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REVIEW

Pancreatic cancer in 2025: Have we found a solution?

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Abstract

Pancreatic cancer is still one of the neoplasms with the worst prognosis. Late presentation at an unresectable or metastatic stage precluding surgery, aggressive biology, and resistance to antiblastic drugs make this disease a formidable foe. The authors, following the path already traced by the previous review, investigate and summarize the breakthroughs of recent years concerning this lethal disease. Areas of progress include improving prevention and early detection strategies, refining molecular understanding of pancreatic cancer, identifying more effective systemic therapies, and improving quality of life and surgical outcomes. No less important is the technological aspect that looks primarily at artificial intelligence.

Key Words: Pancreatic cancer; Early diagnosis; Therapeutic development; Precision medicine; Target therapy; Immunotherapy; Pancreatic surgery

Core Tip: Pancreatic cancer is still one of the neoplasms with the worst prognosis. Late presentation at an unresectable or metastatic stage precluding surgery, aggressive biology, and resistance to antiblastic drugs make this disease a fearsome challenge. This review aims to investigate new strategies for early diagnosis and new therapeutic hopes for improving the still tragic outcomes.

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INTRODUCTION

Pancreatic cancer is one of the deadliest malignancies and poses a significant global health challenge. It ranks 12th in incidence and 6th in cumulative mortality[1]. In the Western world it is the third leading cause of cancer death[2]. Despite advances in healthcare, survival rates have seen little improvement[3]. Retroperitoneal localization, nonspecific symptoms in early stages, and its aggressive biology contribute to the high percentage of patients (51%) presenting with metastatic disease at diagnosis. Additionally, the limited treatment options is due to its desmoplastic and chemoresistant nature[4]. Pancreatic ductal adenocarcinoma (PDAC) accounts for the majority (90%) of pancreatic neoplasms[4]. The 5-year overall survival (OS) rate for pancreatic cancer is 11%, while the cancer-specific survival rate is 13%[3]. The 5-year survival rate varies greatly depending on the stage of the disease at diagnosis, ranging from 44% in patients with localized disease to 3% in patients with metastatic disease[4]. For those with borderline or locally advanced disease, survival is 10%-15%[5]. It should be noted that for patients with stage Ia pancreatic cancer, the 5-year survival rate is 84%[3, 6].

Epidemiology

In high human development index countries such as Europe, North America, Australia/New Zealand, and Japan, the incidence of PDAC is highest, ranging from 7.9 to 9.9 per 100000 people. Conversely, Africa, Central America, and South Asia have the lowest incidence, between 1.5 and 4.6 per 100000 people[7,8]. This difference may be due to the higher prevalence of risk factors associated with higher income levels such as tobacco use, alcohol consumption, obesity, and diabetes as well as an aging population. Pancreatic cancer generally occurs in older adults. The median age at diagnosis is 70 years, with incidence peaking between 65 and 79 years globally[9,10]. Overall, the incidence has increased in recent decades, with a more significant rise observed in individuals under 50 years of age[9,11,12]. It is hypothesized that early-onset PDAC (defined as cases diagnosed between 40 and 55 years of age[13,14]) may represent a distinct clinical and/or biological phenotype, with specific etiologic factors such as genetic and behavioral features, and prognostic implications [11-14]. The more rapid increase in PDAC incidence among young adults may reflect changes in exposures and lifestyle factors like obesity and diabetes[14]. Although early-onset PDAC accounts for a small proportion of cases, it significantly contributes to the disease burden. For example, in the United States, it is estimated that it accounts for at least 20% of potential years of life lost and about 6% of all cancer deaths in this age group[13,14].

Risk factors

Several studies have examined diabetes as a risk factor. It is well established that diabetes is associated with an increased risk of PDAC and that PDAC can have a diabetogenic effect, with half of PDAC patients having diabetes[15,16]. In the first year after the diagnosis of type 2 diabetes, the risk of also being diagnosed with PDAC is 14-15 times higher than in the nondiabetic population. The risk decreases in the second year to 3.5-5.4 times and stabilizes at about 3 times[17]. Prediabetes is associated with a 40% increase in pancreatic cancer risk[18]. Type 2 diabetes significantly increases the overall annual incidence rate of PDAC compared with the general population, with a standardized incidence ratio of 1.54 [19,20]. A recent systematic review suggested that new-onset diabetes, especially when associated with advanced age, a family history of pancreatic cancer, a personal history of gallstones or pancreatitis, and weight loss, is strongly correlated with PDAC and could be used as a basis for further screening strategies[21]. The association of chronic obstructive pulmonary disease or hyperuricemia with diabetes also increases the risk of pancreatic cancer[22,23]. Recent studies have also associated PDAC with conditions such as cutaneous and systemic lupus erythematosus, polycystic ovary syndrome, opium use, chronic intake of proton pump inhibitors, and chronic inflammatory bowel disease[24-29].

Heritability is suspected in 21%-36% of pancreatic cancer patients[30]. This may be due to genetic syndromes (accounting for 20% of cases) or familial pancreatic carcinoma (FPC) (80%). Genetic syndromes that predispose to pancreatic cancer involve genes such as *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2/EPCAM*, *MSH6*, *PMS2*, *STK11*, *PRSS1*, and *TP53*. FPC is defined as a familial cluster-based predisposition in families with at least one pair of first-degree relatives (FDR) affected by PDAC, in the absence of a known genetic syndrome. Individuals with one affected FDR have a 4-fold increased risk, those with two or three affected FDRs face a 6- and 34-fold increased lifetime risk, respectively[31,32].

Screening

Pancreatic cancer screening in the general population is not currently recommended by guidelines[33,34]. However, it is considered in high-risk individuals (HRIs), defined as those with a lifetime risk of PDAC ≥ 5%. These include individuals with genetic syndromes or who meet criteria for FPC[31,33,34]. Besides the traditional criteria for FPC, individuals with three or more diagnoses of pancreatic cancer on the same side of the family, or with at least two affected relatives on the same side (one of whom is an FDR), are considered high risk. Screening methods include magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS). MRI is better for evaluating cystic lesions, while EUS is preferred for detecting solid lesions and parenchymal changes[35]. Guidelines recommend annual screening with EUS and/or MRI[36-39]. The one-year interval is advised because nearly half of all patients develop interval PDAC at a median of 11 months in large cohorts of HRIs. Shorter intervals may be recommended if relevant lesions are detected[36]. The age to start screening depends on the individual's estimated risk. For patients with FPC or a known genetic predisposition and one or more FDRs affected with pancreatic cancer, it is recommended to start screening at age 50 or 10 years before the age of the first affected blood relative. For those at very high risk, earlier screening is recommended, which can begin at age 40 for patients with familial atypical multiple mole melanoma or hereditary pancreatitis, and at age 35 for those with Peutz-Jeghers syndrome. There is no current consensus on when to stop screening. Discontinuation is recommended when the risk of death from causes unrelated to pancreatic cancer is higher than that of pancreatic cancer, or when patients are no

longer candidates for surgical resection.

Screening programs report excellent survival outcomes, with rates ranging from 24% to 73% at 5 years. These findings contrast with sporadically diagnosed PDAC, where 5-year survival rates for all stages reach 11%-13%. Blackford *et al*[3] demonstrated that HRIs who undergo annual or semi-annual EUS and MRI surveillance and receive a diagnosis of pancreatic cancer are more likely to have smaller, lower-stage tumors, lower cancer-specific mortality and better OS. A multimodal approach to surveillance, capable of estimating individual risk by integrating demographic data, clinical examinations, imaging, genomics, biomarkers, and artificial intelligence (AI), would be sensational.

BIOMARKERS AND EARLY DETECTION

Serum biomarkers

Carbohydrate antigen 19-9 (CA19-9) is the most validated serum tumor marker for pancreatic cancer in terms of its diagnostic, prognostic, and surveillance capabilities. However, CA19-9 has a low positive predictive value and isn't used as a screening tool[40]. Other carbohydrate antigens have been evaluated for the early diagnosis of pancreatic cancer, but they haven't found clinical validation. Among new diagnostic tools, circulating cell-free DNA (cfDNA), micro-RNA (miRNA), and exosomes are the most interesting. Hu *et al*[41], studying more than 120 cfDNA methylation biomarkers, identified a panel for PDAC detection. It includes *IRX4*, *KCNS2*, and *RIMS4* and achieved a sensitivity of 86% for patients in the validation cohorts with 100% specificity. Additionally, they identified hundreds of methylated cfDNA biomarkers that differed between PDAC and hepatocarcinoma, colorectal cancer, and gastric cancer. CfDNAs are also being studied in combination with CA19-9 to improve its performance. Ben-Ami *et al*[42] created a panel with CA19-9, tissue inhibitor of metal protease, and cfDNA that showed higher discrimination ability than CA19-9 alone for early-stage PDACs [area under the curve (AUC): 0.86 *vs* 0.82].

