC on EUS appears as a hypoechoic mass, typically with dilation of the proximal pancreatic duct and the border of the lesion may have an irregular contour. This is the best accurate technique for local T and N staging, and for predicting vascular invasion. However, EUS is inferior to CT for evaluation of distant metastases. In addition, the specificity of EUS for excluding vascular invasion in small tumors is limited, particularly when inflammatory changes are present[119].

EUS is mainly used as part of the workup to obtain fine needle aspiration or biopsy material in patients suspected of having a PDAC[120]. EUS is not readily accessible and as a result is considered a complementary modality to the pancreatic protocol CT. Emerging area for endoscopic ultrasound includes the incorporation of elastography. Elastography shows significantly lower elasticity values for PDAC than for normal pancreatic tissue[121]. Incorporation of elastography in the evaluation of solid pancreatic lesions improves diagnostic accuracy[122,123].

Endoscopic retrograde cholangiopancreatography

A meta-analysis demonstrated a 92% sensitivity and 96% specificity of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of PDAC[124]. Findings suggestive of a malignant tumor of the pancreatic head include stenosis or obstruction of the common and pancreatic bile ducts (the "double duct" sign), a pancreatic duct stenosis greater than 1 cm in length, and pancreatic duct obstruction. In addition, ERCP provides an opportunity to collect tissue samples for cytohistologic analysis [124].

Some early-stage pancreatic tumors are not detected by CT, MRI, or EUS. Especially for carcinoma in situ, localized stenosis of the main pancreatic duct is often the only imaging finding. Pancreatic duct imaging evaluation by ERCP and subsequent pancreatic juice cytology are critical for diagnosis.

On the other hand, ERCP is an invasive procedure that can cause acute pancreatitis, bleeding, and cholangitis. Consequently, it has purely therapeutic value for patients with cholestasis due to tumor obstruction of the biliary system and require placement of a biliary stent[125].

Positron emission tomography

The role of positron emission tomography (PET) is limited for PDAC due to the high number of false positives and false negatives[126]. However, the degree of fluorodeoxyglucose (FDG) uptake correlates with histopathology, aggressiveness, and metastatic potential[127,128]. According to a meta-analysis, PET/CT is more accurate than CT in detecting distant metastases. Preoperatively, it may therefore be useful in avoiding unnecessary resection if unexpected metastases are found[129,130]. After treatment, FDG-PET is instead used to detect residual or recurrent cancer. It can also be applied to assess and monitor response to therapy in unresectable or metastatic disease[127,131].

Other molecular imaging agents including overexpressed proteins, signaling pathways, and tumor stroma may also be used[132]. Among these, promising results appear to involve ⁶⁸Ga-cicratide, an integrin $\alpha\beta 6$ -specific radiotracer, which has favorable pharmacokinetics and is capable of detecting pancreatic cancer lesions and monitoring response to therapy[133]. Another molecular imaging method that is of interest for early detection is hyperpolarized MRI. It can identify metabolic aberrations in the pancreas that indicate preneoplasia[134].

Staging laparoscopy

Sub-centimeter metastases of the liver or peritoneum that are rarely visible by CT, MRI or PET may be visualized laparoscopically. Up to one-third of patients thought to be resectable by imaging will be found to be unresectable based upon laparoscopic findings[135,136].

Some experts suggest a selective approach to staging laparoscopy, limiting the procedure to those with the highest likelihood of occult metastatic disease[137,138]. First, this includes tumors of the body or tail of the pancreas that appear potentially resectable by CT scan. Second, it includes large (> 3 cm) primary tumors and patients with a high initial CA 19-9 level (> 100 units/mL)[139].

Biopsy

Biopsy of a pancreatic mass can be performed either percutaneously or *via* EUS. EUS-guided FNA is the best modality for obtaining a tissue diagnosis. EUS-FNA is a safe method with a 0.98% morbidity and a 0.02% mortality. Although the most common adverse events of EUS-FNA include pancreatitis and postprocedural pain, there is also some concern regarding tumor cell seeding[140]. According to a study by Yane *et al* [141] the cumulative needle tract seeding rate at five years was 3.8%. However the preoperative EUS-FNA has no negative effect on recurrence-free survival and OS.

In many cases, the diagnosis will not yet be histologically confirmed. Once PDAC is suspected on imaging studies, the next step is generally a staging evaluation rather than biopsy. Patients who are fit for major surgery and who appear to have potentially resectable PDAC, they do not necessarily need a biopsy before surgery. Biopsy could be indicated if there is evidence of systemic spread or local evidence of unresectability on staging studies. It is also indicated if the patient is unfit for major surgery or if other diagnoses need to be excluded[142,143].

Pancreatic incidentaloma

A 2014 systematic review[144] evaluated 5 studies enrolling patients with incidentalomas and concluded that most solid lesions are malignant. Histologic definition of a solid lesion of the pancreas should be the first option, as opposed to radiologic monitoring alone. It is important to avoid operating on benign solid lesions such as chronic focal pancreatitis or autoimmune pancreatitis.

In case of cystic lesion, surgery is the first option for cystadenomamucinous and IPMN with high-risk stigmata. A recent review defined high-risk stigmata as the presence of obstructive jaundice, vascularized mural nodules ≥ 5 mm, main duct diameter ≥ 10 mm[145].

