Pancreatic cancer

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Pancreatic cancer is frequently a lethal disease with an aggressive tumour biology often presenting with non-specific symptoms. Median survival is approximately 4 months with a 5-year survival of 13%. Surveillance is recommended in individuals with familial pancreatic cancer, specific mutations, and high-risk intraductal papillary mucinous neoplasm, as they are at high risk of developing pancreatic cancer. Chemotherapy combined with surgical resection remains the cornerstone of treatment. However, only a small subset of patients are candidates for surgery. Multi-agent chemotherapy has improved survival in the palliative setting for patients with metastatic disease, as (neo) adjuvant and induction therapy have in patients with borderline resectable and locally advanced pancreatic. Given that pancreatic cancer is predicted to become the second leading cause of cancer-related death by 2030, novel therapies are urgently needed.

Introduction

Pancreatic ductal adenocarcinoma (hereafter: pancreatic cancer) is a lethal disease for most patients with a reported median overall survival of 4 months across all stages of disease.[1,2] This poor survival is driven by aggressive tumour biology and the condition's asymptomatic nature, often resulting in late clinical presentation.[3] As a consequence, just more than half of patients with pancreatic cancer present with metastatic disease at diagnosis.[1] Early systemic spread and the insufficient effect of systemic therapies make systemic disease control challenging, even in patients presenting with radiologically localised disease. Despite the dismal prognosis and small improvements in survival for individuals with pancreatic cancer,[4] the 5-year overall survival has increased over the last 30 years from 4% to 13%.[1] This change is mostly due to improved oncological therapies, surgical techniques, and centralisation of care.[5,6]

Epidemiology

Among all cancers, pancreatic cancer ranks 12th in incidence and 6th in cumulative mortality.[7] Pancreatic cancer is predicted to become the second leading cause of cancer-related deaths in the USA by 2030.[8] The global lifetime risk of developing pancreatic cancer is 0·89% (95% CI 0·88–0·89), ranging from 0·15% (0·13–0·18) in middle Africa to 2·06% (2·04–0·08) in western Europe. The global lifetime risk of death from pancreatic cancer is 0·85% (0·85–0·85).[9] The age-standardised incidence of pancreatic cancer has gradually increased from 6·3 to 6·6 per 100 000 between 2010 and 2019, driven by countries with a middle or low sociodemographic index.[10] The incidence of pancreatic cancer is increasing among young adults with a global age-standardised incidence of 0·2% among adolescents and young adults aged 15–39 years,[11,12] influenced by the growing prevalence of obesity.[13]

Pathogenesis

Pancreatic cancer is the most common solid tumour of the pancreas, comprising more than 95% of all pancreatic neoplasms.[14] This type of cancer originates from normal glandular epithelium that changes into precursor lesions and ultimately invasive cancer.

Approximately 95% of these tumours arise from precancerous lesions called pancreatic intraepithelial neoplasias.[15] Other precursor lesions are pancreatic cysts, including intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. In about half of patients with pancreatic cancer and a concomitant IPMN, the invasive tumour is not derived from IPMN.[15,16] In the general population, pancreatic cysts are estimated to occur in 16% (95% CI 13–18) of individuals, and IPMN is the most common and has the highest risk of malignant transformation.[17] IPMNs with low-risk features has a cumulative incidence of malignant transformation of 8% (4–12) at 10 years, although the risk can be up to 25% (15–36) for patients with high-risk features.[18]

Multiple molecular alterations are observed in pancreatic cancer, which involve activation of oncogenes, inactivation of tumour suppressor genes, and alterations in DNA damage repair genes and homologous repair deficiency genes.[19] Tumorigenesis is entirely somatic in 91% of patients, whereas germline mutations are found in 9% of individuals.[20] The most common somatic mutations are *KRAS* (~88%), *TP53* (61–74%), *CDKN2A* (16–44%), and *SMAD4* (20–22%).[21] The major genetic event in the development of pancreatic ductal adenocarcinoma is the somatic *KRAS* oncogene mutation,[22] which is observed in more than 90% of patients with low-grade pancreatic intraepithelial neoplasia.[23] The *KRAS* mutation remains active during the progression from epithelial cell to invasive cancer, contributing to the processes of proliferation, survival, migration, and invasion. By its effect on the tumour stroma and microenvironment, the KRAS protein plays an important role in the process of metastatic spread and chemotherapy resistance.[22]

Transcriptomic analyses have identified several unique subtypes of pancreatic cancer,[3] for which the categorisation into basal-like and classical subtypes seems to be the most relevant with regard to prognosis and chemotherapy response.[24] Basal-like tumours are enriched for epithelial-to-mesenchymal transition, cell cycle progression, and TGF-þ signalling, and are associated with worse prognosis.[25] Epithelial-mesenchymal transition has been implicated in reprogramming of cancer cells. The

Search strategy and selection criteria

A literature search was done during April 19–22, 2024, on PubMed, Embase, and Cochrane Library, with the aim to identify the most recent English literature with the highest level of evidence published since Jan 1, 2010. Systematic search strategies were designed in collaboration with a clinical librarian, focusing on pathogenesis, risk factors, screening, surveillance, imaging, pathology, biliary stenting, treatment of localised and metastatic pancreatic cancer, and alternative ablative therapies. For all separate search strategies, search terms were: "pancreatic neoplasms", "pancreatic cancer", "pancreatic tumour", "pancreatic ductal adenocarcinoma", "pancreatic adenocarcinoma", "pancreas cancer', 'pancreas neoplasm", "pancreas carcinoma", "pancreas adenocarcinoma", and "pancreas tumour". For the section on pathogenesis, the basic search strategy was extended with the following terms: "molecular", "genomics", "proteomics", "multiomics", "subtyping", "PDAC tumor microenvironment", "pancreatic cancer epigenome", and "tumour associated macrophage". For the section Risk factors, the basic search strategy was extended with the following terms: "smoking", "pancreatitis", "diabetes mellitus", "Peutz–Jeghers Syndrome", "new-onset diabetes", "obesity", "familial pancreatic cancer', "hereditary pancreatitis", "familial melanoma", "lynch syndrome", "intraductal papillary mucinous neoplasms", "mucinous cystic neoplasms", "high-risk individuals", "alcohol", and "lifestyle". In addition to this latter search strategy on risk factors, the search strategy for screening and surveillance, was extended with the following terms: "early detection", "early diagnosis", and "screening". For the section on imaging, the basic search strategy was extended with the following terms: "magnetic resonance imaging", "endosonography", "positron emission tomography", "multidetector computed tomography", "diagnostic imaging", "computed tomography", "endoscopic ultrasonography", "PDAC CT", "accuracy", "staging", "malignancy", "texture analysis", "resectability assessment", and "differentiation". For the section on pathology, the basic search strategy was extended with the following terms: "aspiration", "biopsy", "tissue acquisition", "pancreatic", and "biliary stricture". To identify evidence about endoscopic retrograde cholangiopancreatography, the following terms were used: "endoscopic retrograde cholangiopancreatography", "post endoscopic retrograde cholangiopancreatography", "ERCP", "postoperative complications", "complication rate", "pancreatitis", "accuracy", "pancreas malignancy", and "risk". The following terms were used to identify evidence about biliary drainage: "stent", "biliary stricture", "biliary obstruction", "pancreatic neoplasm", "malignancy", "pancreatic", "cancer", "carcinoma", and "mass". For the section on treatment of metastatic pancreatic cancer, the basic search strategy was extended with the following terms: "drug therapy", "antineoplastic combined chemotherapy", "antineoplastic agent", "cancer chemotherapy", "chemotherapy", "metastatic", "metastasis", "metastases", "advanced", and "survival". For the section on treatment of localised pancreatic cancer, the basic search strategy was extended with the following terms: "neoadjuvant therapy", "induction chemotherapy", "preoperative chemotherapy", "chemoradiotherapy", "preoperative chemoradiotherapy", "adjuvant chemotherapy", "adjuvant chemoradiotherapy", "antineoplastic combined chemotherapy protocols", "resectable", "borderline", "irresectable", "irresectability", "unresectable", "unresectability", "borderline resectable", "locally advanced", "resected", and "resection". For the section local ablative therapy, the basic search strategy was extended with the following terms: "ablation techniques", "electrochemotherapy", "ablation", "ablative", "induction chemotherapy", "resectable", "borderline", "irresectable", "irresectability", "unresectable", "unresectability", "borderline resectable", "locally advanced", "localized", "advanced stages", and "resection". From the identified literature, reference lists and citation records were screened for other relevant literature that was published before Jan 1, 2010, or published after the literature search from April 23, 2024, until Dec 9, 2024.

transition allows these cells to escape into the circulation and facilitates immune evasion, and metastasis.[26]

Pancreatic cancer is characterised by desmoplastic stroma, mainly consisting of an extracellular matrix, vasculature, and cancer-associated fibroblasts. The desmoplastic stroma causes elevated intratumoural interstitial pressure, hampering chemotherapy delivery.[27] Pancreatic cancer cells extend along vessels, nerves, and collagen structures.[28] This extending of cancer cells explains the high rates of perineural (~62%) and lymphovascular (~54%) invasion, which are associated with worse overall survival.[29]

Risk factors

The rising age-adjusted incidence of pancreatic cancer suggests an increasing prevalence of risk factors,[30] in addition to an ageing global population.[31] Various modifiable lifestyle and heritable risk factors for pancreatic cancer are known (table 1).

