Pancreatic cancer

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Pancreatic cancer is a highly fatal disease with a 5-year survival rate of approximately 10% in the USA, and it is becoming an increasingly common cause of cancer mortality. Risk factors for developing pancreatic cancer include family history, obesity, type 2 diabetes, and tobacco use. Patients typically present with advanced disease due to lack of or vague symptoms when the cancer is still localised. High quality computed tomography with intravenous contrast using a dual phase pancreatic protocol is typically the best method to detect a pancreatic tumour and to determine surgical resectability. Endoscopic ultrasound is an increasingly used complementary staging modality which also allows for diagnostic confirmation when combined with fine needle aspiration. Patients with pancreatic cancer are often divided into one of four categories based on extent of disease: resectable, borderline resectable, locally advanced, and metastatic; patient condition is also an important consideration. Surgical resection represents the only chance for cure, and advancements in adjuvant chemotherapy have improved long-term outcomes in these patients. Systemic chemotherapy combinations including FOLFIRINOX (5-fluorouracil, folinic acid [leucovorin], irinotecan, and oxaliplatin) and gemcitabine plus nab-paclitaxel remain the mainstay of treatment for patients with advanced disease. Data on the benefit of PARP inhibition as maintenance therapy in patients with germline *BRCA1* or *BRACA2* mutations might prove to be a harbinger of advancement in targeted therapy. Additional research efforts are focusing on modulating the pancreatic tumour microenvironment to enhance the efficacy of the immunotherapeutic strategies.

Introduction

Pancreatic cancer remains a highly fatal malignancy and is projected to become the second leading cause of cancer death in the USA in the next twenty to thirty years. The 5-year survival rate at the time of diagnosis is 10% in the USA, as approximately 80–85% of patients present with either unresectable or metastatic disease.[1,2] Even for the small subset of patients who are diagnosed with a localised, resectable tumour, the prognosis remains poor with only 20% surviving 5 years following surgery. Over the past decade, advances in diagnostic approaches, perioperative management, radiotherapy techniques, and systemic therapies for advanced disease have made relevant but only modest incremental progress in patient outcomes. New strategies for screening high-risk patients to detect pancreatic tumours at earlier stages are desperately needed to make a clinically significant impact. In this Seminar, we discuss the latest developments in pancreatic cancer with respect to epidemiology and risk factors, pathology, diagnosis, and treatment, and we conclude with future directions in the field over the next several years.

Epidemiology and risk factors

According to the American Cancer Society, approximately 56 000 new cases of pancreatic cancer were diagnosed in the USA in 2019 with an estimated 45 000 deaths, ranking third after lung cancer and colorectal cancer.[1] It is the seventh leading cause of cancer death in both men and women worldwide, accounting for roughly 459 000 new cases and 432 000 deaths according to GLOBOCAN 2018 estimates.[3] It is predicted that pancreatic cancer will soon surpass breast cancer as the third leading cause of cancer death in the European Union.[3] According to Cancer Research UK, it is the tenth most common cancer in the UK and has increased in incidence approximately 10% over the last 10 years. The 2017 Global Burden of Disease Study, a systematic effort to characterise the global burden of various diseases from 1990–2017 across 195 countries and territories, showed a 2·3-fold increase in the global number of cases and deaths from pancreatic cancer with a 3-fold higher incidence in countries with higher social-demographic indices as measured by fertility rates, education and income.[4] Most patients are diagnosed later in life with a median age of 71 years at diagnosis and only 20% of diagnoses occurring before the age of 60.[5,6] Several groups have reported that certain variables, namely race, marital status, and level of insurance affect outcomes in patients diagnosed with this cancer.[7–10]

Modifiable risk factors associated with development of pancreatic cancer include obesity, type 2 diabetes, and tobacco use. A large National Institutes of Health cohort study showed that patients who were overweight or obese (defined by body mass index [BMI] ≥30 kg/m²) had an increased likelihood of developing this cancer compared to patients with normal range BMIs with hazard ratios (HR) of 1·15–1·53.[12] Fatty infiltration of the pancreas has been correlated with development of pancreatic intraepithelial neoplasias, precursors to the development of pancreatic ductal adenocarcinoma.[13] A 2019 study evaluating cancer trends among young adults in the USA showed a disproportionate rise in the

Search strategy and selection criteria

We searched MEDLINE and PubMed databases for relevant randomised trials and other high-quality studies published from Jan 1, 1995, to Dec 31, 2019, with the keywords "pancreatic cancer". We primarily included publications from the past 10 years, but we also selected older high-quality publications for inclusion. Abstracts from meetings were included if they were high quality and presented potentially practice-changing data.

incidence of various obesity-related malignancies, including pancreatic cancer, among patients aged 25–49 years old;[14] however, according to the National Cancer Research Institute, this trend has not yet been observed in the UK. Diabetes has long been correlated with development of pancreatic cancer with a pooled relative risk of 2·1, although pancreatic cancer is also thought to be a risk factor for developing diabetes.[15,16] Approximately 1% of patients over the age 50 with new onset diabetes develop diabetes due to a concomitant pancreatic cancer.[17] Similarly, patients who have been diagnosed with diabetes for less than a year have a 5·4-fold relative risk of developing pancreatic cancer compared with a 1·5-fold increase in risk in patients with long standing diabetes.[17] These data suggest that new onset diabetes might be an important risk factor and harbinger for pancreatic cancer. Estimates suggest that smokers are approximately twice as likely to develop pancreatic cancer compared with their non-smoker counterparts; however, in contrast with other smoking-related malignancies, a unique genetic signature for smoking-related pancreatic cancer has not yet been identified.[18] The European Prospective Investigation into Cancer and Nutrition study showed that patients with a high healthy lifestyle index score (which incorporates smoking, alcohol, physical activity, adiposity, and diet) had a decreased likelihood of developing pancreatic cancer, independent of abstaining from smoking tobacco.[19] Unfortunately, rates of metabolic syndrome continue to rise, particularly in countries with higher socio-economic indices, which might help to partially explain the global rise in incidence and death from this type of cancer despite lower smoking rates in this population.[4]

