Management of pancreatic ductal adenocarcinoma (PDAC): Progress in the past decade and challenges for the future

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Epidemiology

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death in the United States with 41,615 deaths in 2015 as well as in Europe where 128,000 persons are expected to die from this tumor in 2018 [1,2]. Although the worldwide incidence is low with 4.2 per 100 000, and there are important geographic differences (from 7.4 per 100 000 in North America to fewer than 1.5 in Central Africa), the incidence is rising in developed countries such as France, where it nearly doubled between 1982 and 2012 and ranges from 10.2 per 100 000 in men to 6.9 per 100 000 in women [3]. Because the mortality rate will either remain unchanged or moderately increase in upcoming years, PDAC is expected to become the third leading cause of cancer death in the EU by 2025 and the second leading cause of cancer-related death in the United States by 2030 [4,5].

Risk factors

PDAC is more frequent in the elderly and in men (sex ratio=1.5), and the incidence seems to differ depending on the ethnic group. Indeed, the reported incidence rates in the United States suggest a higher risk in the Afro-American population.

Environment and lifestyle: Established risk factors include smoking (with a 2-fold increased risk, accounting for an estimated 20% cases in the developed countries) and diet, with an increased risk associated with high calorie intake, red and processed meat, as well as soft drink consumption. Alcohol consumption of ≥30g/day is also associated with a 20% increased risk of PDAC. On the other hand, fruit and vegetable consumption, as well as physical activity has been shown to be potential protective factors [6].

Predisposing conditions: Medical conditions associated with PDAC include obesity and the metabolic syndrome, a history of diabetes and chronic pancreatitis. In contrast, atopic allergies have been reported to be a protective factor. Several associations have been described but must still be confirmed or are a subject of debate: a history of cholecystectomy, gastrectomy, Helicobacter pylori infection, or non-O blood type. HBV and HCV infections have also been reported to be risks factors [6].

Genetic: A family history of PDAC is associated with a higher risk that increases in relation to the number of relatives concerned and results in an up to 32-fold higher risk in patients with three or more first degree relatives (FDRs) [7]. Although as many as 10% of PDAC are thought to have an inherited component, only a limited number of putative susceptibility genes have been identified to date. Indeed, only 15% of those with a family history of PDAC have an identified germinal predisposing mutation.

The main genes and genetic syndromes known to be associated with an increased risk of PDAC are summarized in Table 1 [7-12].

Improvements in sequencing technologies have resulted in the recent discovery of numerous other germline variants associated with a susceptibility to PDAC and should provide further useful information in the future to improve risk estimations, for earlier diagnosis in patients at risk and for possible personalized treatment [9].

Moreover, germinal mutations may not only be detected in patients with a family history of PDAC but also in a significant proportion of sporadic cases. The frequency of known PDAC-associated mutations in unselected patients in several studies ranges from 3.6% to 20%. For example, Hu et al. [10] recently reported a 5.2% rate of deleterious mutations in six predisposition genes (CDKN2A, TP53, MLH1, BRCA2, ATM, and BRCA1) in 2687 patients with no family history of pancreatic cancer. Systematic pathogenic germline variant (PGV) testing in unselected patients diagnosed for PDAC (with no family or personal history of cancer) identified a significant number of patients with potentially clinically significant mutations that would not have been identified if the current criteria for germline mutation testing had been applied. In two prospective cohorts of 298 and 615 unselected PDAC, only 48% and 59% of PGV carriers would have been identified [13,14]. In addition, some of them can be targeted and represent future potential therapeutic targets (i.e. PARP inhibitors).

Thus, because detection of these mutations could help identify treatments and provide opportunities for the prevention and screening of the relatives of these patients, more appropriate genetic testing criteria are also needed.

Screening

In 2012 the international cancer of the pancreas screening consortium (CAPS) published several statements on the screening of individuals at high risk of familial pancreatic cancer [7]. A conosortium agreement was reached that the following candidates should be screened:

- first-degree relatives (FDRs) of patients with PC with at least two affected FDRs
- patients with Peutz–Jeghers syndrome; and
- patients with p16, BRCA2 and hereditary non-polyposis colorectal cancer (HNPCC) mutation carriers with ≥1 affected FDR.

Screening techniques should include EUS or MR imaging and any surgery should be performed in a high-volume center. No consensus was reached on the age to start or stop screening or the optimal interval for follow-up imaging. A recent meta-analysis of 16 studies including 1551 individuals at high risk of familial pancreatic cancer, reported a pooled proportion of screening goal achievement (defined as the diagnosis of T1N0M0 PDAC, PanIN3 or high grade IPMN) of 1.4% [15]. Because of the high risk of morbidity/mortality of pancreatic surgery, these results show the need for improvement in screening programs. In this same study, the pooled proportion of unnecessary surgeries was 68.1%.

Pre-cancerous lesions

In addition to environmental factors and genetic predispositions, pre-malignant pancreatic lesions include pancreatic intraepithelial neoplasia (PanINs), intraductal papillary and mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Improvement in imaging techniques has resulted in a significant increase in the detection of pancreatic cysts that are mostly found incidentally. Their estimated prevalence is 2%-20% depending on the patient's age and the type of imaging, with a reported prevalence of clinically important lesions of 1% in current guidelines [16].

IPMN is the main preneoplastic pancreatic cystic lesion. These macroscopic lesions are divided into main duct (MD) IPMN and branch duct (BD) IPMN with a reported incidence of malignancies of 70% and 25%, respectively [17,18]. Although early and systematic resection was practiced in the 1990's, ever since the Sendai guidelines in 2006 and the Fukuoka guidelines in 2012, a more conservative approach has been taken, especially for BD IPMN, based on criteria estimating the risk of malignancy. Nevertheless, the limits of these criteria were evaluated in several studies, resulting in a recent update of Fukuoka guidelines in 2017 (Table 2) [17,19].

