Pancreatic adenocarcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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epidemiology and risk factors

In Europe, cancer of the pancreas is the seventh most frequent cancer, accounting for some 2.8% of cancer in men and 3.2% in women. It is the fifth leading cause of cancer-related death with ∼70 000 estimated deaths each year and predicted to become the fourth cause of cancer death in both sexes in due course in the European Union [1, 2]. In men, the estimated annual average incidence rate is 11.6 per 100 000 ranging from 4.7 (Cyprus) to 17.2 (Hungary). Mortality in men is ∼35 000 cases per year. The estimated average incidence rate in women is 8.1 per 100 000 ranging from 2.1 (Cyprus) to 11.4 (Finland). Mortality in women is also ∼35 000 cases per year [3]. Incidence increases with age and the majority of cases are diagnosed above the age of 65. Smoking, obesity and dietary factors such as high consumption of processed meat increase the risk for pancreatic cancer [4, 5] (II).

Pancreatic cancer still has a dismal prognosis. According to the EUROCARE 4 study, the overall 1-year survival rate in Europe ranges from ∼11% in Malta to 28.3% in Belgium; >95% of those affected die of the disease. The high mortality rate is due to late diagnosis, early metastasis and poor response to chemo- and radiotherapy in most cases. Moderate improvement in survival in resectable pancreatic cancer has been achieved by adjuvant chemotherapy. Recently, some improvement in survival in the metastatic setting could be achieved by novel combination chemotherapy (see below).

histology and genetics

The major histological type of pancreatic cancer is ductal pancreatic adenocarcinoma accounting for >80% of pancreatic neoplasms. Other types are acinar cell carcinoma or neuroendocrine tumors. Most ductal pancreatic cancers (90%) are considered sporadic. There are some genetic conditions that are associated with an increased risk of pancreatic cancer, e.g. hereditary pancreatitis, Peutz–Jeghers syndrome, familial malignant melanoma, hereditary breast and ovarian cancer syndrome and Lynch syndrome. Hereditary conditions account for ∼5%–10% of pancreatic cancers.

About 75% of all ductal pancreatic carcinomas occur within the head or neck of the pancreas, 15%–20% in the body and 5%–10% in the tail of the pancreas.

More than 80% of ductal pancreatic cancers exhibit KRAS mutations, predominantly a G12V or G12D mutation. Furthermore, ∼90% of the tumors exhibit deletions, mutations or epigenetic alterations in the CDKN2 gene. Nearly 50% have mutations in the tumor suppressor p53 and also ∼50% exhibit mutations or homozygous deletions in the DPC4/Smad4 gene.

symptoms and diagnosis

Late diagnosis of pancreatic cancer results from a lack of early symptoms of the disease and the fact that even late symptoms are often not characteristic (abdominal or back pain). Currently there are no efficient screening tools available that can be recommended outside a high risk population, e.g. those suffering from the hereditary conditions outlined above. For those, regular endoscopic ultrasound (EUS) that allows the detection of small lesions and magnetic resonance imaging (MRI) is recommended [6, 7]. (III; B)

In case of a tumor of the pancreatic head that compresses the bile duct patients present with painless jaundice. Abdominal pain, back pain or weight loss are usually signs of late-stage disease. Sometimes patients also present with newly diagnosed diabetes or pancreatitis.

For the diagnosis of suspected pancreatic cancer abdominal ultrasound is useful for the initial examination. For further evaluation, EUS, contrast-enhanced multi-detector computed tomography (MD-CT) and MRI combined with magnetic resonance cholangiopancreatography (MRCP) are more appropriate (level of evidence: good clinical practice). EUS,