5–10% of all pancreatic cancers are estimated to be attributable to inherited risk factors.[20] Several familial cancer syndromes that are associated with an increased risk of developing pancreatic cancer have been identified. The Peutz-Jeghers syndrome, resulting from a mutation in the tumour suppressor *STK11* (also known as *LKB1*), results in a 35% increased risk of developing pancreatic cancer.[21] Similarly, hereditary breast-ovarian cancer syndrome, most commonly attributed to mutations in *BRCA1* or *BRCA2*, is associated with an increased risk of developing this type of cancer. Although this risk in patients harbouring a *BRCA1* mutation is relatively small (relative risk [RR] 2·8% *vs* 1·3% in the general population), *BRCA2* mutations are the most common inherited risk factor for pancreatic cancer with a RR of 3·5 for developing the disease.[20,22] Germline mutations in *CDKN2A* (familial atypical multiple mole melanoma) are associated with a 17% increased risk of developing pancreatic cancer.[23] Germline mutations in genes important for the DNA damage response (eg, *ATM*) and DNA repair (eg, *MLH1, MSH2, MSH6* as seen in Lynch syndrome, *PALB2*) are also associated with an increased risk of developing this type of cancer.[21] Patients with Lynch syndrome have an approximately 8·6-fold increased risk of developing pancreatic cancer by age 70 compared with the general public and harbour tumours that exhibit microsatellite instability, uniquely sensitising them to checkpoint inhibitor therapy.[24,25] Chronic pancreatitis is a well known risk factor for developing pancreatic cancer with a 40% lifetime risk of this cancer in patients with hereditary pancreatitis syndromes, associated with mutations in *SPINK1* and *PRSS1*.[21] A study of 3000 patients showed that 5·2% of patients with pancreatic cancer who had no family history of this cancer harboured at least one known inherited pancreatic cancer-predisposing genetic alteration, compared with 7·9% of patients with a positive family history.[26] This finding led to updated recommendations from the American Society of Clinical Oncology and the National Comprehensive Cancer Network to consider germline testing for all patients diagnosed with pancreatic cancer.[27,28]

Histological and molecular characteristics

Most pancreatic cancers are characterised as ductal adenocarcinoma and thus represent malignancy of the exocrine pancreas whereas a minority represent neuroendocrine tumours. Most pancreatic ductal adenocarcinomas arise from precursor lesions, termed pancreatic intraepithelial neoplasias, that progress in a stepwise process through acquisition of genetic alterations and culminate in development of overt pancreatic ductal adenocarcinoma. A minority of pancreatic ductal adenocarcinoma arises from cystic neoplasms such as intraductal papillary mucinous neoplasms (IPMN); however, IPMNs are often found to co-localise with pancreatic ductal adenocarcinoma and might have a distinct genetic signature suggesting divergent development.[29] Molecular characterisation of the progression from grade 1 and 2 pancreatic intraepithelial neoplasia to pancreatic ductal adenocarcinoma has been well described in the literature. Grade 1 and 2 pancreatic intraepithelial neoplasias are characterised by point mutations in the *KRAS* oncogene (found in approximately 90% of pancreatic ductal adenocarcinoma), particularly within codon 12, resulting in constitutive downstream signalling through the RAS and PI3K–AKT pathways and subsequent cell cycle progression and increased cell survival and motility (figure 1). Telomere shortening is a characteristic feature of grade 1 pancreatic intraepithelial neoplasia, perhaps predisposing cells toward developing mutations through chromosomal instability.[30] Early pancreatic intraepithelial neoplasias, particularly grade 2 lesions, are associated with inactivation of two cyclin-dependent kinase inhibitors, *CDKN2A* (and its encoded protein p16) and *CDKN1A* (and its encoded protein p21). Hallmarks of later stages of carcinogenesis, representing grade 3 and grade 4 pancreatic intraepithelial neoplasias, include mutations in the critical tumour suppressor gene *TP53*, observed in

