Pancreatic cancer

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Abstract

Improving the survival of patients with pancreatic ductal adenocarcinoma (PDAC) remains an oncological and surgical challenge. The non-specific nature of presenting symptoms which results in approximately 50% of patients having advanced disease at diagnosis, coupled with its relative chemoresistance have led to persistently poor survival rates. Unfortunately, even long-term outcomes following surgical resection for PDAC remain poor, with only 20% of patients surviving 5 years after pancreatectomy. Patient selection for surgery remains sub-optimal largely due to the absence of consideration of aggressive tumour biology. The benefits of FOLFIRINOX for patients with metastatic disease are now being realized in the adjuvant setting and potentially in the neoadjuvant space coupled with improved understanding of the impact of treatment sensitive molecular subgroups. For all patients with PDAC, management should incorporate multidisciplinary management, and integrated supportive care with comprehensive germline testing becoming increasingly applied. The future will likely see gradual progression to more patient-centred treatment algorithms based on tumour molecular profiling with the aim of improving not only survival outcomes but also quality of life.

Keywords Chemotherapy; germline mutation; molecular profiling; neoadjuvant treatment; palliative care; pancreas cancer; pancreatic ductal adenocarcinoma; pancreatic surgery

Introduction

Approximately 10,500 new cases of pancreatic cancer are diagnosed in the UK annually. While a relatively uncommon cancer, pancreatic ductal adenocarcinoma (PDAC) has overtaken breast cancer as the 3rd most common cause of cancer-related death in Western societies. With an increasing incidence of 0.5%−1.0% per year it is predicted to be 2nd by 2030. PDAC accounts for 90% of pancreatic neoplasms, with other subtypes including neuroendocrine tumours, acinar carcinoma, and rare entities including pancreaticoblastoma.

Despite progress in chemotherapeutic strategies, the long-term outcomes following surgical resection for PDAC remain poor, with only 20% of patients surviving 5 years after pancreatectomy. Patient selection for surgery remains sub-optimal largely due to the absence of consideration of aggressive tumour biology, such that even in the setting of an R0 resection and completion of adjuvant therapy, recurrence can occur within 6 months. In the last 5 years, significant developments in the understanding of the molecular biology underpinning PDAC along with paradigm shifting systemic treatment developments suggest that the nihilism associated with the management of this terrible disease is lifting.

This article reviews the current concepts regarding the diagnosis and management strategies to treat patients with localized pancreatic cancer.

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Epidemiology and screening

Globocan 2020 figures showed approximately half a million new diagnoses of pancreatic cancer were made worldwide, a two-fold rise over three decades. As such, it is the 12th most diagnosed malignancy but the 7th most deadly. Its lethality is evidenced by its mortality/incidence ratio of 90%−100%. Worryingly, its prognosis is unchanged over two decades, largely the result of failure to diagnose early, surgical resection being suitable only for the minority and significant chemotherapy resistance. More common in men (5.5/100,000) than women (4/100,000), PDAC is generally a disease of the elderly, rare before the age of 40, with 80% diagnosed between 60 and 80 years (median 73 years). The incidence is bound to rise as the proportion of those >65 years rises to 16.7% in the next 30 years. Worryingly, the incidence of PDAC in patients under 30 years is rising.

Modifiable and inherited risk factors

Several risk factors for PDAC can be divided into potentially modifiable and those that are not. Amongst multifactorial interactions and lifestyle factors that underlie this disease, cigarette smoking dominates and remains the most consistently reported modifiable risk factor. The carcinogenic effect of tobacco on pancreatic tissue may be explained by the direct action of N-nitrosamines or their secretion into bile and subsequent reflux into the pancreatic duct. The relative risk of PDAC development is 2.5-fold in current smokers and 1.6-fold for previous smokers, when compared to those with no history, with a dose dependent increase in risk also evident. Smoking cessation decreases risk precipitously, approaching that of those with no smoking history after 10 years. It is estimated that up to 20% of PDACs are attributable to cigarette smoking, with such cancers harbouring more genetic aberrations.

Patients with a BMI >30 kg/m^2 have a 1.7-fold increased risk of PDAC compared to those with a normal weight, after correcting for potential confounders including age, smoking and diabetes. Potential mechanisms include hormonal and inflammatory effect of adipose tissue, increased intake of food with carcinogenic metabolites and reduced physical activity. Diets rich in processed meat, high-fructose beverages, and saturated fat are associated with obesity and PDAC.

Type 2 diabetes, often observed in overweight patients, is also linked to PDAC development, with almost 50% of patients diagnosed having concomitant type 2 diabetes mellitus. Indeed, normal blood glucose is observed in just 14% of PDAC patients. The causal relationship between diabetes and pancreatic cancer is complex with a non-linear link between risk and duration of the diagnosis. New onset diabetes (NOD) (within 3 years of

diagnosis) may herald the diagnosis of pancreatic cancer in 1% of cases, reflecting malignancy-induced ß-cell dysfunction, partially secondary to duct obstruction and gland atrophy in addition to peripheral insulin resistance. Longstanding diabetes (>3 years) carries greater risk. Potential mechanisms include hyperglycaemia, hyperinsulinaemia and inflammation. The rising incidence of PDAC in the young may be related to increasing rates of obesity and diabetes. NOD cohorts are currently being targeted for PDAC screening initiatives.

The evidence for alcohol consumption resulting in pancreatic cancer development is confounded by alcohol excess often being accompanied by cigarette smoking. Intake of >9 standard drinks per day increases the risk of pancreatic cancer 1.6-fold compared to non-drinkers. Carcinogenesis can be caused by the metabolite acetaldehyde via pathways including oxidative stress and free radical formation. The role of alcohol is made more complex as it contributes to chronic pancreatitis development.

Cyclical inflammation underlying chronic pancreatitis is presumed to account for the associated 13-fold increased risk for PDAC through formation of cytokines and oxygen radicals leading to DNA damage, subsequent mutations, and malignant transformation. However, only 4% of patients with chronic pancreatitis will develop malignancy over 20 years and this association diminishes with long-term follow-up, therefore screening is not justified. Furthermore, imaging sensitivity of detection of small neoplasms is limited by the fibrosed parenchyma and calcification of chronic pancreatitis. *Helicobacter pylori* infection has been proposed as a risk factor, but evidence is not strong.

An individual with at least two first degree family members with pancreatic cancer has a 7-fold increased risk of the malignancy. Such patients are associated with an inherited predisposition based on familial clustering known as familial pancreatic cancer which constitutes 5%–10% of all pancreatic cancer.

Of these patients, only 25% have had their genetic mutation identified as part of a well-known cancer syndrome such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), familial multiple mole melanoma syndrome (FAMMMS), Li Fraumeni syndrome, hereditary breast and ovarian cancer (HBOC) syndrome, or Peutz–Jeghers syndrome.

The most common germline gene variants that increase susceptibility to PDAC occur in DNA Damage Repair (DDR) genes. The most common variants in PDAC include *BRCA2* (7%), *BRCA1* (1%) (HBOC), and *ATM* (2%) (ataxia telangiectasia). Germline BRCA2 variants are associated with an increased risk for PDAC (OR, 9.07) more commonly than BRCA1 (OR, 2.95) or ATM variants (OR, 8.96). Importantly BRCA1 and BRCA2 germline carriers are known to respond to platinum chemotherapy and PARP inhibitors in multiple tumour types, including early data for PDAC.

Mutation in the DNA mismatch repair gene family (MLH1, MSH2, MSH6, PMS2) results in HNPCC with an 8-fold risk of pancreatic cancer by 70 years. Although uncommon (1% of PDAC patients) it is a therapeutically important group (checkpoint blockade sensitive).