Cigarette smoking is the leading modifiable risk factor of pancreatic cancer with a relative risk (RR) of 1·8 (95% CI 1·7–1·9%) compared with individuals who have never smoked.[34] The age-standardised proportion of all pancreatic cancer deaths attributable to smoking is 21% (95% CI 19–24%), followed by high fasting plasma glucose (9%, 95% CI 2–19%) and high BMI (6%, 95% CI 3—11%).[31] Smoking cessation mitigates the risk,[50] as illustrated by the smaller risk difference among former versus never smokers (RR 1·2, 95% CI 1·1–1·2)—longer smoking cessation time further reduces the risk.[34] Heavy alcohol consumption is associated with an increased risk for pancreatic

	Risk	Recommended surveillance
Modifiable risk factors		
Pancreatitis		
Acute pancreatitis*	SIR=172·8 (95% CI 54·9–544·7)[32]	None
Chronic pancreatitis	SIR=22·6 (95% CI 14·4–35·4)[33]	None
Cigarette smoking	RR=1·8 (95% CI 1·7–1·9)[34]	None
Heavy alcohol intake		
≥60 g/day (*vs* no alcohol intake)	RR=1·6 (95% CI 1·0–2·5)[35]	None
≥9 drinks/day (*vs* abstainers or occasional drinkers <1 drink/day)	OR=1·6 (95% CI 1·2–2·2)[51]	None
Diabetes†	RR=1·5 (95% CI 1·4–1·6)[37]	None
Metabolic syndrome	RR=1·3 (95% CI 1·2–1·5)[38]	None
BMI (for a 5-unit increase)	RR=1·1 (95% CI 1·1–1·1)[39]	None
Inherited risk factors		
Familial pancreatic cancer	SIR=4·9 (95% CI 4·0–5·9)[40]	Surveillance recommended for individuals who have at ≥1 first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer.[41] Initiate surveillance at 50–55 years of age or 10 years earlier than the youngest affected blood relative was diagnosed, whichever is earlier.[41]
Hereditary breast ovarian cancer syndromes		
BRCA1	RR=2·4 (95% CI 1·5–3·7)[42]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
BRCA2	RR=3·3 (95% CI 2·2–5·1)[42]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
PALB2	RR=2·4 (95% CI 1·2–4·5)[44]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
ATM	RR=6·5 (95% CI 4·5–9·5)[45]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *EPCAM* (Lynch syndrome)‡		
MLH1, *MSH2*, or *MSH6*	HR=8·6 (95% CI 4·7–15·7)[46]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
MLH1	OR=6·7 (95% CI 2·5–15·0)[47]	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
MSH2	OR=1·6 (95% CI 0·1–7·5)[47]‡	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
MSH6	OR=2·0 (95% CI 0·8–4·1)[47]‡	Surveillance recommended if ≥1 first-degree blood relative with pancreatic cancer.[41] The 2024 NCCN guideline recommends surveillance if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative.[41, 43]
TP53	RR=6·7 (95% CI 2·5–15·0)[47]	Surveillance is recommended if ≥1 first-degree or second-degree blood relative with pancreatic cancer.[43] Initiate surveillance at the age of 45–50 years or 10 years earlier than youngest pancreatic cancer-affected relative was diagnosed.[43]
CDKN2A (FAMMM)	OR=12·3 (95% CI 5·4–25·6);[47] cumulative incidence of 21% at 70 years[48]	Initiate surveillance at the age of 40 years or 10 years earlier than youngest pancreatic cancer-affected relative was diagnosed.[41,43]
STK11/*LKB1* (Peutz-Jeghers syndrome)	RR=132 (95% CI not reported)[49]	Initiate surveillance at the age of 40 years or 10 years earlier than youngest pancreatic cancer-affected relative was diagnosed, whichever is earlier.[41] The 2024 NCCN guideline recommends surveillance from age 30–35 years.[43]
PRSS1 (hereditary pancreatitis); other genes: *SPINK1*, *CTRC*, *CFTR*, and CPA1	SIR=63·4 (95% CI 45·4–88·5)[33]	Initiate surveillance at the age of 40 years or 20 years after the onset of pancreatitis, whichever is earlier.[41]

ATM=ataxia telangiectasia mutated. CDKN2A=cyclin-dependent kinase inhibitor 2A. FAMMM=familial atypical multiple mole melanoma. HR=hazard ratio. NCCN=National Comprehensive Cancer Network. OR=odds ratio. PALB2=partner and localised breast cancer 2. *PRSS1*=cationic trypsinogen gene. *STK11*=serine threonine kinase 11 gene. RR=relative risk. SIR=standardised incidence ratio. *Acute pancreatitis is associated with pancreatic cancer, more likely as first presentation of the disease instead of being a risk factor to develop pancreatic cancer. †New-onset diabetes is associated with pancreatic cancer, more likely as an (early) symptom than being a risk factor to develop pancreatic cancer. ‡2024 NCCN guideline recommends surveillance for individuals with DNA mismatch repair genes *MLH1, MSH2, MSH6, or EPCAM*.

Table 1: **Main risk factors and surveillance strategies**

cancer.[35,51] The increased risk might attenuate after 10 years of abstinence.[36]

Diabetes is considered to be another risk factor for pancreatic cancer (RR 1·5, 95% CI 1·4–1·6).[37] However, diabetes can also be a prodrome of pancreatic cancer (ie, type 3c or pancreatogenic diabetes).[52] The fact that diabetes can be both a risk factor and a prodome of pancreatic cancer is illustrated by a possibly stronger association of new-onset diabetes (ie, ≤3–4 years) with pancreatic cancer compared with long-standing diabetes (ie, >3–4 years).[53] Elevated HbA1c in individuals with new-onset diabetes is associated with an increased risk of pancreatic cancer.[54] Even in individuals with normal glucose concentrations, increased fasting glucose concentrations are associated with an increased risk of pancreatic cancer.[55] Metabolic syndrome is associated with an increased risk for pancreatic cancer (RR 1·3, 95% CI 1·2–1·5%),[38] in which the risk increases with the individual having more constituent factors.[56,57] Recovering from metabolic syndrome is associated with a reduction of this increased risk.[58]

Pancreatitis is established as a strong risk factor for pancreatic cancer, including chronic pancreatitis (standardised incidence ratio [SIR] 22·6, 95% CI 14·4–35·4), with an increasing cumulative incidence during its disease course.[33] Contrastingly, in patients with acute pancreatitis, the risk of pancreatic cancer is the highest within the first 2 months from symptom onset, as the condition might be a first symptom of pancreatic cancer (HR 172·8, 95% CI 54·9–544·7).[32] The risk gradually decreases over time until the risk disappears 10 years after diagnosis.[32,59]

Heritability is suspected in about 21–36% of patients with pancreatic cancer, although the actual rate is uncertain.[60,61] Familial pancreatic cancer (ie, >1 first-degree relative) is a strong risk factor for pancreatic cancer (SIR 4·9, 95% CI 4·0–5·9).[40] The risk of developing pancreatic cancer is even higher in the case of more affected first-degree family members (≥3 first-degree relatives SIR 10·8, 95% CI 4·7–10·1) compared with having one (SIR 3·46, 95% CI 2·52–4·76) or two (SIR 5.44, 95% CI, 4.07-7.26) first-degree relatives.[40] Furthermore, the risk of developing pancreatic cancer is higher in individuals having a family history of young-onset (ie, <50 years of age) pancreatic cancer.[40] However, germline mutations are found in only about 10% (95% CI 8–12%) of individuals with familial pancreatic cancer.[62] Individuals with a germline mutation have a higher risk of developing pancreatic cancer compared with individuals with a positive family history alone.[63,64] Various mutations and genetic syndromes are associated with pancreatic cancer (table 1).