Regarding miRNAs, the most promising panel consists of mir-5100, mir-642b-3p, and mir-125a-3p, with an AUC of 0.95, a sensitivity of 0.98, and a specificity of 0.97[43,44]. Huang *et al*[45] obtained similar results, reporting a signature composed of miR-132-3p, miR-30c-5p, miR-24-3p, and miR-23a-3p. It was obtained from the analysis of tissue and serum samples from 1273 participants and detected PDAC with promising accuracy (AUC = 0.971).

Excellent results were also obtained with miR-28-3p, miR-143-3p, miR-151a-3p, a panel of 2'-O-methylated miRNAs[43,46]. Exploration of exosomal protein expression has shown promising results in large cohorts[47]. Wei *et al*[48] and Wei *et al*[49] identified significantly elevated levels of the exosomal receptor erythropoietin-producing hepatocellular A2 (EphA2) in 244 pancreatic cancer patients. Indeed, the area under the receiver operating characteristic (AUROC) values for the serum exo-EphA2 diagnostic test were 0.94 and 0.92 compared with healthy controls and benign pancreatic disease, respectively. For early-stage I or II PDAC, these values decreased slightly to 0.92 and 0.90, but the combination of exo-EphA2 with CA19-9 increased the AUROC to 0.96 compared with healthy controls[48,49]. A meta-analysis on the diagnostic accuracy of exosomes in pancreatic cancer revealed that within the subset of exosomal biomarker types, the group with exosomal cell surface proteoglycan showed the highest combined sensitivity (0.96) and specificity (0.90)[50].

Pancreatic juice

Extremely promising results have been obtained by analyzing biomarkers in pancreatic juice. In a recent study, Yachida *et al*[51] created a method to identify resectable PDAC by analyzing *KRAS* mutations in duodenal fluid collected during an esophagogastroduodenoscopy with stimulation of pancreatic juice secretion by secretin. They obtained an AUC of 0.934 in differentiating patients with resectable PDAC from healthy controls. In pancreatic juice, Sakaue *et al*[52] also detected high diagnostic potential for early-stage PDAC in Ex-miR-4516, a PDAC-specific exosomal miRNA. A multicenter prospective study evaluated 14 methylated DNA markers (MDMs) in pancreatic juice (*NDRG4*, *BMP3*, *TBX15*, *C13orf18*, *PRKCB*, *CLEC11A*, *CD1D*, *ELMO1*, *IGF2BP1*, *RYR2*, *ADCY1*, *FER1 L4*, *EMX1*, and *LRRC4*). A panel with 3 MDMs (*FER1 L4*, *C13orf18*, and *BMP3*) alone and in combination with CA19-9 was then studied. Methylated *FER1 L4* had the highest individual AUROC of 0.83. The AUROC for the 3-MDM + plasma CA19-9 model (0.95) was higher than both the 3-MDM PJ panel (0.87) and plasma CA19-9 alone (0.91). With a specificity of 88%, the sensitivity of this model was 89% for all stages of PDAC and 83% for stage I/II PDAC[53].

DIAGNOSIS

Clinical symptoms

The symptoms that manifest in pancreatic cancer are generally vague and nonspecific and depend on the location of the disease. Approximately 70% occur in the head of the pancreas and often present with painless jaundice and exocrine pancreatic insufficiency[5]. In contrast, tumors of the body-tail cause abdominal and back pain. In both cases, symptoms related to cachexia (loss of appetite, weight loss, fatigue) are common. The onset of diabetes or worsening of pre-existing diabetes may be a sign of PDAC. Acute pancreatitis can be a primary manifestation[5]. PDAC is accompanied by a state of hypercoagulability, which can manifest as Trousseau's syndrome, a superficial and migratory thrombophlebitis. Skin manifestations, such as pancreatic panniculitis, may occur as paraneoplastic phenomena.

Imaging

The imaging modality of choice is contrast-enhanced triphasic computed tomography (CT)[54-56]. It consists of the pancreatic, arterial, and portal venous phases. PDAC typically presents as a hypodense lesion, in stark contrast to hyperdense neuroendocrine tumors. Cancer of the head of the pancreas also often causes dilation of both the common bile duct and the main pancreatic duct, a typical feature known as the "double duct sign"[55]. However, some lesions, especially small ones, are isoattenuating and not easily identifiable[56]. It will therefore be necessary to look for indirect findings that suggest the presence of pancreatic cancer, such as dilation of the pancreatic duct with a sharp cut and pancreatic atrophy[57]. In patients with poorly defined masses or contraindications to contrast-enhanced CT, MRI or EUS may be used. MRI is also excellent for characterizing suspected liver metastases, while EUS is useful for assessing lymphovascular involvement. It is also capable of obtaining a definitive cytological or histological diagnosis. Positron emission tomography aims to rule out distant metastases in cases with a high risk of metastatic disease, for example in patients with very high serum CA19-9, regional lymphadenopathy, and large primary tumors[54-58].

Pathology

In patients with suspected metastatic pancreatic cancer, a pathological report of possible metastases must be obtained[54]. In cases of localized neoplasia, a pathological report is necessary when imaging is unable to distinguish between benign and malignant disease, or in patients for whom first-line treatment is chemotherapy[54,58]. EUS with fine needle biopsy is the standard procedure[54,58]. Genetic testing for hereditary mutations is recommended for all patients diagnosed with pancreatic cancer[58]. In the case of advanced or metastatic disease, it is recommended to investigate the molecular profile to guide targeted treatment. The profile to be evaluated includes *BRCA1*, *BRCA2*, DNA mismatch repair deficiency (*e.g.*, *MLH1*, *MSH2*, *MSH6*), and *KRAS* wild type (*KRAS*wt) (*e.g.*, fusion genes such as *NRG* and *NTRK*)[58].

Laboratory

In patients with pancreatic cancer, serum concentrations of CA19-9 and carcinoembryonic antigen (CEA), liver enzymes, and bilirubin are measured. Although the serum CA19-9 biomarker is not reliable for the definitive diagnosis of PDAC, it is valuable as an indicator of possible micro-metastatic disease, for assessing the risk of occult metastases, and for evaluating response to treatment[59].

Staging

The tumor node metastasis classification (tumor, lymph node, and metastasis) is used exclusively to assess prognosis[60]. A more practical classification, useful in everyday life to define the correct therapeutic management, divides pancreatic cancer into resectable, borderline resectable pancreatic cancer (BRPC), locally advanced pancreatic cancer (LAPC), or metastatic. Resectability is defined by anatomical (A), biological (B), and conditional (C) criteria[61,62]. Anatomical resectability is defined by the degree of contact between the tumor and adjacent vascular structures (*i.e.*, the superior mesenteric and portal veins, as well as the celiac, hepatic, and superior mesenteric arteries). It is classified as uninvolved, abutted, or encased. Abutment implies that the tumor has blood vessel involvement of 180° or less, while encased implies circumferential tumor-vessel involvement greater than 180°. Tumors are generally considered resectable when contact with major vessels is minimal or absent. BRPC involves venous involvement and/or partial arterial involvement. Locally advanced PDAC is unresectable at presentation due to vascular invasion[5]. The biological criterion chosen is a CA19-9 value of 500 IU/mL at diagnosis. Above this level, even anatomically resectable tumors should be reclassified as borderline due to their more aggressive behavior and poorer prognosis. The conditional criterion reflects the patient's physiological status and is based on the Eastern Cooperative Oncology Group (ECOG) score. An ECOG score ≥ 2 defines the case as borderline due to the expected poor tolerance to the required surgical and systemic therapy[61,62].

Surgery

Surgical resection is the only potentially curative treatment, but it can only be performed in a limited number of cases, as pancreatic cancer is often diagnosed at an advanced stage. Depending on the location and extent of the tumor, a pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy may be performed. The surgical procedure involves removing the tumor with clear margins and at least twelve lymph nodes (necessary for staging). In recent years, minimally invasive procedures, particularly robotic procedures, have been implemented for pancreatic cancer, based on the assumption of a potential benefit in terms of faster recovery and the possibility for patients to proceed more quickly and more often to adjuvant therapy[63,64]. Pancreatic cancer surgery may require portomesenteric, arterial, and multivisceral vein resection to achieve radical resection. Arterial resection has historically been contraindicated due to the associated increase in morbidity and mortality. It is only considered in young patients in good general health because it can offer a more favorable prognosis than palliative treatment[64].