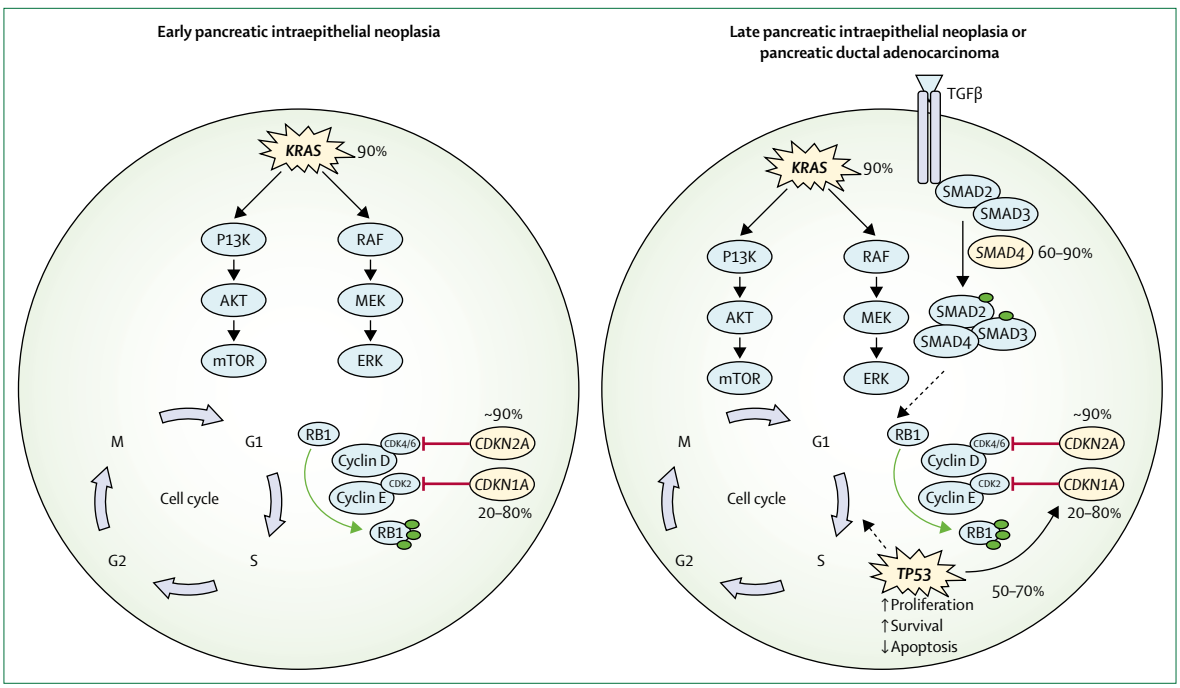

Figure 1: **Molecular pathways disrupted in pancreatic cancer development**
Early pancreatic intraepithelial neoplasias are characterised by mutations in the oncogene *KRAS*, leading to activation of the RAS–RAF and PI3K–AKT pathways—intracellular signalling pathways that regulate the cell cycle. Early lesions are also characterised by inactivation of tumour-suppressor gene *CDKN2A* (and its encoded protein p16) and overexpression of the oncogene *CDKN1A* (and its encoded protein p21), which promotes transition of the cell cycle from the G1 to S phase. In later lesions and eventually in pancreatic cancer, two critical tumour suppressor genes, *SMAD4* and *TP53* are inactivated. Inactivation of *SMAD4* and its encoded protein SMAD4 interrupts canonical signalling downstream of the TGFβ receptor and inactivation of *TP53* and its encoded protein p53 promotes progression through the cell cycle, survival, and inhibition of apoptosis. Frequency of gene alteration is given in percentages. AKT=protein kinase B. CDK=cyclin-dependent kinase. ERK=extracellular signal-regulated kinase. MEK=Mitogen-activated protein kinase. mTOR=mammalian target of rapamycin. P=phosphate. PI3K=phosphoinositide 3-kinase. RB1=retinoblastoma tumour suppressor protein. TGFβ=transforming growth factor β.

50–70% of pancreatic ductal adenocarcinomas, as well as inactivating mutations in *SMAD4*, observed in 60–90% of these malignancies.[31]

Genomic advances have facilitated attempts to further sub-classify pancreatic cancer based upon distinct molecular signatures. Earlier work using gene expression profiling of samples of primary pancreatic ductal adenocarcinoma in conjunction with murine cell lines identified three molecular subtypes of the disease, each exhibiting distinct clinical outcomes: classical, quasi-mesenchymal and exocrine-like.[32] Further work used micro-dissected specimens to separate stroma and normal pancreas from pancreatic ductal adenocarcinoma and identified two molecular subtypes: classical and a basal-like subset.[33] The basal-like subset had similar clinical and molecular characteristics to basal subsets found in other solid tumours, such as breast and bladder cancer. Another categorisation scheme based on a genomic analysis of 456 specimens of pancreatic ductal adenocarcinoma classified tumours into four distinct subtypes: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine.[34] Cross study analyses suggested that the squamous, basal-like and quasi-mesenchymal subsets were molecularly similar and likely to represent the same subset of pancreatic ductal adenocarcinoma. These tumours were also similar in their clinical outcomes, portending a poor prognosis and a poorer response to chemotherapy compared with pancreatic progenitor or classical subsets. Finally, a molecular analysis of 309 resected pancreatic ductal adenocarcinomas confirmed the presence of the pancreatic progenitor and basal-like, squamous, and quasi-mesenchymal subsets.[35] However, this study further characterised the tumour microenvironment and identified 3 additional subsets including desmoplastic, immune classical, and stroma activated subsets.[35] The clinical implications of this work are still in early stages of evaluation and additional studies are needed to help translate these molecular data to inform prognosis and treatment decisions.

Clinical presentation and diagnostic evaluation

Presentation and symptoms

Consistent with the fact that only a minority of patients diagnosed with pancreatic cancer present with surgically-resectable disease, the disease frequently causes few, if any, symptoms before it develops to the advanced stage. Unfortunately, those who do develop symptoms often have non-specific complaints—epigastric or back pain, nausea, bloating, abdominal fullness or change in stool

consistency—symptoms often understandably attributed to alternative, benign causes, which can delay diagnosis.[36,37]

The clinical features that occur with the highest frequency at the time of diagnosis include abdominal pain (40–60%), abnormal liver function tests (~50%), jaundice (~30%), new-onset diabetes (13–20%), dyspepsia (~20%), nausea or vomiting (~16%), back pain (~12%) and weight loss (~10%).[38] A patient's presentation also depends on the location of the tumour within the pancreas (figure 2). Approximately 60–70% of pancreatic tumours arise from the pancreatic head or neck and are more likely to cause biliary obstruction, leading to the classical presentation of a patient with painless jaundice. The positive predictive value of jaundice for diagnosing pancreatic cancer ranges 4–13%.[38] Tumours of the pancreatic body tend to invade local vascular structures including the celiac, hepatic, and superior mesenteric vessels in addition to the portal vein and are more likely to cause back pain on presentation. Pancreatic tail tumours can often grow unimpeded due to fewer anatomical neighbours and tend to be advanced at the time of diagnosis.

Other presenting symptoms include gastric outlet or bowel obstruction, weight loss, anorexia, depression, new-onset diabetes, or venous thrombosis. Malignant obstruction of the pancreatic duct can result in symptoms of pancreatic enzyme insufficiency (post-prandial abdominal pain, flatulence, loose bowel movements and, in severe cases, steatorrhea); malabsorption of fat (and fat-soluble vitamins, with associated deficiency, eg, vitamin D) and occasionally pancreatitis.