Screening and surveillance

Screening for pancreatic cancer in asymptomatic adults is not recommended given the low incidence and the absence of accurate screening modalities.[65] New-onset diabetes is being discussed as a possible indication for screening for pancreatic cancer.[66] Given the low standardised incidence ratio (1·5, 95% CI 1·4–1·6) of pancreatic cancer among individuals with new-onset diabetes together with low capacity of prediction models and the absence of evidence on the survival benefit, screening is currently not recommended.[67,68]

Genetic testing is recommended in individuals at high risk,[69] including people with Li–Fraumeni or Lynch syndrome, familial pancreatic cancer, or relatives with a known pathogenic mutation (table 1).[70,43] The 2024 National Comprehensive Cancer Network (NCCN) guideline emphasizes that patient counselling is crucial when surveillance is considered, considering the potential drawbacks (eg, uncertainty about the benefits, false-positive findings, and costs).[43]

Surveillance aims to detect high-grade precursors or pancreatic cancer at an early stage, generally started after an age of 50 years or 10 years earlier than the age of diagnosis in the youngest affected relative.[41] The recommended screening modalities are endoscopic ultrasonography (EUS) and MRI with magnetic resonance cholangiopancreatography (MRCP) once per year. The diagnostic accuracy of EUS and MRI in detecting high-grade dysplasia or early-stage pancreatic adenocarcinoma seems to be similar.[71] However, the value of MRI/MRCP in addition to EUS is debated.[64] Accurate liquid biomarkers are not available.[72]

In individuals at high risk of pancreatic cancer, the number of patients needed to screen (NNS) to detect a high-risk lesion with EUS or MRI is 135 (95% CI 88–303), although this number is lower in people with a pancreatic

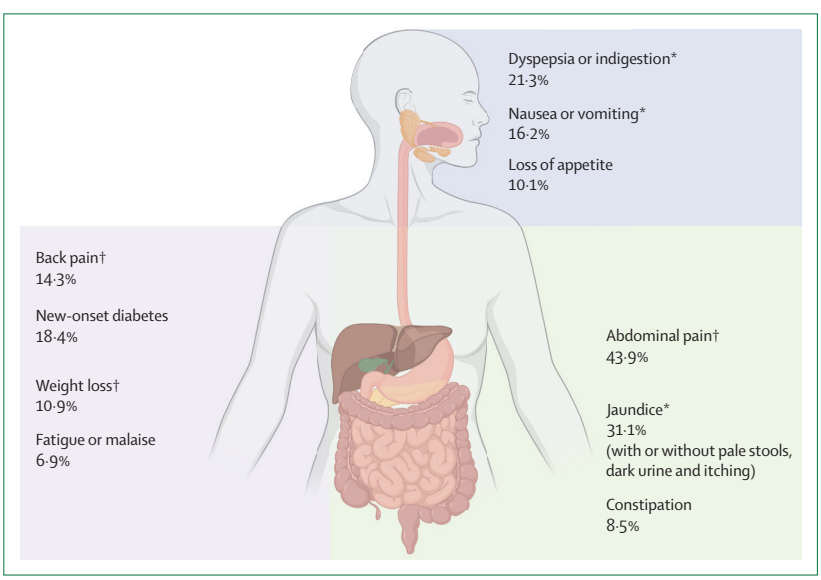


Figure 1: **Symptoms of pancreatic cancer**
Most common symptoms and signs of pancreatic cancer at diagnosis.[79-81] *These symptoms are more often seen in patients with pancreatic cancer located in the pancreatic body or tail compared with pancreatic head tumours. †These symptoms are more often seen in patients with pancreatic cancer located in the pancreatic head compared with pancreatic body or tail tumours.

cancer susceptibility mutation, particularly in individuals with hereditary pancreatitis (NNS=130), Peutz–Jeghers syndrome (NNS=71), and *CDK2NA* germline mutation (NNS=51).[73] Guidelines recommend surveillance for individuals with radiology-based IPMN diagnosis in the absence of an absolute indication for surgery, including radiological (eg, main pancreatic duct size, enhancing mural node size, and cystic growth) and clinical (eg, acute pancreatitis, diabetes de novo) features.[74,75] Individuals at high risk with screening-detected

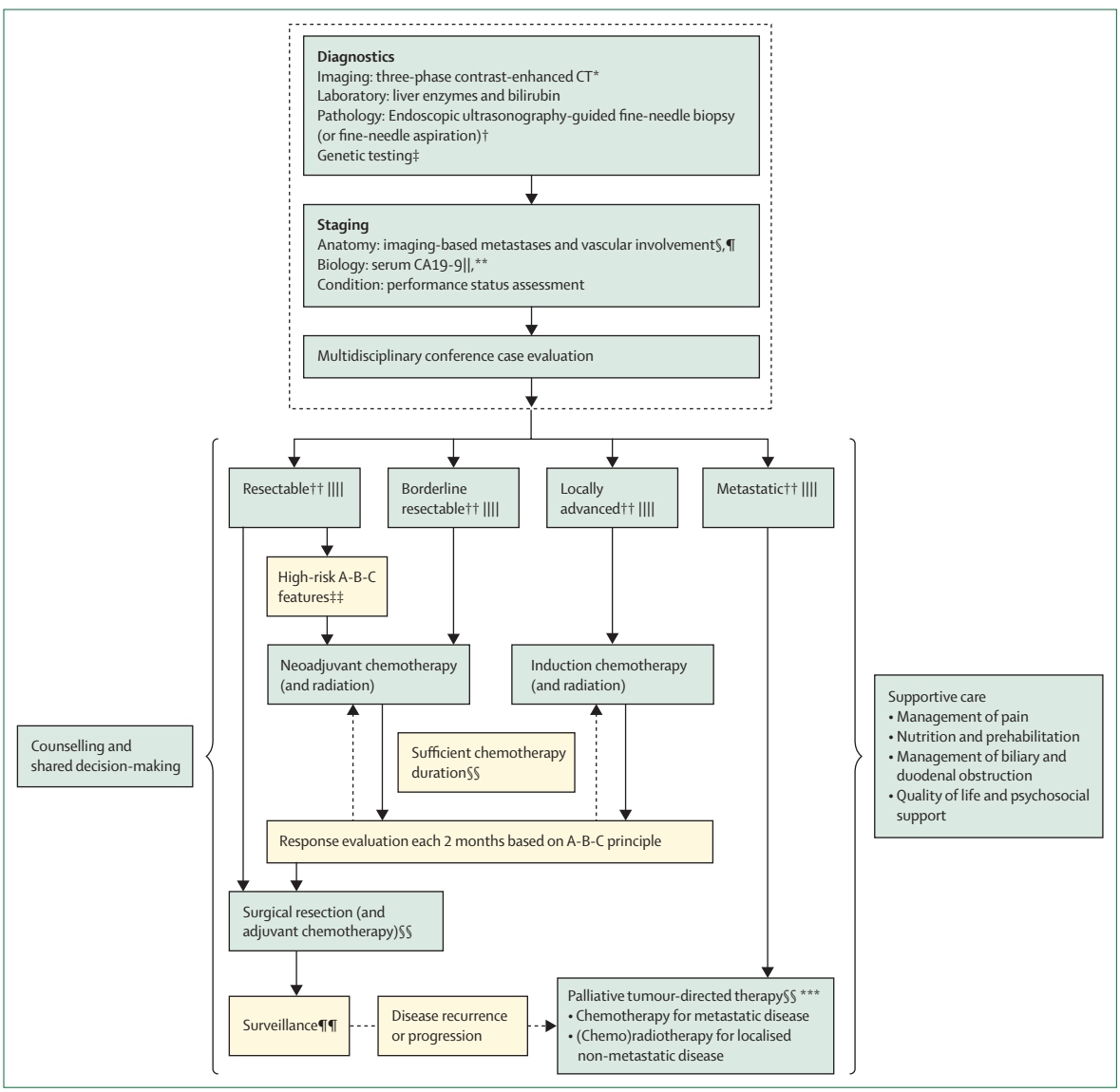


Figure 2: **Clinical workflow for patients with pancreatic cancer**

* Endoscopic ultrasonography (or MRI) should be performed if no mass is visible on three-phase CT or if there is a contraindication for contrast-enhanced CT. †Pathology-proven adenocarcinoma is only required if chemotherapy is considered or if imaging is inconclusive for benign or malignant disease. ‡Genetic testing is indicated in all patients diagnosed with pancreatic cancer, particularly on *BRCA1* or *BRCA2* and microsatellite instability. §The National Comprehensive Cancer Network (NCCN) resectability criteria and American Joint Committee on Cancer Tumour Node and Metastasis classification are mostly used for staging. ¶Liver-MRI, fluorodeoxyglucose positron emission tomography, and staging laparoscopy can be considered in patients with high risk for metastatic disease. ||In case of hyperbilirubinemia, serum carbohydrate antigen 19-9 (CA 19-9) should be measured again after biliary drainage if indicated to obtain an adequate serum CA19-9 level. ** If non-elevated serum CA19-9, alternative biological markers are serum CEA, serum CA-125, and fluorodeoxyglucose positron emission tomography. ††Based on the anatomy-based NCCN resectability criteria (figure 3). ‡‡According to the 2024 NCCN guideline, defined as large primary tumour, large regional lymphadenopathy, markedly elevated serum CA19-9, or excessive weight loss. §§A total of 6 months chemotherapy should be intended. This amount of 6 months chemotherapy is distributed perioperatively in patients who undergo surgery. ¶¶Various follow-up strategies are used, but level-1-evidence about the value of active postoperative surveillance is awaited. ||||Regardless of the resectability status (ie, resectable, borderline resectable, locally advanced, or metastatic), palliative tumour-directed therapy or best-supportive care alone can always be considered based on refractory impaired functional status and patient's preference. ***In patients with locoregional recurrence after surgical resection that is radiologically non-progressive after palliative chemotherapy, locoregional treatment with radiation can be considered.

pancreatic cancer are more likely to have early-stage disease at diagnosis compared with the general population of patients diagnosed with pancreatic cancer. This difference possibly leads to a prolonged overall survival in patients diagnosed with pancreatic cancer revealed via screening.[76] Annual imaging does not preclude failure of surveillance.[77] Almost half of new lesions appear at a median of 11 months from last EUS or MRI/MRCP.[78]

