

Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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incidence and epidemiology

A recent study estimating cancer epidemiology in 2014 (within Europe) showed that pancreatic cancer was the fourth most fatal cancer in men after lung, colorectal, and prostate cancers [1]. Similarly, pancreatic cancer was found to be the fourth most fatal cancer in women after breast, colorectal and lung cancers [1]. With a life expectancy of ~5% at 5 years, the prognosis of this cancer has not improved over the past 20 years, and incidence and mortality rates are very similar. Death due to pancreatic carcinoma is increasing in Europe with the number rising from 75 439 in 2009 to a projected 82 300 deaths in 2014 (+19%) [1]. It usually arises in elderly patients with a mean age at onset of 71 years for men and 75 years for women. The majority of patients with pancreatic cancer progress to either metastatic or locally advanced disease in the asymptomatic phase. Surgical excision is the definitive treatment with a 5-year survival rate (after resection) of ~20%, but it is only possible in 15%–20% of the patients. The opportunity to detect pancreatic cancer, while it remains curable, depends on the ability to identify and screen high-risk populations before their symptoms arise. Defining the treatment strategy for patients suffering from pancreatic carcinoma requires a specialised multidisciplinary team that includes: surgeons, medical oncologists, gastroenterologists, radiation therapists, radiologists, and supportive and palliative care specialists.

The vast majority (>80%) of pancreatic carcinomas are due to sporadically occurring mutations. Only a small proportion (<10%) are due to inherited germline mutations. Germline mutations in *BRCA2*, *p16*, *ATM*, *STK11*, *PRSS1/PRSS2*, *SPINK1*, *PALB2*, and DNA mismatch repair genes are associated with varying degrees of increased risk for pancreatic carcinoma [2].

Familial pancreatic cancers, defined as at least two first-degree relatives with pancreatic cancer, account for only 5%–10% of all pancreatic cancer cases. Mutation in *BRCA2* is probably the most common inherited disorder in familial pancreatic cancer. Other familial syndromes linked to pancreatic cancer are: hereditary pancreatitis, hereditary non-polyposis colorectal cancer, hereditary breast and ovarian cancers, Peutz–Jeghers syndrome, ataxia telangiectasia, familial atypical multiple mole melanoma syndrome and Li–Fraumeni syndrome.

The main acquired risk factors for pancreatic cancer are cigarette smoking (overall relative risk 1.74) and, to a lesser degree, environmental tobacco smoke. The second most modifiable risk factor of pancreatic cancer is obesity. Tumorigenesis is enhanced by excess adipose tissue, probably through the mechanism of abnormal glucose metabolism. Obesity [body mass index (BMI) > 30 kg/m²] is associated with a 20%–40% higher rate of death from pancreatic cancer. Meta-analyses have demonstrated associations between both type 1 and type 2 diabetes mellitus and pancreatic cancer, with odds ratios of ~2.0 and 1.8, respectively [2].

Chronic pancreatitis accounts for ~5% of pancreatic cancers. The most common cause of chronic pancreatitis, in Europe, is excess alcohol consumption. The causal pathway is not clear, however, alcohol consumption by itself is related to an increased risk of pancreatic cancer.

Helicobacter pylori, hepatitis B, and human immunodeficiency virus infection have also been reported to be related to an increase in relative risk of pancreatic cancer, although some confounding factors such as cigarette smoking or alcohol consumption have not always been considered [2].

Dietary factors have been studied extensively, and clearly contribute to the development of pancreatic cancer. Independent of their role in causing obesity: butter, saturated fat, red meat, and processed foods are clearly linked to pancreatic cancer [3]. Conversely, a high fruit and folate intake could reduce the risk of pancreatic cancer [3].

Different chemical substances have been reported to increase the relative risk of developing pancreatic cancer, among these

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Table 1. Major non-genetic risk factors [7]^a

Factor	Relative risk	Attributable fraction
Tobacco	2	11%–32%
<i>Helicobacter pylori</i> infection	1.5	4%–25%
Non-O-blood group	1.4	13%–19%
Diabetes mellitus	1.4–2.2	1%–16%
Obesity	1.2–1.5	3%–16%
Red meat intake	1.1–1.5	2%–9%
Heavy alcohol intake	1.1–1.5	9%
Low fruit and folate intake	0.5–1.0	<12%

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are: chlorobenzoil, chlorinated hydrocarbon, nickel and nickel compounds, chromium compounds, silica dust, and others [4].

A recent pooled analysis of 117 meta-analytical studies [5] assigned a relative risk to a number of these factors improving our understanding of the respective role of each factor (Table 1).

As a summary, it is possible to say that 5%–10% of pancreatic cancers are related to a genetic alteration. Among the remaining 90%, the major risk factors are tobacco, *H. pylori* infection and factors related to dietary habits (BMI, red meat intake, low fruit and vegetables intake, diabetes, alcohol intake). Some factors are difficult to interpret such as chronic pancreatitis, which is known as a risk factor but can be related to alcohol intake. Diabetes is also known as a risk factor but this could be the initial symptom of the disease, and can also be found in chronic pancreatitis. However, about two thirds of the major risk factors associated with pancreatic cancer are potentially modifiable, affording a unique opportunity for preventing one of the deadliest cancers.

key points

- 5%–10% of pancreatic cancers are due to genetic alteration
- The main risk factors are tobacco, and factors related to dietary habits (BMI, red meat intake, low fruit and vegetables intake, diabetes, alcohol intake)

diagnosis and pathology/molecular biology

diagnosis

Early symptoms of pancreatic cancer result from a mass effect. Approximately 60%–70% of pancreatic cancer arises in the head of the pancreas, 20%–25% in the body and the tail, and the remaining 10%–20% diffusely involve the pancreas. Tumours located in the body and the tail are likely to be diagnosed at a more advanced stage than tumours located in the head, as these can develop symptoms related to an obstruction of the common bile duct and/or the pancreatic duct. Common presenting symptoms of pancreatic cancers include jaundice (for tumours of the head), abdominal pain, weight loss, steatorrhoea, and new-onset diabetes. Tumours can grow locally into the duodenum (proximal for tumour of the head and distal for tumour of the body and tail) and result in an upper gastroduodenal obstruction.

key points

- Early symptoms of pancreatic cancer result from a mass effect
- Common presenting symptoms include jaundice, pain, weight loss, steatorrhoea

pathology

Pancreatic cancers arise from both the exocrine and endocrine parenchyma of the gland, however, ~95% occur within the exocrine portion and may arise from ductal epithelium, acinar cells, or connective tissue. Only 2% of tumours of the exocrine pancreas are benign. The most common pancreatic cancer is a ductal adenocarcinoma, which accounts for ~80% of all pancreatic cancers. Microscopically, these neoplasms vary from well-differentiated duct-forming carcinomas (which may be so well differentiated that they mimic non-neoplastic glands) to poorly differentiated carcinomas, with epithelial differentiation demonstrable only on immunolabelling. Ductal adenocarcinomas typically elicit an intense stromal reaction which has been postulated to serve as a barrier to chemotherapy [6]. A number of morphological variants of ductal carcinoma have been characterised, including colloid carcinoma and medullary carcinoma. Other variants of pancreatic cancer, such as adenosquamous carcinoma and undifferentiated carcinomas with osteoclast-like giant cells, are important to recognise because they are associated with a poorer prognosis. On the contrary, acinar cell pancreatic cancers have a slightly better prognosis [7]. Neuroendocrine tumours of the pancreas are the second most frequent pancreatic cancers, but they have a very specific pattern that will not be considered in this paper.