Pancreatoduodenectomy

Open surgery remains the standard of surgical care for pancreatoduodenectomy. While the PLOT[65] and PADULAP[66] trials initially showed potential benefits for laparoscopic pancreatoduodenectomy (LPD), these results were challenged by the Dutch LEOPARD 2 study, which reported an increase in mortality in the laparoscopic group and was therefore discontinued prematurely[67]. A subsequent meta-analysis showed that the successful application of laparoscopic techniques depends on a learning curve[68]. Choi *et al*[69] also found an inferiority of the minimally invasive approach in terms of disease-free survival (DFS) for stage III pancreatic head tumors. Conversely, Giani *et al*[70] demonstrated comparability in oncologic outcomes between open and minimally invasive techniques. In fact, they found the latter was associated with better lymph node harvesting. This is especially true for the robotic technique, as confirmed by a review

of 17831 pancreatoduodenectomies[71] and several single-center retrospective studies[72,73]. The EUROPA trial, a trial including 81 patients randomized to either robotic pancreatoduodenectomy (RPD) or open pancreatoduodenectomy (OPD)[74,75], found that both RPD and OPD were safe, although RPD had a higher complication rate and a longer surgical duration. When comparing laparoscopic and robotic surgery, robotic surgery often prevails. A recent study demonstrated its superiority in terms of conversion rate, blood loss, R0 resection rates, lymph node retrieval (24.2 *vs* 21.9), and length of hospital stay (11 days *vs* 13 days). Additionally, an improvement in DFS from 1 years to 3 years and OS was found in the RPD group compared with the LPD group[76].

Distal pancreatectomy

Unlike pancreatoduodenectomy, minimally invasive distal pancreatectomy (MIDP) is recommended as the standard approach for tumors of the body and tail of the pancreas. It offers advantages in terms of delayed postoperative gastric emptying, functional recovery time, and length of hospital stay compared to OPD[77,78]. In 2023, the study "minimally invasive *vs* open distal pancreatectomy for resectable pancreatic cancer" was published in Lancet, demonstrating the non-inferiority of MIDP compared to OPD in terms of resection rates. Equivalent rates of R0 resection, median lymph node harvest, and intraperitoneal recurrence were found. In addition, the median functional recovery time and length of hospital stay were comparable, as were the one- and two-year survival rates[79,80]. According to a European study[81], the annual use of robotic distal pancreatectomy (RDP) increased from 30.5% to 42.6% and was associated with fewer grade intraoperative events compared to laparoscopic distal pancreatectomy, although with a longer operating time. No significant differences were observed in terms of morbidity and hospital/30-day mortality. RPD was associated with fewer conversions in overweight patients, in cases of previous abdominal surgery, and in cases of vascular involvement [81]. Chen *et al*[82] demonstrated that the RDP group had higher rates of R0 resection, a greater number of lymph nodes removed, and a greater number of vascular resections, indicating that the RDP group underwent more extensive surgery, which could explain the longer hospital stay.

Total pancreatectomy

Total pancreatectomy may be essential to surgically extirpate multicentric pancreatic cancer[83]. Minimally invasive total pancreatectomy and open total pancreatectomy have comparable operative and oncological outcomes[83]. Scholten *et al* [84] reported improved conversion rates for robotic total pancreatectomy at 13.3% *vs* 42% for laparoscopic total pancreatectomy, with otherwise similar outcomes.

Surgery and metastasis

Metastases in PDAC have historically been a contraindication to curative resection. Some studies have reported the technical feasibility and safety of metastasectomy for oligometastatic disease, defined as disease with three or fewer metastatic lesions in the liver, lungs, or both[85-90]. The clinical status of "oligometastasis" is still poorly understood. Its adoption remains controversial, and current evidence is not strong enough to influence guidelines. Metastasectomy is justified when it is safe and offers a benefit in terms of survival or improved quality of life.

Liver and lung

The liver is the most common organ for initial metastatic spread or distant recurrence in patients with pancreatic cancer [88] and the median survival has remained poor compared with other sites of metastases[91]. Frigerio *et al*[92] studied patients with synchronous liver-only metastases (73% had more than two liver metastases). All patients underwent preoperative chemotherapy (63.5% FOLFIRINOX, 36.5% gemcitabine), achieving complete regression of metastatic lesions prior to surgery. In 67.3% of patients, CA19-9 normalization was observed after treatment. With an R0 resection rate of 86.5%, OS from diagnosis was 37.2 months and median DFS after pancreatectomy was 16.5 months. A recurrence occurred in 75% of cases. According to a multivariate analysis, the main factor associated with recurrence was omission of adjuvant therapy. The improvement in OS demonstrates the importance of chemotherapy in helping to select favorable biology[93].

Patients with pulmonary metastases have been shown to have a longer time between pancreatectomy and recurrence and better OS than those with other types of recurrence[94]. Pulmonary metastasectomy has, in recent years, been recognized as a procedure for patients with pancreatic cancer, with reported 5-year survival rates of 31%-70%[95-99].

Peritoneum

Peritoneal carcinomatosis has always been considered incurable and treated palliatively with chemotherapy (median OS: 1.5-17 months[100]). The standard regimens are gemcitabine plus nab-paclitaxel (GnP) or FOLFIRINOX, which modestly increase survival compared to gemcitabine alone[101,102]. However, the median survival for metastatic pancreatic cancer ranges from 4.4 to 11.1 months, regardless of the treatment protocol used[103]. Intraperitoneal chemotherapy significantly increases the surgical conversion rate compared to systemic chemotherapy for peritoneal metastases[104-106]. Hyperthermic intraperitoneal chemotherapy (HIPEC), accompanied by radical surgical resection, has shown favorable oncological outcomes. In a Mayo Clinic study[107], patients with PDAC and isolated peritoneal metastases (peritoneal carcinomatosis index < 7) who completed ≥ 6 months of systemic chemotherapy were retrospectively examined.

Patients undergoing cytoreductive surgery (CRS)/HIPEC were compared with patients undergoing systemic therapy alone. A statistically significant difference in median OS, from diagnosis of peritoneal metastasis, was found (19 months for systemic therapy alone and 41 months for CRS/HIPEC). In addition, OS at 1, 2, and 3 years was 81%, 31%, and 8% for systemic therapy alone, compared with 91%, 66%, and 59% for CRS/HIPEC. From the time of surgery, median OS was 26 months, with OS at 1, 2, and 3 years being 76%, 57%, and 39%, respectively. The median progression-free survival

(PFS) was 13 months. These results suggest that a selected group of patients may benefit from CRS/HIPEC treatment. However, the procedure is not considered the standard of care for PDAC with peritoneal metastases. Further investigation is needed and is currently underway (No. NCT04858009)[108,109].

In addition to HIPEC, there are also other methods of intraperitoneal chemotherapy, namely normothermic intraperitoneal chemotherapy (NIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC). A study compared conventional systemic therapy and NIPEC with paclitaxel, demonstrating improved survival in the intraperitoneal therapy group (17.9 months *vs* 10.2 months). Patients who responded to treatment and underwent conversion surgery then had a median survival of 27.4 and 11.3 months, respectively[106].

PIPAC allows for homogeneous and deep penetration of chemotherapy into the peritoneum through the production of aerosols. In a phase II study, a PIPAC approach was used with the administration of cisplatin and doxorubicin, achieving a median survival of 15.6 months[110]. Di Giorgio *et al*[111] found pathological regression in 50% of cases using PIPAC with oxaliplatin or cisplatin-doxorubicin in patients with peritoneal metastases of pancreatic and biliary origin.

A median survival of 10 months and a 1-year survival rate of 50% were achieved in a phase I study of patients with unresectable peritoneal metastases from various tumors[112,113].

Frassini *et al*[104] systematically reviewed complications following HIPEC, PIPAC, and NIPEC. The incidence of grade III and IV side effects was 5.5%, 5.1%, and 6.2%, respectively. Intraperitonel chemotherapy therefore has the potential to improve outcomes for pancreatic cancer with peritoneal metastases, however, it can only be applied in the clinical trial setting.