Diagnostic techniques and imaging

The recommended initial imaging technique for accurate and timely diagnosis of pancreatic cancer is multidetector CT angiography using a dual-phase pancreatic protocol, which carries a sensitivity of at least 90%.[39,40] Pancreatic tumours typically appear hypodense relative to pancreatic parenchyma, and the dual-phase protocol allows proper visualisation of regional vasculature in order to assess staging and resectability. MRI is an alternative modality that can provide a detailed assessment of the biliary tract (eg, magnetic resonance cholangiopancreatography) and has a higher sensitivity for the detection of liver lesions.[41] Endoscopic ultrasound is frequently used as an adjunctive tool for identifying regional lymph nodes and assessing the relationship of tumours to nearby vascular structures.[42,43] For patients with potentially resectable disease, endoscopic ultrasound with fine needle aspiration is a safe, high-yield approach for tissue confirmation. Upfront systemic therapy or resection must not be delayed if multiple attempts at biopsy are unsuccessful at confirming malignancy. In situations in which tumour infiltration leads to biliary obstruction, endoscopic retrograde cholangiopancreatography allows for biliary stent placement, and itself carries a sensitivity and specificity for the diagnosis of pancreatic cancer in excess of 90%.[44]

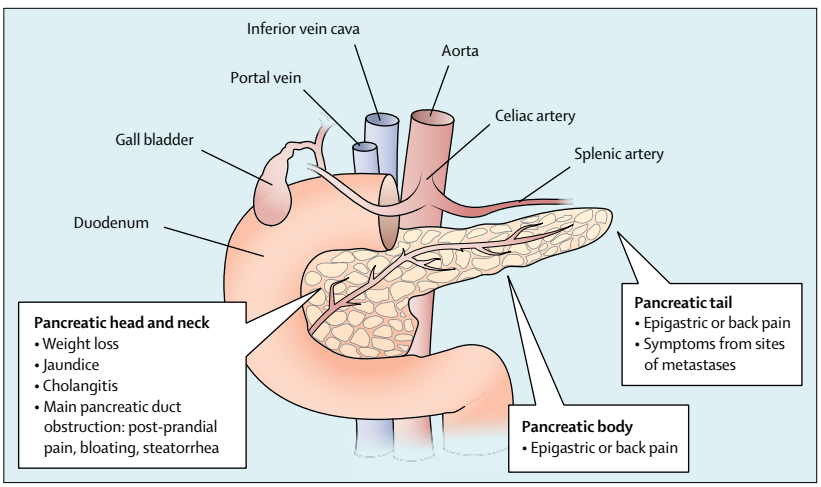

Figure 2: **Common signs and symptoms by site of pancreatic tumour**
Signs and symptoms at the time of presentation with pancreatic cancer depend on the location of the primary tumour within the pancreas. The pancreas is typically anatomically divided into the head, neck, body, and tail.

Routine biliary decompression for patients taken for surgical resection is not recommended because of increases in complications.[4] PET-CT is not routinely indicated in the diagnostic evaluation of pancreatic cancer, but should be considered in patients with high risk for occult metastatic disease, such as those with carbohydrate antigen (CA) 19-9 concentrations out of proportion to their suspected stage.

Serum biomarkers

CA19-9 is a well documented and validated serum biomarker associated with pancreatic cancer, maintaining a sensitivity of 79–81% and specificity of 82–90% for the diagnosis of the disease in symptomatic patients.[46] Carcinoembryonic antigen (CEA) and CA125 are non-specific markers that might be elevated in patients with this cancer. Serial measurement of CA19-9 has a role in monitoring response to systemic treatment in the neoadjuvant or metastatic setting and often is an early reflection of response on imaging.[47–50] Elevated preoperative CA19-9 also can help identify patients whose surgeries are less likely to result in an R0 (microscopically margin-negative) resection and can predict long-term survival after resection.[46,51] CA-19 concentrations might provide prognostic value in patients with inoperable pancreatic cancer.[52,53] Importantly, CA19-9 can be elevated in patients with biliary obstruction, highlighting limitations in this setting.[54]

Screening

At present, no recommendation exists for screening for pancreatic cancer in asymptomatic adults[55] mainly because of low incidence in an unselected population. However, indication of benefit exists in the screening of asymptomatic high-risk individuals.[56–58] A multi-institutional study in the USA screened 225 asymptomatic individuals at high-risk for pancreatic cancer using

endoscopic ultrasound, MRI, or CT.[58] Neoplasms were detected in 85 patients, and MRI and endoscopic ultrasound were both more sensitive than CT for detecting abnormalities. In 2011, the International Cancer of the Pancreas Screening Consortium recommended screening high-risk individuals (eg, carriers of a high risk germline mutation or a positive family history, or both) with endoscopic ultrasound or MRI, or both, though the age to initiate screening and optimal screening intervals remain unclear.[59]

Staging

Patients with pancreatic cancer can be staged according to the eighth edition of the American Joint Committee on Cancer Staging Manual. However, most clinicians use a four-tiered staging system based on tumour resectability (table 1): resectable, borderline resectable, locally advanced, and metastatic.[60–62] In 2017, the International Association of Pancreatology published a modified classification model that expands on the anatomical definition of borderline resectability to account for biological risk and patient condition.[63] Although laparoscopic evaluation of potentially resectable patients in order to rule out occult metastases is not routinely recommended, patients with high risk as determined by equivocal radiographic findings or elevated CA19-9 might benefit from this approach.[64] The decision of optimal management for patients with localised disease should be made with a multidisciplinary team of experienced clinicians.

Treatment

Resectable and borderline resectable

Despite 5-year survival rates of 10–25% for patients who can undergo surgical resection, surgery remains the only treatment that offers curative potential.[65,66] Resectability status should be determined by a multidisciplinary team after evaluation with high-quality cross-sectional imaging. Tumours in the pancreatic head are typically resected with a pancreaticoduodenectomy (Whipple procedure) which includes resection of the pancreatic head, duodenum, proximal jejunum, common bile duct, gall bladder, and a segment of the stomach. In retrospective studies, laparoscopic and robotic-assisted approaches have comparable outcomes in terms of safety when compared with a traditional open surgery.[67–69] In a large review of 322 patients from the Mayo Clinic (Rochester, MN, USA) laparoscopic pancreaticoduodenectomy was associated with less blood loss, reduced length of hospital stay, and improved disease-free survival compared with open surgery.[70] Furthermore, evidence exists that institutions with a high volume of pancreaticoduodenectomy surgeries (ie, at least 30 per year) experience lower post-operative mortality.[71,72] Tumours localised to the body or the tail of the pancreas can be treated with a distal pancreatectomy, often combined with splenectomy. Vascular resections at the time of tumour resection are frequently done to achieve negative surgical margins. In contrast to venous resection, arterial resection might be associated with increased post-operative morbidity and should be considered, if necessary, only at high-volume centers.[73]