These criteria recommend further evaluation (based on endoscopic ultrasound) and surveillance or surgery in patients diagnosed with IPMN. Surgical resection is strongly recommended in any patient in good condition with a high risk of stigmata. Patients should be treated in experienced centers with a high-volume of pancreatic surgery to limit the morbidity and mortality of prophylactic resections.

Large cohorts of patients with pancreatic cysts are being followed to improve knowledge of the natural history and risks of progression in these pre-cancerous lesions.

Table 1. Main genetic diseases predisposing to the development of PDAC

Genetic syndrome	Oncogenic process	Mutation	Percentage among familial PDAC	Relative risk	Cumulative risk of PDAC by age 70%
No family history	-	-	-	1	0.5-1
2 first-degree relatives with confirmed PDAC	Unknown	Unknown	80-85	4-6	5-12
≥ 3 first-degree relatives with confirmed PDAC		Unknown		20-40	40
Hereditary breast and ovarian cancer (HBOC)	DNA Repair	BRCA 2	5-20	2-10	4-5
		BRCA 1	1-5	2-4	3-4
		PALB2, FANC-C/G	1-3	2-6	4-5
Lynch syndrome		hMLH1, hMSH2, hMSH6, PMS 2	1-3	4-8	3-5
Li Fraumeni syndrome	Cell growth and cell cycle control	TP53	<2	?	?
Familial atypical multiple mole melanoma (FAMMM) syndrome		P16/CDKN2A	2-3	10-25	5-25
Peutz-Jeghers syndrome		LKB1/STK11	1-3	100 -130	30-40
Ataxia Telangiectasia		ATM	<2	?	?
Hereditary pancreatitis	Cell injury	PRSS1	1-4	50-80	40-55

Table 2. Consensual clinical and imaging features that should lead to prompt management, according to Fukuoka guidelines [19]

Worrisome features	'High risk stigmata'
- cyst size ≥ 3 cm	- obstructive jaundice
- thickened/enhancing cyst walls	- enhanced mural nodule ≥ 5 mm
- main pancreatic duct size between 5-9 mm	- main pancreatic duct ≥10 mm
- enhancing mural nodule < 5 mm	
- abrupt change in caliber of pancreatic duct with distal pancreatic atrophy	
- lymphadenopathy	
- elevated serum level of CA 19-9	
- rapid rate of cyst growth > 5 mm/2 years	

Diagnosis

Although ultrasound can be used in case of jaundice or abdominal pain as the first imaging technique, a reliable diagnosis cannot be obtained with this method and small pancreatic tumors cannot be excluded [20]. If the diagnosis is suspected clinically or by US, CT and MR imaging are the reference techniques and the characteristics of PDAC are now well known [21]. Although a recent study showed a significant incremental benefit in the diagnosis of pancreatic cancer and a positive influence in the staging and management of patients [18]FDG PET/CT is not recommended [22].

Endoscopic ultrasound can be useful in four situations:

- strong suspicion of PDAC that cannot be visualized on CT or MR imaging

- undetermined pancreatic mass (e.g. differential diagnosis with chronic pancreatitis or pseudo-tumoral auto-immune pancreatitis)

- need for pathological evidence if the diagnosis is doubtful when neoadjuvant treatment is planned in resectable tumors or before proposing chemotherapy in non-resectable tumors when there are no other more easily accessible tumoral lesions.

- an indication for endoscopic retrograde cholangiopancreatography (ERCP) for biliary drainage.

Staging

Once the diagnosis has been made, a chest-abdominal-pelvic CT scan is performed to assess the stage of the cancer. This test should be performed no more than four weeks before any planned surgery for pancreatic cancer to avoid unexpected metastases during the intervention [23]. CT should include three sequences: without contrast administration and after contrast administration during the arterial and portal phases. Tumor resectability depends on the size, the extension and especially vascular involvement of the tumor as well as the presence/absence of distant metastases (Table 3).

There are four tumor subtypes :

- resectable

- borderline resectable

- locally advanced

- metastatic.

Although abdominal magnetic resonance imaging (MR imaging) with cholangio-pancreatographic sequences are as specific and sensitive as CT, this technique is limited by cost and availability and a thoracic CT must still be performed. Liver MR imaging with diffusion sequences is sometimes recommended before surgery of localized tumors to exclude small hepatic metastases that cannot be visualized on CT [8].

Prognostic and diagnostic markers

The poor prognosis of PDAC is mainly due to the difficulty of obtaining an early diagnosis and the limited efficacy of available therapeutics. Although there is a large window for surgical resection before progression from preneoplastic lesions to invasive cancer, the rate of advanced PDAC (stage III or IV) at diagnosis is more than 80%. Because of the lack of reliable markers, no screening programs for PDAC are possible except in those with family risks. CA 19-9 is still the only biomarker used for the diagnosis and management of PDAC.

CA 19-9:

As a diagnostic marker: CA 19-9 has several limitations. It is a sialylated Lewis blood group antigen and can therefore not be used in Lewis a-b- patients who represent approximately 5-10% of this population [24]. Furthermore, the accuracy is reduced by a lack of specificity, and this marker may be elevated in extra-pancreatic malignancies and benign conditions such as cholestasis or diabetes. Thus, CA 19-9 has been shown to be ineffective for screening in asymptomatic populations because of the low positive predictive value. For example, only 4 cases of PDAC were identified in a Korean study including 70,940 asymptomatic patients and in a recent meta-analysis the sensitivity and specificity of CA 19-9 was 78.2% and 82.8%, respectively [25,26].

As a prognostic marker: The prognostic value of CA 19-9 is probably better for therapeutic follow up.