STAGING

The goal of the staging workup is to delineate the extent of disease spread and to identify patients who are eligible for resection with curative intent. Patients with PDAC can be staged according to the eighth edition of TNM system of American Joint Committee on Cancer (AJCC). However, most clinicians use a four-tiered staging system including resectable, borderline resectable, locally advanced (LA), and

metastatic cancer[146,147] (Table 2). In 2017, a classification was published, by the International Association of Pancreatology, which redefines the concept of resectability in relation to biological risk and patient conditions[148]. Table 3 summarizes the different resectability criteria assumed by the different scientific societies.

SURGERY

Surgical resection is the only potentially curative treatment. Unfortunately, PDAC is often diagnosed at an advanced stage and radical surgery could be performed in a very limited number of patients. The surgical interventions that can be performed are different depending on the tumour location and extension. In all cases the operation involves the removal of the tumour with free margins and at least twelve lymph nodes, which are necessary for staging. Tumors of the head require more complex operations, which still have a high operative morbidity. In high-frequency surgical centres mortality after pancreatoduodenectomy (PD) is now less than 2%, but post-operative morbidity remains high, 30%-50%. Anastomotic dehiscences, are the most serious post-operative complication. They are difficult to manage and are unfortunately associated with a still high mortality rate. Tumors of the tail and body require easier operations than head tumors, with a low operative morbidity and mortality. Unfortunately, because of their late symptomatology, they are more frequently unresectable.

Pancreaticoduodenectomy

PD is the classic operation performed for pancreatic tumors of the head or uncinate process. Conventional pancreaticoduodenectomy involves removal of the pancreatic head, duodenum, first 15 cm of the jejunum, common bile duct, gallbladder, and a partial gastrectomy. It is a complex procedure and patients may experience several complications. These complications could be intra-operative or post-operative[149, 150].

The most important intraoperative complication of PD is bleeding. Most patients undergoing PD for PDAC have an obstructive jaundice with associated coagulopathy. Bleeding can occur from multiple sites during the various phases of mobilization and resection, so hemostasis must be monitored and assured before reconstruction begins.

Postoperative complications can be further divided into short-term and long-term complications. The short-term ones are pancreatic fistula, delayed gastric emptying, and postoperative bleeding. The long-term ones are biliary stenosis and cholangitis, pancreatitis, peptic ulcer disease, small bowel obstruction, and incisional hernia[149, 150].

Modifications of the conventional PD procedure have been developed in an attempt to improve outcomes or minimize the morbidity associated with this operation. The pylorus-preserving pancreaticoduodenectomy preserves the gastric antrum, pylorus, and proximal 3 cm to 6 cm of the duodenum. It can decrease the incidence of post-operative dumping, marginal ulceration, and bile reflux gastritis, without negative effect on the morbidity, mortality and long-term survival[151]. Instead, the subtotal stomach-preserving pancreaticoduodenectomy is performed with the aims to preserve as much stomach as possible, minimizing the delayed gastric emptying that are associated with preserving the pyloric ring in the face of vagal denervation. In this procedure, the duodenum, pylorus, and 1 cm to 2 cm of stomach are resected with the pancreatic specimen. Although described, this modification has yet to be validated, and it is uncommonly performed[152].

The "Artery-first" approach is a surgical technique or set of techniques that have in common the dissection of the main arterial vasculature involved in pancreatic cancer, prior to performing any irreversible surgical step (transection of the pancreatic neck or bile duct division). The "Artery-first" approach has the potential to reduce blood loss and increase R0 resection rates and OS, as demonstrated in a recent meta-analysis[153].

Modified child reconstruction aims to reduce the incidence of cholangitis due to digestive reflux through hepatic-digiunal anastomosis. In case of pancreatic-digiunal anastomosis, the hepatic-digiunal anastomosis is made downstream of the previous one. In case of pancreatigo-gastric anastomosis, the hepatic-digiunal anastomosis is made near the previously closed loop. Whatever the type of pancreatigo-digestive anastomosis, the digestive anastomosis (gastro-digiunal or duodeno-digiunal) is made 60 cm downstream of the hepatic-digiunal anastomosis, to reduce digestive reflux into the biliary tract.

Table 2 Resectability criteria

Resectability status		Resectable	Borderline resectable	Locally advanced
Arterial involvement	Celiac artery	None	≤ 180°; > 180°, without involvement of aorta o GDA (body/tail)	>180° (head/uncinate); Solid tumor contact with CA and aorta
	SMA common hepatic artery	None	≤ 180°; Solit tumor contact without extension into CA or hepatic artery bifurcation	> 180°
Venous involvement (portal vein/smv)		None; ≤ 180° contact without contour irregularity	> 180°; ≤ 180° with contour irregularity or thrombosis, with reconstructible PV/SMV; Solid tumor contact with IVC	Unreconstructible PV/SMV due to tumor involvement or occlusion

CA: Celiac artery; GDA: Gastroduodenal artery; IVC: Inferior vena cava; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.

Table 3 Resectability criteria and societies

Vessel involvement	NCCN 2019	MDACC	ACTO	AHPBA/SSAT/SSO
CA abutment (≤ 180°)	Borderline	Borderline	Borderline	Unresectable
CA encasement (> 180°)	Borderline (body/tail); locally advanced (head/uncinate)	Unresectable	Unresectable	Unresectable
SMA abutment (< 180°); SMA encasement (> 180°); CHA abutment or encasement	Borderline; Locally advanced; Borderline	Borderline; Unresectable; Borderline	Borderline; Unresectable; Borderline	Borderline; Unresectable; Borderline
PV/SMV encasement (> 180°) or abutment (≤ 180°) with contour abnormality	Borderline	Borderline	Borderline	Borderline

ACTO: Alliance for Clinical Trials in Oncology; AHPBA: American Hepato-Pancreato-Biliary Association; CA: Celiac artery; CHA: Common hepatic artery; MDACC: The University of Texas MD Anderson Cancer Center; NCCN: National Comprehensive Cancer Network; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SSAT: Society for Surgery of the Alimentary Tract; SSO: Society for Surgical Oncology.