Cystic neoplasms represent 10%–15% of cystic lesions of the pancreas [8]. The most commonly encountered cystic neoplasms include: serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (either cystadenoma or cystadenocarcinoma). Mucinous lesions have potential for malignant progression and/or may harbour a malignancy at the time of diagnosis. The non-mucinous lesions have no malignant potential.

key points

- 95% of pancreatic cancers are adenocarcinomas
- Mucinous lesions of the pancreas have potential for malignant progression

molecular biology

The classical precursor lesions of pancreatic cancer show a ductal phenotype, suggesting their ductal cell of origin. The most frequent precursors are microscopic pancreatic intraepithelial neoplasia (PanIN), followed by IPMN and mucinous cystic neoplasm. PanIN are microscopic (<5 mm) mucinous-papillary lesions, which lead to invasive carcinoma through an adenoma-carcinoma sequence [9]. Similarly, IPMN and mucinous cystic neoplasms become neoplastic by stepwise gene alterations.

Multiple combinations of genetic mutations are commonly found in pancreatic cancers and can be classified as follows:

- Mutational activation of oncogenes, predominantly *KRAS* found in >90% of pancreatic cancers.
- Inactivation of tumour suppressor genes such as *TP53*, *p16/CDKN2A*, and *SMAD4*.

- (iii) Inactivation of genome maintenance genes, such as *hMLH1* and *MSH2*, which control the repair of DNA damage. Most of these mutations are somatic aberrations.

Many efforts to understand the genomics of pancreatic cancer have evolved from the model system and especially cell lines. However, cell lines are poor models of cancer since solid tumour samples consist of a variety of tissues which may comprise only a small proportion of tumour cells. Adjacent to and surrounding these are the other tissues consisting of stroma and endothelial cells. This is particularly the case in pancreatic cancer, since the tumour contains a high content of stromal tissue. An analysis using whole-genome sequencing and copy number variation analysis was recently carried out in 100 pancreatic ductal adenocarcinomas [10]. Chromosomal rearrangements, leading to gene disruption were prevalent, affecting genes known to be important in pancreatic cancer (*TP53*, *SMAD4*, *CDKN2A*, *ARID1A*, and *ROBO2*) and new candidate drivers of pancreatic carcinogenesis (*KDM6A* and *PREX2*). Patterns of structural variation in chromosomes classified pancreatic cancer into four subtypes with potential clinical utility. The subtypes were termed: stable, locally rearranged, scattered, and unstable.

key points

- The most frequent precursors are microscopic PanIN, followed by IPMN and mucinous cystic neoplasm
- Multiple combinations of genetic mutations are commonly found in pancreatic cancers
- Some of the recent genetic mutations discovered could become targetable in the near future

staging and risk assessment

CA 19-9 is not useful for the primary diagnosis of pancreatic cancer [I, E]. An increase in serum levels is seen in almost 80% of the patients with advanced disease. However, in patients not harbouring a functional Lewis enzyme (Le^{a-b-} genotype: 7%–10% of the population), levels of CA 19-9 are typically undetectable or below 1.0 U/ml. Conversely, the level of CA 19-9 is correlated to the level of bilirubin and any cause of cholestasis is able to induce false-positive results. CA 19-9 has a significant value as a prognostic factor and can be used as a marker to measure disease burden and potentially guide treatment decisions. A preoperative serum CA 19-9 level ≥ 500 UI/ml clearly indicates a worse prognosis after surgery [IV, B] (Figure 1).

The imaging work-up must determine the tumour size and precise burden, as well as arterial and venous local involvement. All these factors are part of the TNM classification (Table 2). In case of jaundice due to an obstructive cancer of the head of the pancreas, a metal biliary stent should not be placed before initial work-up, because their use is linked to an increase of post-operative morbidity if it is decided to resect the cancer [III, A]. In case of biliary sepsis, plastic stents should be preferred.

Endoscopic ultrasound (EUS) is now largely used in the staging of adenocarcinoma. A recent meta-analysis study showed that EUS had limited value in the detection of all metastatic lymph nodes [sensitivity (Se) 69%, specificity (Sp) 81%], but was valuable in the detection of vascular invasion (Se 85%, Sp 91%) and prediction of resectability (Se 90%, Sp 86%) [11].

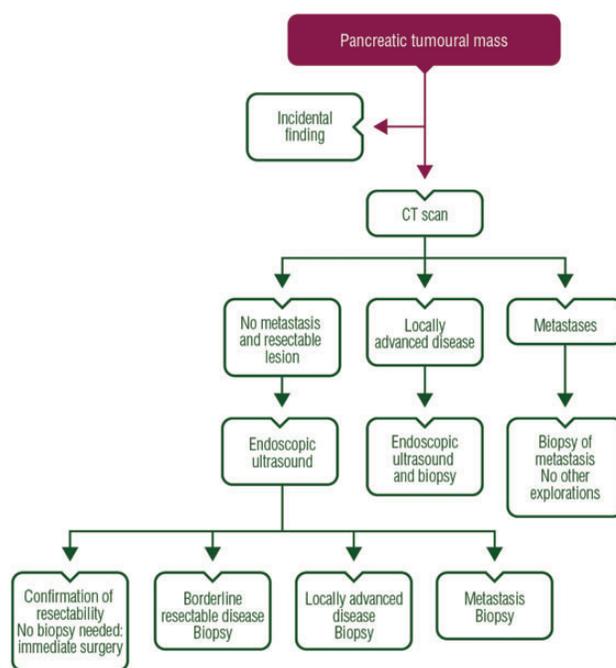


Figure 1. Diagnostic work-up before multidisciplinary decision. CT, computed tomography.

The great advantage of EUS is its ability to provide tissue samples, via fine-needle aspiration, that allow up to 95% diagnostic accuracy (when carried out by an experienced cytopathologist). Aside from allowing the diagnosis of pancreatic adenocarcinoma, this technique also permits the sampling of atypical lymph nodes (portocaval especially) to check for tumours with distant metastasis, a finding which would contraindicate radical resection. Incidental hepatic metastases can also be sampled during the same procedure without introducing any major risk [II, A].