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MD-CT and MRI together with MRCP have the highest sensitivity for the detection of pancreatic cancer and provide additional information on the pancreatic and the bile duct. Furthermore, EUS allows biopsy and/or fine needle aspiration cytology. MD-CT and MRI allow evaluation of invasion of vessels and metastasis (e.g. lymph nodes, liver, peritoneal cavity). Endoscopic retrograde cholangiopancreatography (ERCP) has a role only to relieve bile duct obstruction. However, in the preoperative setting ERCP and biliary stenting should only be performed if surgery cannot be done expeditiously (I; B). A recent trial demonstrated a substantial increase in serious complications in the group undergoing biliary stenting prior to surgery for cancer of the head of the pancreas [8]. Positron emission tomography scanning (PET scan) has no role in the diagnosis of pancreatic cancer since it does not allow a reliable differentiation between chronic pancreatitis and pancreatic cancer [9].

Tumor markers such as CA19.9 are of limited diagnostic value since CA19.9 is not specific for pancreatic cancer and persons lacking the Lewis antigen are unable to synthesize CA19.9. Furthermore, high levels of CA19.9 are also found if a patient is jaundiced with cholestasis. CA19.9 levels are therefore insufficient to make a diagnosis at this time. Baseline CA19.9 can be used to guide treatment and follow-up and may have a prognostic value in absence of cholestasis.

Histological proof of malignancy is only mandatory in unresectable cases or when a neoadjuvant strategy is planned. For patients who will undergo surgery with radical intent, a previous biopsy is not obligatory. Biopsy should be restricted to cases, e.g. in which imaging results of a pancreatic lesion are ambiguous. Here, EUS-guided biopsy is preferred and percutaneous sampling should be avoided due to a lower risk of tumor seeding using EUS guided biopsy [10]. Metastatic lesions can be biopsied percutaneously under ultrasound or CT guidance or during EUS.

staging and risk assessment

The established staging system for pancreatic cancer is the one developed by the TNM committee of the AJCC-UICC (see Table 1). Stage grouping of pancreatic cancer is presented in Table 2. MD-CT or MRI plus MRCP should be used for staging. EUS can complement the staging by providing information on vessel invasion and potential involvement of lymph nodes and is the preferred means to obtain a biopsy of the pancreatic lesion.

MD-CT of the chest is recommended to evaluate potential lung metastases. In the absence of typical symptoms, a bone scan is not useful since only a few patients with pancreatic cancer present with bone involvement at diagnosis. PET scan is currently not routinely recommended for the staging of ductal pancreatic cancer.

The National Comprehensive Cancer Network (NCCN) guidelines provide imaging criteria of borderline resectable and definitely irresectable pancreatic cancers depending upon the extent of vein invasion as well as artery invasion [11].

Laparoscopy may detect small peritoneal and liver metastases changing the therapeutic strategy in <15% of patients. It can be performed before resection in left-sided large tumors and/or in case of high CA19.9 levels or when neoadjuvant treatment is considered. However, the extent of cancer spread in cancer of the pancreas can often be determined accurately only during surgery.

Recent data have shown that upon thorough reevaluation of a resected specimen in many cases a previous R0 resection had to be regarded as R1 [12]. The concept of the circumferential resection margin (CRM) has been established for the analysis

Table 2. Stage grouping of pancreatic cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Table 1. TNM classification for pancreatic cancer

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ[b]
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to the pancreas, >2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

of rectal cancer but can also be adapted to the situation in pancreatic cancer. The definition of the CRM requires a specific pathological procedure to be correctly assessed [13]. Therefore, specific recommendations for the histopathological reporting of carcinomas of the pancreas have been published, e.g. by the British Royal College of Pathologists (http://www.rcpath.org/NR/rdonlyres/954273A2-3F01-4B97-B0F6-C136231DF65F/0/datasethistopathologicalreporting carcinomasmay10.pdf). Here, painting of the CRM of the pancreas with an agreed color code is recommended and the recommended techniques to dissect the surgical specimen are described (Table 3). The CRM status is as a key prognostic factor. However, the rates of margin involvement and local tumor recurrence are often incongruous. Nevertheless, using a standardized, detailed pathology examination protocol, microscopic margin involvement is a common finding in pancreatic carcinoma (>75%) and correlates with survival. There is a controversy over the adequate minimum clearance for pancreatic, common bile duct and ampullary carcinoma. The British guidelines currently recommend that a carcinoma <1 mm from a resection margin is considered to be incompletely excised. Another established prognostic factor is the post-resection CA19.9 level.

treatment options

The only curative treatment of pancreatic cancer is radical surgery. This approach is mainly suitable for patients with early stage of disease mainly stage I and some stage II.