Peutz-Jeghers syndrome is associated with digestive tract hamartomatous polyps and mucocutaneous hyperpigmentation, the result of mutation in STK11/liver kinase B1 (LKB1) gene, a serine threonine kinase affecting multiple pathways in particular cell polarity and metabolism. It is associated with a 132-fold increased risk of PDAC development with a 30%–60% lifetime risk by 70 years as well as small intestine, colorectal, oesophagogastric, lung, breast, ovary, and uterus malignancy.

FAMMMS, the result of a CDKN2A germline mutation, carries a 20- to 34-fold risk of PDAC in addition to melanoma especially when affecting a specific 19-base pair deletion.

Hereditary pancreatitis is an autosomal dominant disorder accounting for 5% of pancreatitis resulting from a mutation in the cationic trypsinogen gene PRSS1, the serine peptidase inhibitor kazal-type 1 (SPINK1) and CPA1 carries a lifetime risk of 25%–40% by 60 years of PDAC development, increasing to 75% with paternal transmission of hereditary pancreatitis.

The National Comprehensive Cancer Network (NCCN) guidelines in 2021 recommended all new diagnosis PDAC patients undergo germline testing with a multi-gene panel including BRCA1/2, ATM, MLH1, MSH2, MSH6, and PMS2. Multi-panel testing rather than hierarchal single-plex gene analysis is recommended for cost and efficiency. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) have published research guidelines for the identification of patients with a potential germ-line mutation who should be referred for genetic consultation.

Molecular profiling

Three potential paths to PDAC via precursor lesions exist: pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN). Of these, the most common and well-studied is PanIN, found in small calibre pancreatic ducts and seen in up to 30% of specimens representing a stepwise mutational acquisition of proto-oncogene and loss of tumour suppressor genes including KRAS, CDKN2A, TP53, and SMAD4 that are responsible for the initiation and maintenance of PDAC, that lead to development of invasive carcinoma from normal ductal cells (Figure 1).

Large scale collaborative whole genome sequencing initiatives (TCGA, ICGC) have revealed that apart from established driver mutations, a few at around 10% prevalence (e.g., *KDM6A*, *RBM10*, *MLL3*), most occur at a rate of less than 5% and therefore PDAC represents a very genomically heterogeneous tumour. Despite the ubiquitousness of *KRAS* mutation in almost 95% of PDAC, only recently have therapeutics successfully targeted certain *KRAS* mutations.

Whole genome sequencing has elucidated key mutational signatures involved in PDAC pathogenesis, notably DDR deficiency and BRCA signalling, which is targetable by platinum-based chemotherapy, and poly (ADP-ribose) polymerase inhibitors ($PARPi_{nh}$) may be effective for patients with pathogenic variants in BRCA1/2 and PALB2.[1] With subsequent approval of targeted therapy in the form of olaparib in select patient with BRCA1/2 germline variants.[2]

Recent molecular classification advances have started to impact clinical practice. Particularly, transcriptomic molecular subtyping of PDAC has consistently identified subgroups, termed squamous (also known as basal) subtype, characterized by epigenetic changes that drive immune evasion and epithelial-to-mesenchymal transition and poor outcome as compared to the classical pancreatic subtype characterized by

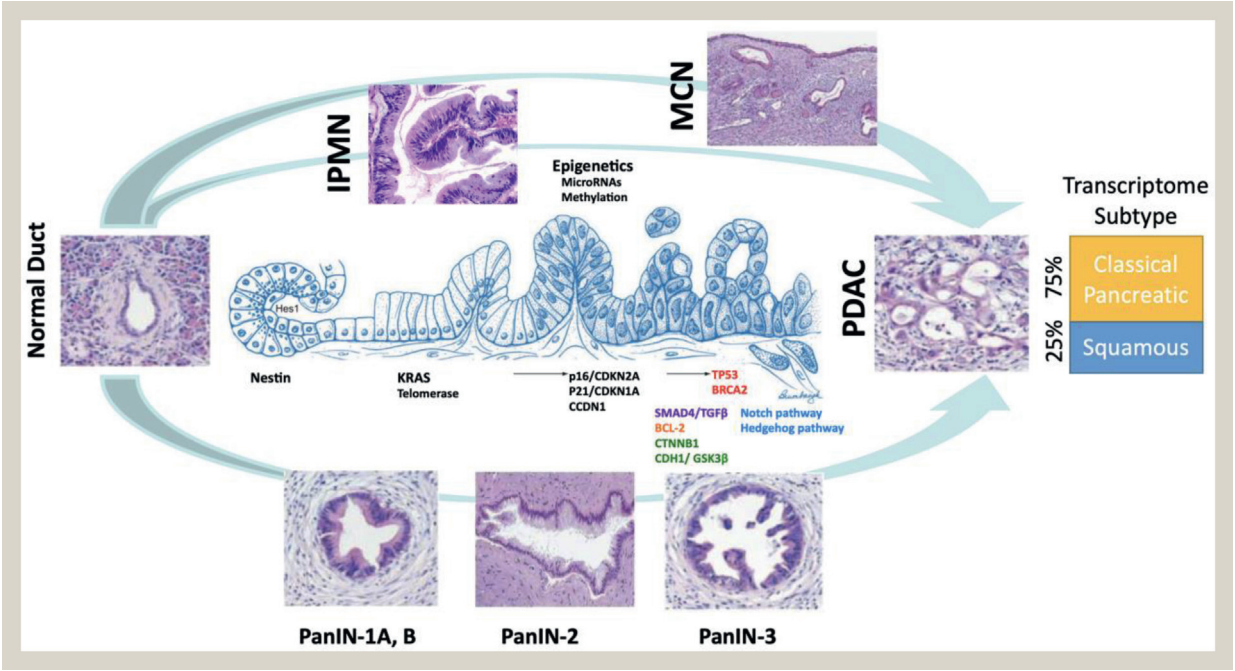

Figure 1 Genetic progression model of pancreatic adenocarcinoma. The progression from histologically normal epithelium to low-grade pancreatic intraepithelial neoplasia (PanIN), to high-grade PanIN, to invasive carcinoma (left to right) appear to associate with the accumulation of genetic alterations. IPMN and MCN are alternative paths to PDAC.

higher level of differentiation and inflammatory cell infiltrate and more favourable prognosis.[3] Platinum chemotherapy response may vary between these subtypes.

Despite development of novel personalized molecular and histological tools that evaluate tumour biology, these metrics have to date failed to integrate into clinical practice. For PDAC, the evolution towards a precision oncology strategy is driven by global initiatives including PRECISION-Panc in the United Kingdom (ISRCTN14879538),[4] and PRECISION-PROMISE in the USA. The selection of therapies according to molecular profile are currently underway in prospective trials based on diagnostic paraffin embedded biopsy material.

Precursor lesions

PanIN are <5 mm intraductal lesions formed by metaplasia of ductal epithelium. They exhibit various degrees of atypia from PanIN-1A, -1B through PanIN-2 to PanIN-3 or carcinoma in situ. Ultimately a small fraction of low grade PanINs transform to malignancy (Figure 1).

MCNs are mucin producing cystic tumours. The columnar epithelium contains mucin rich cells with ovarian like stroma and are oestrogen/progesterone positive. Typically diagnosed in 40- to 50-year-old women, the lesions are typically solitary large cysts not connected to the PD, almost exclusively in the pancreatic tail, unilocular with fine septations and rarely have a rim of calcification. Resection is recommended when >4 cm or if mural nodules are present due to the risk of malignant transformation, although the natural history is poorly defined.