Radiological studies should include computed tomography (CT) angiography at the pancreatic arterial (40–50 s) and portal venous (65–70 s) phases. A consensus statement, describing a standardised reporting template, was recently developed to provide a precise reporting of disease staging and to improve the decision-making process for patients with pancreatic cancer [12]. When assessing vessel involvement, the use of magnetic resonance imaging (MRI) is left to expert discretion. It shows equal benefit to CT scanning with no superiority demonstrated in studies [13]. However, MRI is useful for solving problems such as the detection of hepatic lesions that cannot be characterised by CT [II, A]. MRI and magnetic resonance cholangiopancreatography may also be preferable for cystic neoplasms of the pancreas and to evaluate biliary anatomy [IV, C].

In the majority of cases, pancreatic adenocarcinoma appears in the pancreatic arterial phase on CT examination, as a hypo-attenuating homogeneous mass with indistinct margins. The interruption (with or without dilatation) of the biliary duct is fundamental to specify tumour extension. The presence of calcifications is very unlikely but a cystic part of the tumour can exist, especially when the tumour originates from a degenerating cystic pancreatic lesion. Extra-pancreatic local extension has to be delineated: enlarged lymph nodes (especially in the retroportal space), hepatic or peritoneal nodules are the main metastatic sites.

Table 2. TNM classification 7th edition^a

Primary tumour (T)	
T0 = No evidence of primary tumour	
Tis = Carcinoma <i>in situ</i>	
T1 = Tumour limited to the pancreas, ≤2 cm in greatest dimension	
T2 = Tumour limited to the pancreas, >2 cm in greatest dimension	
T3 = Tumour extends beyond the pancreas but without involvement of the coeliac axis or the superior mesenteric artery	
T4 = Tumour involves the coeliac axis or the superior mesenteric artery (unresectable primary tumour)	
Regional lymph nodes (N)	
NX = Regional lymph nodes cannot be assessed	
N0 = No regional lymph node metastasis	
N1 = Regional lymph node metastasis	
(A minimum number of 10 lymph nodes analysed is recommended.)	
The regional lymph nodes are the peripancreatic nodes which may be subdivided as follows:	
Superior	Superior to head and body
Inferior	Inferior to head and body
Anterior	Anterior pancreaticoduodenal, pyloric (for tumours of head only), and proximal mesenteric
Posterior	Posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
Splenic	Hilum of spleen and tail of pancreas (for tumours of body and tail only)
Coeliac	For tumours of head only
Distant metastasis (M)	
M1	Distant metastasis
^a By permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.	

According to the American Hepato-Pancreato-Biliary Association consensus report, pancreatic ductal adenocarcinoma (when metastases are absent) is classified as resectable, borderline resectable or unresectable [14]. At the time of diagnosis, pancreatic ductal adenocarcinoma is deemed resectable in only 15%–20% of patients.

For arterial vessels, three situations can exist: vessel tumour contact <180° without deformation, more than 180° without deformation, or with deformation (i.e. abutment). For venous vessels, one supplementary situation is described: tear drop deformation at the tumour contact (i.e. distortion). With the use of such criteria, CT or MRI are able to determine the non-resectability of the tumour with a high positive predictive value (>90%), but have an insufficient predictive value to affirm resectability (<50%) [15].

Each vessel—superior mesenteric artery (SMA), coeliac axis, and common hepatic artery—has to be assessed individually with attention paid to local encasement or abutment and a possible anatomic variant, as these can be crucial for the surgical decision making. The portal vein (PV) and the superior mesenteric vein (SMV) are the major trunks; any local involvement, thrombus, or hazy attenuation of the fat surrounding the vessel,

must be described [III, B]. Performance and nutritional status, as well as medical comorbidities, are important considerations for all patients with pancreatic cancer, who are being considered for any major treatment modalities (surgery, chemotherapy, or radiation). Advanced age is not a contraindication for any of these treatments.

Biopsy is indicated for patients requiring a diagnosis, such as patients initiating chemotherapy or chemoradiation. EUS-guided fine-needle aspiration allows preoperative tissue confirmation of malignancy, but fear of tumour cell dissemination along the needle track has limited its use. A recent study has indicated that it could be carried out without consequence on efficacy of surgery [16]. It must be recommended, especially in doubtful cases. Percutaneous biopsy of a liver metastasis can be used in metastatic disease, but percutaneous biopsy of the pancreas is contra-indicated in potentially resectable cases [III, B].

Positron emission tomography/CT does not currently add much staging information in most patients with resectable disease and cannot be recommended; its role will be clarified by on-going studies.

Endoscopic retrograde cholangiography and pancreatography (ERCP) is considered as pathognomonic when it shows a double stop on the main bile and pancreatic ducts. However, ERCP had little diagnostic value over CT or MRI for the evaluation of patients with pancreatic cancer [III, B].

The additional use of staging laparoscopy to exclude peritoneal metastasis in resectable or borderline resectable patients has been suggested by some authors, but it is not generally accepted [14] [IV, C].

key points

- CA 19-9 is the most useful tumour marker in pancreatic cancer [IV, B]
- Staging of the patient is initially done by CT scan
- EUS provides some complementary information and allows biopsy of the tumour [II, A]
- MRI should be discussed, especially in cystic lesions [IV, C]

treatment

At the end of the staging procedures, the tumour can be categorised as resectable, borderline resectable, locally advanced or metastatic disease. A treatment decision must be taken in accordance with these findings, including general and nutritional status considerations.

treatment of localised disease

Surgical resection is the only potentially curative treatment of pancreatic adenocarcinoma. However, at diagnosis, <20% of patients have a resectable tumour. The main goal of surgery is to achieve negative (R0) resection margins. After radiological evaluation, only patients with a high probability of R0 resection are good candidates for upfront surgery.

resectability criteria

An expert consensus group has developed criteria to define tumour resectability, to improve patient selection and the rate of

R0 resections [14, 17, 18]. According to the degree of contact between the tumour and the vessels (PV or SMV, SMA, coeliac trunk, and common hepatic artery), tumours are classified as resectable, borderline resectable or locally advanced [IV, B]. For patients with resectable tumours, upfront surgery remains the standard of care. Patients with borderline resectable tumours have a high probability of R1 resection and, as such, should not be considered as good candidates for upfront surgery. Patients with locally advanced or metastatic disease have to be considered as having unresectable tumours. These criteria (which should be considered when defining resectability) [19] have been adopted in the National Comprehensive Cancer Network (NCCN) guidelines (Table 3) [IV, B].

resection and margins

The location and the size of the tumour determine the type of surgery. Patients with tumours in the head of the pancreas are treated with pancreatoduodenectomy (Whipple procedure). Dissection of the right hemi-circumference of the SMA to the right of the coeliac trunk is recommended to obtain a good medial clearance and to improve the rate of R0 resection [20]. In the event of vein involvement, complete venous resection (PV or SMV) followed by reconstruction to obtain R0 resection is possible. However, PV or SMV resection is associated with a lower rate of R0 resection and poor survival, likely due to the inherent aggressiveness of the tumour [21] [IV, B]. Arterial resections during pancreatoduodenectomy are associated with increased morbidity and mortality, and are not recommended. Frozen sections analysis of pancreatic neck transection and common bile duct transection margins is recommended [IV, E].