Post-operative pancreatic fistula (POPF) is the main and most frequent complication after pancreatic resection surgery. It is caused by leakage of pancreatic juice into the abdominal cavity, which is collected and conveyed to the outside by the drains normally placed at the end of surgery or during postoperative care if necessary. The diagnosis is made on the basis of the quality of the drainage fluid (varying from transparent to coffee-colored to brown) and the value of amylase in the fluid itself, greater than three times the normal limit of serum amylase[149,150].

POPFs are classified into three grades based on clinical impact. Grade A fistulas do not involve any special intervention and do not significantly modify the postoperative hospital stay. Grade B fistulas require a longer postoperative stay, the retention of surgical drains, the possible placement of additional drains under radiological guidance, antibiotic therapy and the use of artificial nutrition (enteral or parenteral). In grade C fistulas, reoperation is required to resolve the complication.

Several methods have been used to reduce the risk of pancreatic fistula, including the use of octreotide, pancreatic duct occlusion, pancreatic duct stenting, pancreaticojejunostomy, anastomosis modification, and pancreaticogastrostomy. The efficacy of octreotide in preventing POPF is still a hotly debated topic. According to a 2020 meta-analysis[154], somatostatin analogs did not affect POPF after PD, but rather appeared to be associated with a lower rate of POPF after distal pancreatectomy. Therefore, reconstruction technique is the most important factor in reducing the risk of this complication. Recently, interesting results concern the blumgart anastomosis (BA), which combines the duct-mucosal principle with the transpancreatic U-suture technique. Unlike other duct-mucosal anastomoses such as Cattell-Warren anastomosis and Kakita anastomosis, U-shaped sutures and horizontal mattress suture technique are used in BA. The difference is that Blumgart's technique involves the placement of 3 to 6 transpancreatic and digestive seromuscular U-sutures to bring the pancreatic stump and jejunum closer together. A meta-analysis conducted by Ricci *et al* [155] demonstrated the ability of BA to reduce the risk of pancreatic fistula compared with non-blumgart duct-to-mucosal anastomoses (non-BA DtoM). The reduction seems clinically significant, with a number needed to treat of 9 which means that one pancreatic fistula can be avoided every ten patients treated with BA instead of non-BA

DtoM[155,156].

Indications for the preoperative treatment of jaundice in patients who are candidates for surgery are still under debate. It increases post-operative complications and should be reserved to patients with cholangitis or with bilirubin levels greater than 15 mg/dL[157].

Distal pancreatectomy

Distal pancreatectomy with splenectomy is the conventional operation for PDAC located in the body or tail of the pancreas. It can provide a margin-negative resection and ensure a sampling of at least 12 regional lymph nodes. A systematic review, that included 29 observational studies, found less blood loss and reduced length of hospital stay in patients operated with laparoscopic approach. However, the laparoscopic technique has some disadvantages that may lead to inadequate resection margins: Technical difficulties, inability to palpate the gland, difficulty in closing the pancreatic stump. Generally, surgeons advocate an open approach when the concern for malignancy is high, reserving laparoscopic resection for benign or premalignant indications[158-160].

Petrucciani *et al*[161] evaluated the prognosis of patients with positive surgical margin (R1). A better OS was observed in patients with R0 margin *vs* R1. However, an extension of the surgical resection following R1 pancreatectomy did not improve long term survival.

Total pancreatectomy

Sometimes, because of the extent or location of the tumor, a total pancreatectomy is required to achieve microscopically negative resection margins[162,163]. However, the metabolic consequences of this procedure, which include permanent exocrine insufficiency and brittle diabetes, have a detrimental impact on the quality of life and long-term survival[164]. A recent study showed a moderately reduced summary score of 76%, compared with a general population score of 86% using the EORTC QLQ-C30 questionnaire to evaluate the overall quality of life. Diarrhea is the most important symptom[165].

Lymphadenectomy

Tomlinson *et al*[166] evaluated the minimum number of lymph nodes removed during pancreatectomy that are essential for proper staging. They consider a number of 15 Lymph nodes as the optimal cut-off. Therefore, the cut-off of 12 lymph nodes reported by Schwarz, represents a more easily threshold value, but sufficient for correct staging.

Standard lymphadenectomy should strive to resect lymph node stations 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b[167].

In some centres, mainly in Japan, surgeons routinely perform extensive lymph node dissection, including all 8, 9, all 12, all 14, 16a2, and 16b1 lymph nodes. A systematic review comparing standard *vs* extended lymphadenectomy demonstrated that there are no differences in OS between the two groups at one, three, or five years. However, the risk of complications was significantly increased after extended lymphadenectomy [168].

Vascular resection

If the pancreatic tumor involves the PV or SMV, pancreatic resection with PV or SMV resection may be considered: (1) When the vascular resection allows for adequate vascular flow; (2) When the tumor does not involve the SMA or hepatic artery; and (3) When an R0 resection can be accomplished. Nevertheless, many surgeons prefer to treat patients with PV or SMV involvement with neoadjuvant systemic chemotherapy before surgery.