IPMNs are mucin producing epithelial neoplasms arising from the main duct (MD), side-branches (SB) or both. Most frequently identified incidentally as a result of increased cross-sectional imaging in 60- to 70-year-old patients with equal sex incidence. Although those cysts occur mostly in the head, they can occur anywhere along the duct. Four histologic subtypes exist (gastric, intestinal, pancreatobiliary and oncocytic). SB-IPMNs are mostly gastric phenotype while the intestinal type is more commonly seen in MD-IPMN progressing into invasive carcinoma (colloid or tubular type). Malignant degeneration is higher in the MD-IPMN (60%) at 5 years compared to SB-IPMN (15%). Risk of malignancy is correlated with clinical and radiological features of the cyst (jaundice, pancreatitis, size, nodules). The Fukuoka guidelines (2017) categorize risk according to 'high-risk stigmata' or 'worrisome features' which attempt to stratify need for surgery or surveillance.[5] Unlike MCN they lack ovarian type stroma. Annual imaging surveillance is recommended; however, there remains no consensus as to optimal surveillance frequency or method. As this is a disease of the elderly, health economic impact must be acknowledged when considering surveillance of a cyst or the remnant pancreas following resection.

Clinical assessment and manifestations

At presentation, 50% of patients have metastatic disease, 30%–35% have locally advanced likely unresectable disease as a result of vascular involvement, while only 20% of patients with PDAC present with disease at an anatomically resectable stage attributable to initially non-specific symptoms. As the tumour grows, compressing or infiltrating surrounding structures, then symptoms develop dependant on tumour location or pattern of metastases. The three most common earliest symptoms include anorexia, indigestion and altered bowel habit.

Tumour location largely dictates symptoms with patients with cancer arising from the head or neck of the pancreas classically presenting with painless obstructive jaundice, pruritus, dark urine and pale stools, the result of distal bile duct compression.

Pain may be present, while vomiting secondary to duodenal obstruction is rarer. Body and tail cancers present later, often infiltrating the retroperitoneum and celiac plexus at presentation causing severe protracted back pain.

PDAC, even in the absence of metastases, is associated with significant weight loss and cachexia, which is multifactorial secondary to anorexia, malabsorption due to pancreatic duct obstruction, and systemic cytokine release. Weight loss of 10% over 6 months prior to admission portends to a poor prognosis.

New-onset diabetes in the absence of obesity is a potentially important warning symptom heralding endocrine failure secondary to PDAC and warrants evaluation.

Rarely, acute pancreatitis can be the primary manifestation of PDAC occurring in about 3% of patients with newly diagnosed PDAC. Interval imaging following resolution of inflammatory change is often necessary to identify the neoplasm.

At the time of diagnosis, the presence and severity of comorbidities must be accurately assessed along with performance status as these will guide subsequent management. Referral to an experienced multidisciplinary team is recommended.

Examination findings at an early stage may be minimal except for signs of weight loss. A tumour in the head of the pancreas may present with a distended gallbladder along with jaundice (Courvoisier's law). Late signs of malignancy would include cachexia, left side supraclavicular lymphadenopathy, palpable liver mass, ascites or umbilical nodule. Paraneoplastic signs may include thrombophlebitis migrans.

Investigations

The aim of investigation of a suspicious pancreatic mass is threefold. Firstly, to detect and distinguish it from other differential diagnoses, including pancreatitis (acute or chronic), neuroendocrine tumours, lymphoma and metastatic intraparenchymal deposits (renal, breast, lung, colorectal and melanoma). Secondly, to determine the relationship with central splanchnic vessels and surrounding organs, and finally to exclude metastases. A streamlined coordinated journey through a potentially complex diagnostic pathway is critical to accelerate the time to diagnosis and management commencement (Figure 2). Strategies include rapid access jaundice clinics, patient navigators and dynamic multidisciplinary team assessment.

CT

A pancreatic protocol CT (Figure 3) is the mainstay investigation for PDAC to determine vascular anatomy and presence of metastases, which occur most frequently in the liver (90%), lymph nodes (25%), lung (25%), peritoneum (20%), and bones (10%). Overall sensitivity is 89%–97% although this falls to as low as 67% for detection of small lesions (<1.5 cm). Slice thickness should be <3 mm and involve two phases. The arterial phase (25–35 s contrast) visualizes the hypo-enhancing lesion which has fibrotic stroma, and the relationship between the tumour and arterial structures (SMA, coeliac axis) and identifies arterial anomalies. The portal venous phase (60–70 s post-contrast) is key for venous assessment. Vessel assessment is categorized as uninvolved, abutted, or encased. Abutment describes tumour that has <180° vessel involvement while encasement describes >180° of circumferential tumour-vessel involvement. Synoptic reporting tools are being developed to assist in this variable nomenclature.

For small (<1.5 cm) or isoattenuating lesions, awareness of secondary signs is vital including abrupt pancreatic duct cut off, distal pancreatic gland atrophy, irregular gland contour, dilated pancreatic and bile ducts, and vascular impingement/encasement. These should trigger further investigations irrespective of the presence of a mass.

EUS

While there is little role for trans-abdominal USS, endoscopic ultrasound (EUS) has become a key component of the PDAC management algorithm. It serves to detect lesions not well visualized on cross-sectional imaging, define tumour-vessel relationship, evaluate lymph nodes and most importantly to secure tissue acquisition. Typical PDAC features include a heterogeneous, hypoechoic solid mass with irregular border. Fine needle biopsies (FNB) outperform fine needle aspiration (FNA) enabling acquisition of tissue with architectural preservation improving diagnostic accuracy, and tissue volume sufficient for clinical trial level molecular profiling. EUS biopsy can be associated with significant complications including haemorrhage (5%), pancreatitis (2%) or perforation (0.03%). Tumour seeding is far rarer than with percutaneous biopsy.

MRI

This involves a contrast enhanced MRI with an MRCP to assess the pancreas, interrogate the bile duct and exclude liver metastasis. PDACs are usually detected as hypointense lesions on T1/2 phases and are hypo-enhancing with contrast. Restricted diffusion weighted imaging increases detection of non-enhancing lesion. Potential advantages over CT include detection of small primary tumours, small liver metastatic deposits and investigation of patients intolerant of CT IV contrast.

18-FDG-positron emission tomography (FDG-PET)

FDG-PET functional imaging can distinguish benign pancreatic lesions, however it has limited spatial resolution and is confounded by inflammation. While not a substitute for CT and not recommended for all PDAC, SIGN and NCCN 2021 guidelines suggest there may be a role in high-risk patients to exclude extrapancreatic metastatic deposits: those with at least borderline disease, marked Ca19-9 elevation, large tumour, and regional lymphadenopathy. More recently this modality may, in the neoadjuvant setting, identify metabolic response in the primary cancer which subsequently correlates with pathological response.

Laparoscopy

Laparoscopy is not mandated as a routine procedure in any guideline. However, it has been found to avoid unnecessary resection in those individuals at high risk of occult metastasis: grossly elevated Ca19-9, equivocal CT findings, borderline disease, large tumours, bulky regional lymph nodes or highly symptomatic patients (weight loss, back pain). Laparoscopic staging should also be considered in patients with locally advanced pancreatic cancer (LAPC) that are considered candidates for radiotherapy or trial protocols as these patients will

