

The management of locally advanced pancreatic cancer: European Society of Digestive Oncology (ESDO) expert discussion and recommendations from the 14th ESMO/World Congress on Gastrointestinal Cancer, Barcelona

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introduction

Pancreatic ductal adenocarcinoma (PDAC) represents a significant cause of morbidity and mortality worldwide. With more than 80 000 deaths from pancreatic cancer predicted for 2013 in pancreatic cancer is the fourth leading cause of cancer death in Europe [1].

About one-third of patients with pancreatic cancer present with locally advanced, unresectable disease. There is no uniform definition of a locally advanced PDAC and resectability of PDAC is sometimes difficult to assess (see below). The majority of locally advanced PDAC will be T4 tumors involving either the superior mesenteric artery or the celiac axis.

One-third of patients with locally advanced PDAC die without evidence of distant metastases [2]. This shows that locally advanced PDAC is a heterogeneous disease with some patients potentially benefitting from local treatments. However, two-third of patients will eventually present with metastatic disease in line with recent data suggesting that a large number of pancreatic tumors exhibit metastases already at a very early stage [3].

This article focuses on the management of locally advanced pancreatic cancer and summarizes the expert discussion, which was organized by the European Society of Digestive Oncology (ESDO) during the 14th European Society of Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer (WCGIC) in June 2012 in Barcelona, Spain. Opinion leaders and experts from different nationalities, selected on scientific merit,

participated in the discussion. In preparation for this expert discussion, a questionnaire was sent to all participants, and the questions, answers and conclusions were rediscussed at the meeting. Expert committee reports reflect clinical experience on top of evidence-based medicine. As such, consensus was not always reached. The main strength, however, of this approach is that more than minimal guidelines are offered, in order to assist clinicians in the process of making treatment choices in daily clinical practice.

clinical assessment and staging of locally advanced pancreatic cancer

Primary diagnosis of locally advanced PDAC is often done by abdominal ultrasound followed by abdominal triple-phase multislice computed tomography (CT).

obtaining pathological proof

In case of suspected locally advanced, unresectable PDAC (LAPC), pathological proof is mandatory to confirm the diagnosis of PDAC and defines the subsequent treatment of the disease. Endoscopic ultrasound (EUS)-guided biopsy is the preferred means of obtaining a pancreatic tissue sample. EUS-FNA histology with immediate formalin fixation is superior to EUS-FNA cytology with regards to diagnostic delay, costs and specimen suitability for molecular studies [4]. Alternatively, a 2-pass approach in EUS-guided FNA with combined histologic–cytologic analysis can be used [5].

staging–imaging

The panel found that dedicated pancreas-specific abdominal multidetector CT can be regarded as the primary staging

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procedure to determine resectability. CT is carried out as a triple-phase multislice CT. Other means such as magnetic resonance imaging (MRI) or EUS are reserved for particular questions. The MRI scan can be useful in case of fatty liver when a CT scan does not allow to detect smaller lesions in the liver or in case vascular invasion remains unclear with CT or EUS. Positron emission tomography (PET) and PET-CT can also be used to detect small metastatic lesions (peritoneum, lymph nodes). However, there is currently not sufficient scientific evidence to recommend the routine use of PET or PET-CT for diagnosis or staging of PDAC. The panel found that PET-CT is an area of future prospective trials for diagnosis and staging of PDAC.

staging laparoscopy

Laparoscopy is not a standard procedure for staging of pancreatic cancer. It may be used in special situations e.g. when there is a suspicion of peritoneal carcinomatosis by CT imaging.

criteria of resectability/irresectability

Surgical resection is the only potentially curative approach to PDAC. The criteria for resectability and borderline resectability have been defined by different groups including the MD Anderson Cancer Center and the NCCN ([6]; http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#pancreatic). The panel accepts the definitions by all these groups. The differences between these definitions are mostly minor and are found in the precise wording (abutment, encasement, infiltration). All definitions are neither completely clear nor evidence based, i.e. supported by appropriate literature of a high level of evidence.

The panel feels a multidisciplinary approach is paramount in assessing resectability. This approach should involve all parties, including surgeons, radiologist, digestive oncologists, gastroenterologists and radiotherapists. All decisions should be taken by the multidisciplinary team and not by a single party.