A systematic review of 12 single-center reports concluded that pancreatectomy with PV/SMV resection is a safe and feasible procedure. It increases the number of patients who can undergo curative surgery and improves long term prognosis in a selected group of patients[169]. However, post-operative morbidity and mortality increase markedly when arterial resections are performed and few data are available to support these procedures[170-172].

Open vs minimally invasive approach

A systematic review identified 27 retrospective studies, including close to 7000 patients who underwent pancreatectomy (1306 minimally invasive, 5603 open)[173]. The laparoscopic approach was associated with longer operative times [mean difference (MD) 71 min], but lower intraoperative blood loss (MD -300 mL). The rate of

lymph node retrieval was significantly higher in the minimally invasive group (MD 1.34 nodes), and the likelihood of an R0 resection was also higher (odds ratio 1.45). Hospital stay, postoperative hemorrhage and wound infection were significantly lower in the laparoscopic group, while the rate of overall mortality, reoperations, vascular resection, pancreatic fistula, delayed gastric emptying and bile leak were similar between the two groups[174-176].

In some high-volume surgical centres, robotic-assisted pancreatic resection has been adopted. Experienced surgeon reported the same morbidity and mortality of open surgery. Decreased blood loss, higher number of adequate lymphadenectomy and improved gastric emptying are reported in some studies. These results may improve OS, but, because robotic-assisted pancreasectomy is still in its infancy, available long-term oncologic outcomes are limited[177-181].

CHEMOTHERAPY FOR RESECTABLE AND BORDERLINE RESECTABLE PANCREATIC CANCER

The only treatment with curative potential for pancreatic cancer is surgery. Five-year survival ranges from 10% to 25%.

For patients with PDAC resectable or borderline resectable, surgical resection is followed by adjuvant chemotherapy. Some high-volume centers also use neoadjuvant therapy in these categories of patients[182,183].

Adjuvant chemotherapy

Several adjuvant chemotherapy regimens have been evaluated in randomized controlled trials[184-190]. Currently, mFFX is the recommended therapy for patients with a good performance status. Gemcitabine (+/- capecitabine) remains a treatment option for patients not sufficiently fit or with contraindications to mFFX[182,191]. Because mFFX has a high toxicity, Brown University Oncology Research Group suggests FOLFOX + nab-paclitaxel (FOLFOX-A) as an alternative[192].

According to a meta-analysis[193], S1 was ranked best for overall and disease-free survival followed by mFFX. Whilst there was no significant difference between S1 and mFFX for OS, S1 had significantly longer disease-free survival (MD 2.8 mo) and was ranked best for lowest overall and haematological grade 3/4 toxicities[194]. However, the results should be interpreted with care, as S-1 has shown good results in the Asian population, but its performance in Caucasians remains unclear due to the different expression of cytochrome P-450.

Adjuvant chemotherapy should be administered between 28 and 59 d after surgery. This timing appears to provide better survival than administering before 28 or after 59 d[182,194].

A 2020 study compared the efficacy between adjuvant chemotherapy and chemoradiation therapy in relation to AJCC stage. Monochemotherapy and combination chemotherapy + chemoradiotherapy (CRT) showed better OS and disease free survival than CRT alone in patients with AJCC stage III, whereas there was no significant difference in OS in patients with AJCC stage I/II[195].

Neoadjuvant chemotherapy

The main purpose of neoadjuvant chemotherapy (NACT) differs according to the stage. For patients with BR-PDAC the objective of the therapy is to decrease tumor size and to control the micro metastases. For patients with primary resectable PDAC the purpose is to increase the proportion of patients receiving chemotherapy, because half of patients undergoing surgery, do not receive adjuvant chemotherapy due to postoperative morbidity or poor general condition[196].

In 2020, important advances were made in this field. For patients with BR-PDAC several studies confirmed the benefits on R0 resection rates and survival of NACT with mFFX[197-200] or multi-agent gemcitabine[201]. Moreover, in the PREOPANC-1 trial, patients receiving neoadjuvant CRT with gemcitabine obtained the same benefits of mFFX[202]. A study of the University of Texas showed that patients who received neoadjuvant CRT had significantly improved R0 resection rates, lymph node resection rates, and locoregional recurrence rates, compared with those who received NACT [203]. Although early data suggest the importance of integrating both NACT and CRT into the treatment, large prospective trial data are lacking[204]. New evidence for a standard regimen for BR-PDAC will be established by the result of the ESPAC-5F trial (ISRCTN89500674)[205].

For primary resectable cancer, the potential benefit of NACT has been validated, particularly when initiated within 6 wk of diagnosis[206]. The SWOG S1505 study observed that patients who received gemcitabine and nab-paclitaxel had a greater pathologic response and median survival comparable to those who received mFFX [207]. Several chemotherapeutic agents for resectable pancreatic cancer are currently being studied in several RCTs[208]. The NorPACT-1 study[209] and the Panache-01 study[210] are evaluating the effect of NACT with mFFX, and the NEONAX study [211] of NACT with 2 cycles of nab-paclitaxel/ gemcitabine.

In the Asian population, treatment regimens differ. The Prep-02/JSAP-05 study demonstrated, in patients with resectable PDAC, that NACT with gemcitabine plus S-1 (GS therapy) improves median OS compared with initial surgery (37 mo vs 27 mo). The resection rate and morbidity of surgery remain the same[212].

