

# Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

S. Cascinu<sup>1</sup>, M. Falconi<sup>2</sup>, V. Valentini<sup>3</sup> & S. Jelic<sup>4</sup>  
On behalf of the ESMO Guidelines Working Group\*

<sup>1</sup>Department of Medical Oncology, Università Politecnica delle Marche, Ancona; <sup>2</sup>Department of Surgery and Gastroenterology, University of Verona, Verona;

<sup>3</sup>Department of Radiotherapy, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>4</sup>Internal Medicine Service, Institute of Oncology and Radiology, Belgrade, Serbia

## 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 range between 8.7 (East) and 7.3 (North and West) per 100 000, and in women between 5.7 (North) and 4.5 (East). Men have approximately a 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 of age to 55 per 100 000/year in patients >65 year of age. Pancreatic cancer is one of the most highly fatal cancers, with >95% of those affected dying of their disease. The high mortality rate is due to the high incidence of metastatic disease at diagnosis. No survival increases have been observed in the last years.

## diagnosis

There are three histological types of pancreatic cancer. Infiltrating ductal adenocarcinomas account for 90% of pancreatic neoplasms, the remaining 10% being represented by acinar cell carcinoma, accounting for <1% of pancreatic cancers (in this type overproduction of lipase may lead to metastatic fat necrosis syndrome, which includes peripheral fat necrosis, eosinophilia and polyarthralgias) and pancreatoblastoma (a tumour 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 EGFR 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 in the general population. However, some patients are at greater risk of developing a pancreatic cancer. The risk of pancreatic cancer is increased significantly (18-fold)

in families with an affected first-degree relative. Pancreatic cancer is associated with several genetic syndromes including hereditary pancreatitis syndrome, hereditary non-polyposis colorectal cancer, hereditary atypical multiple mole melanoma syndrome, hereditary BRCA2-related breast and ovarian cancer and Peutz–Jeghers syndrome. For these patients specific programmes have been established in order to recognize pre-cancerous lesions.

Clinical presentation is generally characterized by weight loss, pain and jaundice. Jaundice predominates in patients with cancer in the head of the pancreas, and pain in patients with tail and body tumours. In up to 10% of patients new onset of diabetes may be the first clinical feature. Pancreatitis may also be the first signal of a 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 CT scan is the preferred imaging modality used for the diagnosis and staging of pancreatic cancer. In addition to the assessment of the primary tumour localization and size, CT is 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 regional lymph nodes, invasion of retroperitoneal structures and intraperitoneal dissemination. Selected cases may benefit from MRI and laparoscopy. The actual role of ERCP is only therapeutic. At the present time, the role of PET scanning in the management of patients with pancreatic cancer is under development.

For small tumours endoscopic ultrasound (EUS) has been reported to be superior to CT. 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 cytological examination.

Tumour 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 patients expected to undergo surgery with radical intent, a previous biopsy is not necessary, and even preoperative percutaneous

\*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;  
E-mail: clinicalrecommendations@esmo.org

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sampling should be avoided. In the presence of metastatic lesions they can be biopsied under ultrasound or CT guidance.

## staging and risk assessment

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. A simpler staging system is often used, based on whether or not it is likely that the cancer can be removed surgically (Table 3).

CT scan is the preferred and more diffuse imaging modality for staging. MRCP may add additional information about both the biliary and pancreatic ducts and the presence or absence of vascular invasion. Moreover it is able to distinguish better than CT a solid from a cystic mass and is indicated in the case of severe liver and renal failures. PET scanning is in development and it should not routinely be recommended at the present time as a staging procedure. EUS may provide useful information about vascular and nodal involvement. Moreover it represents a useful tool in any case in which pathological material is requested. 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 <15% of patients. It can be suggested before resection in left-sided large tumours and/or with high CA19.9 levels or if 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. Specific recommendations for the assessment of margins in surgical specimens, especially the superior mesenteric artery margin have also been published by the AJCC-UICC (sixth edition) and are present in the guidelines of the College of American Pathologists.