CHEMOTHERAPY

Localized pancreatic cancer

The treatment process varies depending on the stage of the tumor. For resectable pancreatic cancer, surgical resection combined with adjuvant chemotherapy is recommended[114]. The most successful regimens are modified FOLFIRINOX (mFOLFIRINOX) and gemcitabine-capecitabine[114-116]. In 2018, the PRODIGE-24/CCTG PA6 study demonstrated that adjuvant therapy with mFOLFIRINOX significantly improves median DFS (21.6 months *vs* 12.8 months) and OS (54.4 months *vs* 35.0 months) compared to gemcitabine alone[114]. In Asia, the S-1 regimen has become the standard of care following the JASPAC 01 study. It is a phase III randomized study conducted in Japan reported that adjuvant chemotherapy with S-1 offered a 5-year OS of 44.1% and a median OS of 46.5 months *vs* 24.4% and 25.5 months for gemcitabine alone[116]. However, S-1 is not as widely used in America and Europe, mainly because the maximum tolerated dose in Caucasians is lower.

It should be noted that one-third of patients do not receive adjuvant chemotherapy, mainly due to postoperative surgical complications[117]. In patients with resectable pancreatic cancer, randomized trials have not consistently shown benefits with the use of neoadjuvant chemotherapy[118]. However, resectability was previously evaluated only from an anatomical point of view. The 2024 National Comprehensive Cancer Network guidelines, considering activity based classification (A-B-C) approach, also provide for the possibility of treating resectable PDAC with neoadjuvant therapy if high-risk disease features are present (*e.g.*, large primary tumor, regional lymphadenopathy, markedly elevated serum CA19-9, and excessive weight loss)[58,119,120]. In patients with resectable pancreatic cancer, the rate of resection after neoadjuvant therapy is 77%[121]. For patients with BRPC, the standard treatment is neoadjuvant chemotherapy, followed by surgical resection and adjuvant chemotherapy[30,54,58]. There are still no conclusive data regarding the best neoadjuvant chemotherapy regimen. The phase III PREOPANC-2 study[122] is very interesting. It highlights how, in patients with resectable pancreatic cancer and BRPC, FOLFIRINOX in the neoadjuvant setting did not improve OS compared to gemcitabine-based chemoradiotherapy[122].

The resection rate after neoadjuvant therapy for BRPC is 61%[121]. Whether the addition of radiotherapy to chemotherapy after induction chemotherapy is an optimal approach remains a controversial issue. At the American Society of Clinical Oncology 2024 meeting, the GABARNANCE study results were presented. This study compared neoadjuvant chemotherapy (gemcitabine + nab-paclitaxel) and chemoradiotherapy (with S-1) for BRPC[123]. The median OS was 23.1 months for chemotherapy and 31.5 months for chemoradiotherapy, with no statistically significant difference. The chemoradiotherapy group showed a delayed survival benefit with a higher 2-year OS (48.2% *vs* 62.8%) and better pathological response (30.4% *vs* 14.3%). Further follow-up is planned to confirm the long-term survival benefits. The PANDAS/PRODIGE44 trial recently showed that adding chemoradiotherapy after initial mFOLFIRINOX treatment for borderline resectable PDAC did not result in an improvement in R0 resection rates or OS[124]. Opposite results were obtained by Yun *et al*[125] in patients with BRPC and vascular involvement. The addition of radiotherapy to neoadjuvant chemotherapy was associated with improved postoperative survival, better local control and R0 resection rate. The authors suggest performing surgery within 4 weeks of radiotherapy to achieve better outcomes.

Patients with LAPC are mainly treated with systemic chemotherapy for 4-6 months, using mFOLFIRINOX or gemcitabine-nab-paclitaxel regimens[54,58]. Trials showed similar OS between the two regimens[126-128]. About 22% of patients initially diagnosed with LAPC undergo resection after induction chemotherapy[121]. Radiotherapy is associated with increased rates of R0 resection and pathological complete response[129-131]. However, few randomized trials have not shown a survival benefit of adding preoperative radiotherapy, as the ALLIANCE A021501[132]. According to a study by Franklin *et al*[133], after multi-agent neoadjuvant chemotherapy and resection for pancreatic cancer, additional adjuvant chemoradiotherapy *vs* adjuvant chemotherapy alone is associated with improved survival for patients with lymphatic-vascular invasion + or grade III tumors. A recent meta-analysis reported that for patients with LAPC who are unlikely to receive resection, neoadjuvant radiotherapy seems to improve OS, PFS, DFS, and recurrence-free survival

[134].

For patients with advanced or metastatic disease, systemic chemotherapy is the mainstay of treatment. For decades, 5-fluorouracil (5-FU) was the only chemotherapy option for treating pancreatic cancer. Subsequently, gemcitabine was approved as a first-line treatment for pancreatic cancer in 1997 and in 2003 a multi-agent regimen (FOLFIRINOX) was successfully used for metastatic PDAC[107]. FOLFIRINOX improves OS, PFS, and overall response rate (ORR) compared to gemcitabine in patients with metastatic pancreatic cancer and good performance status (ECOG). The PRODIGE 4/ACCORD 11 study[102] reported a median OS of 11.1 months in the FOLFIRINOX-treated group and 6.8 months in the gemcitabine-treated group.

According to the PANOPTIMOX-PRODIGE 35 study, median survival without deterioration in quality of life is better with a regimen based on 4 months of FOLFIRINOX followed by leucovorin plus maintenance treatment with 5-FU[135]. Recently, NALIRIFOX (liposomal irinotecan, 5-FU, oxaliplatin, and leucovorin) has been approved by the Food and Drug Administration (FDA) as a first-line treatment for metastatic PDAC[136]. This approval was based on the results from the phase 3 NAPOLI-3 trial, which demonstrated significant improvements in OS (11.1 months *vs* 9.2 months) and PFS (7.4 months *vs* 5.6 months) in comparison with GnP[137]. NALIRIFOX used a lower chemotherapy dosage than FOLFIRINOX and utilized a liposomal formulation to maintain efficacy while reducing toxicity[138]. Additionally, NALIRIFOX utilizes a standardized dosing regimen, whereas mFOLFIRINOX dosing varies depending on the prescriber. NALIRIFOX, however, is more expensive. According to a systematic review and meta-analysis, NALIRIFOX and FOLFIRINOX were associated with similar PFS and OS as first-line treatment of advanced PDAC, although NALIRIFOX was associated with a different toxicity profile. Careful patient selection, financial toxic effects consideration, and direct comparison between FOLFIRINOX and NALIRIFOX are warranted. GnP can be used either in the first line, particularly in patients with a PS that precludes the use of more intensive regimens, or in second-line settings after prior exposure to 5-FU-based regimens in the first line[139].

After chemotherapy, it is necessary to evaluate the response obtained. In restaging, the main radiological parameter considered is the exclusion of progression by metastatic disease, which is a real challenge due to the difficulty in distinguishing residual tumor tissue from fibrosis on CT[58,140]. An A-B-C approach is therefore necessary in the re-evaluation. To consider surgery in patients with BRPC, the serum CA19-9 concentration must be at least stable, while in patients with LAPC, a substantial decrease after induction chemotherapy is necessary[58]. In patients with CA19-9 not elevated at diagnosis, the biological response is assessed by fluorodeoxyglucose positron emission tomography[141]. As can be inferred from the overall complexity, staging, restaging, and subsequent therapeutic decisions must be followed by a multidisciplinary team.

TARGET THERAPY

Homologous recombination deficiency

Mutations in the homologous recombination genes *BRCA1*, *BRCA2*, and *PALB2* are found in 15%-19% of patients with PDAC. In these cases, platinum-based chemotherapy and poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi) have been associated with improved PFS and OS. Wattenberg *et al*[142] reported that PDAC patients with germline *BRCA1* and *BRCA2* mutations had a higher ORR than those without these mutations (71.4% *vs* 13.9%) when treated with FOLFIRINOX. A randomized phase II trial comparing cisplatin-gemcitabine with and without veliparib in patients with *BRCA* and *PALB2* mutations reported ORRs of 74.1% and 65.3%, respectively[143].

In the POLO trial[144], patients with metastatic PDAC with *BRCA1/BRCA2* mutations and stable disease or who responded to treatment after 4 months of platinum-based chemotherapy were randomized to receive olaparib or placebo.

The group receiving olaparib showed longer PFS (7.4 months *vs* 3.8 months). Following this study, olaparib was approved by the European Medicines Agency and FDA as maintenance therapy in patients with metastatic PDAC with *BRCA1/BRCA2* mutations whose disease had not progressed after at least 4 months of first-line platinum-based therapy.