Based on these results, the latest Japanese guidelines recommend GS therapy as standard neoadjuvant therapy for patients with resectable PDAC. In this regimen, patients receive intravenous gemcitabine at a dose of 1000 mg/m² on days 1 and 8, plus oral S-1, twice daily, at a dose based on body surface area (80, 100, 120 mg/d) on days 1-14 every 3 wk for 2 cycles. For patients with BR-PDAC, they recommend NACT, but have refrained from recommending any specific regimens[212-214]. Among several ongoing RCTs on treatments for borderline resectable pancreatic cancer, a Japanese trial is comparing neoadjuvant therapy with gemcitabine plus nab-paclitaxel and CRT therapy with S-1[215].

A subset of patients does not respond to NACT. There is therefore a need to find markers that can predict response to NACT. At the moment the best ones seem to be GRP78, CADM1, PGES2 and RUXF[216] (Table 4).

CHEMOTHERAPY FOR LA PANCREATIC CANCER

Thirty to forty percent of patients with PDAC are initially diagnosed LA PDAC[182, 215]. LA PDAC is still nonmetastatic, but due to the local growth, curative resection is not possible at the time of diagnosis. Treatment involves chemotherapy with regimens that are also used in the metastatic setting, such as mFFX or gemcitabine plus nab-paclitaxel[217-219]. A small percentage of patients, with excellent response to chemotherapy, may become eligible for surgical resection. The majority have incurable disease. A systematic review of studies investigating mFFX in LA-PDAC revealed a median OS ranging from 10.0 mo to 32.7 mo[220], while in the LAPACT study, about the Nab-Paclitaxel + Gemcitabine regimen, OS 18.8 mo[221]. Recently, Kunzmann *et al* [222] compared two different NACT regimens, mFFX and gemcitabine plus nab-paclitaxel. The mFFX was superior in both the conversion rate to surgery (45.0% vs 30.6%) and the rate of R0 resections achieved (74% vs 68%). A subsequent study confirmed that mFFX patients had greater tumor size reduction, fewer positive lymph nodes, longer OS and distant metastasis-free survival compared to the nab-P/G patients[223].

The role of CRT for LA disease is still unclear. According to the LAP07 study, CRT improves the rate of local control but does not prolong survival in patients with LA PDAC after treatment with chemotherapy (gemcitabine with or without erlotinib) [224]. It is unclear whether these conclusions still hold true in the setting of newer combination chemotherapy regimens and improved radiation therapy techniques, such as stereotactic radiation therapy and proton therapy. The PAULA-1 study compared two cohorts of LAPDAC patients treated with stereotactic body radiotherapy (SBRT) ± chemotherapy vs CRT ± chemotherapy in terms of local control, distant metastases-free survival (DMFS), progression-free survival (PFS), OS, and toxicity. Patients treated with SBRT showed higher local control rate and similar OS, DMFS, PFS and toxicity compared to CRT[225].

CHEMOTHERAPY FOR METASTATIC PDAC

Half of patients have metastatic disease at the time of diagnosis. The primary treatment is systemic chemotherapy, with the goal of increasing survival and palliating cancer-related symptoms. Both mFFX and gemcitabine plus nab-paclitaxel improve median OS compared to gemcitabine monotherapy[226,227]. In clinical practice, for patients who are fitter, mFFX is generally preferred, reserving gemcitabine plus nab-paclitaxel as a second-line option if they have adequate performance status[228,229]. For patients who have received first-line gemcitabine and

Table 4 Phase of trial and level of evidence of trial about chemotherapy for resectable and borderline resectable pancreatic ductal adenocarcinoma

Ref.	Phase of trial	Level of evidence
Neoptolemos <i>et al</i> [185]	III	II
Oettle <i>et al</i> [186]	III	I
Neoptolemos <i>et al</i> [187]	III	I
Neoptolemos <i>et al</i> [188]	III	I
Conroy <i>et al</i> [189]	III	I
You <i>et al</i> [195]	III	II
van Roessel <i>et al</i> [198]	IV	II
Versteijne <i>et al</i> [202]	III	II
Ghaneh <i>et al</i> [205]	II	II
Sohal <i>et al</i> [207]	IV	II
Labori <i>et al</i> [209]	III	II
Schwarz <i>et al</i> [210]	II	I
Ettrich <i>et al</i> [211]	II	II
Motoi <i>et al</i> [212]	III	II
UMIN-CTR Clinical Trial[215] (UMIN000026858)	III	II

have progressed, a good option might be the combination of fluorouracil plus leucovorin with nanoliposomal irinotecan[230]. Golan *et al*[231] evaluated patients with metastatic PDAC and BRCA1-2 germline mutation. In these patients, disease progression had not occurred during at least 4 mo of first-line platinum derivative-based chemotherapy. Patients were randomized to receive olaparib or placebo. Olaparib showed a benefit in terms of PFS and a relatively safe toxicity profile. Although AIFA has not yet approved the indication, this study suggests a role for olaparib as maintenance therapy[231].

Finally, we look forward to the results of the AVENGER 500 trial (NCT03504423) to evaluate the efficacy of mFFX with or without CPI-613. CPI613 (devimistat) is an inhibitor of pyruvate dehydrogenase and α -ketoglutarate, key enzymes of the Krebs cycle. It has already shown good results in a phase I study[232].