Measurement of this marker at diagnosis has a good prognostic value. Survival in patients with normal serum levels (<37 U/ml) is better than in those with abnormal levels (32-36 months vs 12-15 months). It is also useful when tumor resection is planned. Serum levels ≤ 100-200 U/ml are suitable for surgery, while higher levels suggest the presence of (micro)metastatic disease. A postoperative decrease >20%-25% or normalization in CA 19-9 serum levels is associated with prolonged survival, as is a decrease after chemotherapy [27,28].

New biomarkers: Because of the limitations of CA 19-9, novel biomarkers are needed. Many approaches are under development to obtain earlier detection, improved predictive value and for follow-up. Some recent advances are described below.

Multi marker panel: To increase both sensitivity and specificity, multimarker panels have been proposed combining different serum proteins (with or without CA 19-9) for improved diagnostic performances [29]. Interesting results have been obtained with combinations including CA 19.9 and REG1+SYCN, thrombospondin A2, or more recently periostin (POSTN) + CA 242 [30-32]. These panels must be validated in large independent validation cohorts before they can be applied in routine practice.

Inflammatory and growth factors: Various inflammatory factors including chemokines, cytokines and growth factors are differentially

Table 3. Imaging features defining borderline and locally advanced PDAC

NCCN 2015		
Vessel	**Borderline**	**Locally advanced**
Superior mesenteric vein/ Portal vein	Contact ≥ 180° Contact < 180° with caliber irregularity of the vein without occlusion and/or tumoral occlusion with possible surgical reconstruction	Tumoral occlusion with no possible reconstruction, or invasion of jejunal principal veins
Superior mesenteric artery	Contact < 180°	Contact ≥ 180°
Common hepatic artery	Short contact, whatever the circumference, without invasion of the coeliac trunk nor of the origin of the CHA, with possible surgical reconstruction	No possible surgical reconstruction
Coeliac trunk	Contact < 180°	Contact ≥ 180°

expressed in patients with cancer, including PDAC. Thus, several panels have been developed combining certain analytes. Recently Mellby *et al.* [33] proposed a proteomic multiparametric analysis including 29 biomarkers (mainly targeting the tumor secretome or immunoregulatory proteins to reflect the systemic response) to discriminate early stage PDAC (I or II) from healthy controls with an AUC/sensitivity/specificity of 0.96/95%/94% and 0.963/95%/93% in two independent cohorts, respectively.

Metabolomics: Several changes occur in metabolic enzymes and there is an accumulation of key intermediates in PDAC as a result of reprogramming by the cancer cell metabolism in response to abnormal metabolic demands. Thus Johannes et al. [34] recently proposed a panel including five metabolites to discriminate early stage PDAC from healthy controls, reporting an AUC of 0.892 and improved results when it was combined with a previously validated biomarker panel (CA 19.9, LRG1, TIMP1) (AUC of 0.924) [35].

Besides serum protein markers, inflammatory, growth factors and metabolomic analysis, there is growing interest in a new field called liquid biopsy.

"Liquid biopsy": The recent discoveries in molecular pathology and the genetic alterations involved in the development and progression of cancer have led to the development of liquid biopsy, which is a promising tool because of the difficulty in biopsing PDAC.

This minimally invasive approach should make it possible to detect and analyze genetic material released from the tumor into the peripheral circulation including circulating tumor cells (CTCs), tumor nucleic acids (ctNAs), tumor RNAs (ctRNAs) and tumor-derived exosomes [36]. This technique is promising for early diagnosis, prognosis and PDAC disease monitoring. It may also provide valuable genomic and molecular information to help determine a non-invasive approach to the mutational landscape or methylation profiles of tumors.

Circulating tumor cells (CTCs): PDAC tumor-derived cells found in the peripheral circulation are highly heterogenous compared to other cancer types, making detection challenging (37). Several techniques have been developed for the detection of CTCs based on physical features, different cell surface proteins, markers or oncogene expression, with varying results. The only detection strategy approved by the FDA in lung cancer at this time (Cellsearch™) seems to be less effective in PDAC. The clinical application of these techniques has been evaluated in several studies, with high variations in sensitivity [37]. Some have reported a correlation with tumor differentiation and overall survival in locally advanced PDAC, as well as a potential prognostic value in resectable and metastatic patients. Unified detection methods and validation in large cohorts are needed to assess the potential use in practice [38,39].

ctDNA: Detection of ctDNA is based on the targeting of tumor specific PDAC mutations (mainly KRAS) in circulating free DNA (cfDNA). This approach has not yet been validated and the sensitivity and specificity must be clarified [37]. Because of the high frequency of KRAS mutations in this tumor, ctDNA detection would theoretically be useful for early detection. Nevertheless, the sensitivity in the study by Bettegowda et al. [38] was disappointing in an evaluation of 155 PDAC, with detectable ctDNA in only 48% of nonmetastatic patients. Several studies have also suggested that the sensitivity of KRAS mutation detection in plasma was low. Moreover, specificity may also be limited because detection rates of over 10% have been reported in patients with chronic pancreatitis [40]. ctDNA detection may be of interest as a prognostic marker in resectable patients and for the early assessment

of treatment response in patients with nonresectable tumors. KRAS mutation detection may also be corrrelated to prognosis and TNM stage in both advanced and resected pancreatic cancers [41,42]. As for CTCs, the clinical application of CTCs is limited by small evaluation cohorts, low sensitivity and the lack of technical standardization.

Methylation profile: In addition to genomic abnormalities, epigenetic alterations in the methylation profile of ctDNA could also be of future interest. Several targets for abnormal DNA methylation associated with PDAC have been identified and combined to improve performance and may become new diagnostic markers in the future [43].

Circulating RNA: Circulating noncoding RNAs (ncRNA), especially miRNA and long non-coding RNA (lncRNA), are other future potential markers [44]. Several studies have identified and tested different circulating miRNA (the most extensively studied is miR-21) and reported their potential value in miRNA panels in both blood and tumor-derived exosomes [45]. miR-107 is especially promising as it may be useful as both a diagnostic marker and therapeutic target of PDAC [46].