Diagnosis

Clinical symptoms

Pancreatic cancer typically causes non-specific symptoms, resulting in a diagnostic delay.[79] Figure 1 shows the incidence of clinical symptoms and signs.[79–81] The only high-risk feature with a positive predictive value of more than 1% is painless jaundice: 13% (95% CI 8–27%) at an age of at least 40 years and 22% (14–52%) at an age of at least 60 years.[80,82] Painless jaundice occurs among 71% of patients with a pancreatic head tumour.[83] Given the low incidence of jaundice in the early phase of the disease course and the non-specific symptoms, it is challenging for primary care physicians to decide on appropriate timing for further investigations.[79] Pancreatic cancer should be considered in differential diagnosis warranting further investigation in people with concomitant conditions including a positive family history of pancreatic cancer,[40] new onset diabetes,[84] or acute or recurrent pancreatitis (figure 2).[32,85]

Diagnostics

Imaging

The imaging modality of choice in individuals with suspicion of pancreatic cancer is a contrast-enhanced three-phase (ie, pancreatic, arterial, and portal venous phase) computed tomography (CT),[69,70] which has a diagnostic accuracy of 89% (95% CI 85–93).[86] Pancreatic cancer in the head often causes dilatation of both the common bile duct and main pancreatic duct (ie, double duct sign).[87] Differentiating between pancreatic cancer and other periampullary carcinomas can be challenging, as illustrated by the 13–32% preoperative misdiagnosis risk among resected pancreatic head adenocarcinomas.[88,89] Pancreatic adenocarcinoma typically appears as a hypodense lesion on CT, in contrast with hyperdense pancreatic neuroendocrine tumours. However, about 5–17% of lesions are isoattenuating on CT, particularly smaller lesions.[90] In the absence of a visible mass, other key findings raising suspicion for pancreatic cancer include pancreatic duct dilatation with an abrupt cutoff and glandular atrophy.[91] MRI[69,70] or EUS[92] can be performed in individuals with a suspected isoattenuated mass or patients with a contraindication for contrast-enhanced CT. MRI aids in characterising liver lesions that are indeterminate on CT and detecting liver metastases that are not visible on CT, given the difference in sensitivity of 83% (95% CI 74–88) for MRI versus 45% (21–71) for CT.[93] Positron emission tomography (PET) can be considered to exclude distant metastases in patients with inconclusive CT or MRI or in individuals at high risk of metastatic disease (eg, highly elevated serum carbohydrate antigen 19–9 [CA19–9], regional lymphadenopathy, and large primary tumour).[69,70,94]

Pathology

In patients with suspected metastatic pancreatic cancer, pathology from possible metastasis should be obtained.[69,70] In case of a localised pancreatic mass (ie, no metastases seen on imaging), pathology is needed when imaging cannot differentiate between benign or malignant disease, or in patients for whom chemotherapy is considered as first-line treatment.[69,70] EUS with fine needle biopsy is preferred over fine needle aspiration,[69,70] considering the higher diagnostic accuracy of fine needle biopsy compared with fine needle aspiration (85%, 95% CI 83–87% *vs* 80%, 95% CI 78–83%).[95]

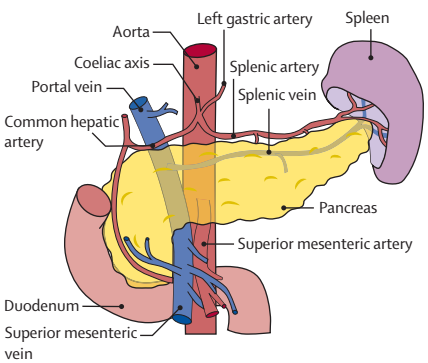
Genetic testing for inherited mutations is recommended by the 2024 NCCN guideline for all patients diagnosed with pancreatic cancer.[70] When tumour-directed treatment is considered in patients with locally advanced and metastatic disease, molecular profiling is recommended to investigate the presence of actionable somatic mutations with therapeutic consequences.[69,70] These include entities such as *BRCA1, BRCA2,* DNA mismatch repair deficiency (eg, *MLH1, MSH2, MSH6*), and *KRAS* wild type (eg, fusion genes such as *NRG* and *NTRK*), despite their low incidences.[21]

Laboratory

Serum CA19–9 (and carcinoembryonic antigen), liver enzymes, and bilirubin concentrations are measured in patients with (suspected) pancreatic cancer. The biomarker serum CA19–9 is routinely used in patients with the suspicion of pancreatic cancer.[69,70] However, serum CA19–9 is inaccurate for establishing a diagnosis of pancreatic cancer, either in screening or to differentiate from other pathologies, because elevated serum CA19–9 can be caused by other benign and malignant pathologies (eg, biliary obstruction, pancreatitis).[96] Moreover, about one-third of patients with pancreatic cancer have non-elevated serum CA19–9 (ie, ≤37 U/mL), including 8% of patients who are non-secretors of CA19–9 (ie, <2 U/mL).[97] Liquid biomarkers with a higher diagnostic accuracy than serum CA19–9 are not available.[72] Despite its limitations for diagnostic purposes, serum CA19–9 is valuable in patients with proven pancreatic cancer as an indicator for micrometastatic disease, risk assessment for occult metastases, and treatment response evaluation.[98,99]

Staging laparoscopy

Staging laparoscopy can be done before initial treatment with chemotherapy or before surgery to detect occult



	Superior mesenteric artery	Coeliac axis	Common hepatic artery	Portomesenteric venous axis
Resectable	No involvement	No involvement	No involvement	≤180° contact without vein contour irregularity
Borderline resectable	≤180° contact	≤180° contact	Any contact without extension to CA or hepatic artery bifurcation*	≤180° contact with vein contour irregularity OR >180° contact without vein contour irregularity or thrombosis, but reconstructable OR Any contact with inferior vena cava
Locally advanced	>180° contact	>180° contact OR any contact of the CA with aortic involvement	Any contact with extension to CA and/or hepatic artery bifurcation	No reconstructable involvement due to tumour contact or occlusion (either due to tumour or bland thrombus)
Metastatic	Distant metastatic disease, regardless of vascular involvement of the primary tumour			

***Figure 3*: Anatomical staging of pancreatic cancer**
Resectability criteria according to the National Comprehensive Cancer Network (NCCN) guideline (version 2.2024)[70] CA=coeliac axis. *Solid tumour contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced common hepatic artery, and the origin of the replaced or accessory artery) and the presence and degree of tumour contact should be noted if present, as it may affect surgical planning.

metastases and thus avoid unnecessary local therapy including surgery.[100] Staging laparoscopy's yield to detect occult metastases has decreased from about 20% in 1988–2006[101] to 15% in 2009–21[102–104] most likely due to improved cross-sectional imaging. Staging laparoscopy should especially be considered in patients with high-risk features[69,70] (eg, indeterminate extra-pancreatic lesions, strongly elevated serum CA19–9, large tumours, pancreatic body or tail cancer, borderline and locally advanced cancer, and ascites).[103,104]

Staging

Approximately 57% of patients with pancreatic cancer present with metastatic disease at the time of diagnosis,[105] with cancer predominantly located in the liver (75–80%), peritoneum (13–30%), lung (15–18%), and extra-regional lymph nodes (12%).[106] In the absence of metastases, the primary tumour is anatomically staged as resectable (RPC), borderline resectable (BRPC), or locally advanced (LAPC), depending on the presence and extent of involvement of peripancreatic major vasculature including the superior mesenteric artery, coeliac axis, hepatic artery branches, and portomesenteric venous axis.[99] The resectability criteria according to the NCCN guideline are most commonly used.[70] Besides this mainly technical classification, the Tumour, Node, and Metastasis classification of the American Joint Committee on Cancer is used for prognostication, both based on imaging-based staging and after resection based on the histopathology.[107] For adequate assessment of vascular involvement, pancreas protocol contrast-enhanced three-phase CT is essential.[69,70] Moreover, the use of a standardised reporting template is important[69,70] because of high inter-observer variability.[108] Imaging for staging should be done within 4 weeks before initiation of treatment and before biliary drainage.[70]

Clinical staging can be further improved by considering not only the anatomical extent of the tumour, but also taking the tumour biology and patients' condition (A-B-C nomenclature) into account.[109–112] When serum CA19–9 concentrations are not elevated, serum carcinoembryonic antigen and CA–125 can be used.[113,114] In patients with cholestasis, serum CA19–9 should be measured after normalisation of bilirubin and close to the initiation of tumour-directed treatment for adequate staging and response evaluation after chemotherapy.

A nationwide observational cohort study including 688 patients with anatomically RPC treated with upfront surgery underlined the clinical relevance of including biology-based resectability criteria. Biology-based borderline resectable disease (ie, serum CA19–9 ≥500 U/mL) was associated with impaired overall survival.[115] This finding was confirmed by a bi-national observational cohort study[111] including 1835 patients with localised pancreatic cancer who started with a (modified) combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin (ie, [m]FOLFIRINOX) as first-line treatment. This study identified anatomical (ie, BRPC and LAPC), biological (ie, serum CA19–9 ≥500 U/mL), and conditional (ie, WHO performance status ≥1) factors at diagnosis as poor prognostic factors for overall survival, giving a range in 5-year overall survival from 5% in presence of the worst A-B-C prognosticators versus 5-year overall survival of 47% in presence of the most favourable A-B-C conditions.[111] This finding underscores the relevance of systematically assessing anatomical, biological, and conditional factors for optimisation of treatment decisions and patient

outcomes. Figure 3 presents the anatomical staging of pancreatic cancer.