STROMA-TARGETING THERAPY

Although chemotherapy is the recommended treatment for patients with advanced PDAC, its efficacy is not satisfactory. The major hurdle is considered the dense dysplastic stroma. The stroma components occupy more than 70% of the total tumor volume. The dense desmoplastic stroma of PDAC leads to vascular compression and a hypoxic microenvironment, which in turn influences drug pharmacokinetics/pharmacodynamics. It also prevents proper action of immune system cells, which are unable to reach the target site. The result is a chemoresistant and immunoresistant tumor[233,234].

One of the major components of the PDAC stroma is hyaluronic acid (HA). HA promotes the survival, proliferation, and migration of tumor cells[235]. HA is a potential therapeutic target using pegylated hyaluronidase (PEGPH20). The HALO-109-202 study demonstrated that PEGPH20, combined with Abraxane (nab-paclitaxel) and gemcitabine, improves progression-free and OS in patients with high HA levels [236]. However, poor results were obtained from the subsequent HALO-109-301 study (NCT02715804). Another element to be acted upon is the Hedgehog signaling pathway, which is generally overactivated in pancreatic cancer. Vismodegib, in combination with gemcitabine or erlotinib, was studied for this purpose. It did not significantly affect survival compared with these two drugs administered as monotherapy[237,238].

In tumors, Angiotensin II activates transforming growth factor- β through the AT1R and stimulates proliferation, so several angiotensin system inhibitors have been used to target PDAC stroma[233]. One study evaluated the efficacy of mFFX combined with losartan in a neoadjuvant regimen in patients with LA PDAC. The therapy was associated with an increased R0 resection rate[239].

A clinical trial evaluated the efficacy of focused ultrasound combined with gemcitabine microbubble delivery in PDAC patients. Patients treated with the combination tolerated multiple chemotherapy cycles of gemcitabine. A prolongation of median survival by almost 9 mo and, in 50% of cases, a reduction in tumor size were observed[240].

Poor results were obtained from stroma depletion in clinical settings. They are due to the fact that, although stroma-targeting therapy enhances the delivery of chemotherapeutic agents, it might also promote tumor chemoresistance and metastasis (a double-edged sword)[241]. According to several experts, future research should focus on the tumor ECM biology, biomarkers correlated with treatment benefit (as ADAM12)[242] and pharmacological agents able to alter the tumor microenvironment (TME). One of the most interesting discoveries in this regard involves clodronate liposomes. They prevent metastasis formation by inhibiting the activity of PDAC-associated macrophages and altering the microenvironment of key organs that are sites of metastatic invasion. They are therefore valuable candidates to be evaluated in combination with target therapy against stroma[243].

IMMUNOTHERAPY

Immune checkpoint inhibitors

Checkpoint inhibitors activates the function “kill the tumor” of the immune system, targeting immune checkpoint molecules (PD-1, PD-L1, CTLA-4) that negatively regulate T-cell function. Although they resulted in remarkable successes in other cancers, ipilimumab, BMS-936559 and tremelimumab showed little efficacy in PDAC [244-247]. The reasons of failure of immune checkpoint inhibitors are the low baseline PD-1+ T-cell infiltration into the tumor and a paucity of neoepitopes[248,249]. Indeed, in a very small subset of PDAC patients with a high burden of microsatellite instability (MSI-high) PD-1 inhibitor is effective and was recently FDA approved[250,251].

Currently, the development of immune checkpoint inhibitors for PDAC is focused on combination therapy with chemotherapeutic agents[252-255].

Therapeutic cancer vaccines

Therapeutic cancer vaccines present of immunogenic tumor antigens to the immune system, resulting in activation of the anti-cancer response. GVAX is an allogeneic vaccine irradiated with tumor cells engineered to express GM-CSF. It was studied alone and in combination with CRS-207 and cyclophosphamide, however it didn't correlate with improved survival[256,257].

More promising results were instead obtained with KIF20A-66[258-260].

K-RAS vaccines have been tested in the past, but data remain unclear and with no prominent advantages in metastatic patients[261-264].

We are currently awaiting the results of some studies: (1) TLP0-001, a phase III study of a dendritic cell (DC) vaccine loaded with WT1 peptides in patients with advanced PDAC refractory to standard chemotherapy[265,266]; (2) A clinical trial using GV1001 with GM-CSF in patients with LA-PDAC in combination with gemcitabine chemotherapy, tadalafil and radiation therapy (NCT01342224); and (3) NCT01836432, NCT02405585 and NCT01072981 evaluating algenpantucel-L in combination with chemotherapy and CRT therapy. They involve patients with borderline resectable and LA unresectable PDAC.

CAR-T cell

CAR-T cell therapy is a type of adoptive cell therapy. CAR-T cells are T lymphocytes that are extracted from a patient's blood sample or from a donor by apheresis, genetically modified to express the receptor for chimeric antigen (CAR), and cultured in the laboratory. They are then re-infused into the patient. The resulting T cells are able to recognize tumor cells and activate the immune system response against the disease[267]. The target antigens of CAR-T cells include mesothelin, prostate stem cell antigen (PSCA), CEA, HER2, MUC-1, and CD133[268,269]. In a study of metastatic PDAC, autologous mesothelin-specific T lymphocytes improved PFS in two patients of the six examined. An additional patient had complete remission of all liver metastases

[270].