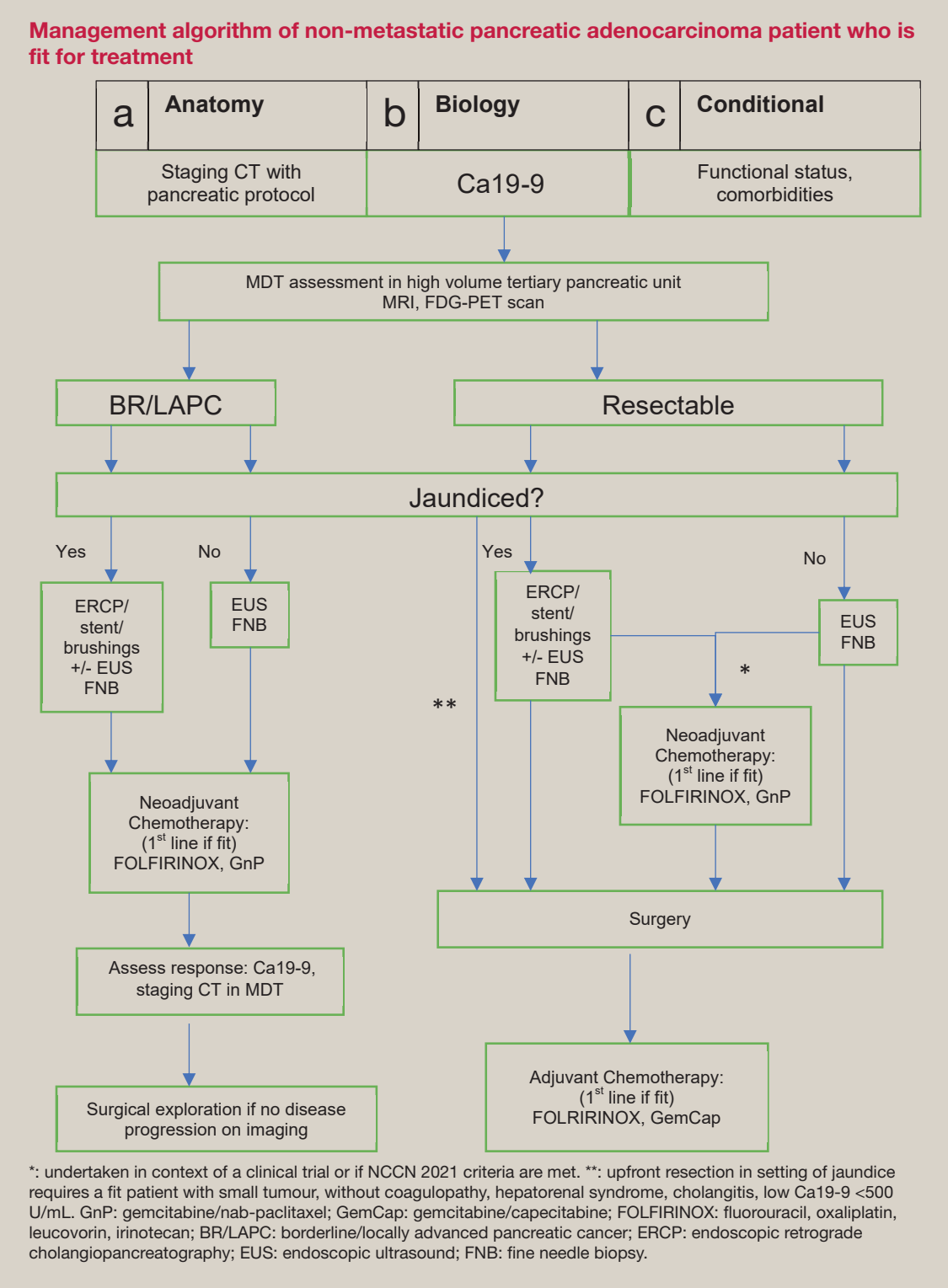

Figure 2

have an incidence of sub-radiological occult disease in approximately 35% of cases.

Serum biomarkers

Serum carbohydrate antigen (Ca) 19-9, is a sialylated Lewis blood group A antigen present in high concentration in patients with PDAC. It is limited as 5% of the population are Lewis antigen negative, in whom it is not detectable. Whilst it has a limited role in diagnosis or screening, it serves as a useful prognostic and predictive biomarker to determine therapeutic response. Notably, preoperative Ca19-9 >1000 U/mL has been found to correlate with increased risk of unresectability or metastasis.

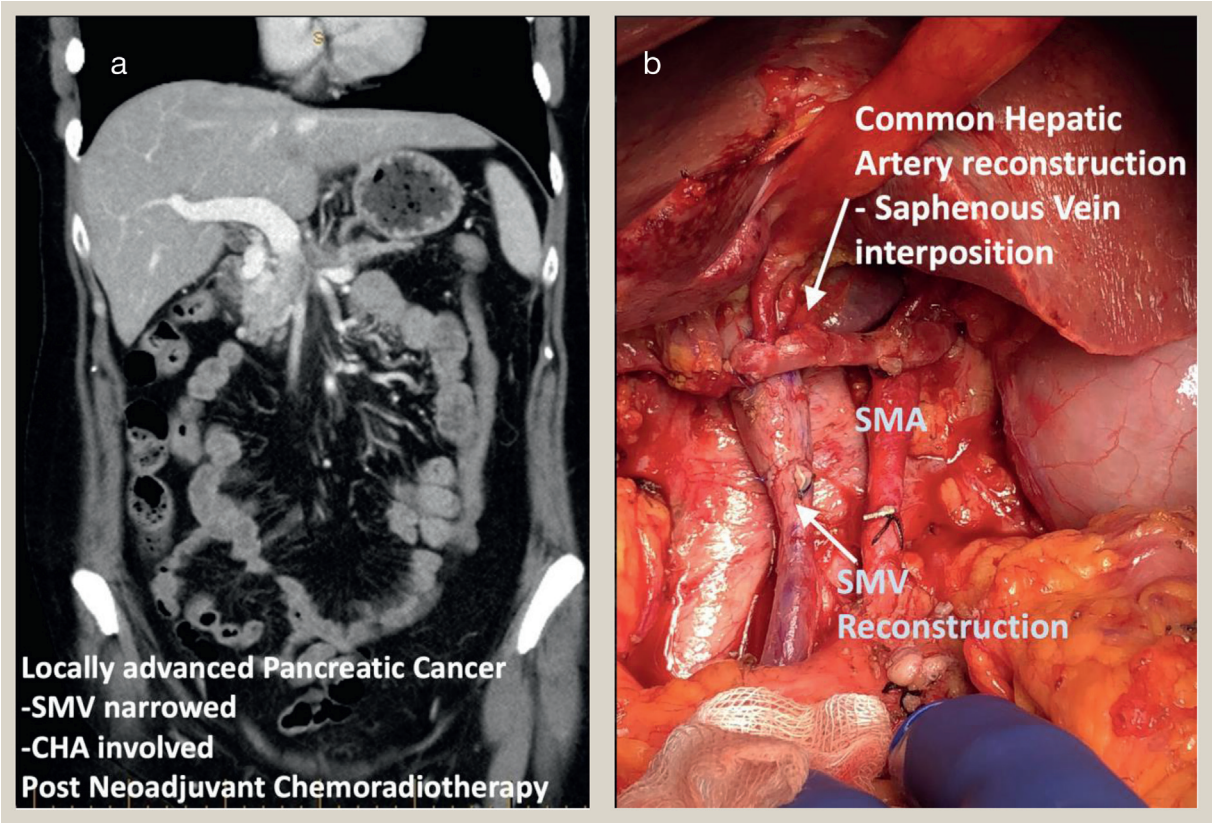

Figure 3 (**a**) Axial CT scan of a hypoattenuating locally advanced pancreatic cancer. (**b**) Post-resection intraoperative image with complex common hepatic artery and SMV reconstruction.

Post-neoadjuvant therapy, a 30% decrease in Ca19-9 is predictive of a 90% chance of progression to surgery. Other investigational blood-based biomarkers, including cell-free DNA, circulating tumour cells and exosomes, may have a future role in monitoring treatment response, therapy resistance and recurrence.

Clinical staging and multidisciplinary management of localized disease

Resectability, defined as the ability to completely remove the tumour, is a fundamental assessment to determine treatment selection for localized PDAC (Figure 4a). The American Joint Committee on Cancer (AJCC) tumour, node, and metastasis classification is used to assess prognosis (Figure 4b). Each case is defined as resectable PDAC, borderline resectable PDAC (BRPC), or locally advanced PDAC (LAPC) based on the degree of tumour contact and invasion into the superior mesenteric artery, hepatic artery, or coeliac vasculature (Figure 4c).