Treatment

Treatment decision making is primarily driven by the stage of disease at diagnosis. Figure 2 shows the clinical workflow for patients with pancreatic cancer.

Metastatic pancreatic cancer

Palliative chemotherapy is the standard of care in patients with metastatic pancreatic cancer, with (m)FOLFIRINOX and gemcitabine-nab-paclitaxel as preferred regimens.[69,70] Table 2 shows key randomised controlled phase 3 trials on palliative chemotherapy regimens. Both (m)FOLFIRINOX and gemcitabine-nab-paclitaxel are superior to gemcitabine alone. Median and 1-year overall survival in the FOLFIRINOX group was 11 months (95% CI 9–13) and 48%, respectively, and 9 months (8–10) and 35% in the gemcitabine-nab-paclitaxel group, compared with a median and 1-year overall survival of about 7 months and 21–22% after gemcitabine alone.[116,117] Therefore, gemcitabine is only reserved for patients with a poor performance status.[116,117] A growing body of evidence suggests that some pancreatic cancer subtypes respond better to FOLFIRINOX, whereas others respond better to gemcitabine-based chemotherapy.[24,124–126] However, randomised trials confirming the clinical effect of these findings are not available.

The international NAPOLI-3 trial showed longer overall survival after NALIRIFOX (ie, 5-fluorouracil with leucovorin, liposomal irinotecan, and oxaliplatin) with a median overall survival of 11 months (95% CI 10–12) and 1-year overall survival of 46% (41–51), compared with a median overall survival of 9 months (8–11) and 1-year

	Population	Comparison	Conclusion
First-line treatment			
Conroy et al (2011)[116] PRODIGE4-ACCORD 11	342 patients with M1 pancreatic cancer, chemotherapy naive, from France	FOLFIRINOX *vs* GEM. In both arms, 6 months of chemotherapy was recommended for patients with response; primary endpoint: OS	In patients with M1 pancreatic cancer, first-line treatment with FOLFIRINOX is superior to GEM considering prolonged OS (median OS of 11 *vs* 8 months [p<0·001] and 1-year OS rate of 48% *vs* 21%), but with higher toxicity after FOLFIRINOX
Von Hoff et al (2013)[117]	861 patients with M1 pancreatic cancer, no previous chemotherapy for M1 pancreatic cancer, from North America, Europe, and Australia	GEM-NAB-PAC *vs* GEM. In both arms, chemotherapy was continued until RECIST progressive disease or unacceptable toxicity; primary endpoint: OS	In patients with M1 pancreatic cancer, first-line treatment with GEM-NAB-PAC is superior to GEM considering prolonged OS (median OS of 9 *vs* 7 months [p<0·001] and 1-year OS rate of 35% *vs* 22% [p<0·001]), but with increased rates of peripheral neuropathy and myelosuppression after GEM-NAB-PAC
Wainberg et al (2023)[127] NAPOLI-3	770 patients with untreated M1 pancreatic cancer from Europe, North and South America, Asia, and Australia.	NALIRIFOX *vs* GEM-NAB-PAC. In both arms, chemotherapy was continued until RECIST progressive disease or unacceptable toxicity; primary endpoint: OS	First-line treatment with NALIRIFOX is superior to GEM-NAB-PAC considering prolonged OS (median OS of 11 *vs* 9 months [p=0·036] and 1-year OS rate of 46% *vs* 40%) with a similar rate of serious adverse events. A comparison with FOLFIRINOX and a cost analysis is lacking
Second-line treatment			
Golan et al (2019)[119] POLO	154 patients with *BRCA1* or *BRCA2* with non-progressive disease after ≥ 4 months first-line platinum-based chemotherapy, from 12 countries	Maintenance olaparib *vs* placebo. The intervention was continued until RECIST progressive disease; primary endpoint: PFS	In patients with M1 pancreatic cancer and a germline *BRCA* mutation, maintenance therapy with olaparib following first-line platinum-based chemotherapy results in prolonged PFS (median PFS of 7 *vs* 4 months; p=0·004 and 1-year PFS rate of 34% *vs* 15%). However, olaparib did not result in prolonged OS (median OS of 19 *vs* 18 months [p=0·68]).
Wang-Gillam et al (2016)[120] NAPOLI-1	417 patients with disease progression including M1 after GEM-based chemotherapy, from Europe, North and South America, Asia, and Australia	Nanoliposomal irinotecan and 5-FU with leucovorin *vs* nanoliposomal irinotecan *vs* 5-FU with leucovorin. In both arms, treatment was continued until disease progression or intolerable toxicity; primary endpoint: OS	In patients with disease progression including M1 after first-line GEM-based therapy; second-line treatment with nanoliposomal irinotecan and 5-FU with leucovorin is superior to 5-FU with leucovorin considering prolonged OS (median OS of 6 *vs* 4 months [p=0·012]) with a manageable safety profile
De La Fouchardière et al (2024)[121] PRODIGE 65-UCGI 36-GEMPAX UNICANCER	211 patients who progressed during or within 3 months after first-line (m) FOLFIRINOX or were intolerant, with M1 disease, from France	GEMPAX *vs* GEM. In both arms, chemotherapy was continued until disease progression, limiting toxicity, or patients' decision; primary endpoint: OS	In patients with M1 pancreatic cancer, who progressed during or within 3 months after completing first-line (m) FOLFIRINOX or were intolerant to this regimen; second-line treatment with GEMPAX does not improve OS compared with GEM (median OS of 6 *vs* 6 months [p=0·41])

5-FU=5-fluorouracil. GEM= gemcitabine. GEM-NAB-PAC=gemcitabine-nab-paclitaxel. GEMPAX=gemcitabine-paclitaxel. M1=metastatic disease. (m)FOLFIRINOX=a (modified) combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin. NALIRIFOX=nanoliposomal irinotecan with 5-fluorouracil, leucovorin, and oxaliplatin. OS=overall survival. PFS=progression-free survival. RECIST=response evaluation criteria for solid tumours. *Key trials are defined as randomised phase 3 trials that are used in the current daily clinical practice.

Table 2: **Key randomised controlled phase 3 trials on palliative chemotherapy in patients with metastatic pancreatic cancer***

overall survival of 40% (35–44) after gemcitabine-nab-paclitaxel.[127] However, randomised trials comparing (m)FOLFIRINOX with either gemcitabine-nab-paclitaxel or NALIRIFOX are lacking. A reconstructed individual patient data and network meta-analysis including only randomised trials found no significant difference in overall survival between (m)FOLFIRINOX and respectively gemcitabine-nab-paclitaxel and NALIRIFOX.[128]

In case of non-progressive disease after 6 months of palliative chemotherapy, treatment can be halted or maintenance therapy can be considered.[70] In patients with a germline *BRCA* mutation, maintenance therapy with the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib after platinum-based chemotherapy is recommended.[69,70] This treatment is associated with prolonged progression-free survival, but without improvement in overall survival,[119,129] In case of disease progression during first-line treatment with (m)FOLFIRINOX, second-line gemcitabine-based chemotherapy should be considered (or vice versa), although randomised trials are scarce and heterogeneous.[250] Two randomised trials[118,120] showed a survival benefit of second-line chemotherapy. The CONKO-003 trial showed that oxaliplatin and 5-fluorouracil with leucovorin was superior to 5-fluorouracil with leucovorin alone in patients diagnosed with advanced pancreatic cancer with disease progression during first-line gemcitabine: median overall survival of 6 months (95% CI 4–7) versus 3 months (3–4).[118] The NAPOLI-1 trial showed that liposomal irinotecan with 5-fluorouracil and leucovorin was superior to 5-fluorouracil and leucovorin: median overall survival of 6 months (5–9) versus 4 months (3–5).[120] The PRODIGE UNICANCER randomised trial, however, showed no difference in overall survival between second-line gemcitabine-paclitaxel compared with gemcitabine alone after first-line (m)FOLFIRINOX with a median overall survival of 6 months (5–7) in both arms.[121]

Toxicity of multi-agent chemotherapy causing serious adverse events is common with rates of 60–76% with (m)FOLFIRINOX, 50–86% with gemcitabine-nab-paclitaxel, and 87% with NALIRIFOX.[117, 122, 127, 130-132] Most common are haematological events (eg, neutropenia, leukopenia, and thrombocytopenia), fatigue, peripheral neuropathy, diarrhoea, nausea, and vomiting.[117, 122, 127, 130- 132] Chemotherapy-related toxicity can frequently be managed with dose reduction, which does not seem to affect the efficacy of FOLFIRINOX, although level-1 evidence is not available.[133] Despite its toxicity, (multi-agent) chemotherapy is associated with prolonged or even improved quality of life due to reduction of disease-related symptoms,[134,135] particularly in patients with a lower performance status and quality of life at baseline.[136] Outside clinical trials, patients with metastatic pancreatic cancer have a median overall survival of 2 months and a 1-year overall survival rate of 8%, because the vast majority of patients never receive chemotherapy because of frailty, rapid disease progression, or some degree of fatalism.[2]

In a small subset of patients with some tumour profiles, specific regimens could be considered, such as (m)FOLFIRINOX or gemcitabine–cisplatin for patients with a *BRCA or PALB2* germline mutation,[126,137] or adding pembrolizumab to first-line chemotherapy in the presence of microsatellite instable or mismatch-repair deficient tumours.[138] First-line treatment with targeted therapy of tropomyosin receptor kinase inhibitors larotrectinib or entrectinib is recommended in patients with a *KRAS* wild type with *NTRK* gene fusion.[139,140] The availability of personlised treatments for small subsets of patients underlines the importance of genetic testing and molecular profiling in patients with pancreatic cancer in daily clinical practice and for clinical trials.[69,70]

Localised pancreatic cancer

Multimodal treatment

The cornerstone of the treatment for localised pancreatic cancer is surgical resection combined with chemotherapy.[141] The timing of chemotherapy and the chances for surgery depend on the tumour resectability.