Combination of immunotherapy drugs was experienced and showed good results over time. Le *et al*[271] compared the efficacy of Ipilimumab as monotherapy (arm 1) and Ipilimumab in combination with GVAX (arm 2) in patients with already treated PDAC. Combination therapy showed an increase in median OS (5.7 mo *vs* 3.6 mo) and 1-year OS (27% *vs* 7%). Chung *et al*[272] evaluated the combination of Pembrolizumab with modified p53-expressing Ankara vaccinia virus (p53MVA). Three of eleven patients experienced disease stabilization by 30, 32, and 49 wk. Good OS and PFS results were also obtained using DC and cytokine-induced killer cell immunotherapy in combination with S-1 chemotherapy, compared with chemotherapy or supportive care alone[256].

Several trials of immunotherapy-based treatment combinations with targeted agents are ongoing for patients with pancreatic cancer[273-275].

Oncolytic viruses

Oncolytic viruses are modified therapeutic drugs that selectively infect and self-replicate in tumor cells with tumor-dissolving effect. They also activate the anti-tumor immunity and change the TME from an immunosuppressed state to an immune-activated state. Furthermore, oncolytic viruses have the advantages of specificity, low toxicity, and low drug resistance[276]. Adenovirus, Herpes Simplex Virus, Protoparvovirus, Reovirus and Vaccinia Virus have been tested. However most of the studies have shown unsatisfactory results. The only positive results derive from ParvOryx02 (NCT02653313). A single-arm study published in 2020 showed an encouraging efficacy of pembrolizumab in combination with Pelareorep and chemotherapy in patients progressed after first-line treatment[277-281] (Table 5).

GENETIC MUTATION AND TARGET THERAPY

Some genetic alterations produce cellular changes in neoplastic cells that are potentially therapeutically targetable. BRAF mutations occur in 1%-3% of PDAC. They showed to be targetable in metastatic colon cancer where the combination of Encorafenib and Cetuximab has recently been approved[282,283]. Encorafenib and Cetuximab should also be evaluated in PDAC. Furthermore, pancreatic tumors with NTRK gene fusions can be treated with tropomyosin receptor kinase inhibitors[284, 285]. Similarly, some wild-type Kras pancreatic tumors hosting somatic NRG1 gene fusions respond to treatment with a kinase inhibitor of the HER family[286,287].

However, the results of the targeted therapies have been unsatisfactory, mainly due to the low life expectancy. There is no time to sequence the tumors and develop a treatment based on mutations[288].

The exceptions were the germline alterations. Patients with mutations of BRCA1, BRCA2 or PALB1 are remarkably sensitive to treatment with DNA cross-linking agents, such as platinum-based drugs, and poly(ADP-ribose) polymerase (PARP) inhibitors[289-291]. Patients with Lynch syndrome (MSI-high) respond well to treatment with immune checkpoint inhibitors[292-294] and those with ATM mutations could respond to the drugs, targeting the ATR-checkpoint kinase 1 (Chk1) pathway [295,296].

The elephant in the targeted therapy room remains Kras[297]. It has been considered "undrinkable"[297-299] because the protein lacks an efficient small-molecule binding pocket and has a high affinity for cellular guanosine triphosphate (GTP), which is highly concentrated in the cytoplasm. Furthermore, other than the GTP/GDP binding pocket, KRAS has no other pockets for small-molecule inhibitor binding. A druggable variant of Kras appears to be G12C. Enormous progress has been made in this regard and several drugs (AMG 510, MRTX849, JNJ-74699157 and LY3499446) are currently in clinical trials[299]. The importance of these can be deduced from the fact that 95% of pancreatic cancers harbor mutations in the Kras gene (the four Kras mountains, TP53, CDKN2A and SMAD4 present in > 50% of tumors)[300,301]. Although Kras G12C mutations are only a small fraction of Kras mutations in PDAC, these drugs represent a chance to take down a previously thought invincible adversary.

PANCREATIC CANCER AND GUT MICROBIOTA

Recent studies have shown the gut microbiota (GM) may play a role in the

Table 5 Phase and level of evidence of trials about immunotherapy for pancreatic ductal adenocarcinoma

Ref.	Phase of trial	Level of evidence
Royal <i>et al</i> [245]	II	II
Brahmer <i>et al</i> [246]	I	I
O'Reilly <i>et al</i> [247]	II	II
Tumeh <i>et al</i> [248]	II	III
Le <i>et al</i> [250]	II	II
Le <i>et al</i> [251]	II	II
Wainberg <i>et al</i> [252]	I	II
Weiss <i>et al</i> [253]	Ib/II	II
National Institute of Public Health[254] (JapicCTI-184230,ONO-4538)	II	II
Wang-Gillam <i>et al</i> [255]	II	II
Le <i>et al</i> [257]	IIb	I
Asahara <i>et al</i> [258]	I/II	II
Suzuki <i>et al</i> [259]	II	III
Miyazawa <i>et al</i> [260]	II	II
Wedén <i>et al</i> [261]	IV	III
Toubaji <i>et al</i> [262]	I	III
Abou-Alfa <i>et al</i> [263]	I/II	III
Cohn <i>et al</i> [264]	I	III
Katsuda <i>et al</i> [265]	III	I
Katsuda <i>et al</i> [266]	I/II	II
Beatty <i>et al</i> [270]	I	III
Le <i>et al</i> [271]	Ib	II
Chung <i>et al</i> [272]	I	III
Wang-Gillam <i>et al</i> [273]	I	III
Reiss <i>et al</i> [274]	II	III
Desai <i>et al</i> [275]	Ib/II	Ongoing trial
Chang <i>et al</i> [278]	I	III
Noonan <i>et al</i> [279]	II	II
Mahalingam <i>et al</i> [280]	Ib	III

development of PDAC and its response to therapy. GM alterations result in reduced mucus thickness, leading to decreased antimicrobial defenses and increased exposure to bacterial components such as LPS, flagellin, single or doubled DNA and CpG DNA. These agents activate Toll-like-receptors and trigger chronic inflammation that are related to carcinogenesis. Moreover, inflammation and dysbiosis lead to mutation of Kras, that accelerates carcinogenesis, activating nuclear factor- κ B pathway[302-304].