The role of systemic therapy in patients with resectable and borderline resectable disease has been most studied in the post-operative setting. The European Study Group for Pancreatic Cancer (ESPAC)-1 trial initially established the role of adjuvant chemotherapy with the combination of fluorouracil and folinic acid (leucovorin) improving median overall survival compared with no chemotherapy after surgery.[74] After the ESPAC-3 trial confirmed the efficacy of adjuvant gemcitabine, the ESPAC-4 study randomly assigned patients to adjuvant gemcitabine with or without capecitabine, an oral fluoropyrimidine.[75–77] The results, published in 2017, showed an increased median overall survival from 25·5 months to 28 months (HR 0·82; 95% CI 0·68–0·98; p=0·032) with the doublet. In 2018, the results of the PRODIGE-24 trial were published, comparing 6 months of adjuvant modified fluorouracil plus leucovorin, oxaliplatin and irinotecan (mFOLFIRINOX) to gemcitabine monotherapy.[78] The

	Resectable		Borderline resectable		Locally advanced	
	MDACC	IAP	MDACC	IAP	MDACC	IAP
Superior mesenteric artery	No extension; normal fat plane between tumour and artery	No tumour contact	Tumour abutment ≤180° of artery circumference	Tumour contact <180° without deformity or stenosis	Encased (>180° involvement)	Tumour contact or invasion of ≥180°
Celiac axis or hepatic artery	No extension	No tumour contact	Short-segment encasement or abutment of common hepatic artery	Tumour contact with common hepatic artery without contact of the proper hepatic artery or celiac artery	Encased and no technical reconstructive option	Tumour contact or invasion of ≥180° or contact or invasion of the proper hepatic artery
Superior mesenteric vein or portal vein	Patent	No tumour contact or unilateral narrowing	Short-segment occlusion with suitable vessel above and below	Tumour contact of ≥180° or bilateral narrowing or occlusion, not exceeding inferior border of duodenum	Occluded and no technical reconstructive option	Bilateral narrowing or occlusion exceeding inferior border of duodenum

MDACC=MD Anderson Cancer Center. IAP=International Association of Pancreatology.

Table 1: **MDACC and IAP criteria for resectability of pancreatic cancer[61,62]**

	Recommended management	Evidence	Comments
Resectable	Surgical resection → 6 months of postoperative chemotherapy or preoperative chemotherapy with or without chemoradiotherapy → surgical resection → postoperative chemotherapy	Adjuvant gemcitabine plus capecitabine[74] and mFOLFIRINOX[78] both showed improved OS in phase 3 studies; neoadjuvant chemotherapy is increasingly used, with retrospective data suggesting improved survival,[84] but lack of strong evidence precludes routine use	Consider mFOLFIRINOX only for patients with ECOG performance status of 0 or 1; if preoperative chemotherapy is given, total duration of chemotherapy should be 6 months; advise clinical trial enrolment
Borderline resectable	Same as for resectable	Subgroup analysis from PREOPANC-1 study showed improved survival with preoperative chemotherapy and chemoradiotherapy[85]	Same as for resectable
Locally advanced	Systemic chemotherapy → surgical resection for down-staged patients	Multiple phase 2 and 3 studies of first-line systemic chemotherapy for locally advanced disease show benefit of induction chemotherapy[86]	For non-operative patients not progressing on chemotherapy, consider consolidative chemoradiotherapy or treatment break; no OS benefit found for chemoradiotherapy in this setting;[91] advise clinical trial enrolment
Metastatic	Systemic chemotherapy	FOLFIRINOX[92] or gemcitabine plus nab-paclitaxel[93] as first-line regimens in phase 3 studies showed improved OS when compared to gemcitabine alone	Consider FOLFIRINOX only for patients with ECOG performance status of 0 or 1; supportive care is a crucial component of management of advanced pancreatic cancer; advise clinical trial enrolment

mFOLFIRINOX=modified FOLFIRINOX (5-fluorouracil, folinic acid [leucovorin], irinotecan, and oxaliplatin). OS=overall survival. ECOG=Eastern Cooperative Oncology Group.

Table 2: **Authors' guidelines for pancreatic cancer treatment**

combination therapy increased disease-free survival from 12·8 to 21·6 months (HR 0·58; 0·46–0·73; p<0·001) and median overall survival from 35 to 54·4 months (HR 0·64; 0·48–0·86; p=0·003). Based on these data, 6 months of adjuvant mFOLFIRINOX is the recommended therapy for patients with a good performance status after resection of pancreatic ductal adenocarcinoma of any stage (table 2). In 2019, the APACT study concluded that 6 months of adjuvant gemcitabine plus nanoparticle albumin-bound paclitaxel (nab-paclitaxel) did not improve disease-free survival compared with gemcitabine alone.[79] Gemcitabine with or without capecitabine remains a treatment option for patients with contraindications to mFOLFIRINOX or those with suboptimal performance status. The timing of initiation of chemotherapy with respect to surgery has been evaluated in retrospective studies with a 2019 analysis suggesting that patients who began adjuvant therapy between 28 and 59 days of surgical resection had better survival than those who began before 28 or after 59 days.[80]

Despite limited high-level evidence to support its use, many high-volume centres use neoadjuvant therapy in patients with resectable and borderline resectable disease. Goals of preoperative systemic therapy include excluding patients with rapidly progressive disease who would probably not benefit from a major surgical procedure and potentially increasing the chance of achieving an R0 resection. Multiple single-arm studies have shown the safety of neoadjuvant therapy.[81–83] A retrospective review of resected patients found that patients who received neoadjuvant therapy had improved overall survival compared with those who received adjuvant therapy (34 *vs* 19 months; p=0·003).[84] In 2020, the final results of the phase 3 PREOPANC-1 study[85] were published, in which neoadjuvant chemoradiation with gemcitabine was compared with immediate surgery in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma. Although there was no statistically significant difference in survival, neoadjuvant chemoradiation was associated with a higher R0 resection rate and prolonged disease-free survival. In a subgroup analysis, patients with borderline resectable pancreatic cancer experieneced increased overall survival with neoadjuvant therapy.[85] Several studies are currently being done to compare neoadjuvant therapy with upfront surgical resection followed by adjuvant therapy.