Tumor-derived exosomes: Exosomes are small extracellular vesicles in the peripheral circulation whose components, proteins and nucleic acids from cancer cells may be useful as diagnostic and prognostic biomarkers. Glypican 1, a cell surface proteoglycan is specifically enriched on the surface of cancer-derived exosomes and has been reported by Melo et al. [47] to be a "near perfect" tool for discriminating PDAC patients from healthy controls and benign pancreatic diseases, with an AUC of 1.0.

Immunosorbent: Immunology has recently revolutionized many cancer treatment options and it could also provide other applications for prognostic markers in the future. The immunosorbent assay (an immune score quantification of tumors based on total tumor-infiltrating T-cell counts and cytotoxic tumor-infiltrating T-cell counts), which has already been validated in colorectal cancer, was evaluated in a Finnish study including 108 patients with PDAC undergoing surgical resection [48]. Results showed a significant correlation to survival, independent from TNM stage [49]. Further studies are needed in PDAC to determine whether the results in colon cancer could be applicable to obtain reliable new markers, as a guide to adjuvant treatment after surgery, for example.

Treatment

Resectable tumors

Only 10% to 20% of patients are eligible for curative surgery. Multidisciplinary decisions should be based on a recent imaging assessment, i.e. a CT scan less than three to four weeks old. To achieve R0 resection, surgery should be performed in a high-volume center to minimize both morbidity and mortality [50]. The increasing incidence of PDAC makes it urgent to improve surgeon training and develop both intermediate and high-volume centers.

The role of neo-adjuvant treatment (chemotherapy alone or with radiation therapy) must still be defined.

The goal is to:

- induce a tumoral response and favor R0 resection

- provide an observation period to identify aggressive tumors with early metastatic progression

- treat potential micro-metastatic disease early

- test both tumor chemosensitivity and patient tolerance

Two main trials are in progress:

- NEOPAC: phase 3 trial investigating the efficacy of neo-adjuvant gemcitabine/oxaliplatin (or FOLFIRINOX after an amendment) chemotherapy plus adjuvant gemcitabine versus adjuvant gemcitabine only in patients with resectable tumors. The results are pending (NCT01314027) [47].

- PRODIGE 48 (PANACHE-01): open, non-comparative, randomized, multicenter phase II study designed to assess the safety and efficacy of two types of neo-adjuvant chemotherapy (FOLFIRINOX or FOLFOX) followed by surgery vs. direct surgery (NCT02959879).

The duration of adjuvant chemotherapy in patients who receive neoadjuvant treatment must also be defined defined and the role of radiation therapy must be prospectively assessed.

Up to 80% of patients who undergo surgery for localized PDAC will develop local or metastatic relapse [52]. Thus, adjuvant treatment has been systematically proposed since 2000 and should ideally begin within three months after surgery [53]. Since 2010, adjuvant gemcitabine has been the standard-of-care based on the ESPAC-3 trial which showed similar survival but less toxicity than with adjuvant 5-fluorouracil/folinic acid [54]. In 2017, the ESPAC-4 trial showed that gemcitabine plus capecitabine was superior to gemcitabine (28 vs 25.5 months, HR: 0.82, p:0.032) [55]. The results of the PRODIGE 24 trial were recently presented at the 2018 ASCO annual meeting. Compared to gemcitabine, modified FOLFIRINOX (mFOLFIRINOX) improved both disease-free (median: 21.6 vs 12.8 months, HR:0.58, p<0.001) and overall (median: 54.4 vs 35, HR:0.64, p=0.003) survival, respectively. Thus, FOLFIRINOX should be considered the new standard of care for ECOG 0-1 European and American patients [56]. The Japanese JASPAC 01 trial also showed that S1 was superior to gemcitabine and S1 is therefore the reference adjuvant treatment in Japan [57]. Addition of targeted therapy (erlotinib or sorafenib) to gemcitabine failed to

improve overall and disease-free survival [58,59]. Finally, the results of the phase III APACT trial (gemcitabine plus *nab*-paclitaxel versus gemcitabine) are pending. Figure 1 summarizes the progression of median overall survival in resected PDAC.

There is no clear consensus on the role of adjuvant radiotherapy (some studies have even suggested a deleterious effect on survival), and it is therefore not recommended [60-62].

Borderline and locally advanced tumors

Borderline tumors: A tumor is classified as borderline in the presence of limited vascular contact and the risk of R1 resection is not negligible with first line surgical treatment in these cases. Thus, induction treatment may be considered the best option. Some recent studies reported that induction therapy with FOLFIRINOX was effective for the R0 resection rate, pathological response and overall survival [63,64]. The PRODIGE 44 (PANDAS) trial is an ongoing randomized phase II study assessing the efficacy of induction chemotherapy by modified FOLFIRINOX followed or not by chemoradiotherapy. Indeed, the use of radiation therapy combined with capecitabine as a radiosensitizer seems to increase the pathological response [64].

There are no existing data on adjuvant treatment in operated patients who have received induction chemotherapy. Follow-up CT scan after induction treatment is difficult, especially to predict R0 resection. Resection may be R0 or even N0 even with an unchanged imaging status by the NCCN classification [65]. It has been shown that a major pathological response can be predictive of survival [63].

Overall, a large prospective randomized trial is needed to clearly evaluate the role of induction therapy in these patients.