Several bacterial products are considered potential carcinogens. Cyclomodulins promote tumorigenesis through active interference with host cell cycles. Colibactin and Bacteroides fragilis toxin act synergistically with Escherichia coli to create double-stranded DNA damage[305]. E. coli cytotoxic necrotizing factor and CagA lead to uncontrolled cell proliferation, while cytolytic distending toxin and cycle inhibitory factor participate in genetic alterations and induce hyperploidy even in the absence of cell division[306]. The presence of an Helicobacter pylori infection and high concentrations of Fusobacterium spp and Porphyromonas gingivalis (bacteria generally present in the oral cavity) are associated with an increased risk of pancreatic cancer [307-310].

Moreover, other studies correlated a large number of microbes with immune suppression, downregulation of tumor suppressive pathways and the upregulation of oncogenic pathways[311].

Dysbiosis is also related to obesity, chronic pancreatitis and diabetes, well-established risk factors of PDAC[312,313].

Because it participates in drug metabolism and biotransformation and immune regulation, the GM is implicated in the efficacy of chemotherapeutic agents[314]. The innate immune response activated by the GM potentiates the action of oxaliplatin [315]. Gentamicin activity may be reduced by the enzymes pyrimidine nucleoside phosphorylase and cytidine deaminase, which are produced by Gamma-proteobacteria and mycoplasmas within PDAC. Thus, these data suggest the possibility of modulating GM to counteract the chemoresistance characteristic of pancreatic cancer [316].

Intratumoral microorganisms can play a key role in anticancer therapy[317]. Indeed, they can stimulate host immune responses with positive or negative impacts on therapy. *Gammaproteobacteria*, *Escherichia Coli* and *Fusobacteria* are most commonly present in PDAC. Gamma proteobacteria contain the enzyme CDD which could be responsible for the ineffectiveness of gemcitabine[318]. *Escheria Coli* is capable of inducing chemical changes in the structure of gemcitabine, fludarabine, cladribine, and CB1954[319]. The desmoplastic response induced by tumor cells is dependent on MyD88. It is activated by *Fusobacterium* species.

The intratumoral microbiota thus emerges as a major proponent of the chemo-immunoresistant phenotype of pancreatic cancer and is related to long-term survival in PDAC patients.

PROGNOSIS

The most important prognostic factor is tumor stage. The median survival time after resection for patients with stage IA, IB, IIA, IIB, and III was 38, 24, 18, 17, and 14 mo, respectively[320]. Other factors may influence the prognosis of PDAC after surgery: Surgical margin status, tumor grading, presence of lymphatic invasion, preoperative and postoperative serum levels of CA 19-9, and cigarette smoking[321-329]. Squamous subtypes have a poor prognosis. They are enriched with TP53 and KDM6A mutations, upregulation of TP63ΔN transcriptional network, hypermethylation of pancreatic endoderm cell fate determining genes[330].

Several studies have investigated novel factors influencing prognosis: (1) Increased expression of CDK1 and CCNA2 is associated with poor prognosis, although they may be potential therapeutic targets[331]; (2) The autophagy regulatory genes MET and RIPK2 play a prognostic role in PDAC[332]; (3) High expression of GPDAC2, GPDAC3 and GPDAC5 has been significantly associated with favorable survival[333]; (4) High expression of Hic-5 is negatively correlated with postoperative survival time, as Hic-5 stimulates tumor proliferation, migration, and invasion[334]; (5) PRMT1 promotes pancreatic cancer growth by increasing cellular β-catenin levels and predicts poor prognosis[335]; (6) Patients with first recurrence in the lung have a better prognosis than patients with first recurrence in the liver[336]; (7) Increased levels of ZIP4 correlate with poorer survival. ZIP4 inhibits the expression of the gemcitabine transporter ENT1, so that cells take up smaller amounts of the drug. Activation of this pathway participates in the chemoresistance of pancreatic cancers[337]; (8) The highly upregulated in liver cancer (HULC) lncRNA distinguishes patients with pancreatic cancer, patients with benign pancreatic disease, and healthy subjects and correlates with TNM stage. Subjects with low HULC expression have significantly higher 3- and 5-year OS than those with high expression. Therefore, HULC lncRNA could be considered an effective marker for the diagnosis and prognosis of PDAC[338]; (9) Upregulation of TYMS leads to unfavorable OS and RFS[339]; and (10) The GINS complex has four subunits, encoded by the GINS1, GINS2, GINS3, and GINS4 genes, all of which are overexpressed in PDAC. The expression of each member is associated with the histological grade of PDAC and is a negative prognostic marker[340].

CONCLUSION

Pancreatic cancer is a very treacherous, dangerous enemy and the results are still very unsatisfactory. But we have not given up. Research is running fast on many paths, without losing its enthusiasm. It is proof that we are encircling it, and at the end, we

will win. The success of a fight is linked to the ability to move from one failure to another without losing one's enthusiasm.

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