Locally advanced disease

At least one third of patients with pancreatic cancer present with locally advanced disease, typically due to extensive vascular involvement that precludes surgical resection. The treatment for this group of patients primarily involves systemic chemotherapy with regimens that have been approved in the metastatic setting, such as gemcitabine plus nab-paclitaxel or FOLFIRINOX.[86,87] Although a small minority of these patients with an excellent response to chemotherapy might become eligible for surgical resection, the vast majority have incurable disease. The multicentre phase 2 LAPACT study assessed induction gemcitabine plus nab-paclitaxel in patients with locally advanced disease followed by investigator's choice of continued chemotherapy, chemoradiation, or surgery for patients without disease progression.[88] Median time to treatment failure was 9·0 months (90% CI 7·3–10·1) with a median overall survival of 18·8 months (15·0–24·0). Notably, 17 of the 107 enrolled patients had surgical resection, with 7 patients achieving an R0 resection. The role of chemoradiation for patients with locally advanced disease is somewhat controversial as studies have yielded mixed results.[89,90] The results of the LAP07 trial, published

in 2016, concluded that chemoradiation did not prolong survival in patients with locally advanced pancreatic cancer after treatment with systemic chemotherapy (gemcitabine with or without erlotinib), though patients who were treated with chemoradiation experienced improved local control rates and an increased time without treatment.[91] Whether these conclusions still apply in the setting of novel combination chemotherapy regimens and improved radiotherapy techniques such as stereotactic body radiation therapy and proton therapy is not clear.

Metastatic disease

Approximately 50% of patients present with distant metastases at the time of diagnosis. Systemic chemotherapy remains the primary treatment modality with the purposes of palliating cancer-related symptoms and prolonging life. FOLFIRINOX was compared with the previous standard-of-care, gemcitabine, in a randomised phase 3 trial of 342 patients with untreated metastatic pancreatic cancer.[92] The combination regimen improved median overall survival from 6·8 to 11·1 months (HR 0·57; 95% CI 0·45–0·73; p<0·001). Two years later, the results of another first-line phase 3 study were published comparing gemcitabine plus nab-paclitaxel with gemcitabine monotherapy.[93] Median overall survival in the chemotherapy doublet arm was 8·5 months compared with 6·7 months in the monotherapy arm (HR 0·72; p<0·001). Although first-line FOLFIRINOX and gemcitabine plus nab-paclitaxel have never been compared in a head-to-head clinical trial, real-world retrospective analyses indicate that younger, fitter patients are more likely to receive FOLFIRINOX and tend to have improved overall survival compared with gemcitabine plus nab-paclitaxel.[94,95] Gemcitabine monotherapy remains an option for patients whose performance status or comorbidities preclude combination chemotherapy.

Germline or somatic mutations in the *BRCA1* or *BRCA2* genes are present in 5–9% of patients with pancreatic cancer.[34,96,97] Data from pancreatic and ovarian cancer indicate that response to PARP inhibition appears to be most pronounced in patients with mutated *BRCA1* or *BRCA2* genes who are platinum-sensitive.[98,99] These findings led to the phase 3 POLO study evaluating the role of maintenance olaparib, a PARP inhibitor, in patients with germline *BRCA1 or BRCA2* mutations who were not progressing after at least 16 weeks of first-line platinum-based chemotherapy.[100] Compared with placebo, olaparib improved median progression-free survival from 3·8 to 7·4 months (HR 0·53; p=0·004). No difference in overall survival between the groups was found, although the survival data had not reached maturity at the time of publication. In December, 2019, olaparib gained approval in the USA for use in this setting—the first biomarker-based targeted therapy approved for pancreatic cancer.[101]

The only second-line therapy for metastatic pancreatic cancer that has shown a survival advantage in a phase 3 study is the combination of fluorouracil plus leucovorin with nanoliposomal irinotecan. In the NAPOLI-1 trial, patients with metastatic disease who had progressed on gemcitabine-based therapy were found to have an increased median overall survival with fluorouracil plus leucovorin with nanoliposomal irinotecan compared with fluorouracil plus leucovorin (6·1 *vs* 4·2 months, HR 0·67; p=0·012).[102] For patients who progressed on first-line FOLFIRINOX, gemcitabine-based chemotherapy is an appropriate second-line option for patients with an adequate performance status for chemotherapy.

Supportive care

Supportive care is a crucial component of the management of patients with advanced pancreatic cancer. Pain is an almost universal symptom, even in early-stage disease. Management options include opioid-based pharmacotherapy and interventions such as celiac plexus neurolysis.[103,104] Relief of biliary obstruction with stenting can reduce the risk of cholangitis and ensure the safe administration of chemotherapy, with metal stents preferred to plastic stents due to improved patency and potentially lower infection risk.[105] Patients with cholangitis often present acutely ill, an appearance which can be mistaken for progression of advanced pancreatic cancer, and should be managed for their potentially reversible infection. Venous thromboembolism is a well described source of morbidity and potential mortality in patients with pancreatic ductal adenocarcinoma, and although evidence does support the consideration of prophylactic rivaroxaban, the decision should be made on an individual basis after balancing potential benefit with risks of bleeding complications.[106,107] Depression, anxiety, anorexia, and weight loss are also common symptoms that must be addressed by clinicians managing patients with pancreatic cancer, and pharmacologic management should be strongly considered in appropriate patients. Main pancreatic duct obstruction can result in exocrine pancreatic insufficiency manifesting with symptoms of abdominal pain, bloating, and steatorrhea. Pancreatic enzyme supplementation can improve fat absorption and these symptoms. At the time of diagnosis with metastatic disease, American Society of Clinical Oncology guidelines recommend goals of care and advanced directive discussion with full assessment of symptoms, psychological status, and social support, usually necessitating palliative care consultation.[108] In a retrospective study in Canada, palliative care involvement was associated with reductions in admission to the intensive care unit, chemotherapy near death, multiple visits to the emergency department, and hospitalisations.[109]