In patients with RPC, upfront surgery followed by 6 months of adjuvant chemotherapy is the standard of care,[69,70] as randomised trials have not shown superior overall survival with the use of neoadjuvant chemotherapy.[142] Randomised trials on neoadjuvant therapy versus upfront surgery were designed based on purely tumour anatomy-based resectability criteria. In light of the shift towards an A-B-C approach, the 2024 NCCN guideline also provides the option to treat RPC with neoadjuvant therapy, including for patients with high-risk A-B-C disease features (eg, large primary tumour, regional lymphadenopathy, markedly elevated serum CA19–9, and excessive weight loss),[70] which at least might reduce the risk of futile surgery.[143] In patients with RPC, the rate of resection after neoadjuvant therapy is 77% (95% CI 71–83).[144] After upfront surgery, the preferred adjuvant regimens are (m)FOLFIRINOX, gemcitabine–capecitabine, and in Asia the S-1 regimen.[145–147] Although the 2024 NCCN guideline proposes to consider to use adjuvant chemoradiation, the benefit on overall survival shown by randomised controlled trials is conflicting.[148,149] Table 3 presents randomised phase 3 trials on adjuvant chemotherapy. After pancreatic cancer surgery, about 33% of patients do not receive adjuvant chemotherapy, mainly due to impaired functional recovery caused by surgical complications.[153] This ommission might have less or no effect in patients who already received preoperative chemotherapy,[154] but clearly worsens survival in individuals undergoing upfront surgery.[155]

In patients with BRPC, the standard of care is neoadjuvant chemotherapy (with or without radiotherapy) followed by surgery and eventually adjuvant chemotherapy to complete 6 months chemotherapy.[69,70] Randomised controlled trials

	Population	Comparison	Conclusion
Upfront surgery with or without adjuvant chemotherapy			
Oettle et al (2007)[151] CONKO-001	354 patients who underwent R0 or R1 resection for localised pancreatic cancer from Germany and Austria	Adjuvant GEM (6c) *vs* no adjuvant therapy; primary endpoint: DFS	Adjuvant therapy with GEM is superior to no adjuvant therapy considering prolonged DFS (median DFS of 13 *vs* 7 months [p<0·001] and 5-year DFS rate of 17% *vs* 7%) and prolonged OS (median OS of 23 *vs* 20 months [p=0·01] and 5-year OS rate of 21% *vs* 10%). Therefore, adjuvant chemotherapy is preferred in patients undergoing upfront surgery for localised pancreatic cancer
Upfront surgery followed by different adjuvant chemotherapy regimens			
Neoptolemos et al (2017)[147,152] ESPAC-4	730 patients from the UK, Germany, France, and Sweden who underwent R0 or R1 resection for localised pancreatic cancer	Adjuvant GEM-CAP (6c) *vs* adjuvant GEM (6c); primary endpoint: OS	Adjuvant GEM-CAP is superior to GEM considering prolonged OS (median OS of 32 *vs* 28 months [p=0·031] with 5-year OS rate of 32% *vs* 25%). Therefore, GEM-CAP is preferred over GEM as adjuvant regimen following upfront surgery for localised pancreatic cancer. However, trials comparing GEM-CAP with either (m) FOLFIRINOX or GEM-NAB-PAC are not available
Uesaka et al (2016)[146] JASPAC 01	385 patients from Japan who underwent R0 or R1 resection for localised pancreatic cancer	Adjuvant S-1 (4c) *vs* adjuvant GEM (6c); primary endpoint: OS	Adjuvant S-1 is superior to GEM considering prolonged OS (median OS of 47 *vs* 26 months [p<0·0001] and 5-year OS rate of 44% *vs* 24%). Therefore, S-1 is preferred over GEM as adjuvant regimen after upfront surgery in Japanese patients with localised pancreatic cancer
Conroy et al (2018)[131,145] PRODIGE 24-ACCORD and CCTG PA	493 patients from France and Canada who underwent R0 or R1 resection for localised pancreatic cancer	Adjuvant (m)FOLFIRINOX (12c) *vs* adjuvant GEM (6c); primary endpoint: DFS	Adjuvant mFOLFIRINOX is superior to GEM considering prolonged OS (median of 54 *vs* 36 months [p=0·001] and 5-year OS rate of 43% *vs* 31%), although mFOLFIRINOX is associated with increased toxicity. Therefore, mFOLFIRINOX is preferred over GEM as adjuvant regimen in fit patients after upfront surgery for localised pancreatic cancer. However, trials comparing mFOLFIRINOX with either GEM-NAB-PAC or GEM-CAP are not available
Tempero et al (2022)[130] APACT	866 patients who underwent R0 or R1 resection for localised pancreatic cancer from North America, Europe, Australia, and Asia	Adjuvant GEM-NAB-PAC (6c) *vs* adjuvant GEM (6c); primary endpoint: DFS	Adjuvant GEM-NAB-PAC does not improve DFS compared with GEM (median DFS of 19 *vs* 19 months [p=0·18]), although the OS is prolonged after GEM-NAB-PAC (median OS of 42 *vs* 38 months [p=0·023] and 5-year OS rate of 38% *vs* 31%). Based on the prolonged OS, GEM-NAB-PAC could be considered as preferred adjuvant regimen in fit patients compared with GEM. However, trials comparing GEM-NAB-APC with either (m)FOLFIRINOX or GEM-CAP in the adjuvant setting following upfront surgery are not available
Preoperative chemotherapy followed by surgery with or without adjuvant chemotherapy			
No phase 3 randomised controlled trials			

C=cycle. CAP=capecitabine. DFS=disease-free survival. GEM=gemcitabine. GEM-NAB-PAC=gemcitabine-nab-paclitaxel. OS=overall survival. (m)FOLFIRINOX=a (modified) combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin. R0=microscopically radical resection. R1=microscopically non-radical resection. *Key trials are defined as randomised phase 3 trials that are used in the current daily clinical practice.

Table 3: **Key randomised controlled phase 3 trials on adjuvant chemotherapy after surgery for patients with localised pancreatic cancer***

showed superior overall survival with neoadjuvant therapy compared with upfront surgery followed by adjuvant therapy.[156] However, evidence is inconclusive about the optimal neoadjuvant chemotherapy regimen, optimal number of cycles, and benefit of subsequent adjuvant chemotherapy.[99] See appendix (p 1) for randomised phase 3

See **Online** for appendix

trials on neoadjuvant therapy versus upfront surgery in patients with (B)RPC. The resection rate after neoadjuvant therapy for patients with BRPC is 61% (95% CI 55–66).[144]

Patients with LAPC are primarily treated with systemic chemotherapy for 4–6 months. The most common regimens are (m)FOLFIRINOX and gemcitabine-nab-paclitaxel.[69,70] However, randomised controlled phase 3 trials on different chemotherapy regimens such as neoadjuvant or induction therapy for patients with localised pancreatic cancer are still not available. Three phase 2 randomised controlled trials[157–159] showed similar overall survival between neoadjuvant or induction (m)FOLFIRINOX and gemcitabine-nab-paclitaxel for localised pancreatic cancer. The preliminary published results from the PREOPANC-2 phase 3 trial found that neoadjuvant FOLFIRINOX did not improve overall survival compared with gemcitabine-based chemoradiotherapy in patients with (B)RPC.[160] In the subset of patients with LAPC who are candidates for surgical resection after induction chemotherapy, evidence is inconclusive, particularly about the optimal number of cycles and the benefit of subsequent adjuvant chemotherapy.[99] About 22% (95% CI 17–29) of patients initially diagnosed with LAPC undergo resection after induction chemotherapy.[144] The resection rates of BRPC and LAPC after systemic chemotherapy are lower on the population level, due to referral bias.[161,162]

Current guidelines allow for the possibility to administer additional (chemo)radiotherapy after neoadjuvant or induction chemotherapy,[69,70] including stereotactic body radiotherapy (SBRT), which allows for precise and therefore higher dosing compared with conventional external beam radiation.[163] Radiotherapy is associated with increased rates of a microscopically radical (ie, R0) resection and pathological complete response.[164,165] Randomised trials, however, have not shown a survival benefit of adding preoperative radiotherapy (appendix p 2). Moreover, the ALLIANCE A021501 phase 2 randomised controlled trial showed longer 18-month overall survival after neoadjuvant mFOLFIRINOX alone compared with mFOLFIRINOX combined with hypofractionated radiotherapy in patients with BRPC: 67% (95% CI 56–79) versus 47% (36–63).[166]