Subsequently, the RUCAPANC2 study[145] demonstrated that rucaparib can improve median OS, reaching 23.5 months. Reiss *et al*[145] identified *BRCA* or *PALB2* reversion variants that restore the function of the corresponding proteins in patients whose disease had progressed during maintenance therapy with PARPi. Patients with these variants developed rapid resistance to PARPi and had worse outcomes than those without reversions, with PFS of 3.7 months *vs* 12.5 months and OS of 6.2 months *vs* 23.0 months. Future research should focus on developing treatment options for pancreatic cancer patients who are resistant to PARPi and platinum-based therapies[146].

New studies are evaluating the use of olaparib as adjuvant therapy (APOLLO/EA2192, No. NCT04858334), melphalan (No. NCT04150042) and pidnarulex (No. NCT04890613).

KRAS-mutated PDAC

In PDAC, 90%-92% of cases have a driver mutation in the *KRAS* oncogene, which classifies PDAC genomically into two subtypes, *KRAS* mutant (*KRAS*mut) and *KRAS*wt PDAC[8,39]. In pancreatic cancer, the most common *KRAS* mutations are *KRAS* G12D (40%), followed by G12V (29%), G12R (15%), and less commonly G12C (approximately 1%)[147]. Currently, no FDA-approved therapies exist specifically for *KRAS*mut PDAC.

Adagrasib and sotorasib are small-molecules, covalent inhibitors that irreversibly and selectively bind *KRAS* G12C, trapping it in its inactive guanosine diphosphate-bound state. Adagrasib and sotorasib demonstrated good results in patients with *KRAS* G12C mutations in the CodeBreak 100 and KRYSTAL-1 trials, respectively[75,147,148]. Additional *KRAS* G12C inhibitors in clinical trials include JDQ443 (No. NCT04699188), JAB-21822 (No. NCT05002270), D-1553 (No. NCT04585035), GDC-6036 (No. NCT04449874), LY3537982 (No. NCT04956640), and BI-1823911 (No. NCT04973163).

MRTX-1133, a novel inhibitor targeting *KRAS* G12D mutations, is in phase I clinical trials and has shown promising preclinical data[149]. A phase I trial (No. NCT05737706) is currently exploring the use of MRTX-1133 in *KRAS* G12D advanced solid tumors[150]. Another promising molecule is RMC-6236, which targets multiple *RAS* variants[151]. The phase I RMC-6236-001 study enrolled patients with advanced tumors harboring mutations at codon 12 of *KRAS* (*KRAS* G12X), excluding *KRAS* G12C, after progression on at least one standard therapy option[152]. The most recent updated analysis showed that the 14 + week disease control rate in *KRAS* G12X mutated PDAC was 87% with a median PFS of 8.1 months. Patients with metastatic PDAC and *KRAS* G12X mutation in the second-line setting, achieved a median PFS of 8.5 months and a median OS of 14.5 months. The response rate for patients harboring *KRAS* G12X mutations was 29% in the second-line group and 22% in the third line and beyond. Lower outcomes were reported in patients harboring any *RAS* mutation. These promising results have led to the initiation of RASolute 302 (No. NCT06625320), a phase 3 randomized trial for second-line metastatic PDAC regardless of *RAS* status[153]. IMM-1-104, a mitogen-activated protein kinase (MAPK) pathway inhibitor, can induce universal *RAS* inhibition and it is currently being explored in *RAS* mutant solid tumors[154]. A trial (No. NCT05585320) exploring it as monotherapy or in combination with GnP or mFOLFIRINOX in patients with locally advanced or metastatic PDAC is ongoing.

New and very interesting clinical trials are underway on indirect targets to block *KRAS*. A phase I trial in patients with advanced *KRAS*-mutated cancers is evaluating the safety and efficacy of BI1701963, an inhibitor of the nucleotide exchange factor *SOS1*, alone and in combination with trametinib, a MAPK pathway inhibitor (No. NCT04111458)[155,156]. Multiple studies (No. NCT04418661, No. NCT04330664, and No. NCT03634982) are investigating combinations to block Src homology 2-containing protein tyrosine phosphatase 2, a tyrosine phosphatase necessary for *KRAS* activation, and ASP3082 (No. NCT05382559), capable of binding ubiquitin ligase E3 and *KRAS* G12D, thus allowing the ubiquitination of the latter and its degradation by the proteasome[157-159]. Lastly, RMC-7977 is a highly selective inhibitor of the active guanosine triphosphate-bound forms of *KRAS*, *HRAS*, and *NRAS*, with affinity for both mutant and wild-type variants. It has shown promising results in preclinical models[160,161].

KRASwt PDAC

*KRAS*wt PDAC can harbor other mutations, including rare gene fusions involving *FGFR2*, *RAF*, *ALK*, *RET*, *MET*, *NTRK1*, *ROS1*, *ERBB4*, *NRG1*, and *FGFR3*, among others. Although these genetic fusions are uncommon, they can offer an opportunity for personalized therapeutic approaches. Zenocutuzumab recently received FDA approval for advanced or metastatic *NRG1* fusion-positive pancreatic cancer[75,162]. *BRAF* V600E is rare, present in approximately 3% of PDAC cases. The combination of dabrafenib and trametinib, which targets *BRAF* V600E mutations, was investigated in the NCI-MATCH trial and the ROAR basket trial, demonstrating efficacy and a manageable toxicity profile[163]. In 2022, the FDA granted accelerated approval for the use of this combination in adult and pediatric patients (≥ 6 years) with unresectable or metastatic *BRAF* V600E-positive solid tumors who had progressed after prior therapy and lacked other suitable options. Additionally, selpercatinib, a kinase inhibitor targeting *RET* fusions, has received FDA accelerated approval based on promising results in *RET* fusion-positive solid tumors, non-small cell lung cancer, medullary thyroid cancer, and thyroid cancer[164,165]. A phase II trial (No. NCT04390243) is currently investigating the combination of encorafenib, a *BRAF* inhibitor, and binimetinib, a mitogen-activated protein kinase kinase inhibitor, in patients with pretreated metastatic PDAC with somatic *BRAF* V600E mutations. Furthermore, in 2024, the FDA granted accelerated approval to fam-trastuzumab deruxtecan for adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive (immunohistochemistry 3 +) solid tumors, based on data from the DESTINY-PanTumor2 trial[166]. Larotrectinib and entrectinib are recommended as first-line treatment options for locally advanced or metastatic pancreatic cancer with *NTRK* fusions[167,168]. Repotrectinib, a newer *NTRK* inhibitor, received accelerated FDA approval in 2023, showing promising results in the TRIDENT trial[75,169,170].

Uncontrolled cell division in pancreatic cancer causes high levels of replicative stress and stimulates activation of the ataxia telangiectasia and Rad3-related serine/threonine kinase-checkpoint kinase 1 (CHK1)-*WEE1* pathway[170,171]. The inhibition of this pathway is currently under investigation. The use of a single agent has shown poor efficacy and significant myelosuppression[172]. Better results were obtained by combining the SRA737 CHK1 inhibitor with gemcitabine. In this case, although the ORR was 10.8%, the therapy was well tolerated with few side effects[173]. In preclinical models, PARPi-resistant pancreatic cancer cells have been shown to be highly sensitive to the *WEE1* inhibitor adavosertib[174]. In a phase I study, the combination of radiotherapy with gemcitabine and adavosertib in patients with advanced pancreatic cancer demonstrated a median PFS of 9.4 months and a median OS of 21.7 months[175]. An interesting target for PDAC is *FGFR2* fusions. Stein *et al*[176], in 2024, showed a case series of four *FGFR2* fusion-positive metastatic PDAC patients who achieved durable responses with fibroblast growth factor receptor inhibitors. REFOCUS is a phase I/II trial evaluating the highly selective *FGFR2* inhibitor, RLY-4008, in patients with intrahepatic cholangiocarcinoma and other advanced solid tumors (No. NCT04526106)[177]. Another target currently being explored is methylthioadenosine phosphorylase (MTAP) or *CDKN2A*-deleted cancers, including pancreatic cancer. AMG 193, a *PRMT5* inhibitor targeting MTAP or *CDKN2A*-deleted tumors, showed promising antitumor activity and a favorable safety profile in a phase I study involving 80 patients with MTAP-deleted solid tumors[178]. AMG 193 is currently being evaluated in clinical trials in combination with chemotherapy in patients with MTAP-deleted PDAC (No. NCT06360354).

