Pancreatic cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

In Europe, cancer of the pancreas is the 10th most frequent cancer, accounting for some 2.6% of cancer in both sexes, and the eighth leading cause of cancer-related death with ~65 000 deaths each year. In men, the annual incidence rates ranged between 8.7 (East) and 7.3 (North and West) per 100 000, while in women between 5.7 (North) and 4.5 (East). Men have an approximately one-half greater age-adjusted incidence rate than women. Incidence increases steeply with age from 1.5 per 100 000/year in patients 15–44 years old to 55 per 100 000/year in patients >65 years of age. Pancreatic cancer is one of the most highly fatal cancers, with >95% of those affected dying of their disease.

diagnosis

Histologically there are three types of pancreatic cancer. Infiltrating ductal adenocarcinomas account for 90% of pancreatic neoplasms, the remaining 10% being represented by acinar cell carcinoma (in this type overproduction of lipase may lead to metastatic fat necrosis syndrome, which includes peripheral fat necrosis, eosinophilia and polyarthralgias) and pancreatoblastoma (a tumor occurring mainly in children). More than 90% of pancreatic cancers carry mutations in the *K-ras* oncogene, a fact that negatively affects therapeutic use of epidermal growth factor receptor blocking agents.

Early detection of pancreatic cancer is unfortunately an infrequent situation at the present time. Consequently, there are no current screening programmes that can be recommended.

Clinical presentation is generally characterized by jaundice in patients with cancer of the head of the pancreas, and pain in patients with tail and body tumors. In up to 10% of patients new onset of diabetes may be the first clinical feature.

Pancreatitis may also be the first signal of pancreatic neoplasia, especially in the elderly when there is no obvious cause such as gallstones or alcohol abuse. Another important feature of pancreatic cancer is weight loss.

Currently spiral CT is the prefered imaging modality for the diagnosis and staging of pancreatic cancer. In addition to the assessment of the primary tumor localization and size, CT scans are used to evaluate major vessels adjacent to the pancreas for neoplastic invasion or thrombosis, as well as, to evaluate hepatic or distant metastases, enlargement of peripancreatic or regional lymph nodes, invasion of retroperitoneal structures and intraperitoneal dissemination. Selected cases may benefit from MRI and laparoscopy.

Endoscopic retrograde cholangio-pancreatography (ERCP) is a useful tool in diagnosing suspected pancreatic cancer. For example if a patient has obstructive jaundice and no mass lesion is seen on CT scan then ERCP can be both diagnostic and therapeutic. Magnetic resonance cholangio-pancreatography (MRCP) also provides information about 3D anatomy and gives additional information about the presence of absence or vascular invasion.

At the present time, the role of PET scanning in the management of patients with pancreatic cancer is under development. For small tumors endoscopic ultrasound (EUS) has been reported to be superior to CT and because of this, it may be useful in family screening protocols. An additional aspect of the application of endoscopic technology includes the ability to combine EUS with fine needle aspiration cytologic examination. Tumor markers such as CA19.9 are of limited diagnostic value (it is not specific for pancreas cancer and persons lacking the Lewis antigen are unable to synthesize CA19.9), although they are often taken as a baseline in order to guide treatment and follow-up. Pathological proof of malignancy is mandatory in unresectable cases or when preoperative treatment is planned. For candidates for surgery, biopsy is not necessary and even preoperative percutaneous sampling should be avoided. In the presence of metastatic lesions they can be biopsied under ultrasound or CT guidance.

staging and risk assessment

The risk of pancreatic cancer is increased significantly (18-fold) in families with an affected first-degree relative. Pancreatic

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cancer is associated with several genetic syndromes including hereditary pancreatitis syndrome, hereditary non-polyposis colorectal cancer, hereditary atypical multiple mole melanoma syndrome, hereditary BRCA-2-related breast and ovarian cancer and the Peutz–Jeghers syndrome.

The most widely used staging system for pancreatic cancer is the one developed by the TNM committee of the AJCC-UICC, and is presented in Table 1. Stage grouping of pancreatic cancer is presented in Table 2.