Categorizing localized disease is subjective and best performed by a multidisciplinary team, including surgeons, clinical oncologists, radiologists, and medical oncologists. Nomenclature is variably used between centres such that several classifications of resectability exist, resulting in challenges when comparing results between centres or clinical trials.

Tumour resectability is typically based on anatomical assessment alone; however, increasingly the definition is being broadened to acknowledge that resectability requires assessment of biological (Ca19-9) and conditional (comorbidity) dimensions[6] (Figure 2).

Adjuvant chemotherapy

Despite the nihilism associated with outcome following surgical resection of PDAC, significant impact has been achieved through incremental adjuvant therapy trials. Therefore, administration is strongly recommended for all patients within 12 weeks of R0/R1 resection. The principal chemotherapeutic agents are antimetabolites, including gemcitabine/fluorouracil and DNA-damaging agents, e.g. oxaliplatin or irinotecan.

The efficacy of adjuvant chemotherapy in resected PDAC was defined in the ESPAC-1 study (2004) that assessed the impact of adjuvant 5FU and chemoradiotherapy on survival[7] (Table 1). There was a clear benefit of adjuvant chemotherapy (20% 5-year survival in adjuvant group compared to 8% in no treatment) and deleterious effect of chemoradiotherapy (CRT). The CONKO-001 trial demonstrated a clear survival benefit of gemcitabine over observation alone (20.7% with gemcitabine vs 10.4% surgery alone).[8]

Following on from the ESPAC-3 trial which demonstrated outcome equivalence of 5FU/leucovorin and gemcitabine but with a more favourable side-effect profile in the latter, in 2017 ESPAC-4 reported the doublet of gemcitabine/capecitabine having superior survival of 28 months compared to 25.5 months for gemcitabine alone.[9]

A paradigm shift in adjuvant therapy came in 2018 with the multicentre PRODIGE-24 trial combining FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX), which was successful in the metastatic setting, as an adjuvant therapy for resected PDAC compared to gemcitabine for 6 months. Notably this group had a low serum

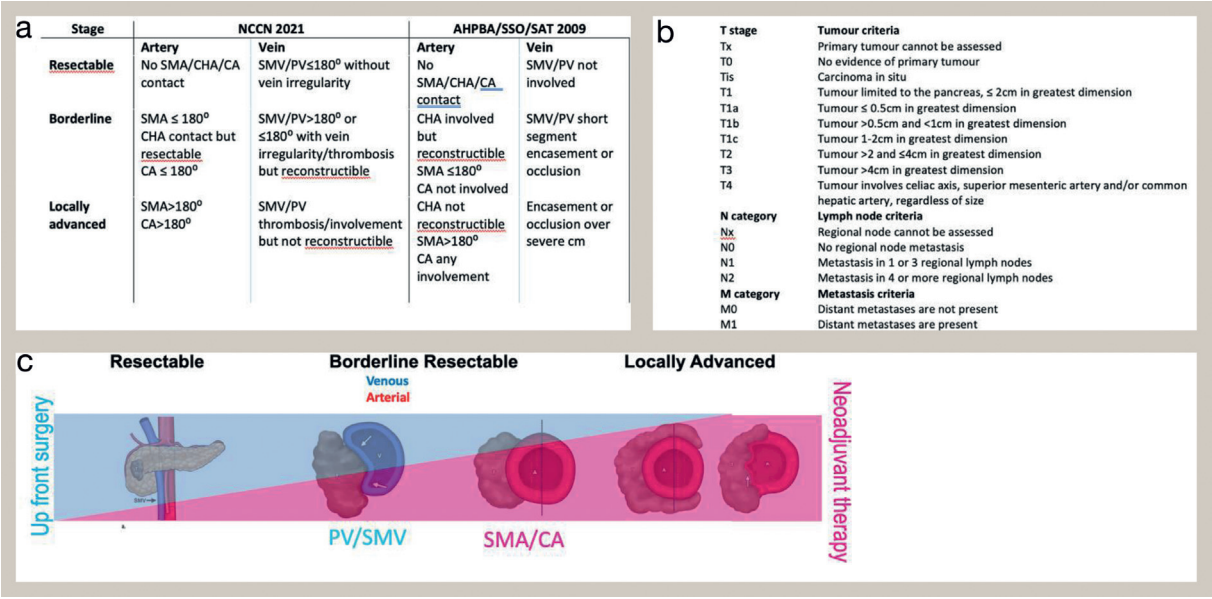

Figure 4 (**a**) Comparison of imaging based criteria between resectable, borderline and locally advanced pancreatic ductal adenocarcinoma. (**b**) American Joint Committee on Cancer staging of pancreatic adenocarcinoma, 8th edition (2017). (**c**) Role of neoadjuvant according to NCCN criteria. Abbreviations: NCCN – National Comprehensive Cancer Network; AHPBA – American HepatoPancreatoBiliary Association; SSO – Society of Surgical Oncology; SSAT – Society for Surgery of the Alimentary Tract; SMA – superior mesenteric artery; CHA – common hepatic artery; CA – coeliac artery.

Ca19-9 (<180 U/mL) and an excellent performance status. Encouraging outcomes occurred in both groups relative to prior adjuvant trials with gemcitabine, likely reflecting inclusion of highly selected patients: patients treated with mFOLFIRINOX had an overall survival (OS) of 54.4 months, compared with 35 months in gemcitabine (HR, 0.64 [95% CI: 0.48–0.86]).[10] Increased adverse events limit mFOLFIRINOX to patients with excellent performance status, leaving gemcitabine/capecitabine for the rest. The role of adjuvant radiotherapy following PDAC resection remains controversial and is not supported by older trial data.

The recent APACT study compared Nab-paclitaxel/Gem combination therapy (successful in metastatic disease) with single agent gemcitabine as adjuvant treatment. Despite improved OS (41.8 months) in the combination arm compared to the monotherapy arm (37.7 months), it failed to meet its primary endpoint of prolonged DFS.[11]

To date adjuncts to traditional chemotherapy have failed to impact survival in the adjuvant setting including the CONKO-005 trial of erlotinib and gemcitabine.

Resectable and borderline disease

Currently NCCN 2021 guidelines recommend adjuvant therapy in those who do not undergo neoadjuvant therapy (NAT). Whilst adjuvant combination therapies can result in improved overall survival, there are potential limitations associated with this strategy. Notably, up to 50% of patients do not start or complete adjuvant chemotherapy because of significant surgical morbidity or deconditioning. Additionally, primary resection is associated with an R1 margin positive rate of 75%. Subsequently 25% of patients develop recurrence within 6 months leading to an overall 10 year OS of <4% for those who get upfront surgery. Therefore, PDAC is increasingly being regarded as a systemic disease. Neoadjuvant therapy has the potential to eradicate occult metastatic disease and increase the number of patients eligible for successful multimodality therapy. Recent trials have demonstrated that patients can successfully complete neoadjuvant mFOLFIRINOX therapy (SWOG S1505).[12] Furthermore, NAT has been shown to achieve successful downstaging to achieve an increased R0 resection rate.