Age is no criterion to select patients for a surgical approach. Elderly patients do benefit from radical surgery. However, comorbidity can be a reason to abstain from an otherwise possible resection especially in patients older than 75–80 years.

The major goal of surgery is the R0 resection (I; A). In case of tumors of the pancreatic head, partial pancreatico-duodenectomy is the treatment of choice. Preservation of the pylorus does not confer a survival advantage for the patients [14]. Cancer of the pancreatic body or tail is usually treated by distal resection of the pancreas. In some cases total pancreatectomy is required.

A critical issue is to define resectability in pancreatic cancer. It is recommended to refer to the NCCN criteria for resectability/irresectability [11]. If the tumor is deemed not resectable, the aim of treatment is prolongation of survival and palliation of symptoms related to the disease by optimal local control and control of metastatic growth.

R0 resection can be possible despite infiltration of the tumor into neighboring organs (e.g. the duodenum). Infiltration of the portal or superior mesenteric vein can still allow an R0 resection, but confers a worse prognosis. Infiltration of the celiac artery or the superior mesenteric artery by the tumor rarely allows a R0 resection of the tumor and should therefore be regarded as non-curative surgery. There is no proven indication and no clear recommendation for such operations.

In pancreatic cancer there is no evidence that extended lymphadenectomy is beneficial. Standard lymphadenectomy comprises dissection of the lymph nodes of the hepatoduodenal ligament, the common hepatic artery, the portal vein, the right sided celiac artery lymph node and

lymph nodes at the right half of the superior mesenteric artery. The lymph node ratio (LNR, number of involved LN/number of examined LN) should be indicated since an LNR ≥ 0.2 is a negative prognostic factor [15] (III; B).

adjuvant treatment

Postoperatively, 6 months of gemcitabine (GEM) or 5-fluorouracil (5-FU) chemotherapy are recommended on the basis of three randomized trials [16–18] (I; A). There is no substantial difference in terms of disease-free survival or overall survival (OS) in a formal comparison between adjuvant 5-FU and GEM. Adjuvant chemotherapy either with GEM or with 5-FU using the Mayo Clinic bolus 5-FU schedule improves the 5-year survival rate from ~9% to 20% in R0/R1 resected patients. However, GEM treatment is associated with less toxic side-effects compared to bolus 5-FU [17]. Patients do also benefit from adjuvant/additive chemotherapy after R1 resection [18].

The role of adjuvant chemoradiation is controversial as reported in a few randomized phase III trials, particularly in the negative ESPAC-1 trial [16]. Since there is no proof of any advantage of adjuvant or additive chemoradiation as compared to adjuvant/additive chemotherapy alone, chemoradiation in the adjuvant or additive setting should only be performed within randomized controlled clinical trials (I; B).

neoadjuvant chemotherapy or chemoradiotherapy

In case of resectable pancreatic cancer neoadjuvant chemotherapy, radiotherapy or chemoradiation should only be performed within clinical trials (III; B). However, the majority of patients relapse after resection of pancreatic cancer with metastases and it is increasingly recognized that many pancreatic cancers metastasize rather early during carcinogenesis. Thus, neoadjuvant strategies could be useful in patients with resectable tumors and patients should be encouraged to join clinical trials in this setting.