CT scan is the preferred imaging modality for staging. MRI does not offer a clear advantage over CT scanning, while PET scanning is in development and it should not be recommended at the present time as a staging procedure. While chest X-ray is usually recommended in the evaluation of patients, bone scan is not useful since only a few pancreatic patients present with bone involvement at diagnosis.

Laparoscopy may detect small peritoneal and liver metastases changing the therapeutic strategy in ∼25% of patients. It can be suggested before resection in left-sided large tumors or if a neoadjuvant treatment is planned.

However, from a practical standpoint, the extent of cancer spread in cancer of the pancreas can often be determined accurately only during surgery. Therefore a simpler staging system is often used, based on whether or not it is likely that the cancer can be removed surgically.

The prognosis of patients who have undergone radical resection for pancreatic adenocarcinoma depends mainly on radical surgery and the presence of negative resection margins. Pathological stage is another important parameter. Less well-defined prognostic factors are the biological features of the tumor such as tumor DNA content. An important

consideration is the previous experience of the hospital team and the skill of the surgeon.

treatment plan

The treatment of pancreatic cancer is undertaken with two different aims. The first is radical surgery for patients with early stage disease, mainly stage I and partially II. In all other cases, the aim of treatment is the palliation of the several distressing symptoms related to this cancer. It is possible to define some treatment strategies according to tumor stage.

stage I

For this stage disease, the standard treatment option is radical pancreatic resection. A pylorus-preserving pancreaticoduodenectomy is the procedure of choice for patients with pancreatic head tumors; a modified Whipple procedure preserving distal stomach and pylorus is another option. The most common surgical approach for tumors of the pancreatic body and tail is a distal pancreatectomy which also routinely includes splenectomy. Postoperatively six cycles of 5-fluorouracil (5-FU) or gemcitabine chemotherapy may be suggested on the basis of two randomized trials. A combination of 5FU and radiotherapy may be suitable for individual clinical use in patients with R1 resection based on the data from a recent meta-analysis of adjuvant randomized trials.

stage IIA

Most patients with stage II pancreatic cancer have tumors that are technically unresectable; nevertheless, when feasible,

Table 1. The American Joint Committee on Cancer (AJCC) tumor–node–metastasis system for cancer of the pancreas

T categories	
TX	The main tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma *in situ* (very few tumors are found at this stage)
T1	The cancer has not spread beyond the pancreas and is <2 cm (∼0.75 inch) across
T2	The cancer has not spread beyond the pancreas but is >2 cm across
T3	The cancer has spread from the pancreas to surrounding tissues near the pancreas but not to blood vessels
T4	The cancer has extended further beyond the pancreas into nearby large blood vessels
N categories	
NX	Regional lymph nodes cannot be assessed
N0	Regional lymph nodes (lymph nodes near the pancreas) are not involved.
N1	Cancer has spread to regional lymph nodes.
M categories	
MX	Spread to distant organs cannot be assessed
M0	The cancer has not spread to distant lymph nodes or to distant organs
M1	Distant metastasis is present

Table 2. Stage grouping for cancer of the pancreas

Stage 0 (Tis, N0, M0)	The tumor is confined to the top layers of pancreatic duct cells and has not invaded deeper tissues. It has not spread outside the pancreas.
Stage IA (T1, N0, M0)	The tumor is confined to the pancreas and is <2 cm in size. It has not spread to nearby lymph nodes or distant sites.
Stage IB (T2, N0, M0)	The tumor is confined to the pancreas and is >2 cm in size. It has not spread to nearby lymph nodes or distant sites.
Stage IIA (T3, N0, M0)	The tumor is growing outside the pancreas but not into large blood vessels. It has not spread to nearby lymph nodes or distant sites.
Stage IIB (T1–3, N1, M0)	The tumor is either confined to the pancreas or growing outside the pancreas but not into nearby large blood vessels. It has spread to nearby lymph nodes but not distant sites.
Stage III (T4, any N, M0)	The tumor is growing outside the pancreas into nearby large blood vessels. It may or may not have spread to nearby lymph nodes. It has not spread to distant sites.
Stage IV (any T, any N, M1)	The cancer has spread to distant sites.