Microsatellite instability and deficiency mismatch repair proteins (MSI-H/dMMR) are associated with increased immunogenicity and significant responsiveness to immune checkpoint inhibitors (ICI)[179,180]. Based on positive outcomes from clinical trials involving 504 patients across different cancer types (KEYNOTE-158, KEYNOTE-164, KEYNOTE-051), the FDA granted full approval for pembrolizumab monotherapy for patients with unresectable MSI-H/dMMR solid tumors in second-line settings and beyond[180-182]. However, MSI-H/dMMR occurs in only 1% of PDAC cases, and its use remains debated. Results from the KEYNOTE-158 trial indicated lower responses (18.2%) in PDAC patients treated with pembrolizumab compared to other non-colorectal cancers (31%-48.5%)[180]. Real-world data from

retrospective studies conducted at the Mayo Clinic and from the Association des Gastro-Enterologue Oncologues European cohort demonstrated better outcomes[183,184] and support the use of ICIs in this patient population, especially if MSI-H/dMMR is discovered.

The junctional protein claudin 18.2 is overexpressed in gastric and pancreatic tumors. Zolbetuximab, a monoclonal antibody against claudin 18.2, in combination with chemotherapy has shown promising results in terms of PFS and OS in both the phase III SPOTLIGHT and GLOW studies in patients with claudin 18.2-positive gastric and gastroesophageal junction tumors (No. NCT03504397 and No. NCT03653507). A randomized study is currently evaluating the combination of GnP with or without zolbetuximab in patients with claudin 18.2-positive metastatic pancreatic cancer (No. NCT03816163). A phase I study (No. NCT05482893) is evaluating PT886, a bispecific antibody that targets claudin 18.2 and cluster of differentiation (CD) 47, in patients with unresectable or metastatic gastric tumors, gastroesophageal junction tumors, and pancreatic cancer[185].

High levels of αvβ5 integrins are expressed in human PDAC but not in healthy tissues. A non-randomized study evaluated the use of certepetide (CEND-1), a peptide that specifically targets αv integrins, administered in combination with GnP in 31 patients with previously untreated metastatic PDAC[186,187]. ORR was 59%, PFS was 9.7 months, and median OS was 13.2 months[186]. Based on these results, a randomized, double-blinded phase II trial is currently enrolling patients (No. NCT05042128) in Australia and New Zealand. In the United States, CENDIFOX (No. NCT05121038) is an ongoing phase Ib-IIa trial of CEND-1 in combination with neoadjuvant FOLFIRINOX in pancreatic, colorectal, and appendiceal cancers[188]. The target therapy for PDAC has been summarized in Table 1.

IMMUNOTHERAPY

Cancer vaccine

Vaccines and miRNA therapies can target *KRAS*. The AMPLIFY-201 study (No. NCT04853017) is evaluating the adjuvant regimen ELI-002, a therapeutic vaccine targeting *KRAS*-mutated tumors, for patients with *KRAS* G12D, G12R PDAC and colorectal tumors who are in a state of minimal residual disease with a high risk of recurrence[189]. Reductions in CEA and CA19-9 were observed in 79% of patients, while clearance of minimal residual disease was observed in 21%. Multifunctional m*KRAS*-specific T cell responses were observed in 80% of patients[190]. Regarding miRNAs, a phase I study (No. NCT03608631) is also exploring the use of mesenchymal stem cell-derived exosomes loaded with small interfering RNAs targeting *KRAS* G12D for patients with metastatic *KRAS* G12D-mutated PDAC[191]. Studies involving GVAX, a cancer vaccine that uses genetically modified tumor cells to stimulate the immune system, are also ongoing in PDAC patients. Urelumab, a monoclonal antibody against CD137, showed pharmacodynamic activity indicating $CD8^+$ T cell activation in patients with metastatic or locally advanced solid tumors, enhancing responsiveness to ICIs and boosting immunogenicity. Another ongoing trial is evaluating the combination of urelumab with GVAX and nivolumab [programmed cell death protein 1 (PD-1) antagonist] in patients with resectable PDAC (No. NCT02451982)[192]. GVAX + nivolumab + urelumab increases intratumoral $CD8^+$ $CD137^+$ cells and demonstrates improved DFS and OS compared to GVAX and GVAX + nivolumab, although not statistically significant. Further studies are obviously needed to confirm these positive results.

Very interesting phase I studies are No. NCT04117087 and No. NCT04161755. The first is currently evaluating a vaccine based on long synthetic peptides combined with ipilimumab and nivolumab in patients with resected PDAC. This vaccine targets six common m*KRAS* gene mutations: G12D, G12R, G12V, G12A, G12C, and G13D. The second study explored the use of cevumeran, a personalized messenger RNA neoantigen vaccine, in patients with resectable PDAC, in a regimen that also includes atezolizumab and mFOLFIRINOX. At a median follow-up of 18 months, patients who responded to the vaccine demonstrated significantly longer recurrence-free survival than non-responders[193]. Currently, a randomized phase II trial (IMCODE003) is underway to evaluate mFOLFIRINOX with or without autogene cevumeran in resected PDAC (No. NCT05968326).

Oncolytic virus therapy

A phase I/II study reported an ORR of 44% and a disease control rate of 94% with the combination of intratumoral injections of LOAd703, an oncolytic adenovirus, and standard chemotherapy with nab-paclitaxel/gemcitabine in patients with unresectable or metastatic PDAC (No. NCT02705196)[194].

The combination of the reovirus pelareorep and pembrolizumab, on the other hand, showed modest efficacy with a clinical benefit rate of 42%. However, led to significant immunological changes in $CD8^+$ T cells and $CD4^+$ regulatory T cells during treatment in patients who responded to therapy (No. NCT03723915)[195].

Finally, a clinical trial will evaluate the efficacy of talimogene laherparepvec, administered endoscopically, for the treatment of locally advanced or metastatic pancreatic cancer refractory to at least one chemotherapy regimen (No. NCT03086642).

Chimeric antigen receptor

Chimeric antigen receptor (CAR) T-cell therapy involves the use of receptors expressed on genetically modified T cells, which are able to recognize specific surface antigens on tumor cells and thus kill them[196]. It is a promising approach, especially against tumors that are resistant to standard therapies. The antigens currently being studied for CAR-T therapy in pancreatic cancer are mesothelin, CEA, *MUC1*, epidermal growth factor receptor (EGFR), CD133, and claudin 18.2[172,197].