The International Study Group of Pancreatic Surgery [18] has recently recommended adhering to the guidelines from British Royal College of Pathologists (RCPath) for specimen examination and the R1 definition (margin <1 mm). They advise surgeons to identify the following margins: anterior, posterior, medial, or superior mesenteric groove, SMA, pancreatic transection, bile duct, and enteric. Tumour clearance should be given for all seven margins [IV, B].

For patients with tumours in the body or tail of the pancreas, distal pancreatectomy, including the resection of the body and the tail of the pancreas and the spleen, is usually carried out. Radical anterograde modular pancreatectomy, with dissection of the left hemi-circumference of the SMA, to the left of the coeliac trunk, is recommended to ensure R0 resection [22] [IV, A].

Some recent studies show that minimally invasive techniques (laparoscopy) can reduce the morbidity of pancreatectomies without having a negative impact on cancer outcome [23]. However, data relating to these techniques are insufficient, particularly in relation to oncological results [24]. Therefore, open surgery remains the standard of care [II, C].

lymphadenectomy

In pancreatic cancer, extended lymphadenectomy is not recommended. Standard lymphadenectomy for pancreatoduodenectomy should resect the following lymph nodes:

- Suprapyloric (station 5)
- Infrapyloric (station 6)

- Anterosuperior group along the common hepatic artery (station 8a)
- Along the bile duct (station 12b)
- Around the cystic duct (station 12c)
- On the posterior aspect of the superior (station 13a)
- On the inferior portion of the head of pancreas (station 13a)
- On the right lateral side of SMA (station 14a and 14b)
- On the anterior surface of the superior (station 17a) and inferior portion of the head of pancreas (station 17b)

For tumours of the body and tail of the pancreas, removal of the following lymph nodes is recommended:

- At the splenic hilum (station 10)
- Along the splenic artery (station 11)
- The inferior margin of pancreas

Standard lymphadenectomy should involve the removal of ≥ 15 lymph nodes to allow adequate pathologic staging of the disease. The total number of lymph nodes examined and lymph nodes ratio (number of involved lymph nodes/number of lymph nodes examined) should be reported in the pathologic analysis [25] [IV, A].

age and pancreatectomy

Some authors have proposed a score that accurately predicts the risk of perioperative mortality in patients undergoing pancreatic resection. This surgical outcomes analysis and research (SOAR) pancreatectomy score is calculated based on preoperative factors (http://www.umassmed.edu/surgery/toolbox/panc_mortality_custom/) [26] [IV, C].

preoperative biliary drainage

A recent prospective and randomised trial demonstrated an increased complication rate associated with routine preoperative biliary drainage [27] [I, E]. However, patients in the trial had a total bilirubin level below 250 $\mu\text{mol/l}$. Therefore, the correct approach in patients with higher levels remains undefined. If jaundice is present at diagnosis of pancreatic carcinoma, endoscopic drainage should only be carried out preoperatively in patients with active cholangitis, or in those whom resection for cure cannot be scheduled within 2 weeks of diagnosis, and in those with a bilirubin level below 250 $\mu\text{mol/l}$.

adjuvant treatment after surgical resection

Considering the poor results of surgery alone in pancreatic carcinoma, many efforts involving chemotherapy, radiotherapy or both have been made to improve the 5-year survival of these patients.

adjuvant chemotherapy

Postoperative adjuvant chemotherapy was evaluated in several randomised trials. In the ESPAC-1 multicentre randomised trial, a 2×2 factorial design, 289 patients treated with curative resection and complete gross resection received one of four therapeutic modalities: exclusive adjuvant chemotherapy [bolus 5-fluorouracil (5-FU) and folinic acid], chemoradiation only (split course 40 Gy plus 5-FU), or chemoradiation followed by chemotherapy or surveillance alone [28]. Patients who received chemotherapy had a longer median survival (20.1 versus 15.5

Table 3. Definition of resectability according to NCCN guidelines [19]

Resectability status	Arterial	Venous
Resectable	No arterial tumour contact [coeliac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)]	No tumour contact with the superior mesenteric vein (SMV), or portal vein (PV) or <180° contact without vein contour irregularity
Borderline resectable	<p>Pancreatic head/uncinate process</p> <ul style="list-style-type: none"> • Solid tumour with CHA without extension to coeliac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA ≤180° • Presence of variant arterial anatomy (e.g. accessory right hepatic artery) and the presence and degree of tumour contact should be noted if present as it may affect surgical planning <p>Pancreatic body/tail</p> <ul style="list-style-type: none"> • Solid tumour contact with the CA of <180° • Solid tumour contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery (some members prefer these criteria to be in the unresectable category) 	<ul style="list-style-type: none"> • Solid tumour contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessels proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumour contact with the inferior vena cava (IVC)
Unresectable	<ul style="list-style-type: none"> • Distant metastases <p>Pancreatic head/uncinate process</p> <ul style="list-style-type: none"> • Solid tumour contact with SMA >180° • Solid tumour contact with the CA >180° • Solid tumour contact with the first jejunal SMA branch <p>Body and tail</p> <ul style="list-style-type: none"> • Solid tumour contact with the SMA and CA • Solid tumour contact with the CA and aorta 	<p>Pancreatic head/uncinate process</p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) • Contact with most proximal draining jejunal branch into SMV <p>Body and tail</p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

months, $P = 0.009$) compared with patients who did not. The results of the CONKO-001 trial comparing gemcitabine to observation confirmed the benefit of adjuvant chemotherapy [29]. Gemcitabine administered for 24 weeks improved disease-free survival (13.4 versus 6.9 months, $P < 0.001$) and overall survival (OS) (22.8 versus 20.2 months, $P = 0.005$). The ESPAC-3 trial compared the administration of adjuvant chemotherapy with six cycles of either fluorouracil and folinic acid or gemcitabine [30]. No difference in OS, recurrence-free quality of life or survival was observed. Recent information suggests that gemcitabine may only be effective in patients with the enzymatic equipment to transport gemcitabine into the tumour cell (hENT1) and metabolically activate it [31]. Unfortunately, there is no sufficiently reliable commercial immunohistochemical antibody allowing the routine use of this test before giving gemcitabine, and this is still not a factor when selecting a chemotherapy regimen. At present, both 5-FU/folinic acid and gemcitabine can be considered as a standard of care [I, A].