In case a nonmetastatic pancreatic cancer is deemed not resectable, the panel recommends particularly to low-volume centers to obtain a second opinion by the MDT of a tertiary referral center. A clear correlation between the experience and volume of the expert team and center and the outcome of patients with pancreatic cancer has been demonstrated.

arterial infiltration

celiac trunk. There is no indication for pancreatic cancer resection in case of celiac trunk infiltration by the tumor. While surgery can be technically feasible in case of infiltration of the celiac trunk, perioperative morbidity and mortality is increased and survival is not substantially improved for the majority of patients [7–9].

superior mesenteric artery and hepatic artery. Pancreatic cancer should also not be resected in case of infiltration of the superior mesenteric artery (more than 180° of circumferential involvement) or the hepatic artery by the tumor because an R0 resection is unlikely to be achieved in these situations. Infiltration of the splenic artery does not prevent resection of a pancreatic cancer [8].

venous infiltration

In general, postoperative survival is less compromised, if venous vessels are infiltrated by the tumor compared with tumor infiltration of arterial vessels.

portal vein. The portal vein can be resected upon infiltration, if it can be reconstructed. This is likely to be the case when the portal vein is only compressed by the tumor. However, reconstruction is less likely to be possible in case of portal vein occlusion and pseudocavernomatous transformation or in case of tumor infiltration of the portal vein over >2 cm [10–12].

superior mesenteric vein. The superior mesenteric vein can be resected in case of tumor infiltration given that its reconstruction is possible [13]. Again, this is more likely in case of compression or stenosis and less likely in case of occlusion or infiltration of the vein by the tumor [11, 14].

visceral metastases

Surgery is not indicated in case of visceral metastases or peritoneal carcinomatosis. In these cases, resection of the primary tumor does not improve the patients' prognosis [15, 16].

lymph node metastases. The panel agrees that there is some difficulty in assessing lymph node involvement by the tumor by conventional CT or MRI imaging. In case of doubt whether a lymph node is involved or not, EUS-guided FNA is recommended. Regional and distant lymph node involvement in pancreatic cancer is defined by the TNM classification.

Suspected lymph node involvement is regarded as resectable, if it is limited to regional lymph nodes. There is no survival benefit if distant lymph nodes (e.g. para-aortic lymph nodes) are resected [17]. Common hepatic artery lymph node metastases are also associated with worse prognosis [18].

Upon completion of the staging procedure, it should be possible to classify tumors as resectable, borderline resectable, unresectable/locally advanced or unresectable/metastatic.

treatment strategies in locally advanced PDAC

Locally advanced PDAC can in principle be divided into three different types: resectable tumors, borderline resectable tumors and locally advanced, clearly not resectable tumors. In resectable pancreatic cancer, standard treatment is resection followed by adjuvant chemotherapy. Neoadjuvant therapeutic strategies are appealing but not standard in this setting and subject of current clinical trials.

In case of borderline resectable pancreatic cancer, the panel recommends neoadjuvant chemotherapy or chemoradiotherapy (CRT) followed by resection, if there is a chance to achieve an R0 resection. So far, there are no markers available that would allow to predict whether a pancreatic tumor will respond to a particular neoadjuvant treatment, so that an a priori unresectable tumor becomes resectable. In case of clearly unresectable locally advanced pancreatic cancer, the panel recommends chemotherapy.

The panel particularly focused on borderline resectable tumors and clearly unresectable locally advanced PDAC.

borderline resectable PDAC

So far, there is also not enough evidence available to define an optimal therapeutic algorithm in case of borderline resectable PDAC—upfront surgery, neoadjuvant chemotherapy or neoadjuvant chemoradiation followed by surgery. A randomized trial is mandatory in this setting and is currently under preparation (ESPAC 5).

If CRT is used outside of clinical trials, the following radiation protocol may be recommended: RT (50.4–54 Gy) with conventional fractionation of 5×1.8 Gy/week. Radiation should be combined with chemotherapy. Gemcitabine or capecitabine or 5-fluorouracil (5-FU) are the preferred options. Capecitabine seemed to offer less toxicity and possibly more efficacy in a randomized phase II trial [19, 20]. If gemcitabine is used, a relatively low dose should be used, e.g. 300–350 mg/m² weekly.

If chemoradiation is used for locally advanced PDAC, there are two options after completion of the CRT: option 1 is observation and close follow-up, option 2 is maintenance treatment with chemotherapy. The panel currently prefers option 1, but finds that option 2 should be studied in prospective trials.

The panel finds it difficult to define an optimal chemotherapy regimen with the intention of tumor downsizing/downstaging and achieving secondary R0 resectability. The recently published FOLFIRINOX protocol or the combination of nab-paclitaxel plus gemcitabine as examined in the MPACT trial may be options, since these protocols achieve rather high tumor response rates of 31.6% and 23%, respectively, compared with 7%–9% with gemcitabine alone [21, 22]. However, both randomized phase III trials included only patients in the metastatic setting and no patients with locally advanced disease. Furthermore, these trials included only patients with a bilirubin level ≤ 1.5 -fold ULN (FOLFIRINOX trial) or \leq ULN (MPACT trial). So far, there are only case series of patients with locally advanced or borderline resectable pancreatic cancer using these regimens, so that a strong conclusion cannot be drawn on the question whether these combination chemotherapy protocols are superior in achieving downsizing/downstaging and subsequent secondary R0 resection of locally advanced/unresectable PDAC compared with gemcitabine monotherapy or CRT regimens. Other possible chemotherapy combinations are 5-FU or capecitabine plus cisplatin or oxaliplatin.