In case of larger tumors and/or tumors with vessel encasement that are borderline resectable or technically non resectable, patients may benefit from neoadjuvant chemotherapy or chemoradiotherapy to achieve downsizing of the tumor and may convert the tumor to become resectable. However, the optimal neoadjuvant strategy is still under investigation and there is so far no standard protocol for neoadjuvant chemoradiotherapy in Europe. In the case of borderline resectable patients, a neoadjuvant chemotherapy approach may be able to identify a subgroup of patients unlikely to benefit from surgical resection. Patients who develop metastases during neoadjuvant chemotherapy or who progress locally are not candidates for secondary surgery [19] (IV; B)

Intraoperative radiotherapy (IORT) is still experimental and cannot be recommended for routine use.

In patients with unresectable tumors, GEM treatment in conventional dosing (1000 mg/m^2 over 30 min) is recommended [20, 21] (I; A). Trials comparing

chemoradiation with chemotherapy alone reported contradictory results [22] and one phase III trial was in favor of using chemotherapy as first line treatment [23]. A suggestion for the treatment of patients with locally advanced pancreatic cancer arose from a retrospective analysis of patients enrolled in the GERCOR studies and from a systematic review of trials of chemoradiation in locally advanced pancreatic cancer. Patients treated with GEM not progressing after 3 months of treatment and with a good performance status (PS) achieved an improvement in survival with the addition of chemoradiation [24]. These data have to be confirmed in a prospective trial.

treatment in stage IV

For patients with metastatic disease, GEM is a reasonable choice and was the standard chemotherapy until recently. Patients receiving GEM have a median survival of 6.2 months and a 1-year survival rate of 20% [25] (I; B). Combinations of GEM and other cytotoxic agents, such as 5-FU or capecitabine, irinotecan, cis- or oxaliplatin, do not confer a major advantage in survival even in large randomized phase III trials and should not be used as standard first line treatment of locally advanced or metastatic pancreatic cancer (I; B). Meta-analysis of randomized trials with a combination of GEM and platinum analogues or of GEM and capecitabine suggested a survival benefit for these combinations for patients with a good PS [25–27]. In contrast, an Italian phase III trial examining GEM/cisplatin did not confirm a survival benefit for the combination GEM/cisplatin [28].

A recent phase III trial using a combination of 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) has shown a response rate of 31.6%, a median survival of 11.1 months (hazard ratio 0.57, 95% confidence interval 0.45–0.73), and 1-year survival rate of 48.4% in the FOLFIRINOX arm [29]. FOLFIRINOX also delayed deterioration of quality of life. In this trial, patients >75 years were excluded and eligibility was restricted to PS 0 and 1.60% of patients had cancers of the body and tail of pancreas. Only 15.8% in the FOLFIRINOX arm and 12.9%, in the GEM arm, respectively, had biliary stents. The FOLFIRINOX protocol is more toxic than GEM: Grade 3/4 side effects were 45.7% neutropenia, 4% febrile neutropenia, 12.7% diarrhea and 9% sensory neuropathy. About 42% of the patients required granulocyte-colony stimulating factor (G-CSF). Nevertheless, the FOLFIRINOX protocol confers a significant improvement in the OS of patients with stage IV pancreatic cancer and can be considered as a novel therapeutic option for patients ≤75 years of age with a good PS (0 or 1) and a level of bilirubin ≤1.5 ULN (I; B).

Combinations with targeted therapies have been disappointing. However, a combination of GEM and the EGFR tyrosine kinase inhibitor erlotinib has been approved by the United States Food and Drug Administration (FDA), and European Medicines Agency (EMA) on the basis of a randomized trial [30]. This combination showed a modest overall gain in median survival of 2 weeks, but a significant advantage in terms of long-term survival in the subgroup of patients who developed skin rash when taking erlotinib. The high economic costs of the treatment and the lack of

efficacy in the majority of patients question the role of this combination for a general use in patients with metastatic pancreatic cancer. As only patients who exhibit a significant skin rash within 8 weeks of treatment appear to benefit from this combination [30, 31], patients with metastatic pancreatic cancer can be treated with a combination of GEM and erlotinib, but treatment with erlotinib is only continued if patients develop skin rash within the first 8 weeks of treatment (V; B). At the moment there is no evidence supporting the use of any other biological in pancreatic cancer including cetuximab, bevacizumab or other angiogenesis inhibitors [32, 33].