The phase 3 PREOPANC trial has demonstrated a potential role for chemoradiotherapy in resectable/BRPC neoadjuvant gemcitabine-based chemoradiation followed by surgery or initial surgery, both followed by adjuvant gemcitabine.[13] This demonstrated prolonged OS observed in the predefined subgroup of 113 patients with BRPC treated with neoadjuvant chemoradiotherapy (17.6 vs 13.2 months). The phase 2 randomized ALLIANCE A021501 trial evaluated perioperative modified FOLFIRINOX with or without neoadjuvant stereotactic body radiotherapy in 126 patients with BRPC.[14] However, the addition of radiotherapy failed to prolong survival. Current guidelines support neoadjuvant chemotherapy with or without radiotherapy as an option in both BRPC and LAPC. Assessment by a multidisciplinary team to determine eligibility for surgical resection in BRPC and LAPC is vital. The ESPAC-5(Feasibility) study has completed, reporting that neoadjuvant chemotherapy with either gemcitabine plus capecitabine or FOLFIRINOX had the better survival compared with immediate surgery for patients with borderline resectable PDAC.[15] The PREOPANC2 study[18] reported at ESMO 2023, demonstrated equivalence between neoadjuvant FOLFIRINOX and neoadjuvant chemoradiotherapy; however, the full study results are yet to be reported.

The benefit of NAT in resectable PDAC is currently undergoing evaluation. Proponents of this approach suggest it identifies the cohort of patients with aggressive disease biology who progress early. Potential limitations include minimal tumour response

Population characteristics and outcomes in pancreatic adenocarcinoma randomized clinical trials

Trials	Year	Setting	No. of patients	Age (years)	Study regime	Comparator regime	Primary end point	Median Survival Study vs Comparator (months)
ESPAC-1[7]	2004	Adjuvant	289	61	CRT (5FU+RT) vs No CRT	Chemo vs Obs	2 years SR	CRT vs no CRT: 15.5 vs 16.1 (NS) Chemo vs Obs: 19.7 vs 14 (Sig)
ESPAC-3	2012	Adjuvant	1088	63	FU/L	Gemcitabine	OS	23 vs 23.6 (NS)
CONKO-001[8]	2013	Adjuvant	368	62	Gemcitabine	Obs	DFS	13.4 vs 6.7 (Sig)
ESPAC-4[9]	2014	Adjuvant	732	65	Gemcitabine/ Capecitabine	Gemcitabine	OS	28 vs 25.5 (Sig)
PRODIGE 24[10]	2018	Adjuvant	493	64	FOLFIRINOX	Gemcitabine	DFS	54.4 vs 35.0 (Sig)
APACT[11]	2021	Adjuvant	866	64	GnP	Gemcitabine	DFS	41.8 vs 37.7 (NS)
SWOG S 1505[12]	2021	Neoadjuvant (Resectable)	102	64	FOLFIRINOX	GnP	OS	22.4 vs 23.6 (NS)
PREOPANC[13]	2020	Neoadjuvant (Resectable, Borderline)	246	56	Gemcitabine based CRT	Gemcitabine	OS	16 vs 14.3 (NS)
ALLIANCE A021501[14]	2021	Neoadjuvant (Borderline)	126	65	FOLFIRINOX FOLFOX	FOLFIRINOX, SBRT or HIGRT FOLFOX	18 m OS rate	31 vs 17.1 m (Sig)
SCALOP[15]	2013	Neoadjuvant (Locally Advanced)	74	65	Gemcitabine based CRT	Capecitabine based CRT	PFS	13.4 vs 15.2 (Sig)
PRODIGE[16]	2011	Metastatic	342	61	FOLFIRINOX	Gemcitabine	OS	11.1 vs 6.8 (Sig)
MPACT[17]	2013	Metastatic	861	63	GnP	Gemcitabine	OS	8.5 vs 6.7 (Sig)
POLO[2]	2019	Metastatic (BRCA)	154	57	Olaparib	Placebo	PFS	7.4 vs 3.8 (Sig)
ESPAC5[15]	2022	Neoadjuvant (Resectable, borderline)	90	64	Gemcitabine plus Capecitabine	Immediate surgery vs FOLFIRINOX vs Capecitabine-based Chemoradiotherapy	Recruitment rate and resection rate	Gemcitabine plus Capecitabine: NE Immediate surgery: 10.7 FOLFIRINOX:NE Capecitabine-based Chemoradiotherapy: NE
PREOPANC-2[18]	2023	Neoadjuvant (Resectable, borderline + Resectable)	375		Neoadjuvant FOLFIRINOX (FFX arm)	Neoadjuvant gemcitabine-based chemoradiotherapy (CRT ARM)	OS	21.9 FFX vs 21.3 CRT (ǂNS)
NORPACT[19]	2024	Neoadjuvant (Resectable)	140	68	Neoadjuvant FOLFIRINOX (FFX arm)	Immediate surgery	OS	23.0 FFX vs 34.4 UFR (NS)

Abbreviations — CRT: chemoradiotherapy; SBRT: stereotactic body RT; HIGRT: hypofractionated image guided RT; L: leucovorin; GnP: gemcitabine/nab-paclitaxel; FOLFIRINOX: fluorouracil, oxaliplatin, leucovorin, irinotecan; R: resectable, B: borderline; LA: locally advanced, Sig: statistically significant; NS: not statistically significant. DFS: disease free survival, PFS: progression free survival, OS: overall survival, NE: not evaluable.

Table 1

based on radiology assessment for most patients. Inadequate tumour response may enable disease progression and loss of opportunity for resection. The multidisciplinary neoadjuvant journey faced by a patient is complex, requiring pre-treatment biopsy, endoscopic biliary stenting which for a patient with resectable PDAC carries risk of pancreatitis (7%), cholangitis (26%), stent occlusion (15%) and postoperative wound infection in 13% following resection. Following NAT, a 30% reduction in Ca19-9 level is predictive of a 90% chance of progression to resection. On restaging CT, it remains difficult to differentiate tumour from post-neoadjuvant fibrosis. Instead, the metabolic response on FDG PET/CT may be a better surrogate of pathologic response, although not all tumours are FDG avid. Therefore, disease stability on imaging after perioperative therapy should prompt surgical exploration to determine resectability (Figure 5).

The phase 2 SWOG S1505 RCT compared two combination neoadjuvant strategies (mFOLFIRINOX and gemcitabine/nab-paclitaxel) in resectable PDAC. While there was also no significant difference between the DFS, it did highlight a high pathological response of 33% and supported the ability of patients to

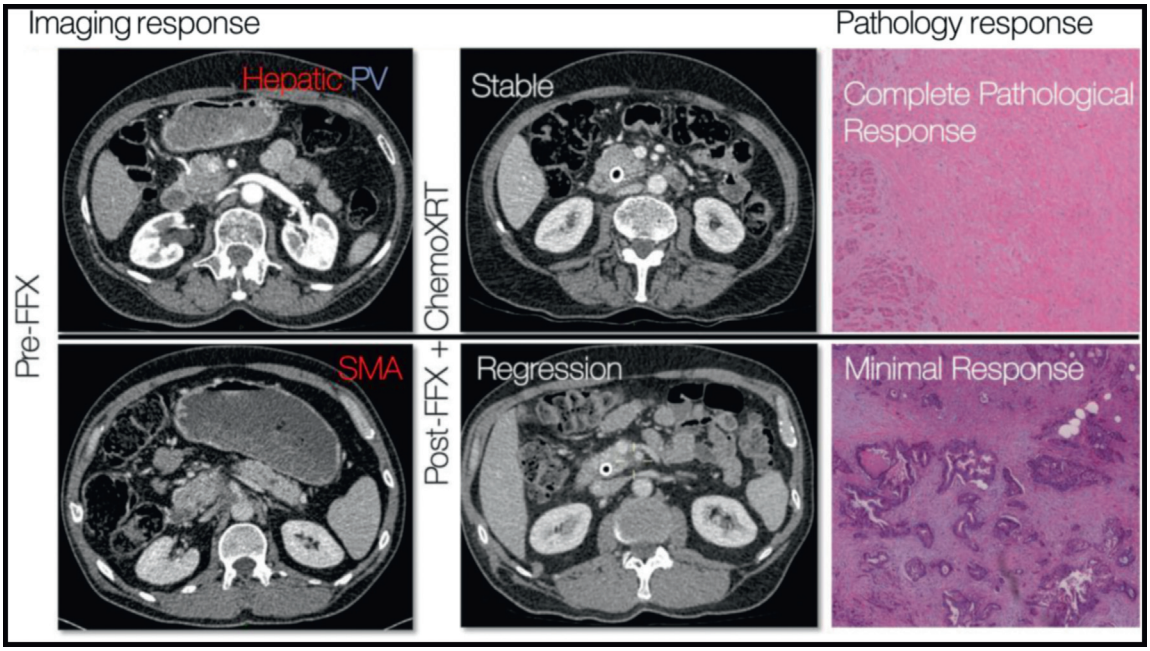

Figure 5 Challenges of interpreting post-neoadjuvant therapy CT scans as final histopathology response is not always representative of the degree of imaging response.

undergo resection without prohibitive complications. However, it also highlighted that 25% of patients with NAT therapy did not progress to surgery because of disease progression or toxicity.