The panel strongly supports the notion that all options in this setting, CRT as well as chemotherapy should be examined in prospective trials.

assessment of secondary resectability

The assessment of secondary resectability should be done using EUS, MD-CT or MRI and laparoscopy in case of suspected peritoneal carcinomatosis. Secondary resectability should always be assessed by a multidisciplinary team. The panel considers it useful particularly for low-volume centers to obtain a second opinion from a tertiary referral center in case of doubt whether secondary resectability has been achieved.

locally advanced, unresectable PDAC

Treatment options for LAPC are in principle CRT or chemotherapy (CT). Until recently, there was an intense discussion on the best strategy. The major argument against RT/CRT was that

PDAC is, in many cases, already a metastatic disease at the time of diagnosis, even if metastases are not yet detectable with imaging [3]. Therefore, a strategy where only those tumors would be subjected to CRT that remained local during initial chemotherapy seemed logical. Indeed, retrospective analyses suggested that CRT in patients with LAPC controlled after induction CT could be superior to continuing CT [23, 24]. However, there is no clear role anymore for CRT in locally advanced, clearly unresectable PDAC, even if disease can be controlled (and kept local) with initial chemotherapy. This is due to the results of the LAP07 trial that examined the role of CRT after disease control with 4 months of gemcitabine in patients with LAPC. This trial showed that administering CRT (54 Gy and capecitabine 1600 mg/m²/day) after gemcitabine treatment was not superior to continuing gemcitabine chemotherapy [25]. Whether a prolonged disease control with chemotherapy, more intense chemotherapy regimens or CRT with gemcitabine are more efficacious in this setting is the subject of a current trial (CONKO 007). Data from this and other trials have to be awaited before CRT after CT can be finally assessed in locally advanced PDAC, but this concept is clearly no current clinical standard in this situation. Of course, RT has a role in specific cases of locally advanced PDAC for control of pain.

There is also no general consensus on the most optimal chemotherapy in locally advanced, clearly unresectable PDAC. Until recently, gemcitabine was the standard regimen with a median overall survival in locally advanced PDAC of about 10 months [26]. However, more recently, FOLFIRINOX and the combination of gemcitabine and nab-paclitaxel have been shown to lead an improved outcome in patients with metastatic pancreatic adenocarcinoma [21, 22]. Although specific studies are not yet available, it is likely that these combination regimens may also lead to an improved outcome in patients with locally advanced pancreatic cancer, who are fit, have a good performance status, a good organ function and who are willing to accept potentially more toxicity for a modest benefit.

conclusions and clinical research agenda

Locally advanced PDAC is difficult to assess. Conventional staging does fail when it comes to the assessment of resectability of a given tumor since e.g. arterial infiltration suggested by CT imaging may not be found upon surgical exploration of the tumor. There is a definite need to improve imaging of locally advanced disease to better differentiate upfront borderline resectable from the clearly unresectable tumors. Locally advanced PDAC is also a heterogeneous disease. In one-third of the patients, the tumor will remain local and may therefore be amenable to local therapeutic strategies such as CRT. The recent studies could not demonstrate the benefit of CRT over chemotherapy in locally advanced pancreatic cancer. However, there are currently no biomarkers that allow to securely predict whether a locally advanced PDAC will remain local or metastasize. The mutational status of the DPC4 tumor suppressor gene has been reported to be of value in differentiating local from metastatic disease [2]. However, these data were obtained in a comparatively small cohort of patients and need to be confirmed prospectively before DPC4 as a single marker can be used for stratification in the clinical setting.

In many clinical trials, locally advanced PDAC has been examined together with metastatic PDAC. Given the heterogeneous biology of locally advanced PDAC, it may be useful to examine these tumors in distinct clinical trials, since, at least in some cases, R0 resectability and consequently longer survival can be achieved. Furthermore, the panel feels that there are currently shortcomings in the development of novel agents for the treatment of PDAC since often novel agents with innovative mechanisms of action are used in trials as if they were merely cytotoxic agents. For example in case of locally advanced PDAC with its substantial desmoplastic reaction, treatment algorithms that aim at depleting the stroma before the application of cytotoxic chemotherapy may be useful.

disclosure

The authors have declared no conflicts of interest.

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