Currently, there is no firmly established standard chemotherapy for patients after progression on first-line treatment. The combination of 5-FU and oxaliplatin has been shown to confer a benefit in the second line setting after first-line GEM in a small clinical trial and can be considered as a treatment option in this setting [34] (II; B). In patients treated with first-line FOLFIRINOX who can receive second-line chemotherapy after progression, GEM can be considered as an option (V; B).

Despite some progress, enrollment of patients with pancreatic cancer in clinical trials for all lines of treatment should be encouraged to further improve the systemic treatment of this disease.

Predictive biomarkers for chemotherapy efficacy are presently carefully studied. hENT1 and dCK expression have been recently reported as being predictive for the benefit of adjuvant GEM treatment [35, 36]. However, the methodology to assess these markers has to be standardized and these biomarkers have to be examined in prospective trials.

palliative therapy

Jaundice is common (70%–80%) in cancers involving the pancreatic head. A Cochrane analysis shows that endoscopic stenting is the preferred procedure in unresectable patients since it is associated with a lower frequency of complications than percutaneous insertion of stents and it is as successful as the surgical biliodigestive anastomosis but has a shorter hospital stay [37] (I; A). Metal prostheses should be preferred for patients with a life expectancy of >3 months since they present fewer complications (occlusion) than plastic endoprostheses. In case plastic stents are used they should be replaced at least every 6 months to avoid stent occlusion and ascending cholangitis. When endoscopic treatment is not possible, percutaneous transhepatic biliary drainage is recommended.

The European Society for Clinical Nutrition and Metabolism guidelines [38] state that in non-surgical well-nourished oncologic patients routine parenteral nutrition is not recommended because it has proved to offer no advantage and is associated with increased morbidity. Nevertheless, short-term parenteral nutrition is commonly accepted in patients with acute gastrointestinal complications from chemotherapy and radiotherapy, and long-term (home) parenteral nutrition will sometimes be required for patients with radiation enteropathy. In incurable cancer patients the guidelines recommend home parenteral nutrition in hypophagic/(sub)