Locally advanced tumors (LAPC): Although this may seem surprising, gemcitabine is still the reference treatment 21 years after it became available [66]. There was no significant difference in overall survival with the addition of erlotinib to gemcitabine compared to gemcitabine alone [67]. Results obtained with FOLFIRINOX are promising, and the results of the NEOPAN study, a prospective
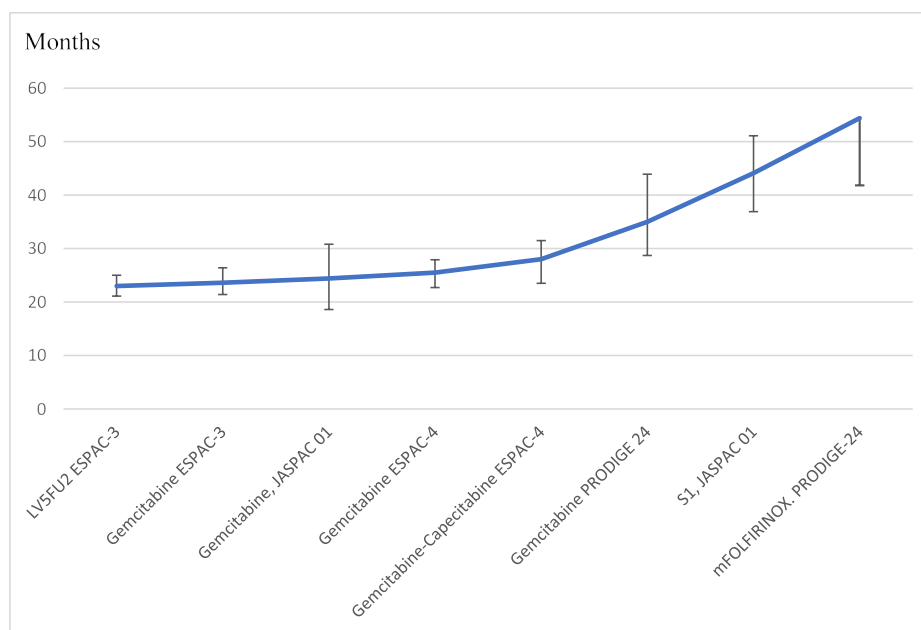

Figure 1. Evolution of median overall survival from 2001 to 2018 according to adjuvant treatment in resected PDA

randomized phase III trial comparing this combination to gemcitabine are awaited [68,69].

The preliminary results of the LAPACT phase II study assessing the efficacy and safety of nab paclitaxel plus gemcitabine were reported at the 2018 ASCO meeting and showed promising antitumor activity with an overall response and disease control rates of 33% and 78% respectively with good tolerance and quality of life. In addition, induction chemotherapy allowed tumor resection in 16/107 patients (15%), almost half with R0 resection [70].

There is no consensus on the role of radiotherapy in LAPC [71]. While some studies have reported a benefit in overall survival with chemoradiotherapy compared to chemotherapy alone, the LAP07 trial found no significant difference [67,72,73]. Capecitabine seems to be superior and less toxic than gemcitabine as a radiosensitizer [74]. It is now generally accepted that a period of induction chemotherapy is needed prior to radiation therapy to detect patients with rapid metastatic progression. One important goal is to propose a therapeutic break until progression in patients who can stop chemotherapy after radiation [65]. In the presence of a major tumoral response without the development of metastases, surgery can be proposed to certain highly selected patients.

Metastatic cancer

First line: Since it was introduced in 1997, gemcitabine has been the reference treatment in metastatic tumors [64]. For nearly 15 years, almost all combinations of gemcitabine with other drugs have failed to improve results. Indeed, several meta-analyses have showed that the toxicity of doublet chemotherapy offsets the marginal benefit to overall survival and may even be harmful in patients with poor performance status [75,76].

The combination of gemcitabine to targeted therapy has failed in numerous studies except for the combination of gemcitabine and erlotinib which was found to have a statistically significant but clinically irrelevant gain in overall survival (< 1 month) [77-79]. The lack of efficacy of erlotinib in the LAP07 trial in LAPC confirmed the limited role of this drug in pancreatic cancer [67]. The major advancement came in 2010 from the phase III PRODIGE-4/ACCORD-11 trial. The FOLFIRINOX combination was found to be highly superior to gemcitabine (OS 11.1 vs 6.8 months, HR=0.57, p<0.001). This protocol was limited to patients younger than 75 years of age in good condition (PS 0-1) and without cholestasis (bilirubin <1.5 fold the upper normal value) [80]. More adverse events occurred in the FOLFIRINOX group, especially febrile neutropenia (5.4%).

A retrospective study then suggested that a lightened, modified FOLFIRINOX (suppression of 5-FU bolus) had an improved safety profile with similar efficacy [81]. The results of the PANOPTIMOX study recently presented at the 2018 ASCO annual meeting showed that maintenance with LV5FU2 is feasible and as effective as the continuation of FOLFIRINOX in patients with metastatic PDAC controlled after 4 months of induction chemotherapy with FOLFIRINOX [82]. These strategic trials are important to optimize the quality of life of patients by limiting (neuro)toxicity as much as possible.

In 2013, the combination of nab-paclitaxel and gemcitabine was also shown to be superior to gemcitabine alone for overall survival (8.5 vs 6.7 months, HR=0.72, p< 0.001) in the phase III MPACT trial [82]. Patients with a Karnofsky performance-status score of 70 or more were eligible.

A comparison of FOLFIRINOX and gemcitabine-nab-paclitaxel has not been performed to date. Some studies have suggested that the FOLFIRINOX combination is superior [83,84].

Finally, gemcitabine alone should be proposed in patients with PS 2 and in patients with PS 3-4, the best support care is recommended [8].

Second line: About 50% of patients are eligible for a second line of treatment following tumor progression with first line therapies. Fluorouracil plus nanoliposomal irinotecan (or fluorouracil plus irinotecan) is the preferred second-line therapy in patients with PS 0-1 who have received first-line treatment with gemcitabine plus nab-paclitaxel. This combination has been shown to be superior to flurorouracil plus folinic acid in the phase III NAPOLI trial (OS 6.1 vs 4.2 months, HR=0.67, p=0.012) [85].