Future directions

Pancreatic cancer remains one of the deadliest malignancies, responsible for substantial morbidity and mortality worldwide. The sobering reality is that most patients have advanced or metastatic disease at diagnosis, and thus efforts are underway to improve early detection. As

	Disease setting	Type	Primary outcome	ID
DDR				
Veliparib plus FOLFOX6	Metastatic	Phase 1/2	DLT	NCT01489865
Niraparib in patients with germline or somatic DDR mutations	Locally advanced, metastatic	Phase 2	PFS	NCT03601923
Niraparib after previous chemotherapy (NIRA-PANC)	Metastatic	Phase 2	ORR	NCT03553004
Rucaparib maintenance in patients with germline or somatic *BRCA* or *PALB2* mutations	Locally advanced, metastatic	Phase 2	Safety	NCT03140670
Immunotherapy				
Personalised tumour vaccine plus atezolizumab followed by FOLFIRINOX	Resectable	Phase 1	Safety	NCT04161755
Intratumoural talimogene laherparepvec	Locally advanced, metastatic	Phase 1	MTD	NCT03086642
huCART-meso with or without cyclophosphamide	Locally advanced, metastatic	Phase 1	Safety	NCT03323944
Intratumoural interleukin 12 transduced oncolytic virus plus chemotherapy	Metastatic	Phase 1	Safety	NCT03281382
TAA specific cytotoxic T lymphocytes	Resectable, locally advanced, or metastatic	Phase 1/2	Tolerability, safety	NCT03192462
LOAd703 (oncolytic adenovirus) and gemcitabine plus nab-paclitaxel with or without atezolizumab	Locally advanced, metastatic	Phase 1/2	DLT	NCT02705196
Concurrent capecitabine plus RT with or without pembrolizumab	Resectable, borderline resectable	Phase 1/2	DLT, TIL characterisation	NCT02305186
Neoadjuvant FOLFIRINOX plus SBRT with or without losartan and nivolumab	Resectable, borderline resectable, or locally advanced	Phase 2	% R0 resection	NCT03563248
Neoadjuvant GVAX with or without cyclophosphamide	Resectable	Phase 2	Safety, T-cell characteristics	NCT00727441
Nivolumab and cabiralizumab plus SBRT	Locally advanced	Phase 2	Safety, resection rate	NCT03599362
Anetumab ravtansine	Locally advanced, metastatic	Phase 2	RR	NCT03023722
GVAX and cyclophosphamide plus SBRT	Locally advanced	Phase 2	DMFS	NCT02648282
GVAX and cyclophosphamide with or without nivolumab plus urelumab (CD-137 agonist)	Resectable	Phase 2	IL17A production from lymphoid aggregates	NCT02451982
Chemotherapy with or without cabiralizumab and nivolumab	Locally advanced, metastatic	Phase 2	PFS	NCT03336216
FOLFOX with or without pegilodecakin	Metastatic	Phase 3	OS	NCT02923921
Tumour targeted				
MVT-5873 (anti-CA19-9) with or without chemotherapy	Locally advanced, metastatic	Phase 1	MTD	NCT02672917
Gemcitabine and nab-paclitaxel plus afatinib	Metastatic	Phase 1	Afatinib MTD	NCT02975141
Gemcitabine and nab-paclitaxel plus BYL719 (PI3K inhibitor)	Locally advanced, metastatic	Phase 1	MTD	NCT02155088
Gemcitabine and nab-paclitaxel plus SGT-53 (p53 cDNA)	Metastatic	Phase 2	PFS	NCT02340117
SM-88 and MPS (methoxsalen, phenytoin, and sirolimus) *vs* chemotherapy	Metastatic	Phase 2/3	OS	NCT03512756
Gemcitabine with or without masitinib	Locally advanced, metastatic	Phase 3	OS	NCT03766295
Microenvironment targeted				
Gemcitabine and nab-paclitaxel plus CPI-613	Locally advanced or metastatic	Phase 1	MTD	NCT03435289
Gemcitabine and nab-paclitaxel plus ADI-PEG 20 (pegylated arginine deaminase)	Locally advanced, metastatic	Phase 1	Safety	NCT02101580
Gemcitabine plus nab-paclitaxel with or without olaratumab	Metastatic	Phase 1/2	Safety, OS	NCT03086369
Neoadjuvant gemcitabine plus nab-paclitaxel with or without FG-3019	Locally advanced	Phase 1/2	Safety, resection rates, RR, 1-yr PFS or OS	NCT02210559
Pamrevlumab (anti-CTGF) and gemcitabine plus nab-paclitaxel	Locally advanced	Phase 2	OS, % R0 resection	NCT03941093
FOLFIRINOX with or without ramucirumab	Locally advanced, metastatic	Phase 2	PFS	NCT02581215
FOLFIRINOX with or without CPI-613	Metastatic	Phase 3	ORR, PFS	NCT03504423

CTGF=connective tissue growth factor. DDR=DNA damage response. DLT=dose limiting toxicity. DMFS=distant metastasis free survival. FOLFIRINOX=5-fluorouracil, folinic acid [leucovorin], irinotecan, and oxaliplatin. FOLFOX6=5-fluorouracil, folinic acid [leucovorin], and oxaliplatin. GVAX=granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic tumour cells. IMRT=intensity modulated radiation therapy. MTD=mean tolerated dose. OS=overall survival. PFS=progression-free survival. ORR=overall response rate. PI3K=phosphoinositide 3-kinase. RR=response rate. SBRT=stereotactic body radiation therapy. TAA=tumour associated antigen. TIL=tumour infiltrating lymphocytes.

