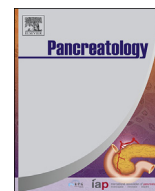




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Pain in pancreatic ductal adenocarcinoma: A multidisciplinary, International guideline for optimized management

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ABSTRACT

Abdominal pain is an important symptom in most patients with pancreatic ductal adenocarcinoma (PDAC). Adequate control of pain is often unsatisfactory due to limited treatment options and significant variation in local practice, emphasizing the need for a multidisciplinary approach. This review contends that improvement in the management of PDAC pain will result from a synthesis of best practice and evidence around the world in a multidisciplinary way. To improve clinical utility and evaluation, the evidence was rated according to the GRADE guidelines by a group of international experts. An algorithm is presented, which brings together all currently available treatment options. Pain is best treated early on with analgesics with most patients requiring opioids, but neurolytic procedures are often required later in the disease course. Celiac plexus neurolysis offers medium term relief in a substantial number of patients, but other procedures such as splanchnicectomy are also available. Palliative chemotherapy also provides pain relief as a collateral benefit. It is stressed that the assessment of pain must take into account the broader context of other physical and psychological symptoms. Adjunctive treatments for pain, depression and anxiety as well as radiotherapy, endoscopic therapy and neuromodulation may be required in selected patients. There are few comparative studies to help define which combination and order of these treatment options should be applied. New pain therapies are emerging and could for example target neural transmitters. However, until better methods are available, management of pain should be individualized in a multidisciplinary setting to ensure optimal care.

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Introduction and methods

Pancreatic ductal adenocarcinoma (PDAC) presents in different ways and often at an advanced stage. Abdominal pain is an important presenting symptom in about 60% of patients [1] and

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becomes a feature in almost all patients at some stage during the course of the disease. It is a common disabling symptom with several causes, and often difficult to treat, requiring multidisciplinary management for effective control. Pain is also a major predictor of outcome and survival. A striking ubiquitous pathological feature of PDAC is perineural invasion, which might explain its propensity to cause pain.

Recently published guidelines reveal a lack of standardized assessment and management of pain associated with PDAC. Most recommendations for its management are offered within selected specialties, reflecting significant variation in practice and thus emphasizing the need for a multidisciplinary approach. The variation in recommendations may simply reflect customary practice, but also the paucity of evidence on which to base the recommendations.

This review contends that improvement in the management of PDAC pain will result from a synthesis of best practices and evidences from around the world, to integrate the many treatment options, including pharmaceuticals, endoscopic and endosonographic interventions, surgery, neurolysis, neuromodulation, radiotherapy, psychotherapy, nursing and supportive care. Accordingly, the authors were selected to include a wide range of specialists with clinical and research experience in cancer pain management within relevant specialties. The authors were assigned to make recommendations on PDAC pain related issues and giving best available evidence. To improve clinical utility, most recommendations were framed for routine clinical practice. To score the strength of the evidence a modified GRADE method was used (<http://www.uptodate.com/home/grading-tutorial>). Finally, the level of agreement for the stated recommendation was determined by the authors independently voting on-line. Further details relating to methodology and a fuller discussion are available (supplementary material on-line).

Pathogenesis of pain in PDAC

The pathogenesis of pain in PDAC is multifactorial and encompasses neuropathic, visceral and somatic mechanisms. Quality assessment: moderate; Recommendation: moderate; Agreement: strong

The majority of patients with PDAC experience a chronic pain syndrome that is multifactorial in origin [2]. It entails neuropathic mechanisms due to neural infiltration by cancer cells. However, the pathogenesis of pain in PDAC is additionally complex in most cases with evidence of cross talks between pancreatic nerves, vascular system, pancreatic stellate cells and cancer cells. This is reflected in management that should target several mechanisms. In addition, pain can be due to invasion of other visceral and somatic structures. For details and references, see supplementary material.

Pain assessment in PDAC

Pain should be assessed in the context of many other physical and psychological symptoms, with an emphasis on severity, quality, distress and functional consequences. Although there has been focus on pain intensity, pain interference with quality of life should also be addressed. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Pain should be assessed in the context of other multiple physical and psychological symptoms, with an emphasis on severity, quality, distress and functional consequences from a patient's perspective [3]. As pain in PDAC shares mechanisms with those in chronic pancreatitis, assessment tools used in this disease may be adopted to patients with pancreas cancer [4]. Numerical scales, such as the visual analogue scale, are commonly applied to assess the intensity

of pain, but should be combined with a standardized registration of the temporal pain pattern [5]. Patients with PDAC have a very high prevalence of depressed mood, which is higher than other cancers with similar prognoses [6] and in many cases disturbed sleep and fatigue should also be recorded [7]. Pain assessment should also be supplemented with measurement of quality of life (QoL) using instruments such as the Short-Form Health Survey 36 (SF-36) and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [8,9].

Secondary reasons for pain

Pain due to complications associated with treatment and side effects of medication is frequent and should always be considered as additional reason for pain, especially because treatment is often effective. Quality assessment: low; Recommendation: moderate; Agreement: strong

Adverse effects and complications due to surgery, endoscopic, pharmacological and oncological treatments are important causes of morbidity in many patients and should be considered as additional sources of pain (Table 1). As management is often effective, these causes of pain should not be overlooked. Pain can be due to chemotherapy and irradiation, and related to neuropathy and enteritis [10]. Anastomotic and peptic ulcers are common and there should be a low threshold for endoscopic diagnosis. Although strong opioids are often used to relieve pain, they have the potential to produce substantial side effects, including constipation, abdominal pain and opioid induced hyperalgesia that can mimic pain due to PDAC (see section on analgesics). Complications of surgical and endoscopic treatments can also be the cause of pain. These include anastomotic leaks, intra-abdominal collections, acute pancreatitis, perforation and adhesions [11]. Obstruction of the bile duct is almost universal in PDAC of the head of pancreas, while obstruction of the duodenum occurs in up to a quarter of these patients. In patients with unresectable, metastatic and recurrent PDAC, biliary and gastric outlet obstructions are best managed with self-expanding metal stents without the need for surgical bypass, because they have been demonstrated to be safe and effective [12]. Abdominal discomfort can be due to maldigestion following pancreatic resection from a possible combination of exocrine pancreatic insufficiency, bile acid malabsorption and bacterial overgrowth [4,12]. Advanced PDAC may cause pain due to direct invasion into adjacent organs but also from metastases, most commonly to bone, liver and lung [13].

Pain management algorithm

Pain management in PDAC should be individualized, multidisciplinary and follow an algorithm. Quality assessment: moderate; Recommendation: strong; Agreement: strong

Pain management in PDAC should be individualized, but it will also depend on local expertise and skills. In many clinical settings, the treatment of pain follows traditional approaches and several treatment modalities are often overlooked. There is an overall consensus by pain specialists that optimal management of cancer pain should be multidisciplinary [13]. This is illustrated in Fig. 1, where most treatment options are included. The different treatments are often started in parallel, although the sequence of treatments will often depend on stage of PDAC and availability of treatment modalities and expertise. Hence, the algorithm in Fig. 1 shall not be regarded as definitive but as guidance. With a multidisciplinary approach, it is imperative that patients have rapid access to a lead health care professional to coordinate disciplines and taking overall responsibility. Ideally,

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