Further recently reported clinical trials investing the role of neoadjuvant therapy for resectable PDAC include the NorPACT phase 2 trial (NCT02919787),[19] which failed to show a survival benefit from neoadjuvant FOLFIRINOX in resectable PDAC compared with upfront surgery. This study highlighted the challenges of implementation of neoadjuvant FOLFIRINOX strategies. A similar format is being tested in the Alliance A021806 trial (NCT04340141) comparing perioperative mFOLFIRINOX and adjuvant mFOLFIRINOX.

LAPC

LAPC is a non-metastatic yet non-operable disease at diagnosis, with only approximately 20% of patients likely to have sufficient tumour response from NAT to become eligible for successful surgical resection, however this may require complex venous or arterial reconstruction and therefore only fit patients with stable Ca19-9 are suitable (Figure 2). To achieve control, initial treatment generally consists of chemotherapy, mFOLFIRINOX or gem/nab-paclitaxel. The role of radiotherapy in this setting remains controversial with the SCALOP trial demonstrating superiority of capecitabine combined with radiotherapy compared with gemcitabine combination.[20]

Surgery

Pancreaticoduodenectomy or Whipple's procedure is required for tumours in the pancreatic head while neck, body, and tail tumours require a distal pancreatectomy. Pancreaticoduodenectomy includes resection of the duodenum, gallbladder, bile duct and head of the pancreas with peri-pancreatic lymph nodes, antrectomy in a 'classic' Whipple, or the pylorus may be left in situ in the case of 'pylorus-preserving' pancreaticoduodenectomy (Figure 6). Pancreatic reconstruction is most commonly a 2-layer duct to mucosa pancreaticojejunostomy with at least a single drain placed close to this anastomosis. While the vast majority are performed open, minimally invasive laparoscopic, or robotic assisted approach can be employed. The latter is gaining traction although a significant learning curve must be overcome to achieve parity with open resection. Following neoadjuvant treatment, dense fibrosis can generate an incredibly hostile operative environment which can be difficult to distinguish from tumour infiltration.

En bloc resection and reconstruction of the portal vein/SMV in patients with tumour invasion can be used to obtain a margin-negative resection. It can be performed safely if well planned and experienced pancreatic or vascular surgeons are involved. This undertaking results in a similar prognosis as in patients whose tumours do not invade the vein and is standard therapy for patients with BRPC if necessary.

An SMA first approach is an increasingly adopted strategy to devascularize the head of the pancreas prior to venous transection and is particularly useful in the post-neoadjuvant setting.

The challenge of pancreatic surgery is often the result of the postoperative morbidity. Postoperative pancreatic fistula (POPF) is the most significant complication due to the added risk of sepsis from undrained collection, resulting in haemorrhage (GDA pseudoaneurysm). Unless recognized and treated early they are associated with significant mortality.

The ISGPS has defined POPF as drain amylase on day 3 or later being greater than 3 times that of the serum level graded in severity from Grade A to C. A Fistula Risk Score system has been devised to predict likelihood of POPF. Variables include gland texture, pathology, pancreatic duct diameter and blood loss.[16]

Vital to optimal surgical outcomes has been development of a multidisciplinary management approach including early integration with clinical nurse specialist care, surgical 'fast-track' for

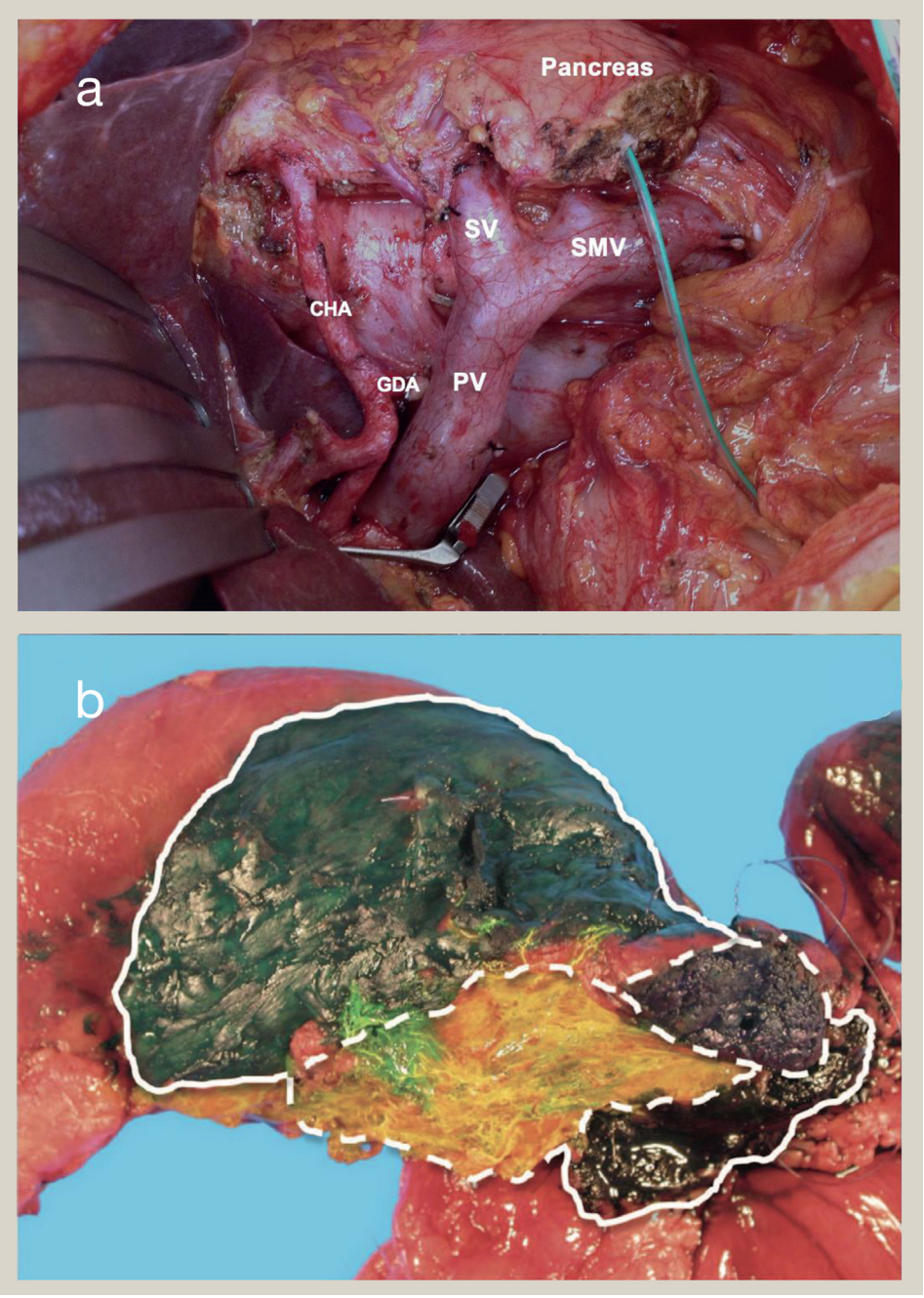

Figure 6 (**a**) Intraoperative view following resection of pancreaticoduodenectomy specimen. Transected pancreas with catheter in small pancreatic duct, bull-dog clip on transected common hepatic duct. PV – portal vein; SMV – superior mesenteric vein; CHA – common hepatic artery; GDA – gastroduodenal artery (transected). (**b**) Inking of the specimen clearly identifies the medial resection margin including the SMV groove (yellow), which lies below the pancreatic transection margin (blue) and separates the posterior resection margin (black) from the anterior pancreatic surface (green).