Table 3. Staging of pancreatic cancer based on resectability

Resectable	The cancer is still localized to the pancreas (or has spread just beyond it) and the surgeon is able to remove the entire tumor.
Locally advanced–unresectable	Too much cancer tissue is present in nearby blood vessels or has spread beyond the pancreas to permit complete surgical removal of the cancer, although it has not yet spread to distant organs. Surgery would only be carried out to relieve symptoms or problems such as obstruction of the bile duct or intestinal tract.
Metastatic	Spread to distant organs has been identified and surgery would only be carried out to relieve symptoms or problems such as obstruction of the bile duct or intestinal tract.

pancreatectomy can be considered a standard approach while unresectable patients may benefit from palliative bypass of biliary obstruction (head of pancreas) and/or palliative bypass of intestinal obstruction. Patients should be encouraged to participate in clinical trials for neoadjuvant treatment.

Indication of adjuvant chemotherapy or in combination with radiation therapy is similar to stage I.

stage IIB and III

The majority of patients with stage IIB and III pancreatic cancer have tumors that are technically unresectable, due to local invasion of blood vessels. For a long time chemoradiotherapy was offered to these patients. A relevant suggestion for the treatment of patients with locally advanced pancreatic cancer arose from a retrospective analysis of 181 patients enrolled in the GERCOR studies. In fact, patients treated with gemcitabine and not progressing after 3 months of treatment and with a good performance status achieved an improvement in survival with the addition of radiochemotherapy.

stage IV

Treatment with gemcitabine may be a reasonable choice. The use of a combination of gemcitabine with other cytotoxic agents, such as 5FU, irinotecan, cisplatin and oxaliplatin, is not supported by an advantage in survival apart from capecitabine since this combination showed a survival advantage in a trial although it was not confirmed in another one. A combination of gemcitabine and platinum analogues may be chosen for young patients and with a good performance status based on a meta-analysis of randomized trials with these chemotherapeutic agents. Another therapeutic possibility is a combination of gemcitabine and erlotinib, recently approved by FDA and EMEA on the basis of a randomized trial from the NCI of Canada. However, the very modest survival gain (about 2 weeks) and the high economic costs of the treatment question the role of this combination in metastatic pancreatic cancer. At the moment there is no evidence supporting the use of either cetuximab or bevacizumab in the overall setting of pancreatic cancer.

There is no standard chemotherapy for patients who have progressed in first-line treatment. Consideration to enrolment in clinical trials should be considered for patients who remain fit.

palliative therapy

Jaundice is common (70–80%) in cancers involving the pancreatic head. For unresectable patients, endoscopic stent placement is the preferred procedure since it is associated with lower frequency of complications than percutaneous insertion and it is as successful as the surgical procedure but has a shorter hospital stay. Metal prostheses should be preferred for patients with a life expectancy of >3 months since they present fewer complications (occlusion) than plastic endoprostheses. 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 provided palliation in this setting. In some cases, proximal obstruction may be overcome by the use of an expandable metal stent. The role of prophylactic gastroenterostomy remains controversial. In fact, only 13–15% of patients will require gastroenterostomy during the course of disease; it should not be performed as standard procedure but can be a reasonable 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 routes of administration should be considered for patients who have impaired swallowing or gastrointestinal obstruction. Percutaneous celiac plexus 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 a 1 month to 1 year duration of effect.

response evaluation and follow-up

Patients should be followed at each cycle of chemotherapy for toxicity and evaluated for response to chemotherapy every 2 months. Clinical benefit and CA19.9 may be useful tools to assess the course of disease in the metastatic setting. Imaging procedures such as CT scan may be indicated mainly in locally advanced disease in order to rule out the presence of metastases and to add radiotherapy to the treatment plan.

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 advantage in an earlier detection of recurrences.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given

in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

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