Patients with PS 0-1 who have received FOLFIRINOX as a first-line treatment can receive gemcitabine alone or associated with nab-paclitaxel as second-line therapy [8]. The results of L-asparaginase combined with cytotoxic chemotherapy (depending on the first line treatment) were promising in the randomized phase II GRASPANC-01 trial and are now being tested in a phase III trial (TRYBECA) [86].

Currently, despite controversial data, fluorouracil plus oxaliplatin can be considered the second-line therapy option in patients who remain in good condition after undergoing first-line treatment with gemcitabine-based chemotherapy. A randomized phase 3 trial (CONKO-003) showed the efficacy of OFF (oxaliplatin, fluorouracil, folinic acid) on overall survival (5.9 vs 3.3 months, p=0.01) compared to FF (without oxaliplatin) [87]. However, this benefit was not confirmed in the PANCREOX phase III randomized trial comparing mFOLFOX6 to FU-Leucovorin [88]. Patients with a PS of 2 may receive second-line therapy with gemcitabine or fluorouracil after evaluation in a multidisciplinary meeting.

There is currently no available robust data about third-line therapy.

Therapeutic research pathways

Although the new cytotoxic chemotherapy regimens discussed above have recently become available with improved outcomes, new therapeutic options are urgently needed. As mentioned, the benefit of targeted therapies remains very limited [84,85].

Thus, researchers have been investigating new concepts and pathways, based on growing knowledge of the molecular mechanisms involved in PDAC carcinogenesis and its microenvironment properties. This has led to the development of new approaches to obtain effective antitumoral effects [89].

Molecular pathology: Improvements in molecular biology have resulted in the development of molecular classifications of PDAC to identify subgroups of patients and potential clinical applications. Since 2011, several classifications have been published using different techniques to characterize the tumor and its microenvironment, revealing a significant heterogeneity among PDAC [90-92].

Waddell et al. [93] performed deep whole-genome sequencing of 100 PDAC and confirmed the well-known mutated genes in PDAC (KRAS, TP53, CDKN2A, SMAD4). They classified these tumors into four subtypes based on their structural variation profile, as stable (20%), locally rearranged (30%), scattered (36%) and unstable (14%). The unstable subtype was characterized by a high genomic instability suggesting defects in DNA maintenance systems, and a high correlation between this subtype and a BRCA mutational signature (previously described associated with deleterious mutations in *BRCA1* or *BRCA2* in

breast, ovarian and pancreatic cancer) was observed. Further analysis of the outcome in these patients revealed a high sensitivity to platinum-based chemotherapy regimens, paving the way to predicting platinum responsiveness in a subpopulation of patients.

In the next step more consensual, unified molecular classifications should be established and several technical challenges in deep whole-genome sequencing must be solved before this approach can be used in clinical practice.

Microenvironment: PDAC displays a marked desmoplastic stromal reaction, that is often greater than the epithelial component of the tumor itself. This complex structure is composed of extra-cellular matrix (ECM) components and various cell types in which cancer associated fibroblasts (CAFs) and especially pancreatic stellate cells (PSC) appear to play a major role. They are responsible for ECM overproduction and secreting various factors resulting in a fibrotic and hypoxic microenvironment. Thus, these elements have been identified as important pro-tumoral partners of cancer cells in PDAC, promoting tumor growth, invasion, metastasis and resistance to chemotherapy [94]. Stromal abundance and activity are correlated to survival, suggesting that desmoplasia may play a prognostic role in PDAC and providing a potential new target for therapeutic strategies [95]. Several **WHAT?** are being developed to interfere with signaling pathways involved in this desmoplastic reaction by targeting the TGFβ pathway or Focal-adhesion Kinases. Retinoic acid and vitamin D, which have both been shown to induce PSC quiescence in pre-clinical models, are also under evaluation. Another promising approach directly targets one of the ECM components, hyaluronic acid (HA). PEGPH20 is a PEGylated human recombinant hyaluronidase enzyme leading to the degradation of stromal HA and a decrease in interstitial pressure, thus promoting intra-tumoral perfusion and exposure to chemotherapy [96]. The 109-202-HALO randomized phase II study evaluated the combination of PEGPH20 with gemcitabine plus *nab*-paclitaxel chemotherapy as first-line treatment in patients with metastatic PDAC. Overall progression-free survival was significantly improved with combination therapy (HR: 0.73, *p*=0.049), but especially in patients with HA-high tumors (HR: 0.51; *p*=0.048) [97]. A phase III study of PEGPH20 including HA high patients alone is ongoing (NCT02715804). Surprisingly, the addition of PEGPH20 to mFOLFIRINOX appeared to be detrimental (HR=0.48) in a study of SWOG (NCT 019599139) by Ramathan et al. [98] probably because of the toxicity of the backbone chemotherapy.

BRCA mutation carriers: BRCA mutation carriers are the exception in PDAC and the only subset of patients in whom personalized treatment is close [11]. PDAC associated with the germline BRCA2 mutation is found in 4% -17% of families with a family history of PDAC history and occurs in 10% of BRCA 2 families with an increased risk of 3 to 6-fold compared to non-carriers. The prevalence of the germline BRCA2 mutation in apparently sporadic PDAC is 4%-7%, and 10-20% in the Jewish Ashkenazi population. The BRCA 1 and 2 genes are key regulators of the homologous recombination (HR), a high-fidelity repair system of double-strand DNA breaks and DNA cross-linking damages induced by DNA-damaging agents [11]. BRCA 2 loss of function induces multiple spontaneous chromosomal aberrations and genetic instability. Thus, therapeutics that exploit the inability of BRCA2-mutated tumors to repair DNA may be beneficial in these subsets of patients. Two main applications have been reported and evaluated thus far.