adjuvant chemoradiation

Three randomised trials compared the benefits of adjuvant chemoradiation after pancreatic resection against surveillance alone. A first trial by the GastroIntestinal Tumour Study Group evaluating chemoradiation (40 Gy + 5-FU) was stopped prematurely after the treatment of 40 patients. An interim analysis revealed a low rate of inclusion and a significant difference in survival in favour of the chemoradiation arm. After the many criticisms made against this

first trial, the EORTC trial compared chemoradiation with simple surveillance after pancreaticoduodenectomy. In the subgroup of 114 patients with pancreatic tumour(s), the survival benefit for adjuvant chemoradiation was not significant. The ESPAC-1 trial has even suggested a deleterious effect of adjuvant chemoradiation, with recurrence-free survival of 10.7 months in the chemoradiation group versus 15.2 months in its absence ($P = 0.04$) [28]. Even in R1 patients, no benefit was observed with adjuvant chemoradiation. Thus, no chemoradiation should be given to patients after surgery except in clinical trials [I, E].

recommendations for treatment of localised disease

- A multidisciplinary team is necessary
- Tumour clearance should be given for all seven margins identified by the surgeon [IV, B]
- Standard lymphadenectomy should involve the removal of ≥15 lymph nodes to allow adequate pathologic staging of the disease [IV, A]
- Adjuvant treatment is done with either gemcitabine or 5-FU folinic acid [I, A]
- No chemoradiation should be given to patients after surgery except in clinical trials [I, E]

treatment of non-resectable disease

In 30%–40% of patients, while the tumour is confined to the pancreatic region, resection is not feasible, mainly due to

vascular invasion. The division of this subgroup of patients into two different categories has been shown recently but it is not always easy to define.

borderline resectable lesions

Tumours are considered resectable upon good response to neoadjuvant treatment including induction chemotherapy, preoperative chemoradiation or a combination of both. Small retrospective studies and two meta-analyses, including patients with both borderline and resectable lesions, have reported an even better survival for these patients than for those with immediately resectable tumours [32, 33]. While the heterogeneity of the trials on neoadjuvant therapy in borderline resectable pancreatic cancer limits the power of any conclusion, many individual series demonstrate improved R0 resection rates and promising survival rates. The majority of studies used full-dose radiotherapy paired either with capecitabine, 5-FU or reduced doses of gemcitabine, or even a combination of gemcitabine plus oxaliplatin. It is impossible at this time to recommend any chemoradiation treatment other than the classical combination of capecitabine and radiotherapy [IV, C]. To improve the disease control and to intensify the treatment of the systemic disease, it has recently been proposed to begin treatment with chemotherapy before starting chemoradiation. Again, due to heterogeneity of the small retrospective series, it is very difficult to recommend a specific schedule of treatment, although some series have reported better survival using a multimodal strategy than that observed with upfront surgery in patients with clearly resectable tumours [34]. Recent chemotherapy regimens, such as FOLFIRINOX [folinic acid (leucovorin)/5-FU/irinotecan/oxaliplatin], have already shown promising results in small series of patients with borderline resectable lesions [30%–45% of objective response rate (ORR)]. A trial, which was stopped prematurely, reported interesting response rates, median progression-free survival (PFS) and OS for patients treated with chemotherapy (gemcitabine) followed by chemoradiation (gemcitabine, 5-FU, cisplatin) versus chemoradiation alone [35]. However, this small trial does not allow any definite conclusions to be drawn. Patients with borderline resectable lesions should be included in clinical trials wherever possible. If this is not feasible, a period of chemotherapy followed by chemoradiation and then surgery appears to be the best option [IV, B].

recommendations for treatment of borderline resectable disease

- Patients with borderline resectable lesions should be included in clinical trials wherever possible
- In routine practice, if the patient is not included in a trial, a period of chemotherapy (gemcitabine or FOLFIRINOX) followed by chemoradiation and then surgery appears to be the best option [IV, B]

locally advanced disease

When the patient has no metastases and the tumour is not considered as borderline resectable, the tumour is defined as truly locally advanced (Table 3). Treatment of this group of patients remains highly controversial. Regardless of the treatment strategy, the average OS for these patients remains low (<1 year) in the oldest studies. However, in the recent LAP07 trial [36], which included only patients with locally advanced disease,

the overall median survival of the patients treated with chemotherapy alone was 16 months. This may be related to more active treatment of the patients diagnosed with metastasis.

When compared with best supportive care, chemoradiation showed a benefit in terms of survival in a small phase III trial [37].

Old trials suggested the superiority of chemoradiation over radiotherapy and chemotherapy alone, which was confirmed by meta-analyses [38] [I, B].

Concerning the comparison with chemotherapy alone, while poor-quality randomised trials have suggested a benefit in favour of chemoradiation, two recent trials showed opposite results. In a French trial using an obsolete regimen of chemoradiation (50 Gy + 5-FU cisplatin), the survival was better in the gemcitabine alone arm (13 versus 8.6 months [39]). In another trial, comparing chemoradiation with gemcitabine plus radiotherapy versus gemcitabine alone, the OS was significantly improved in the chemoradiation arm (11.1 versus 9.2 months) yet toxicity also increased by combining the treatment modalities [40] [II, C].

While many trials have evaluated the best combined regimen of chemotherapy and radiotherapy, no clear definition has been made of a standard of care. For instance, it has been suggested that gemcitabine could be a better sensitiser and chemotherapeutic agent to combine with radiotherapy than fluoropyrimidines in the treatment of locally advanced pancreatic cancer. However, evidence from one randomised trial favoured capecitabine as less toxic and more active than gemcitabine in this setting [41] [I, E].

In an attempt to combine the advantages of both chemotherapy and chemoradiation, the use of chemoradiation in patients showing no sign of progressive disease after 3 months of chemotherapy alone was suggested to be beneficial. However, no clear advantage in favour of the chemoradiation was found in a recent large randomised trial investigating this strategy. This trial was planned to include 722 patients, and was stopped for futility after the inclusion of 449 patients (only 269 assessable for the main end point, OS). They were treated with 4 months of gemcitabine ±erlotinib (first randomisation) and then randomised to receive either two supplementary months of gemcitabine or chemoradiation [36]. The median OS showed no improvement in the chemoradiation group (15.2 versus 16.4 months) even though local tumour control did seem a little bit better in this group [I, D]. Several small retrospective and prospective studies have suggested that FOLFIRINOX may be able to obtain an interesting response rate in this population, and may have rendered some patients with locally advanced cancers resectable. However, it is too early to recommend this treatment and trials are ongoing. Thus, the standard of care for these patients currently remains as 6 months of gemcitabine [I, B].

recommendations for treatment of locally advanced disease

- The standard of care is 6 months of gemcitabine [I, A]
- A minor role of chemoradiation in this subgroup of patients has been observed [I, A]
- It is impossible to recommend any chemoradiation treatment other than the classical combination of capecitabine and radiotherapy [IV, C]

treatment of advanced/metastatic disease

palliative and supportive care

Before even considering systemic chemotherapy, patients with metastatic pancreatic cancer may need interventions to provide relief of biliary and/or duodenal obstruction, malnutrition, and pain.