The prognosis of patients who have undergone radical resection for pancreatic adenocarcinoma depends mainly on presence of negative resection margins. Tumour size, nodal involvement and histological grade are strong prognostic factors. Recently the prognostic role of post-resection CA19.9 has been confirmed. Less well-defined prognostic factors are the biological features of the tumour such as tumour 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 of disease, mainly stage I and some stage 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 the tumour stage.

### stage I

For this stage disease, the standard treatment option is radical pancreatic resection. For patients with pancreatic head tumours

a pylorus-preserving pancreaticoduodenectomy is the procedure of choice which is a modified Whipple procedure preserving distal stomach and pylorus. The most common surgical approach for tumours 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 (GEM) chemotherapy may be suggested on the basis of two randomized trials. Recently, it was reported that there was no substantial differences in terms of disease-free survival or overall survival in a formal comparison between 5-FU and GEM as adjuvant therapy in pancreatic adenocarcinoma. The role of adjuvant chemoradiation (CT-RT) is controversial as reported in a few randomized Phase III trials. 5-FU-based chemoradiation following GEM chemotherapy as described in the RTOG 97-04 protocol may be an option for individual clinical use, especially in patients with tumours of the pancreatic head, large tumour diameter (>3 cm) and in patients with R1 resection as reported in a meta-analysis of adjuvant randomized trials.

### stage II A

Most patients with stage II pancreatic cancer who have tumours that are technically unresectable may benefit from palliative bypass of intestinal obstruction followed by chemotherapy or chemoradiation as described for stages IIB and III. Nevertheless, when feasible, pancreatectomy can be considered a standard approach. Patients should be encouraged to participate in clinical trials for neoadjuvant treatment as recently published results from Phase II studies conducted on preoperative GEM-based chemoradiation seemed to indicate that the neoadjuvant approach can identify a subgroup of patients unlikely to benefit from surgical resection, without compromising survival in patients who ultimately undergo surgery.

Recently the role of intraoperative radiotherapy (IORT) has been addressed in a joint analysis of European centres. The association of preoperative radiotherapy with IORT was associated with improved local control and overall survival, especially in patients with a lower trend to systemic disease spread. Nevertheless, at this time we cannot recommend it as a routine treatment in clinical practice.

Indications for 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 have tumours that encase blood vessels. Patients who present borderline resectable disease may benefit from preoperative therapy (chemoradiation or induction chemotherapy followed by chemoradiation) in order to increase the rate of R0 resections.

In patients with unresectable disease 5-FU chemoradiation can be considered. However, two recent trials which compared chemoradiation with chemotherapy alone reported contradictory results. A relevant 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. In fact, patients treated with GEM and not progressing after 3 months of treatment and with a good performance status achieved an improvement in survival with the addition of chemoradiation.

### stage IV

While treatment with GEM may be a reasonable choice, the use of a combination of GEM and other cytotoxic agents, such as 5-FU, irinotecan, cisplatin and oxaliplatin, is not supported by an advantage in survival apart from capecitabine. However, this combination showed a survival advantage in a trial although it was not confirmed in another one. A meta-analysis of randomized trials with a combination of GEM and platinum analogues seemed to suggest a role for this combination for young patients with good performance status. Nevertheless, the results of a large randomized trial comparing GEM alone with GEM plus cisplatin, presented at the last ASCO meeting, failed to show any benefit for the combination. Another therapeutic possibility is a combination of GEM and erlotinib, recently approved by the FDA and EMEA on the basis of a randomized trial from the NCI of Canada. However, the very modest survival gain (~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. The CONKO 003 study has shown a benefit in the second line setting therefore 5-FU/oxaliplatin should be considered as standard. Since the treatment results even in first line are still disappointing the enrolment in clinical trials should be considered not only for second line therapy but for all lines.

### 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 endoprotheses.

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. Also hypofractionated radiotherapy may be delivered to these patients in order to improve pain control and reduce analgesic consumption.

Percutaneous celiacplexus 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 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.

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