Platinum salts and radiation therapy: DNA-targeting cytotoxic agent platinum salts induce double-strand breaks that are not fixed in BRCA2 mutated tumors, which lack HR repair resulting in the accumulation of DNA damage leading to cell death. Thus, as suggested by Waddell et al. [93] prolonged survival could be expected with platinum-based treatments in this population. Numerous studies have reported prolonged survival in ovarian and breast cancers in BRCA mutation carriers who receive platinum salts and several retrospective case series have found a similar effect in BRCA2 mutation carriers with advanced PDAC [99,100]. Nevertheless, BRCA2 mutated tumors become resistant to platinum salts over time.

PARP inhibitors: olaparib, rucaparib, veliparib, ABT-888: An alternative to the HR system used in BRCA mutated tumors is another, lower fidelity DNA repair mechanism: the base excision repair complex that relies on an enzyme, the poly-ADP-ribose polymérase PARP. Thus, PARP inhibitors (PARPi) have been developed to deprive BRCA mutated (BRCAm) cells from this alternative repair mechanism to favor cell death due to the accumulation of DNA damage. The results of several studies evaluating PARPi monotherapy in BRCA2 mutation carriers have been promising. Two phase II studies including 23 and 19 patients with BRCAm, pretreated, advanced PDAC reported interesting response rates (21.7% and 15.8%) and disease control rates after PARP inhibitor monotherapy (olaparib or rucaparib) [100,101]. Although a third study testing veliparib as a single agent in 16 BRCAm pretreated patients did not report any confirmed response, tumoral control was found ≥ 8weeks in 25% of patients [102].

PARPi are also expected to be beneficial in combination with cytotoxic chemotherapies. A phase 1 study evaluating PARPi in combination with gemcitabine showed a non-significant but interesting doubled overall response rate (27% vs 14%) compared to gemcitabine alone. The BRCA status was only known in a few patients in this study (10/23) [103]. Another phase I study evaluated the association of veliparib with gemcitabine and cisplatin in two cohorts of untreated advanced PDAC, one with BRCA mutations (n=9), the other without (n=7). The objective response rate in the BRCAm cohort was 77.8% (7/9) vs 0% in the BRCA wildtype (wt) arm. Overall survival in the BRCAm and BRCAwt arms was 23.3 months and 11 months, respectively [104]. Phase II and III studies evaluating PARPi as monotherapy or in association with chemotherapy in larger populations of PDAC are ongoing (NCT02677038, NCT01585805, NCT01489865). For example, the POLO study is evaluating the potential efficacy of olaparib as maintenance therapy in patients with sporadic PDAC and BRCA germline mutations (NCT02184195).

As suggested in several studies including the work by Connor et al. [105] PDAC associated with deficiencies in HR repair are not limited to germline BRCA gene mutations. Other genes pooled as "BRACness phenotype" related to DNA maintenance defects may be targeted by these therapies in future clinical trials [106].

Other research pathways: Some of the other approaches being investigated to develop new treatments include:

- RAS pathway inhibition, as activating KRAS mutations are present in >90% of PDAC and are known to play a key role in PDAC carcinogenesis.

- Targeting the abnormal cancer cell metabolism because the significant needs of cancer cells for energy and tumor microenvironment constraints result in adptative cellular mechanisms which are potential therapeutic targets.

- Immune therapies.

Some of the main results and ongoing trials in these fields are summarized in Table 4.

Table 4. Main therapeutic research pathways for PDAC

The RAS pathway	Tumoral metabolism	The stroma	Immune therapies
- **MEK inhibitors** (pimasertib) **Negative studies** in association with Gemcitabine [122]. Modest benefit with the association MEKi + mTORi in phase Ib study [123]. - **interfering RNAs**: Encouraging pre-clinical studies [124], phase II ongoing in association with chemotherapy in locally advanced PDAC (NCT01676259) - **Oncolytic viruses: Reolysin** Disappointing results in association with chemotherapy [125,126]. Encouraging results in association with CPI in a phase IB trial (NCT02620423) Pre-clinical: - **CRISPR-Cas** technology: anti tumoral efficacy demonstrated in vitro and in vivo [127] - **Seven-In-Absentia Homolog (SIAH)** inhibition: Tumorigenesis complete blockage of pancreatic cancer cells in pre clinical models [128].	- **L-asparaginase:** PFS and OS benefit reported in the phase II GRASPANC trial [86] Phase III ongoing. - **Off label treatments** [129]: • **Vitamin C** Phase I with encouraging results, phase II beginning **Hydroxychloroquine** Several trials ongoing (NCT01978184; NCT01128296; NCT01506973; NCT01494155). Disappointing results in human studies, one interim report from a phase II study with encouraging results [130].	- **Pegvorhyaluronidase alfa (PEGPH20)** Positive phase II study [131]. International phase III study (HALO 301) ongoing (NCT02715804). - **The TGF B pathway** • **TGFB ligand inhibitor: Trabedersen (AP12009)** Encouraging OS in phase I/II study [132]. • **TGFB receptor inhibitor: Galunisertib (LY2157299)** Interesting results in two phase II studies (NCT01373164) [133]. Phase IB study ongoing in association with Durvalumab (NCT02734160). - **Focal-adhesion kinase (FAK) inhibitors:** Phase I clinical trials beginning with FAK inhibitor Defactinib (PF-04554878 or VS-6063) associated with CPI in pancreatic cancer and other tumors (NCT02546531, NCT02758587) - **Retinoic acid:** Phase IB study ongoing evaluating ATRA associated with Gem-Abraxane in advanced or metastatic pancreatic cancer (EudraCT2015-002662-23). - **Vitamin D:** Clinical trials combining paricalcitol with chemotherapy are ongoing (NCT02030860), as well as a phase II study combining paricalcitol with immunotherapy (NCT03331562).	- **Vaccine: GVAX** Inefficient as monotherapy. Interesting results combined with Ipilimumab in a phase IB study [134]. Multiple associations with GVAX plus CPI currently tested (NCT02243271, NCT02451982, NCT03161379, NCT03190265, NCT02648282). - **CCL2-CCR2 chemokine axis**: CCR2 inhibitor (PF-04136309) reached promising results in a phase Ib study [135] - **CPI combinations:** phase II trial ongoing comparing tremelimumab plus durvalumab in association with gem-nab-paclitaxel vs chemotherapy alone (NCT02879318) - **CPI in associations with:** • **GVAX** • **MEKi** Encouraging results in metastatic MSS KRASm colorectal cancers, clinical trial ongoing in PDAC (NCT03193190) • **Evofosfamide (TH 302)** Currently tested in a phase I study in association with ipilimumab (NCT03098160) • **FAKi** Phase I and I/IIA studies ongoing evaluating the association of defactinib and CPI in solid tumors including PDAC (NCT02546531 and NCT02758587). • **TGFBi** Phase IB study ongoing evaluating Galunisertib plus Durvalumab (NCT02734160). • **PEGPH20** Evaluation in association with Atezolizumab in a phase I/II trial (NCT03193190) • **Vitamin D** Phase II trial currently evaluating pembrolizumab with or without paricalcitol for maintenance in stage IV PDAC (NCT03331562)