In the event of a biliary obstruction due to a pancreatic tumour, the endoscopic placement of a metallic biliary stent is strongly recommended. The endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy [42] [II, B].

Duodenal obstruction is preferentially managed by endoscopic placement of an expandable metal stent when possible, and is favoured over surgery [42] [IV, B].

Pain is also considered to be a major priority in these patients and it is observed in almost all patients with advanced pancreatic carcinoma. It must be managed aggressively following standard guidelines on pain treatment, without any major specificity due to the location of the disease [43]. However, radiotherapy can be used at this stage to control the coeliac pain induced by a primary pancreatic tumour. Oral supplementation of pancreatic enzyme has been suggested to help control pain; though this has never been proven by a randomised study and should not be considered as a reason to prescribe such drugs. The input of a pain control specialist is often mandatory.

Coeliac plexus block (CPB) can lead to pain control and frequently to a decrease in the total amount of systemic drugs and their side-effects. The endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy [42] [II, B].

While it was classically done percutaneously, one new way to perform CPB is represented by EUS guidance. Previous studies have suggested a decrease in success rate when there is evidence of disease outside the pancreas, such as coeliac or portal adenopathy. CPB should be carried out in the presence of resistant pain and only if the clinical condition of the patient is not poor.

recommendation for palliative and supportive care in advanced/metastatic disease

- Duodenal obstruction is preferably managed by endoscopic placement of an expandable metal stent when possible, and is favoured over surgery [42] [IV, B]

oncologic treatment

Over the past two decades, the development of improved systemic treatments has been a top priority for pancreatic cancer. In 1997, gemcitabine monotherapy was established as the standard of care, after being shown to offer greater clinical benefit and a small survival improvement over weekly 5-FU therapy [44] [II, A]. Since then, gemcitabine chemotherapy combinations have been intensely evaluated. Despite frequently encouraging early-phase data, phase III trials have not given confirmatory results. These combinations have included cytotoxic agents such as irinotecan, 5-FU, cisplatin, oxaliplatin and capecitabine. Three separate meta-analyses [45] reported a statistically significant survival advantage of combination therapy compared with gemcitabine alone [I, C]. Capecitabine and cisplatin-based combinations have

produced the greatest benefit. However, due to the low level of evidence, there have been no clear changes in the daily clinical management of these patients. Even with modern agents such as tyrosine kinase inhibitors or monoclonal antibodies against various targets, the results of large phase III trials evaluating the addition of these drugs to gemcitabine have been disappointing. The targeted therapies tested have included bevacizumab, cetuximab, aflibercept, and anti-insulin growth factor agents. The exception is the combination of gemcitabine and the EGFR tyrosine kinase inhibitor erlotinib, which gained regulatory approval following a 12-day improvement in median survival compared with gemcitabine alone in a large randomised trial [46]. Arguably, however, this duration of survival prolongation is clinically irrelevant for most patients; therefore, erlotinib has not been widely used in this disease. The inefficacy of erlotinib in locally advanced disease which was shown in the LAP07 trial [36] is an additional argument against the use of this drug for this indication.

Major improvements in the treatment of metastatic disease came with the demonstration of the efficacy of a 5-FU-based triplet chemotherapy. The FOLFIRINOX regimen has proven superior to gemcitabine alone, in terms of efficacy, despite an increase in toxicity [47]. This trial included patients who were selected based on their ability to receive this aggressive chemotherapy [Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and normal or subnormal serum bilirubin level]. The median OS was 11.1 months in the FOLFIRINOX group compared with 6.8 months in the gemcitabine group [hazard ratio (HR) for death, 0.57; 95% confidence interval 0.45–0.73; $P < 0.001$]. Median PFS and ORR were also statistically better with FOLFIRINOX than with gemcitabine. More adverse events were noted in the FOLFIRINOX group; 5.4% of patients in this group had febrile neutropaenia. FOLFIRINOX is an option for the treatment of patients with metastatic pancreatic cancer and good performance status [I, A]. After decades of failed randomised trials that have tried to add a drug to gemcitabine alone, a recent trial has shown positive results, demonstrating that the combination of gemcitabine plus nab-paclitaxel is better than gemcitabine alone in metastatic patients [48]. A total of 861 patients were randomly assigned to receive nab-paclitaxel plus gemcitabine or gemcitabine alone. The median OS was 8.5 months in the nab-paclitaxel–gemcitabine group compared with 6.7 months in the gemcitabine group (HR for death, 0.72). Both median PFS and response rate were improved in the nab-paclitaxel–gemcitabine group compared with gemcitabine alone. In the nab-paclitaxel–gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days [I, A].

There are no data concerning a direct comparison of FOLFIRINOX and Gem-nab-paclitaxel. An indirect comparison of the two regimens may suggest a slightly greater activity but also higher toxicity of FOLFIRINOX. No specific data favours the use of one regimen over the other in a defined subgroup of patients. Thus, either of these two options can be offered to patients with serum bilirubin levels less than 1.5× upper limit of normal (ULN) and good performance status (ECOG 0-1) [I, A].

In conclusion, it can be considered that there are three options to treat patients with a metastatic pancreatic cancer according to their general status:

- 1) For patients with performance status of 3/4, with significant morbidities and a very short life expectancy: only

- symptomatic treatment can be considered. Even chemotherapy with gemcitabine cannot be considered for such patients.
- 2) In very selected patients with ECOG performance status 2 due to heavy tumour load, gemcitabine and nab-paclitaxel can be considered for best chance of response [II, B].
 - 3) For patients with performance status of 2 and/or bilirubin level higher than $1.5 \times \text{ULN}$: monotherapy with gemcitabine could be considered [I, A]
 - 4) If the performance status of the patient is 0 or 1 and the bilirubin level is below $1.5 \times \text{ULN}$ two types of combination chemotherapy—the FOLFIRINOX regimen or the combination of gemcitabine and nab-paclitaxel—should be considered [I, A]

The efficacy of the treatment has to be evaluated every two months with a comparative CT scan. The treatment has to be stopped if a RECIST progression is observed and second-line treatment has to be discussed.

second-line treatment

A first randomised trial (168 patients) has shown, in patients with advanced gemcitabine-refractory pancreatic cancer, that second-line 5-FU, folinic acid and oxaliplatin, significantly extend the duration of OS when compared with 5-FU, folinic acid alone [49]. These results have not been confirmed by a more recent Canadian trial [45]. Very recently, combination of MM-398, a nanoliposomal encapsulation of irinotecan, and 5-FU, folinic acid has shown an improvement of OS (6.1 versus 4.2 months), PFS and ORR in the intent-to-treat population over 5-FU/LV alone. Second-line therapy of pancreatic cancer has to be considered in terms of risk benefit for the patient. If the general status remains correct, considering the conflicting results on the use of oxaliplatin, MM-398 when available in all countries may be the best option for second-line treatment of these patients [II, B].

specific treatment of rare forms

Patients with pancreatic cancer related to BRCA1 or BRCA2 mutations have been shown to be more sensitive to platinum salt treatment. These patients may be good candidates for FOLFIRINOX or even 5-FU cisplatin producing more DNA adducts [50], while trials with PARP inhibitors are ongoing in this specific population.