Response evaluation after chemotherapy is challenging due to the inability to differentiate between key tumour tissue and fibrosis on CT, illustrated by the sensitivity and specificity of CT to predict on R0 resection of 78% (95% CI 68–86) and 60% (44–74), respectively.[167] Excluding disease progression by metastatic disease is the main radiological parameter assessed at restaging.[70] The poor ability of CT to differentiate between tumour tissue and fibrosis underlines the importance of an A-B-C approach at restaging. Serum CA19–9 concentration needs to be stable at least after neoadjuvant therapy for patients with (B)RPC,[69,70] whereas a substantial decrease after induction chemotherapy is required in patients with LAPC according to the 2024 NCCN guideline.[70] Diverging targets for a sufficient serum CA19–9 response are described, either based on the relative response and absolute concentrations at restaging.[168,169] Fluorodeoxyglucose positron emission tomography before and after chemotherapy can be used to assess biological disease response, particularly in patients with non-elevated serum CA19–9 concentrations at diagnosis.[170,171] Considering the complexity, it is crucial that staging, restaging, and subsequent treatment decision making are done by a multidisciplinary tumour board.[70]

Surgery

Surgery combined with systemic chemotherapy provides by far the best chance to achieve long-term overall survival. However, after surgical resection 5-year overall survival is still only 17%.[172] This is due to high rates of locoregional and distant recurrence; 48% at 12 months and 86% at 5 years postoperatively.[173,174] Predicting early recurrence is difficult as the presence of unfavourable parameters does not preclude long-term overall survival.[29,175] High-level evidence about the oncological benefit of active surveillance strategies after surgical resection is not available.[176]

The most common resection is a pancreatoduodenectomy,[177] followed by left pancreatectomy (ie, distal pancreatectomy)[178] and total pancreatectomy.[179] Pancreatoduodenectomy is associated with a 90-day major morbidity rate of 26% and a mortality of 5%.[180] A lower failure to rescue rate is seen in high-volume centres with experienced multidisciplinary teams and round-the-clock interventional radiology and interventional endoscopy services.[181] Pancreatic cancer surgery might require portomesenteric venous, arterial, and multivisceral resections[182–184] to obtain a radical resection.[185,186] Therefore, centralisation of pancreatic cancer surgery is highly advocated,[6,187] as higher hospital volumes are associated with lower surgical mortality.[181] Pancreatic surgery is associated with risks of endocrine and exocrine insufficiency of, respectively, 22% and 43% after pancreatoduodenectomy,[188,189] 23% and 12% after left pancreatectomy,[189,190] and 100% after total pancreatectomy.[191]

Open surgery via laparotomy is standard of care,[69] but minimally invasive surgery (ie, either laparoscopic or robot-assisted) is increasingly used in patients without vascular involvement, as minimally invasive surgery might enhance functional recovery.[70] The feasibility and safety of laparoscopic pancreatic surgery compared with an open approach, specifically for patients with pancreatic cancer, has been shown for pancreatoduodenectomy and left pancreatectomy, whereas level-1-evidence for robotic pancreatic surgery is awaited.[192,193]

Local ablative therapy

Local therapies have been and are being studied in patients with studies in patients with LAPC after induction chemotherapy in whom extensive vascular involvement, poor tumour biology, or insufficient performance status preclude surgical resection. International guidelines

propose to consider palliative (chemo)radiotherapy to achieve local disease control.[69,70] Ablative radiotherapy including SBRT has shown promising locoregional control and survival, but level-1 evidence is awaited.[194] Randomised controlled trials[195,196] found no survival benefit for irreversible electroporation and radiofrequency ablation in patients with LAPC.

Supportive care

Supportive care comprises multiple domains including management of pain, nutrition and rehabilitation, management of biliary and duodenal obstruction, and quality of life and psychosocial support.[197]

Attention to symptoms is important considering their modifiability and effect on quality of life.[198] Abdominal or back pain is reported in up to 62% of patients before diagnosis.[199] This pain can be multifactorial including perineural invasion, ingrowth in surrounding visceral structures, and metastases, requiring a multidisciplinary evaluation.[200] In case pharmacological therapy is insufficient to control tumour-related pain, interventions such as coeliac plexus neurolysis and radiation should be considered.[70] Coeliac plexus neurolysis is mainly indicated in patients with a short life expectancy considering this therapy's temporal effect of about 1–3 months.[201] Palliative SBRT possibly reduces pain and improves quality of life for a longer time period.[194]

Screening for malnutrition should be standardised as approximately 63% of patients with pancreatic cancer have cachexia at diagnosis.[202] Prehabilitation including physical training and dietary consultation is important to prepare patients for tumour-targeted treatment.[203] The APACap GERCOR randomised trial[204] in patients with advanced pancreatic cancer showed the positive effect of adapted physical activity training on global health status, functioning, and symptoms without effect on chemotherapy treatment and survival. A contributing factor to the development of weight loss and cachexia is pancreatic exocrine insufficiency. Exocrine insufficiency occurs in about 72% (95% CI 55–86) of patients with advanced pancreatic cancer[205] and requires pancreatic enzyme replacement therapy, according to the 2024 European guideline.[206] However, a standardised approach regarding malnutrition screening, dietary consultation, and pancreatic enzyme replacement therapy is often missing in the daily clinical practice.[207,208] Considering the high incidence of exocrine insufficiency in patients with pancreatic cancer (particularly when located in the pancreatic head), the diagnosis of exocrine insufficiency can be made on symptoms (eg, diarrhoea, steatorrhea, bloating, abdominal cramps, and flatulence) and nutritional status alone.[206] Malnutrition can also be caused by a gastric outlet or duodenal obstruction, which can be managed with a surgical or endoscopic gastrojejunostomy after securing biliary drainage, as a gastrojejunostomy is typically superior to a duodenal stent.[70,209]

In patients with cholestasis, biliary drainage is advised in individuals being scheduled for neoadjuvant or induction therapy, having delay of upfront surgery with more than 2 weeks, having symptoms of cholangitis or fever, or having severe symptomatic jaundice.[69,70] Biliary drainage is preferably performed via endoscopic retrograde cholangiopancreatography (ERCP) with placement of a self-expandable metal stent, considering its longer patency compared with plastic stents.[210,211]

Diabetes is common with a prevalence of approximately 30% in the general population of individuals with pancreatic cancer. Diabetes should be recognised and appropriately managed in this group of patients.[202] In addition, new-onset diabetes might occur after pancreatic surgery.[188,190,191] Management of diabetes after total pancreatectomy is particularly challenging with a negative effect on quality of life. However, the long-term quality of life outcomes after total pancreatectomy are similar compared with patients undergoing partial pancreatectomy.[212]

Psychological support is relevant considering the high prevalence of depression (31%; 95% CI 20–42) and anxiety (20%; 9–32) of patients with pancreatic cancer.[213] In the 6 months before and after diagnosis, the rates of depression are even higher (up to 70% before and 80% after diagnosis).[214] The involvement of informal caregivers (eg, relatives) should not be forgotten as anxiety and depression among patients' relatives during the disease course occurs in about 33% and 12–32%, respectively.[215]

Future directions

Further improvements in the care of patients with pancreatic cancer are urgently needed.

First, tumour markers of improved accuracy are needed for early disease detection, assessment of treatment response, patient selection, and prognostication. Circulating tumour DNA has shown promising results, being associated with survival at time of diagnosis and after treatment.[216]

Second, pancreatic cancer in the head often requires biliary drainage through ERCP. However, ERCP results in acute pancreatitis in about 10% (95% CI 9–11%) and cholangitis in about 3% (1–6%) of patients,[217] which might worsen the patient's condition and delay neoadjuvant therapy or upfront surgery.[218] An EUS-guided transduodenal biliary drainage, as alternative to ERCP, can avoid acute pancreatitis. A meta-analysis including five randomised trials showed that EUS-guided biliary drainage was associated with a lower stent dysfunction, similar technical success rate, and no pancreatitis,[219] but this approach has not yet been included in international guidelines.[69,70] Furthermore, the EUS-guided gastroenterostomy is being studied to manage gastric outlet and duodenal obstruction as alternative to surgical gastroenterostomy.[220]

Third, results are awaited from randomised trials investigating the value of neoadjuvant therapy for patients

with RPC and the optimal neoadjuvant and induction therapy for patients with BRPC and LAPC. These trials assess various strategies including total neoadjuvant therapy, the optimal number of cycles of chemotherapy, different multi-agent chemotherapy regimens, and the added value of radiotherapy. Moreover, randomised trials are needed to investigate the value of second-line neoadjuvant and induction chemotherapy in patients with biochemical or radiological locoregional disease progression.[221] Even though about one-fifth of patients diagnosed with LAPC are resected after (m)FOLFIRINOX or gemcitabine-nab-paclitaxel, with 5-year overall survival rates up to 20–25%,[222] the survival benefit of subsequent surgery remains unclear.[223]