Table 3: **Selected ongoing clinical trials**

detailed in our Seminar, current guidelines recommend screening only in patients deemed high risk for developing pancreatic cancer (defined as having two or more first-degree relatives with this cancer or carrying a known germline genetic variant associated with an increased risk of developing pancreatic cancer, or both factors). Several groups are determining the validity of liquid biopsies as a less invasive modality for early detection but circulating tumour DNA is detectable in only approximately 50% of patients with localised disease.[110] Thus, efforts to use circulating tumour DNA have so far been limited by low sensitivity and specificity.

Advancements in surgical technique offer an opportunity to improve outcomes for patients with locally advanced disease. The advent of neoadjuvant chemotherapy and improvements in venous and arterial reconstruction have rendered some tumours previously designated as inoperable, operable. Similarly, preoperative radiation therapy using newer delivery modalities (eg, stereotactic body radiation therapy) and ablative radiation therapies might also have a role in improving outcomes in patients with locally advanced disease.

Finally, more effective systemic therapies are desperately needed for patients with metastatic disease. To that end, patients with adequate performance status should be considered for clinical trials in both the front-line and pre-treated settings. Efforts to translate latest advances in the molecular characterisation of pancreatic cancer into targeted therapeutics is an active area of ongoing research. The Know Your Tumor programme is a collaboration between industry and academia with the goal of determining whether targeted therapy based on actionable molecular changes can improve outcomes in patients with pancreatic cancer. Most patients in the study had metastatic disease, and approximately 50% of patients had molecular profiles that identified so-called actionable genetic changes (ie, those hypothesised to confer sensitivity to a certain therapy).[111] Published data from this programme showed that patients receiving a matched therapy based upon their actionable molecular alterations had a superior overall survival compared with those who received unmatched therapy (2·58 *vs* 1·51 years, HR 0·34 [95% CI 0·22–0·53]; p=0·004).[112] These data provide real-world evidence that tailoring therapy based upon the molecular characteristics of each patient's tumour is both feasible and can improve outcomes. Molecular profiling of pancreatic cancers is not yet ubiquitous and has traditionally been limited by poor quality and yield of nucleic acid from traditional fine needle aspirations. However, the increasing use of endoscopic ultrasound with fine needle biopsy has improved tissue and molecular integrity, likely to facilitate more widespread molecular profiling.[113]

For more on the **Know Your Tumor programme** see https://www.pancan.org/for-healthcare-professionals/know-your-tumor/

Research aimed at targeting the crosstalk between tumour cells and the tumour microenvironment continues to offer promise in the treatment of pancreatic cancer. Immune checkpoint inhibitors, for example, have shown durable clinical benefit in a wide range of malignancies, but unfortunately this benefit has not yet translated to pancreatic ductal adenocarcinoma,[114] partly due to this tumour's complex, highly immunosuppressive microenvironment. Its microenvironment comprises high numbers of myeloid-derived suppressor cells, T-regulatory cells, alternatively-activated macrophages (M2 macrophages) and cancer associated fibroblasts, all of which function to dampen effective anti-tumour immune responses and promote tumour cell proliferation, survival, and invasion.[115] Targeting the suppressive myeloid compartment using a CD40 agonist antibody, which serves to activate and polarise macrophages toward an M1 phenotype (anti-tumour) and away from a M2 (pro-tumour) phenotype has shown preclinical benefit. Data from a small phase 1b study of metastatic pancreatic cancer patients using a CD40 agnostic antibody, gemcitabine and nab-paclitaxel with or without nivolumab showed an impressive response rate of 58% in the first-line setting.[116]

The pancreatic ductal adenocarcinoma tumour microenvironment is also characterised by a dearth of high quality, infiltrating effector T cells. Several vaccine-based studies are ongoing to induce infiltration of effector T cells. One such approach uses granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic tumour cells to induce T cells against a broad repertoire of pancreatic cancer antigens but has yet to result in improved clinical outcomes.[117] Effective immunotherapeutic strategies are likely to necessitate a multifaceted approach that involve strategies to induce infiltration of T cells (eg, vaccine-based approaches), combined with immunostimulatory approaches (eg, checkpoint inhibitors) as well as strategies to target the immunosuppressive microenvironment (eg, CD40-agonist antibodies).

It is worth noting the disappointing results of several recent clinical trials involving the addition of novel therapies to chemotherapy. Among these agents were PEGPH20, an enzyme targeting stromal hyaluronic acid, pegilodecakin, a pegylated IL-10, ibrutinib, a Bruton's tyrosine kinase inhibitor, and napabucasin, a STAT3 inhibitor aiming to target so-called cancer cell stemness.[118–121] Several other novel therapeutic targets are under active investigation (table 3). One such molecule, named CPI-613 (devimistat) is an inhibitor of two key enzymes of the tricarboxylic acid cycle, pyruvate dehydrogenase and a-ketoglutarate.[122] This approach exploits the relative dependence that pancreatic cancer cells have on mitochondrial metabolism. A phase I study of CPI-613 in combination with FOLFIRINOX showed an objective response rate of 61%, which served as the basis for the ongoing phase 3 AVENGER 500 trial evaluating the efficacy of FOLFIRINOX with or without CPI-613 (NCT03504423).[123] Another novel approach targets the heterogeneously dense pancreatic stroma that results in decreased vascular perfusion and drug delivery. Losartan, the angiotensin-receptor blocker, has been shown to decrease collagen and hyaluronan production in the

pancreatic cancer stroma, which subsequently results in decreased shear stress and improved drug delivery.[124] Losartan is being evaluated in clinical trials in combination with chemotherapy, immunotherapy, and radiation in patients with pancreatic cancer (NCT03563248, NCT04106856).

Conclusion

Pancreatic cancer remains a devastating malignancy with limited options for effective therapy. Improvement in patient outcomes will depend on multidisciplinary advances in imaging, surgical techniques, radiation, and systemic therapies. Although clinical progress has been slow, our understanding of the molecular biology of pancreatic ductal adenocarcinoma and the tumour microenvironment continues to expand and will eventually inform rational therapeutic approaches that will result in clinical benefit.

Contributors

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Declaration of interests

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