Table 3. Summary of recommendations

Screening	• Currently there are no efficient screening tools available that can be recommended outside a high risk population, e.g. those suffering from hereditary conditions. For those, regular EUS that allows the detection of small lesions and MRI is recommended
Diagnosis	• Abdominal ultrasound is useful for the initial examination • For further evaluation, EUS, contrast-enhanced MD-CT and MRI combined with MRCP are more appropriate • ERCP has a role only to relieve bile duct obstruction • In the preoperative setting ERCP and biliary stenting should only be performed if surgery cannot be done expeditiously • PET scan has no role in the diagnosis of pancreatic cancer • Baseline CA19.9 can be used to guide treatment and follow-up and may have a prognostic value in absence of cholestasis • For patients who will undergo surgery with radical intent, a previous biopsy is not obligatory. Biopsy should be restricted to cases, e.g. in which imaging results of a pancreatic lesion are ambiguous. Here, EUS guided biopsy is preferred and percutaneous sampling should be avoided • Metastatic lesions can be biopsied percutaneously under ultrasound or CT guidance or during EUS
Staging	• The established staging system for pancreatic cancer is the one developed by the TNM committee of the AJCC-UICC • MD-CT or MRI plus MRCP should be used for staging. EUS can complement the staging by providing information on vessel invasion and potential involvement of lymph nodes and is the preferred means to obtain a biopsy of the pancreatic lesion • MD-CT of the chest is recommended to evaluate potential lung metastases • In the absence of typical symptoms, a bone scan is not useful since only a few patients with pancreatic cancer present with bone involvement at diagnosis. PET scan is currently not routinely recommended for the staging of ductal pancreatic cancer • Laparoscopy may detect small peritoneal and liver metastases changing the therapeutic strategy in <15% of patients. It can be performed before resection in left-sided large tumors and/or in case of high CA19.9 levels or when neoadjuvant treatment is considered • Using a standardized, detailed pathology examination protocol, microscopic margin involvement is a common finding in pancreatic carcinoma (>75%) and correlates with survival
Treatment	• The only curative treatment of pancreatic cancer is radical surgery. This approach is mainly suitable for patients with early stage of disease mainly stage I and some stage II • Elderly patients do benefit from radical surgery. However, comorbidity can be a reason to abstain from an otherwise possible resection especially in patients older than 75–80 years • In case of tumors of the pancreatic head, partial pancreatico-duodenectomy is the treatment of choice • Cancer of the pancreatic body or tail is usually treated by distal resection of the pancreas. In some cases total pancreatectomy is required • It is recommended to refer to the National Comprehensive Cancer Network criteria for resectability/irresectability [11] • In pancreatic cancer there is no evidence that extended lymphadenectomy is beneficial. Standard lymphadenectomy comprises dissection of the lymph nodes of the hepatoduodenal ligament, the common hepatic artery, the portal vein, the right sided celiac artery lymph node and lymph nodes at the right half of the superior mesenteric artery. The LNR (number of involved LN/number of examined LN) should be indicated since an LNR ≥0.2 is a negative prognostic factor • Postoperatively, 6 months of GEM or 5-FU chemotherapy are recommended • Patients do also benefit from adjuvant/additive chemotherapy after R1 resection • Chemoradiation in the adjuvant or additive setting should only be performed within randomized controlled clinical trials • In case of resectable pancreatic cancer neoadjuvant chemotherapy, radiotherapy or chemoradiation should only be performed within clinical trials • Neoadjuvant strategies could be useful in patients with resectable tumors and patients should be encouraged to join clinical trials in this setting • In case of larger tumors and/or tumors with vessel encasement that are borderline resectable or technically non resectable, patients may benefit from neoadjuvant chemotherapy or chemoradiotherapy to achieve downsizing of the tumor and may convert the tumor to become resectable • Patients who develop metastases during neoadjuvant chemotherapy or who progress locally are not candidates for secondary surgery

Continued

Table 3. *Continued*

	• Intraoperative radiotherapy is still experimental and cannot be recommended for routine use
	• In patients with unresectable tumors, GEM treatment in conventional dosing (1000 mg/m^2 over 30 min) is recommended
	• For patients with metastatic disease, GEM is a reasonable choice and was the standard chemotherapy until recently
	• Combinations of GEM and other cytotoxic agents, such as 5-FU or capecitabine, irinotecan, cis- or oxaliplatin, do not confer a significant advantage in survival even in large randomized phase III trials and should not be used as standard first line treatment of locally advanced or metastatic pancreatic cancer
	• The FOLFIRINOX protocol confers a significant improvement in the OS of patients with stage IV pancreatic cancer and can be considered as a novel therapeutic option for patients ≤75 years of age with a good PS (0 or 1) and a level of bilirubin ≤1.5 ULN
	• Patients with metastatic pancreatic cancer can be treated with a combination of GEM and erlotinib, but treatment with erlotinib is only continued if patients develop skin rash within the first 8 weeks of treatment
	• The combination of 5-FU and oxaliplatin can be considered as a treatment option in the second line setting after first-line GEM
	• In patients treated with first-line FOLFIRINOX who can receive second-line chemotherapy after progression, GEM can be considered as an option
Palliative therapy	• Endoscopic stenting is the preferred procedure in unresectable patients
	• Metal prostheses should be preferred for patients with a life expectancy of >3 months. In case plastic stents are used they should be replaced at least every 6 months to avoid stent occlusion and ascending cholangitis
	• When endoscopic treatment is not possible, percutaneous transhepatic biliary drainage is recommended
	• Pro-kinetics such as metoclopramide can be useful to speed gastric emptying
	• Duodenal obstruction may be overcome by the use of an expandable metal stent
	• Patients who present with severe pain must receive opioids. Morphine is generally the drug of choice. Usually, the oral route is preferred in routine practice. Parenteral or transdermal routes of administration should be considered for patients who have impaired swallowing or gastrointestinal obstruction
	• In some cases, hypofractionated radiotherapy may be delivered to these patients in order to improve pain control and reduce analgesic consumption
	• Percutaneous or per-EUS celiacoplexus blockade can be considered, especially for patients who experience poor tolerance of opiate analgesics
Response evaluation in the palliative setting	• Patients should be followed at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 8 weeks
	• Clinical benefit and ultrasound may be useful tools to assess the course of disease in the metastatic setting
	• When performing abdominal ultrasound patients should be monitored for the presence of ascites that can indicate peritoneal disease
Follow-up after surgical treatment	• A follow-up schedule should be discussed with the patient and designed to avoid emotional stress and economic burden for the patient
	• In the case of elevated preoperative serum CA19.9 levels the assessment of this marker could be performed every 3 months for 2 years and an abdominal CT scan every 6 months

EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; FOLFIRINOX, 5-FU, irinotecan and oxaliplatin; 5-FU, 5-fluorouracil; GEM, gemcitabine; LNR, lymph node ratio; MD-CT, multi-detector computed tomography; PET scan, positron emission tomography scanning.

obstructed patients. A recent phase II study suggests a benefit for additional parenteral nutrition (APN) in patients with advanced pancreatic cancer and progressive cachexia with respect to stabilization of the nutritional status [39]. However, so far there are no data on the impact of APN on survival and larger trials are required to define the benefit and the optimal starting point of APN in patients with advanced pancreatic cancer.

Fewer than 5% of patients with pancreatic cancer present with duodenal obstruction, while gastric outlet obstruction may be more common during the course of disease. Neither chemotherapy nor radiotherapy provide palliation in this setting. Pro-kinetics such as metoclopramide can be useful to speed gastric emptying. Duodenal obstruction may be overcome by the use of an expandable metal stent. The role of prophylactic gastroenterostomy remains controversial. It should not be performed as standard procedure, but can be a choice for individual patients.

Patients who present with severe pain must receive opioids. Morphine is generally the drug of choice. Usually, the oral

route is preferred in routine practice. Parenteral or transdermal routes of administration should be considered for patients who have impaired swallowing or gastrointestinal obstruction. In some cases, hypofractionated radiotherapy may be delivered to these patients in order to improve pain control and reduce analgesic consumption. Percutaneous or per-EUS celiacoplexus blockade can be considered, especially for patients who experience poor tolerance of opiate analgesics. Analgesic response rates as high as 50%–90% are reported with 1 month to 1 year duration of effect.

response evaluation in the palliative setting

Patients should be followed at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 8 weeks. Clinical benefit and ultrasound may be useful tools to assess the course of disease in the metastatic setting. When performing abdominal ultrasound patients should be monitored for the presence of ascites that can indicate peritoneal disease.

follow up after surgical treatment

There is no possibility of cure, even for recurrences diagnosed early, so a follow-up schedule should be discussed with the patient and designed to avoid emotional stress and economic burden for the patient. In the case of elevated preoperative serum CA19.9 levels the assessment of this marker could be performed every 3 months for 2 years and an abdominal CT scan every 6 months. However, it is important to bear in mind that there is no clear advantage in an earlier detection of recurrences.

conflict of interest

Prof. Van Cutsem has reported: research funding to the University of Leuven from Amgen, Bayer, Merck Serono, Novartis, Roche and Sanofi. Prof. Rougier has reported: honoraria from Sanofi Aventis, Amgen, Keocyte, Merck Serono, Pfizer, Roche and Lilly; advisory board for Sanofi Aventis and Keocyte.

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