Pancreatic carcinoma with acinar cells seems to have a better prognosis. There is no specificity for the treatment of these patients at this time; therefore, the FOLFIRINOX regimen can be used. Pancreatic acinar cell carcinoma has recently shown recurrent RAF fusions and frequent inactivation of DNA repair genes [51]: these could be targetable in the near future and lead to new treatment options.

recommendations for oncological treatment of advanced/metastatic disease

- Biliary stenting: the endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy [II, B]
- Pain control is mandatory and frequently needs the help of a pain specialist

- If the performance status is 3/4, with significant morbidities and a very short life expectancy: only symptomatic treatment can be considered
- In very selected patients with ECOG performance status 2 due to heavy tumour load, gemcitabine and nab-paclitaxel can be considered for best chance of response [II, B]
- If the performance status of the patient is 2 and/or the bilirubin level is higher than $1.5 \times \text{ULN}$: a monotherapy with gemcitabine should be considered [I, A]
- If the performance status of the patient is 0 or 1 and the bilirubin level is below $1.5 \times \text{ULN}$ two types of combination chemotherapy—the FOLFIRINOX regimen or the combination of gemcitabine and nab-paclitaxel—should be considered [I, A]

personalised medicine

Among the validated drugs for pancreatic cancer, there is currently no relevant biomarker used in the medical decision making and none should be used in clinical practice.

Emerging data from sequencing initiatives in pancreatic cancer are unveiling a vast array of molecular aberrations and also a significant inter- and intra-tumoral heterogeneity [52]. This introduces major challenges when trying to identify the most relevant targeted therapy. The most frequent genes harbouring genetic aberrations in pancreatic cancer are KRAS, TP53, CDKN2A, and SMAD4. Among the numerous biomarkers tested in pancreatic cancer, some deserve particular attention.

Loss of SMAD4 expression in pancreatic cancer has been associated with a poorer prognosis [53], which could be useful for prognostic stratification and therapeutic decision making.

BRCA2, PALB2, ATM, or mismatch repair (hMLH1 and MSH2) gene mutations, which subsequently cause a DNA damage repair deficiency, might be more sensitive to platinum or PARP inhibitors.

Secreted protein acidic and rich in cysteine (SPARC) expression in the peritumoural stroma has been associated with a longer OS in patients receiving nab-paclitaxel + gemcitabine, compared with those receiving gemcitabine alone. However, this was not confirmed upon analysis of the data from the MPACT phase III trial.

STK11 acts as a tumour suppressor gene, germline mutations of STK11 are associated with Peutz-Jeghers syndrome. *In vitro* data and case reports suggest that mTOR inhibitors demonstrate anti-tumour activity [54].

The hedgehog pathway is an early and late mediator of pancreatic cancer tumour genesis [55]. Smoothed inhibitor sari-degib, which failed to provide any benefit in tests on non-selected pancreatic cancer, might be of particular interest among patients with hedgehog signalling activation. Mutations in PTCH are known to activate hedgehog signalling in experimental models, and are detected in 2% of patients with pancreatic cancer.

The human equilibrative nucleoside transporter 1 (hENT1) is responsible for the intracellular uptake of the prodrug gemcitabine into tumour cells. While tumour hENT1 expression is thereby presumed to be a predictive biomarker of gemcitabine efficacy, contradictory data render its exact role unclear. In the ESPAC-3 trial, patients with high pancreatic hENT1 expression, treated with gemcitabine, had a longer survival compared with those with a low expression [56]. In the phase III AIO-