Fourth, pancreatic resections are increasingly performed minimally invasively.[224] However, evidence about robot-assisted surgery specifically in patients with pancreatic cancer is awaited, and the indications and selection criteria for minimally invasive pancreatic surgery remain a topic of debate.[225]

	Population	Comparison	Conclusion
Extracellular matrix targeting			
Van Cutsem et al (2020)[229] HALO 109–301	494 patients with untreated, hyaluronan-high, M1 pancreatic cancer from North America, Europe, and Asia	GEM-NAB-PAC + PEGPH20 *vs* GEM-NAB-PAC with placebo. In both arms, treatment was continued until disease progression or unacceptable toxicity. Primary endpoint: OS	First-line treatment GEM-NAB-PAC + PEGPH20 does not improve OS (median OS of 11 *vs* 12 months [p=0·97]) compared with GEM-NAB-PAC, although the objective response rate is higher after GEM-NAB-PAC + PEGPH20
Checkpoint inhibitors			
Hecht et al (2021)[230] SEQUOIA	567 patients with M1 pancreatic cancer having GEM-refractory disease from North America, Europe, and Asia	PEG + FOLFOX *vs* FOLFOX. Primary endpoint: OS	Second-line treatment with FOLFOX + PEG does not improve OS (median OS of 6 *vs* 6 months [p=0·66]) compared with FOLFOX alone in patients with GEM-refractory M1 disease
Tyrosine kinase inhibitors			
Hammel et al (2016)[231] LAP07	442 patients with AJCC TNM stage III (6th edition) from France, Australia, New Zealand, Belgium, and Sweden	Preoperative GEM (4c) *vs* preoperative GEM-ERL (4c), followed by second randomisation when response evaluation criteria in solid tumours non-progressive disease for GEM (6 weeks) *vs* CAP-EBRT (54 gray in 30 fractions over 6 weeks). Primary endpoint: OS	Preoperative GEM + ERL does not improve OS (median OS of 12 *vs* 14 months [p=0·09]) compared with GEM alone
Sinn et al (2017)[232] CONKO-005	436 patients with primary resectable pancreatic cancer who underwent R0 resection, from Germany	Adjuvant GEM + ERL (6c) *vs* adjuvant GEM (6c). Primary endpoint: DFS	Adjuvant GEM + ERL does not improve DFS (median DFS of 11 *vs* 11 months [p=0·26]) and OS (median OS of 25 vs 27 months with 5-year OS rate of 25% *vs* 20% [p=0·61]) compared with adjuvant GEM alone
Tempero et al (2021)[233] RESOLVE	424 patients diagnosed with M1 pancreatic cancer being chemo-naive from North America, Europea, and Asia	Ibrutinib + GEM-NAB-PAC *vs* GEM-NAB-PAC with placebo. Primary endpoint: OS and PFS	First-line treatment GEM-NAB-PAC + ibrutinib does not improve OS (median OS of 10 *vs* 11 months [p=0·32]) and PFS (median PFS of 5 *vs* 6 months [p<0·0001])
Immunotherapy			
Hewitt et al (2022)[234]	303 patients with BRPC and LAPC from North America	Neoadjuvant or induction therapy using FOLFIRINOX or GEM-NAB-PAC (with radiation) + HAPa *vs* neoadjuvant or induction therapy using FOLFIRINOX or GEM-NAB-PAC (with radiation). Primary endpoint: OS	Adding HAPa to neoadjuvant or induction therapy using FOLFIRINOX or GEM-NAB-PAC does not improve OS (median OS of 14 *vs* 15 months) compared with FOLFIRINOX or GEM-NAB-PAC alone
Anti-mitochondrial targeting			
Philip et al (2024)[235] AVENGER 500	528 patients with untreated M1 pancreatic cancer from North America, Europe, and Asia*	Devimistat (CPI-613) + mFOLFIRINOX *vs* mFOLFIRINOX. In both arms, treatment was continued until disease progression or unacceptable toxicity. Primary endpoint: OS	First-line treatment devimistat + mFOLFIRINOX does not improve OS (median OS of 11 *vs* 12 months [p=0·66]) compared with mFOLFIRINOX alone

AJCC=American Joint Committee on Cancer. BRPC=borderline resectable pancreatic cancer. C=cycle. CAP=capecitabine. DFS=disease-free survival. EBRT=external beam radiotherapy. ERL=erlotinib. FOLFOX=5-fluorouracil with leucovorin and oxaliplatin. GEM-NAB-PAC=gemcitabine-nab-paclitaxel. HAPa=algenpantucel-L (HyperAcute-Pancreas). GEM=gemcitabine. LAPC=locally advanced pancreatic cancer. M1=metastatic disease. mFOLFIRINOX=modified combination of 5-fluorouracil with leucovorin, irinotecan, and oxaliplatin. NAB-PAC=nab-paclitaxel. OS=overall survival. PEG=pegilodecakin. PEGPH20=pegvorhyaluronidase alfa. PFS=progression-free survival. R0=microscopically radical resection. TNM=Tumour, Node, and Metastasis. *Inclusion was allowed if previous (neo)adjuvant treatment was completed ≥6 months before disease recurrence.

Table 4: **Randomised controlled phase 3 trials on targeted therapy in patients with pancreatic cancer**

Fifth, a subset of patients present with synchronous oligometastatic disease, mostly defined as having three or fewer metastatic lesions in the liver, lung, or both.[226] Highly selected patients might benefit after extensive chemotherapy from locoregional treatment, such as radiation, resection, or ablation of the metastatic lesions,[227] eventually combined with resection of the primary tumour, with a reported median overall survival of 16 months (95% CI 12–23).[226] Ongoing randomised trials have to clarify the added value of local therapy in this setting.[227] The EXTEND randomised phase 2 trial showed a benefit of metastasis-directed therapy with systemic chemotherapy compared with systemic chemotherapy alone in patients with oligometastatic pancreatic cancer: median progression-free survival was 10 months (5–14) versus 3 months (2–5, p=0·030).[228]

Sixth, targeted therapy for pancreatic cancer remains a major challenge. Table 4 presents clinical phase 3 trials on targeted therapy for pancreatic cancer. Clinicals trials should determine the added value of routine genetic and transcriptomic tumour profiling (eg, basal-like *vs* classic subtype, *SMAD4A*, *BRCA1*, *BRCA2*, and *GATA6*) to determine sensitivity to specific chemotherapy regimens, given the growing evidence suggesting a difference in chemosensitivity between tumour subtypes.[24,124-126,236,237] Since about 88% of pancreatic adenocarcinomas have a *KRAS* mutation,[21] *KRAS* inhibitors hold a high potential for treatment in patients with this mutation.[238] Although direct *KRAS* inhibition in pancreatic cancer has historically been challenging, in the last few years advances in *KRAS*-directed therapies offer hope for improved outcomes with the use of $KRAS^{G12D}$ and *RAS-GTP*.[239,240] Additionally, approximately 12% of tumours are $KRAS^{WT}$ with numerous targetable alterations including gene fusions and amplifications and a higher rate of microsatellite instability, which opens up various treatment possibilities.[21,241] These developments illustrate the importance of genetic and molecular tumour profiling for clinical trials in patients diagnosed with pancreatic cancer.

Seventh, pancreatic cancer is a so-called immunologically cold tumour. Wherefore, previous immunotherapy trials did not show prolonged survival,[242,234] except for the less than 1% of patients who had a DNA mismatch deficient tumour,[243] for which immunotherapy with checkpoint inhibition leads to promising survival.[138,244,245] However, there are first signs that this dogma might be broken in the near future, with novel generation immunotherapies in combination with chemotherapy and radiotherapy.[246,247] Furthermore, mRNA-based individualised neoantigen-specific and dendritic cell-based immunotherapy in the adjuvant setting is promising.[248,249]

Conclusions

Pancreatic cancer is a highly lethal disease due to its aggressive tumour biology that frequently presents with non-specific symptoms and has a high rate of metastatic disease at diagnosis. A multidisciplinary approach is mandatory to adequately stage and treat patients with pancreatic cancer with tumour-targeted therapy and concomitant supportive care. Chemotherapy combined with surgical resection is the cornerstone of treatment, but only a small set of patients are candidates for surgery. Given the complexity of pancreatic cancer care, patients should be managed at expert centres. The introduction of multi-agent chemotherapy, either as palliative chemotherapy for metastatic disease or as (neo)adjuvant or induction therapy in patients with localised pancreatic cancer, has improved the survival of patients with pancreatic cancer. Given the prospect that pancreatic cancer will become the second leading cause of cancer-related deaths by 2030, there is an urgent need for novel tumour-targeted therapies with promising results from new generation immunotherapies and *KRAS*-directed therapies.

Contributors

TFS, AAJ, and AO were responsible for the conception, design, execution of the literature reviews, interpretation of data, and drafted the manuscript. BGK, TS, JWW, and MGB were responsible for the conception and design, interpretation of data, drafting of the manuscript, and revising the manuscript critically for important intellectual content.

Declaration of interests

AO has received a grant from Bayer Yakuhin to conduct an observational study assessing the clinical impact of gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging. All other authors declared no competing interests.

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