Table 1 Summary of target therapy

Category	Details
Homologous recombination deficiency	Prevalence: Mutations in homologous recombination genes (*BRCA1*, *BRCA2*, *PALB2*) are found in 15%-19% of patients with PDAC. Therapeutic response: Patients with HRD show improved PFS and OS after platinum-based chemotherapy and PARPi. Retrospective analysis: In a study of patients treated with FOLFIRINOX, the ORR was significantly higher in *BRCA1*/*BRCA2* mutated patients (71.4%) compared to non-mutated patients (13.9%). Platinum-based therapy response: A separate retrospective study reported an ORR of 58% in patients with germline *BRCA* and *PALB2* mutations compared to 21% in the control group
PARPi trials	POLO trial: This trial evaluated olaparib as maintenance therapy for patients with germline *BRCA1*/*BRCA2* mutations who had stable or responding disease after 4 months of platinum-based chemotherapy. The study found a significant increase in PFS (7.4 months for olaparib *vs* 3.8 months for placebo), although there was no significant difference in OS (19 months for olaparib *vs* 19.2 months for placebo). FDA approval: Olaparib has been approved as maintenance therapy for platinum-sensitive metastatic PDAC patients with *BRCA1*/*BRCA2* mutations whose disease has not progressed after at least 16 weeks of first-line platinum-based treatment. RUCAPANC2 trial: This phase II single-arm trial demonstrated that rucaparib, administered as maintenance therapy in patients with advanced pancreatic cancer harboring germline or somatic *BRCA* or *PALB2* mutations, achieved a median OS of 23.5 months. Reversion variants: In a study by Reiss *et al*[145], 16.6% of patients whose disease progressed on maintenance PARPi developed *BRCA* or *PALB2* reversion variants, which restored the function of the *BRCA* or *PALB2* proteins. Patients with these reversion variants experienced rapid resistance to PARPi (PFS of 3.7 months *vs* 12.5 months; $P = 0.001$) and had significantly poorer OS (6.2 months *vs* 23.0 months; $P < 0.0001$)
KRAS mutations	Prevalence: *KRAS* mutations are present in 90%-92% of PDAC cases, classifying them into *KRAS*mut and *KRAS*wt subtypes. Common mutations: The most frequent *KRAS* mutations include G12D (40%), G12V (29%), G12R (15%), and G12C (approximately 1%). Therapeutic challenge: Currently, there are no FDA-approved therapies specifically targeting *KRAS*mut PDAC, making it a significant area of unmet medical need
KRAS G12C inhibitors	Inhibitors: Adagrasib and sotorasib are small-molecule covalent inhibitors that irreversibly bind to *KRAS* G12C, trapping it in its inactive guanosine diphosphate-bound state. Clinical trials: Both inhibitors have shown promising results in patients with *KRAS* G12C mutations in the CodeBreak 100 and KRYSTAL-1 trials, demonstrating efficacy and manageable safety profiles. Other inhibitors: Additional *KRAS* G12C inhibitors currently in clinical trials include JDQ443 (No. NCT04699188), JAB-21822 (No. NCT05002270), D-1553 (No. NCT04585035), GDC-6036 (No. NCT04449874), LY3537982 (No. NCT04956640), and BI-1823911 (No. NCT04973163)
KRAS G12D inhibitors	MRTX-1133: A novel inhibitor specifically targeting *KRAS* G12D mutations, currently in phase I clinical trials, has shown promising preclinical data. RMC-6236: This inhibitor targets multiple *RAS* variants and is undergoing a phase I study. The most recent analysis indicated a 14 + week disease control rate of 87% in patients with *KRAS* G12X mutations, with a median PFS of 8.1 months. RASolute 302 trial: A phase 3 randomized trial evaluating the efficacy of RMC-6236 in second-line metastatic PDAC, regardless of *RAS* status, is currently ongoing
KRAS wild-type PDAC	Genetic fusions: *KRAS*wt PDAC can harbor rare gene fusions involving *FGFR2*, *RAF*, *ALK*, *RET*, *MET*, *NTRK1*, *ROS1*, *ERBB4*, *NRG1*, and *FGFR3*, which may provide opportunities for personalized therapeutic approaches. FDA approvals: Zenocutuzumab has received FDA approval for advanced or metastatic *NRG1* fusion-positive pancreatic cancer. The combination of dabrafenib and trametinib, targeting *BRAF* V600E mutations, was investigated in the NCI-MATCH trial and the ROAR basket trial, demonstrating efficacy and a manageable toxicity profile. Ongoing trials: A phase II trial (No. NCT04390243) is currently investigating the combination of encorafenib (a *BRAF* inhibitor) and binimetinib (a MEK inhibitor) in patients with pretreated metastatic PDAC with somatic *BRAF* V600E mutations
Microsatellite instability	Prevalence: MSI-H/dMMR occurs in only 1% of PDAC cases, which limits the applicability of immunotherapy. Therapeutic response: Pembrolizumab has been granted full FDA approval for unresectable MSI-H/dMMR solid tumors based on positive outcomes from clinical trials (KEYNOTE-158, KEYNOTE-164, KEYNOTE-051). However, response rates in PDAC patients treated with pembrolizumab were lower (18.2%) compared to other non-colorectal cancers (31%-48.5%). Real-world data: Retrospective studies from the Mayo Clinic and the AGEO European cohort suggest better outcomes for MSI-H/dMMR PDAC patients, supporting the use of immune checkpoint inhibitors

HRD: Homologous recombination deficiency; PDAC: Pancreatic ductal adenocarcinoma; PFS: Progression-free survival; OS: Overall survival; PARPi: Poly (adenosine diphosphate-ribose) polymerase inhibitors; ORR: Overall response rate; FDA: Food and Drug Administration; *KRAS*mut: *KRAS* mutant; *KRAS* wt: *KRAS* wild type; MSI-H/dMMR: Microsatellite instability and deficiency mismatch repair proteins; AGEO: Association des Gastro-Enterologue Oncologues.

Several phase I clinical trials have reported partial responses in a small number of patients[198-200]. The phase I study (No. NCT02159716) examined lentivirus-transduced CAR-T cells targeting mesothelin in patients with metastatic pancreatic cancer. Of the five patients, three showed no response and two had disease stabilization for only two to three months. Further disappointing results were obtained in a phase I study (No. NCT01869166) that evaluated EGFR CAR-T cells after a chemotherapy regimen based on nab-paclitaxel plus cyclophosphamide. The median PFS and OS obtained were 3 and 4.9 months, respectively[198].

Research is currently underway with fully human anti-mesothelin CAR (No. NCT03054298 and No. NCT03323944). Several phase I studies[199-203] have evaluated the use of autologous CAR-T cells against claudin 18.2. They reported poor results in terms of efficacy, with only a small percentage of patients achieving partial response or disease stabilization, and significant hematological toxicity[204].

Apparently more promising results have been obtained with anti-*MUC1* CAR-T cells, which have demonstrated effective targeting and cytotoxicity in xenotransplantation models[205]. *MUC1* overexpression is generally a negative prognostic factor as it is associated with metastatic disease and multiple drug resistance.

Two studies (No. NCT05239143 and No. NCT04025216[206-208]), were conducted to evaluate the clinical application of anti-*MUC1* CAR-T cells. Numerous clinical trials have been registered for the use of *EPCAM*-specific CAR-T cells in individuals with pancreatic cancer (No. NCT04151186 and No. NCT03013712) and *ROBO1*- and *MUC1*-specific CAR-natural killer cells (No. NCT03941457 and No. NCT02839954)[208].

In general, immunotherapy has revolutionized the field of oncology. However, in the case of pancreatic cancer, studies (preclinical and clinical) have highlighted the role of the tumor microenvironment (TME) as an obstacle to CAR-T cell therapy. Other limitations that hinder the effectiveness of CAR-T cells in pancreatic cancer are heterogeneous antigen expression and cell-mediated toxicities.

Genetically modified T cells therapy (T cell receptor-engineered T-cell therapy)

The latest development involves T cells engineered to express T cell receptors (TCRs) capable of recognizing tumor antigens[209]. Chiorean *et al*[210] have registered a study of the safety and efficacy of *MSLN*-specific autologous T cells in patients with stage IV pancreatic cancer (No. NCT04809766). *MSLN*-specific autologous TCR T cells are used in combination with bendamustine, cyclophosphamide, and fludarabine. The primary objective is to evaluate safety and dose-limiting toxicities. ORR, PFS, and OS are also being examined. The goal is to achieve a meaningful ORR of 20% among the 15 participants[210].

Recent discoveries in immunotherapy

Recent discoveries in the field of immunotherapy involve the CD39/CD73 axis and bispecific antibodies (BsAbs). CD39 and CD73 are ectonucleotidases that allow the accumulation of extracellular adenosine, which suppresses the immune system in both innate and adaptive responses. The anti-CD73/CD39 antibodies currently being investigated are oleclumab or MEDI9447 (anti-CD73; No. NCT02503774), TTX-030 (anti-CD39; No. NCT03884556), and CPI-006 or mupadolimab (anti-CD73; No. NCT03454451)[211] alone or in combination with other ICIs[212].

BsAbs are specialized antibodies designed to act effectively on two specific antigens simultaneously[213]. BsAbs have been developed for pancreatic cancer treatment, with examples such as anti-EGFR × HER2[214], anti-CD3 × CEA[215], MCLA-128 (anti-HER2 × HER3 BsAb; zenocutuzumab)[216], anti-CD3 × EGFR BsAb[217], anti-CD3 (Vγ9TCR) × HER2/Neu[218], XmAb22841 [anti-*LAG3* × cytotoxic T-lymphocyte-associated protein 4 (CTLA-4); No. NCT03849469], XmAb-23104 (anti-PD-1 × inducible co-stimulatory molecule)[219], and KN046 (anti-CTLA-4 × programmed cell death ligand 1)[220].

Based on the poor results with single-agent immunotherapy or target therapy, several researchers are recently trying to achieve increased outcomes with combinations of drugs with different mechanisms.

Dual immunotherapy

PDAC with biallelic loss of *BRCA1* and *BRCA2* genes has greater sensitivity to ICIs[221] than wild-type tumors because it has a higher mutation burden. A retrospective study evaluated patients with platinum-refractory metastatic pancreatic or biliary carcinoma with mutations in homologous recombination genes who were treated with ipilimumab and nivolumab, achieving a complete response in 4 out of 12 cases, a partial response in 1 case, and stable disease in 2 cases[222]. However, these results have not been confirmed by the recent Checkmate 032 study[223].