Supportive care

Supportive care must play a central role in PDAC patients, whatever the tumor stage and should begin early, during the diagnostic process. Briefly, supportive care must consider and manage the following complications: pain, malnutrition, biliary and/or digestive obstructions, depression and anxiety and venous thromboembolism. Supportive care is absolutely necessary to optimize the general condition of patients so that they can receive potentially effective but aggressive treatments.

Pain management: Pain is a frequent symptom in patients with non resectable PDAC. It can be severe, thus preventing the appropriate administration of antitumoral treatments. Both the nociceptive and neuropathic components of pain should be carefully evaluated. Pharmaceutical analgesics are used according to the WHO three-step ladder and anti-epileptic drugs such as gabapentin and pregabalin should be included in case of neuropathic pain [107]. Pain can

sometimes be refractory to opioids leading to dose escalation and potentially deleterious side effects. Besides opioid rotation, locoregional treatments such as coeliac plexus neurolysis guided by endoscopic ultrasound can be discussed, keeping in mind the possibility of rare but potentially severe pancreatic complications (acute pancreatitis, abcess) or even paraplegia. Coeliac plexus neurolysis is performed by injecting absolute alcohol into the coeliac plexus neural network of ganglia. A meta-analysis showed a significant reduction in pain at four weeks that was not maintained at eight weeks [108].

Venous thromboembolism: Primary thromboprophylaxis can be proposed in high risk patients as defined by the Khorana Score (Table 5) [109].

Malnutrition: Over 80% of PDAC patients report weight loss at diagnosis and over a third of these patients report a weight loss > 10 % of their initial body weight [110].

Table 5. Prediction of the risk of thrombosis in patients with cancer

Patients characteristics	RISK SCORE
Very high-risk primary cancer type (stomach, pancreas)	2
High-risk primary cancer type (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥ 350000/mm³	1
Hemoglobin level < 10g/dl or use of red cell growth factors	1
Prechemotherapy leucocyte count > 11000/mm³	1
Body mass index ≥ 35 kg/m²	1
High-risk score ≥3; Intermediate-risk score=1-2; Low-risk score=0	

A recent study revealed that nutritional support provided within three months after diagnosis could improve survival. More than 60% of patients had a high malnutrition risk at baseline, which was correlated with poorer PS [111]. Therefore, patients should be screened for malnutrition at diagnosis and nutritional support, if necessary, should be begun early on. Based on the ESPEN guidelines, nutritional intervention to increase oral intake is recommended in cancer patients who are able to eat but are at risk of being malnourished [112]. This includes dietary advice, treatment of symptoms and disturbances impairing food intake (nutrition impact symptoms) as well as oral nutritional supplements. Restrictive diets or fasting should be avoided in patients with PDAC as it can worsen weight loss and generate sarcopenia [113]. When oral nutrition remains inadequate despite nutritional interventions, enteral nutrition should be preferred to parenteral nutrition, unless there is a contra-indication (occlusion). When oral food intake has been decreased severely for a prolonged period of time, nutritional support should be increased slowly over several days with regular assessment of potassium, magnesium and phosphate level to prevent a refeeding syndrome.

Physical activity: Many patients ask if adapted physical activity (APA) is feasible and safe during cancer treatment while others do not even imagine being able to practice APA. It has been proven that exercise is not only safe but has a positive effect on health-related quality of life and fatigue both during and after treatment as well as on treatment tolerance and adherence in patients with cancer [114-116]. Moreover, in breast-cancer and colon-cancer patients, physical activity is associated with reduced specific and non-specific mortality [117]. Indeed, preliminary evidence showed that exercise may favorably influence circulating levels of insulin, insulin-related pathways, inflammation and immunity [118-120].

The APA program should be individualized according to the patient's physical fitness, exercise preferences, psychological function and expectations, the tumor characteristics (stage, treatment, and tolerance) and the social environment. A combined aerobic exercise and resistance-training program should be favored. Patient adherence to the APA program is crucial for its efficacy. However, the effect of physical activity has not been examined specifically in patients with PDAC. Two prospective and randomized trials are in progress to assess its potential effect on both fatigue and quality of life in patients with unresectable (APACaP) or resected PDAC (APACaPOp) [121].

Conclusion

While significant progress has been made in the management of PDAC over the past decade, the rate of long-term survivors remains very low. Sustained efforts in all fields are still strongly needed to improve the prognosis of this devastating disease.

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