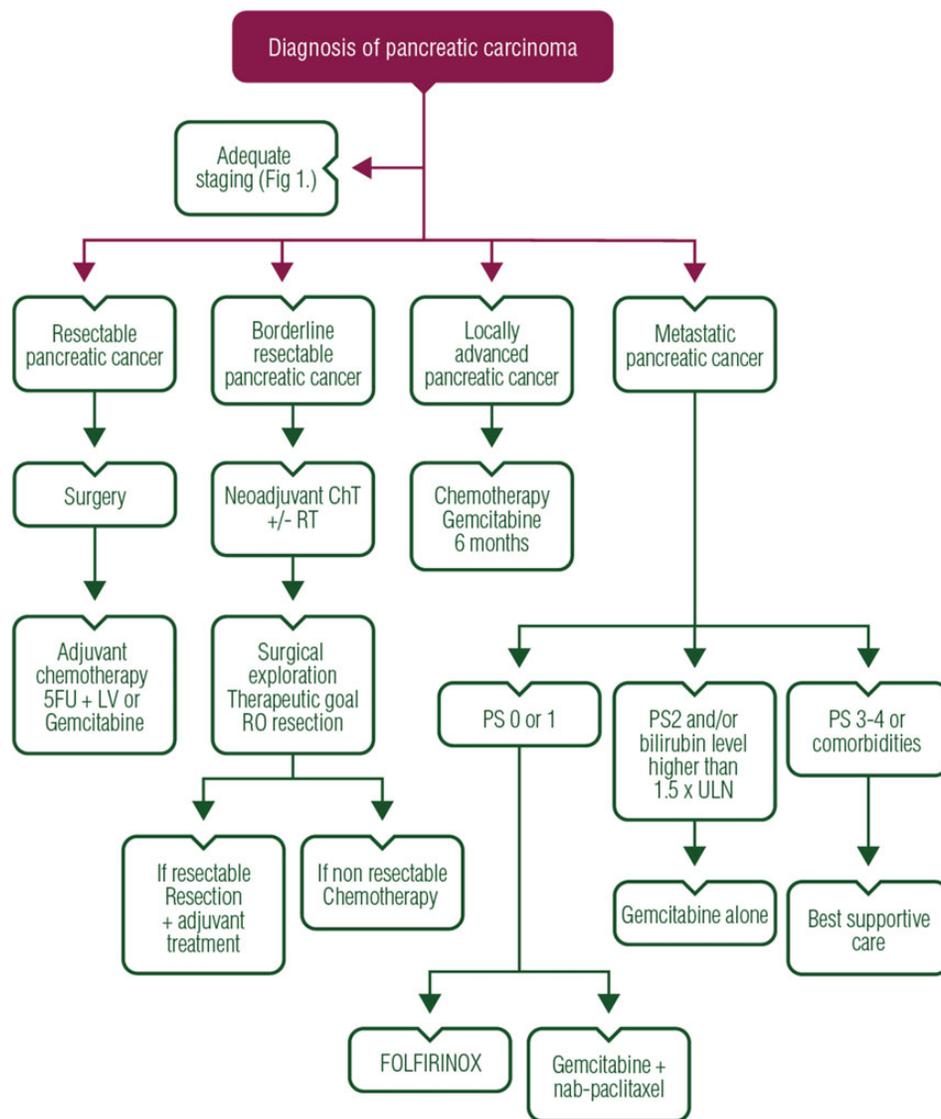


Figure 2. Treatment strategy. ChT, chemotherapy; RT, radiotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; PS, performance status; ULN, upper limit of normal.

PK0104 trial, a phase III trial that compared gemcitabine/erlotinib followed by capecitabine with capecitabine/erlotinib followed by gemcitabine, no difference in OS was found with respect to hENT1 expression [57].

In the recent whole-sequencing analysis [10], a significant proportion of tumours harboured focal amplifications, many of which contained druggable oncogenes (ERBB2, MET, FGFR1, CDK6, PIK3R3, and PIK3CA), but at low prevalence among individual patients. Genomic instability co-segregated with inactivation of DNA maintenance genes (BRCA1, BRCA2, or PALB2) and a mutational signature of DNA damage repair deficiency. Of eight patients who received platinum therapy, four of five individuals with these measures of defective DNA maintenance responded.

key points

- A few targetable mutations have been identified in pancreatic cancer

- There is no role today for personalised medicine in this cancer [IV, C]

follow-up and long-term implications

Considering the poor prognosis of the disease upon diagnosis of a recurrence, there is no evidence that regular follow-up after initial therapy with curative intent has any impact on the outcome. Follow-up visits should concentrate on symptoms, nutrition, and psycho-social support.

recommendations for follow-up

- There is no evidence that regular follow-up after initial therapy with curative intent is useful [IV, D].

summary of recommendations

An overview of recommendations related to therapy is given in Figure 2 and Table 4.

Table 4. Summary of key points and recommendations

Incidence and epidemiology
<ul style="list-style-type: none"> • 5%–10% of pancreatic cancers are due to genetic alteration • The main risk factors are tobacco, and factors related to dietary habits (BMI, red meat intake, low fruit and vegetables intake, diabetes, alcohol intake)
Diagnosis
<ul style="list-style-type: none"> • Early symptoms of pancreatic cancer result from a mass effect • Common presenting symptoms include jaundice, pain, weight loss, steatorrhea
Pathology
<ul style="list-style-type: none"> • 95% of pancreatic cancers are adenocarcinomas • Mucinous lesions of the pancreas have potential for malignant progression
Molecular biology
<ul style="list-style-type: none"> • The most frequent precursors are microscopic PanIN, followed by IPMN and mucinous cystic neoplasm • Multiple combinations of genetic mutations are commonly found in pancreatic cancers • Some of the recent genetic mutations discovered could become targetable in the near future
Staging
<ul style="list-style-type: none"> • CA 19-9 is the most useful tumour marker in pancreatic cancer [IV, B] • Staging of the patient is initially done by CT scan • EUS provides some complementary information and allows biopsy of the tumour [II, A] • MRI should be discussed, especially in cystic lesions [IV, C]
Treatment of localised disease
<ul style="list-style-type: none"> • A multidisciplinary team is necessary • Tumour clearance should be given for all seven margins identified by the surgeon [IV, B] • Standard lymphadenectomy should involve the removal of ≥ 15 lymph nodes to allow adequate pathologic staging of the disease [IV, A] • Adjuvant treatment is done with either gemcitabine or 5-FU folinic acid [I, A] • No chemoradiation should be given to patients after surgery except in clinical trials [I, E]
Treatment of non-resectable disease: borderline resectable lesions
<ul style="list-style-type: none"> • Patients with borderline resectable lesions should be included in clinical trials wherever possible • In routine practice, if the patient is not included in a trial, a period of chemotherapy followed by chemoradiation and then surgery appears to be the best option [IV, B]
Treatment of non-resectable disease: locally advanced disease
<ul style="list-style-type: none"> • The standard of care is 6 months of gemcitabine [I, A] • A minor role of chemoradiation in this subgroup of patients has been observed [I, A] • It is impossible to recommend any chemoradiation treatment other than the classical combination of capecitabine and radiotherapy [IV, C]
Treatment of metastatic disease
<ul style="list-style-type: none"> • Palliative and supportive care: duodenal obstruction is preferably managed by endoscopic placement of an expandable metal stent when possible, and is favoured over surgery [V, B] • Biliary stenting: the endoscopic method is safer than percutaneous insertion and is as successful as surgical hepatojejunostomy [II, B]

- Pain control is mandatory and frequently needs the help of a pain specialist
- For patients with performance status of 3/4, with significant morbidities and a very short life expectancy: only symptomatic treatment can be considered
- In very selected patients with ECOG performance status 2 due to heavy tumour load, gemcitabine and nab-paclitaxel can be considered for best chance of response [II, B]
- For patients with performance status of 2 and/or bilirubin level higher than $1.5 \times$ ULN: a monotherapy with gemcitabine could be considered [I, A]
- If the performance status of the patient is 0 or 1 and the bilirubin level is below $1.5 \times$ ULN two types of combination chemotherapy—the FOLFIRINOX regimen or the combination of gemcitabine and nab-paclitaxel—should be considered [I, A]

Personalised medicine

- A few targetable mutations have been identified in pancreatic cancer
- There is no role today for personalised medicine in this cancer [IV, C]

Follow-up and long-term implications

- There is no evidence that regular follow-up after initial therapy with curative intent is useful [IV, D]

BMI, body mass index; PanIN, pancreatic intraepithelial neoplasia; IPMN, intraductal papillary mucinous neoplasm; CT, computed tomography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; 5-FU, 5-fluorouracil; ULN, upper limit of normal; ECOG, Eastern Cooperative Oncology Group.

Table 5. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [58].

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. The relevant literature has been selected by the expert authors. A summary of recommendations is given in Table 4. Levels of evidence and grades of recommendation have been applied using the system shown in Table 5. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

MD has reported participation in advisory boards and at symposiums with Celgene. TS has reported participation to advisory boards and at symposiums with Celgene and research funding from Celgene. JLVL has reported participation to advisory boards and at symposiums with Celgene and research funding from Celgene. The other authors have reported no potential conflicts of interest.

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