Combination of immunotherapy plus target agents or chemotherapy

In a recent phase Ib/II trial (PARPVAX trial), patients who had not progressed on platinum-based first-line therapy were randomized to receive niraparib plus nivolumab or niraparib plus ipilimumab as maintenance therapy[224]. The results were promising, with a 6-month PFS of 20.6% in the niraparib plus nivolumab group and 59.6% in the niraparib plus ipilimumab group. Based on these encouraging data, several studies are in progress. New results from the POLAR study on metastatic PDAC were presented at the European Society for Medical Oncology 2024 congress[225]. Patients were treated with pembrolizumab plus olaparib and were enrolled in three different cohorts: (1) Homologous recombination deficiency (HRD) patients with BRCA1/BRCA2 or *PALB2* mutations; (2) Patients with non-core HRD mutations such as *ATM*; and (3) Patients with no HRD but with a high response to platinum therapy. Cohort A showed the most promising results, with 64% of patients without PFS at 6 months and a disease control rate of 90%. Based on the POLO study[170] and the immunostimulatory capacity of PARPs[226-228], the SWOG0G2001 study (No. NCT04548752) is evaluating the combination of olaparib and pembrolizumab *vs* olaparib alone with the primary objective of increasing median PFS.

Clinical trials are also examining PARPis combined with FOLFIRI (No. NCT02498613). These combinations may increase the sensitivity to PARPis for a larger population than that with *BRCA* mutations. These approaches are highly innovative and still need to be evaluated in well-designed clinical trials.

Stroma target therapy

The main obstacle to old and new therapies is the TME. The TME constitutes the majority of the tumor complex (approximately 70% of the total volume), while only a small percentage is represented by PDAC neoplastic cells. The pancreatic TME consists of numerous populations of fibroblasts, a dense extracellular matrix, and immune cells with suppressive function. The result is a desmoplastic stroma that compresses vascular structures and creates a hypoxic environment, thereby affecting the pharmacokinetics and pharmacodynamics of therapy. The dense component also prevents immune system cells from reaching the target site. What we are therefore faced with is a chemoresistant and immunoresistant tumor[229]. Targeting fibrosis in pancreatic cancer is crucial due to its significant impact on treatment efficacy. For this reason, several studies are evaluating the use of standard treatments with new agents against stromal components, such as pamrevlumab, a new monoclonal antibody that binds to connective tissue growth factor (No. NCT04229004), or a pegylated recombinant hyaluronidase (No. NCT02715804). Other interesting studies are NCT03727880 and STARPAC [230]. The first evaluates the use of pembrolizumab with defactinib, a focal adhesion kinase inhibitor, as neoadjuvant and sequential adjuvant therapy in patients with high-risk resectable PDAC[172]. The second is a multicenter, randomized, controlled clinical trial in LAPC that tests whether a combination of standard gemcitabine and nab-paclitaxel che-

motherapy and trans-retinoic acid to act on the stroma can prolong PFS and allow surgical resection[230].

Pancreatic cancer and AI

Recent advances in AI have shown encouraging results in: (1) Detecting and segmenting the pancreas and pancreatic lesions; (2) Classifying lesions as benign or malignant; and (3) Developing predictive models for early diagnosis[231].

Cao *et al*[232] developed an approach to detect and classify pancreatic lesions with high accuracy using non-contrast CT with AI (like PANDA). PANDA was trained on a dataset of over 3000 patients and achieves an AUC of 0.986-0.996 for lesion detection in a multicenter validation. It outperforms the average performance of radiologists by 34% in terms of sensitivity and 6% in terms of specificity for PDAC identification and achieves a sensitivity of 93% and a specificity of 99% for lesion detection in a validation involving 20530 consecutive patients. In particular, PANDA shows non-inferiority compared to radiological reports using contrast-enhanced CT and could potentially serve as a new tool for large-scale screening for pancreatic cancer.

Equally good results were obtained in studies conducted in China[233,234]. Si *et al*[233] developed a deep learning model with an average accuracy for all tumor types of 82.7%, and independent accuracies of identifying intraductal papillary mucinous neoplasm and PDAC of 100% and 87.6%, respectively.

With AI, the diagnostic efficiency of EUS images has also been significantly improved, especially in the diagnosis of autoimmune pancreatitis[235,236]. A case in point is the model developed by Marya *et al*[235], trained using static images and videos from EUS examinations on patients. The model achieves high levels of sensitivity and specificity in differentiating autoimmune pancreatitis from PDAC, from normal pancreas, and from chronic pancreatitis.

In addition to imaging, AI is exploring the integration of clinical data to create predictive models that can identify individuals at high risk of developing PDAC, enabling more targeted screening programs and, potentially, the implementation of noninvasive tests for early diagnosis. Placido *et al*[237] analyzed clinical data from 6 million patients, including 24000 with PDAC in the Danish National Patient Registry and 3 million patients, with 3900 cases of PDAC, in the United States Department of Veterans Affairs databases.

The best-performing model was able to predict the onset of pancreatic cancer within 36 months of initial diagnosis based on data extracted from electronic medical records with an AUROC curve of 0.879.

AI is also optimizing therapeutic planning. AI can analyze the genetic and molecular profile of the tumor, combining it with the clinical characteristics of the patient, to predict the response to different chemotherapies or targeted therapies. This data-driven approach makes it possible to select the most effective treatment regimen for the individual patient, avoiding ineffective treatments and reducing toxicity[238]. For example, AI algorithms can identify specific mutations and suggest approved or clinical trial drugs that target them. AI is accelerating the discovery of new therapeutic targets. By analyzing vast databases of tumor genomes, proteomes, and clinical data, AI can identify novel signaling pathways involved in PDAC growth and progression, suggesting potential drugs that block them[239]. This includes finding new strategies to overcome drug resistance, a persistent problem in PDAC treatment. AI is not only improving clinical practice, it is also revolutionizing the way researchers study pancreatic cancer. The amount of data generated by "omics" technologies (genomics, transcriptomics, proteomics, metabolomics) is immense. AI is indispensable to integrate and analyze complex data, identifying patterns and correlations that lead to new biological discoveries and understanding of disease mechanisms[240].

Although AI models are making progress and have had noteworthy practical triumphs, there are significant obstacles to their application in clinical practice[241]. First, statistical limitations such as the retrospective study model, inability outside the trained domain, unintentional confounding, use of selectively chosen images for algorithm training reflecting possible selection bias, false positive (FP) and false negative detections. A major disadvantage of addressing FP detections is that there is no obvious cause for FP detections to improve model capabilities[242]. The complexity of AI-based approaches hinders their usefulness in "explaining" their decision-making or predictions. The problem of limited knowledge of why a particular decision is made is called the "black box" problem[243]. For clinicians to adopt and trust AI models in everyday clinical practice, they must be reliable, interpretable, and explainable. Second, limitations relate to input data size and standardization. AI models are typically trained on small datasets, and the algorithmic approach varies from one medical center to another. Small data sets cause measurement errors and overfitting. Integrating AI into routine clinical practice is difficult due to the current lack of adequate facilities for standardization and validation. Different AI technologies require different types of data and are trained in different environments, which may not reflect the actual patients encountered in community hospitals[244].

Therefore, it is necessary to design and define uniform processes for data collection, processing, storage, replication, and analysis. In addition, experts from institutions located in different geographical areas should collaborate to establish benchmarks for AI-based diagnosis. Finally, there are ethical and legal aspects. To date, AI-assisted image analysis and machine learning neural networks in disease diagnosis and prediction have only provided an "opinion", as the responsible physician retains complete authority over the decisions to be made. Scientists and engineers are making tremendous progress in the use of AI in their fields, achieving task autonomy or conditional autonomy and, ultimately, complete automation. The responsible party remains unclear if an algorithm makes a mistake with potentially fatal consequences.

CONCLUSION

The most recent data registry reports an overall 5-year survival rate for pancreatic cancer of 12%, up from 6% for patients diagnosed in 2004. However, for metastatic disease, the 5-year survival rate has only increased from 2% to 3%, suggesting

minimal progress, while for localized disease it has increased from 24% to 46%. It is important to note that only 14% of patients are diagnosed at a resectable stage, meaning that the survival rate for most patients remains unchanged. Survival rates for metastatic disease at 4, 3, and 2 years have not increased, but 1-year survival has increased from 14% to 22% (2004-2019). These trends suggest progress in short-term outcomes[244]. The resilience and ability of PDAC to withstand significant stresses underlies the nearly uniform fate of ultimate progression. The microenvironment surrounding PDAC, the main proponent of the tumor's intrinsic therapeutic resistance, contains potentially crucial information about treatment vulnerabilities[245]. In summary, 2025 does not mark the discovery of a single solution for pancreatic cancer. Rather, we are in an era of incremental but fundamental advances that are gradually shifting the needle in favor of patients. The integration of a multimodal approach that embraces personalized screening, advanced diagnostics, innovative surgery, and increasingly targeted therapies will be the key to transforming the prognosis of this devastating disease. There is still a long way to go, but the foundation for a more promising future has been laid.

FOOTNOTES

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