jaundiced patients, pre-habilitation strategies including physiotherapy and occupational therapy input, anaemia and nutritional optimization (including pancreas enzyme replacement therapy, enhanced recovery after surgery protocols and increasing use of patient-reported outcome measures to enhance quality of life. Centralization of cancer services over the last decade has demonstrated the best outcomes are attained by high-volume surgeons who perform more than 20 pancreaticoduodenectomy procedures per year. The Dutch pancreas group have reported not only a reduction in perioperative mortality following pancreaticoduodenectomy but also an increase in the number of patients resected along with improved overall survival in high-volume centres.

The reasons underlying this improvement are multifactorial, with the multidisciplinary infrastructure present in large academic centres key to the improved postoperative outcomes described, including specialized anaesthetists, gastroenterologists and radiologists along with established postoperative care pathways present in high-dependency and intensive care units. Nursing and medical staff are primed for early identification of complications

with rapid management thereafter (e.g. CT angiogram if blood present in drain).

Supportive care approaches for pancreatic cancer

Unfortunately, only 20% of patients with a diagnosis of PDAC will receive resection and therefore best supportive care by a multidisciplinary team consisting of clinical nurse specialists, dieticians, oncologists, palliative care, surgeons and endoscopists should be integrated with therapeutic management of PDAC to maximize length of life, quality of life, and most importantly symptom control. Focus should be given to psychosocial requirements, thrombosis prevention, nutrition, pancreatic endocrine and exocrine insufficiency and analgesia for all patients with any stage of disease.

Biliary drainage

While small anatomically resectable PDAC, clear of all vessels, can undergo upfront resection or 'fast track' resection, these represent 10%–20% of the patients referred. Even amongst those patients, only a fraction are suitable for surgery due to frailty, comorbidity, very elevated bilirubin, coagulopathy, or malnourishment. Biliary decompression usually via an endoscopic route is required for temporization and optimization prior to definitive treatment for most symptomatic patients.

A landmark multicentre RCT compared outcomes of upfront resection with stenting followed by delayed surgery within 6 weeks.[17] The complication rate was significantly higher in the biliary drainage group (74%) than the early surgery group (39%). Whilst the surgery related complication rate was similar between groups, there was a high-risk of ERCP complications (46%). This study employed plastic stents which are now less commonly employed in favour of covered self expanding metallic stents (SEMS), which are associated with a lower incidence of cholangitis and rarely require replacement particularly with the increased utilization of neoadjuvant algorithms. When the bile duct cannot be cannulated endoscopically, percutaneous drainage is an option, with subsequent internalization to provide palliation.

Advanced cases of pancreatic cancer at the head, neck and uncinate process can present with gastric outlet obstruction. Treatment includes palliative gastrojejunostomy or endoscopic stenting, the choice being dependent on fitness, prognosis, and anatomical factors. Although there has been a trend for patients who have an expected favourable prognosis being offered surgery, recently endobiliary metallic stent placement has been shown to have noninferior efficacy and greater durability relative to gastrojejunostomy enabling shorter time to palliative chemotherapy.[21]

For patients with metastatic pancreatic cancer, a good performance status and adequate biliary drainage, should be offered palliative chemotherapy in the form of FOLFIRINOX.[22] A potentially less toxic alternative is gemcitabine/nab-paclitaxel, a regimen that has been shown to improve median survival in patients with reduced performance status.[23] However, gemcitabine/cisplatin should be offered in the presence of BRCA/PALB mutations. Gemcitabine monotherapy offers some improved survival benefit, but careful consideration should be given to treatment if performance is limited. While previous trial evidence was based on unselected therapy allocation, in contrast, the POLO (Pancreas Olaparib Ongoing) trial validated a biomarker, germline BRCA1/2 variation, prompting the US FDA approval of the $PARP_{inh}$ olaparib. The drug or placebo was administered as a maintenance treatment in patients with a germline BRCA1/2 variation and metastatic PDAC following initial platinum-based chemotherapy and was approved based on a progression-free survival benefit, however no difference in overall survival was evident.[2]

There is minimal evidence for survival benefit of 2nd line therapy if performance status is maintained and careful consideration should be given for clinical trial recruitment if available.

Surveillance

The value of routine surveillance after resection of PDAC remains unclear, and expert guidelines offer conflicting recommendations with CT and Ca19-9 on an annual basis being a common strategy. A recent meta-analysis suggested that surveillance after resection for PDAC appears to detect more disease at an asymptomatic stage. Data from these non-randomized trials also suggest that treatment rates and survival may be superior in patients where recurrence is detected when asymptomatic.[24] Early confirmation of recurrence may allow 2nd line chemotherapy options or recruitment to trial protocols. Following pancreaticoduodenectomy, up to 75% of patients suffer exocrine dysfunction and 25% develop diabetes mellitus, therefore surveillance provides opportunity to optimize for insufficiency and instigate dietician input.

Future directions

Tremendous progress in our understanding of PDAC has been achieved in the last 5 years. It is envisaged that soon transcriptomic subtype, in addition to genomic characterization, will be determined preoperatively and facilitate patient centred algorithms to improve outcomes for patients with all stages of PDAC. There features have potential to personalize both treatment allocation and prognosis. Molecular aberrations, including *KRAS* will be increasingly targeted in combinatorial strategies with systemic chemotherapy and drugs focused on the immune tumour microenvironment. Ultimately, surgery may be a less common treatment modality, reserved for only those patients with definite biologically localized disease for whom it will bring hope of long-term survival. ◆

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Practice points

- Established risk factors including cigarette smoking, elevated BMI, diabetes mellitus and alcohol excess are significant modifiable risk factors for PDAC
- The 2021 National Comprehensive Cancer Network (NCCN) guidelines recommended all patients with a new diagnosis of PDAC should undergo germline testing with a multi-gene panel including BRCA1/2, ATM, MLH1, MSH2, MSH6, and PMS2
- Key investigations for patients with PDAC include Ca19-9 and a CT pancreas protocol. EUS/FNB is used for tissue acquisition, although postprocedural pancreatitis (<2%) can preclude timely treatment
- Recent advances in transcriptome molecular pathology and classification (squamous and classical pancreatic) and genomic (DNA damage repair pathway) profiling of PDAC have affected clinical practice
- Vascular staging defines each case as resectable PDAC, borderline resectable PDAC, or locally advanced PDAC based on the degree of tumour contact and invasion into the superior mesenteric/portal vein, hepatic artery, or coeliac vasculature
- The benefits of FOLFIRINOX for patients with metastatic disease are now being realized in the adjuvant setting and potentially in the neoadjuvant space, coupled with improved understanding of the impact of treatment sensitive molecular subgroups
- An SMA-first approach is an increasingly adopted strategy to devascularize the head of the pancreas prior to venous transection and is particularly useful in the post-neoadjuvant setting
- Postoperative pancreatic fistula is the most significant complication due to the added risk of sepsis from undrained collection, resulting in haemorrhage (GDA pseudoaneurysm). Unless recognized and treated early, they are associated with significant mortality