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Gastrointestinal Cancer

Pancreas Cancer-Associated Pain Management

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Abstract

Pain is highly prevalent in patients with pancreas cancer and contributes to the morbidity of the disease. Pain may be due to pancreatic enzyme insufficiency, obstruction, and/or a direct mass effect on nerves in the celiac plexus. Proper supportive care to decrease pain is an important aspect of the overall management of these patients. There are limited data specific to the management of pain caused by pancreatic cancer. Here we review the literature and offer recommendations regarding multiple modalities available to treat pain in these patients. The dissemination and adoption of these best supportive care practices can improve quantity and quality of life for patients with pancreatic cancer. ***The Oncologist*** 2021;26:e971–e982

Implications for Practice: Pain management is important to improve the quality of life and survival of a patient with cancer. The pathophysiology of pain in pancreas cancer is complex and multifactorial. Despite tumor response to chemotherapy, a sizeable percentage of patients are at risk for ongoing cancer-related pain and its comorbid consequences. Accordingly, the management of pain in patients with pancreas cancer can be challenging and often requires a multifaceted approach.

Introduction

Prevalence and Significance

Pancreas cancer may be the 11th most common cancer in the U.S., but it is the third leading cause of cancer death overall [1]. The most commonly presenting symptoms in patients with pancreas cancer are pain (abdominal or referred to the lower mid-back), jaundice, and weight loss [2]. Pain may occur secondary to obstruction of the duodenum and/or, more likely, secondary to perineural tumor invasion or nerve impingement [3, 4]. Symptom burden among patients with cancer can result in limitations in daily activities, poor functioning, disability, and overall impairment in quality of life (QOL) [5]. Proper management of symptoms, including pain, can greatly affect a patient's ability to tolerate treatment protocols and improve his or her overall QOL.

The Pancreatic Cancer Action Network maintains a patient registry where patients are enrolled and voluntarily complete a health and symptoms survey. Preliminary analysis of survey respondents over a 2.5-year period (2016–2018) determined that 93% of the patients reported having pain related to the diagnosis of pancreas cancer and that 83% of those reported moderate to severe pain intensity levels [6]. This is similar to previously reported data indicating that pain is the third most common symptom after weight loss and jaundice [7]. About 90% of these patients reported discussing pain with their health care provider (HCP), and most then received recommendations or prescriptions to reduce pain intensity. Despite this, almost 50% of the respondents reported visits to the emergency room for symptoms related to pain, and 33% were hospitalized at least once for pain management.

Several recent reports have established that cancer-related pain affects patient survival in pancreatic and other cancers [8–11]. Poorly managed pain is associated with decreased caloric intake, poor sleep quality, and reduced or limited occupational and social activities. Inadequately

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treated pain can significantly affect a patient's eligibility and tolerance for chemotherapy. Conversely, patients with less pain intensity and pain of shorter duration are reported to have a better QOL and longer survival [12, 13].

About 30% of the patients reported ongoing pain after initiation of tumor treatment or evidence of tumor reduction [14, 15]. So, despite response to chemotherapy, a sizeable percentage of patients will have ongoing abdominal pain. Here we review the pathophysiology and medical management of pain; possible local/focused therapies, such as radiation and nerve blocks; and selected complementary and alternative medicine therapies.

Pathophysiology

The pathophysiology of pain in pancreas cancer is complex and multifactorial. Accordingly, the management of pain in patients with pancreas cancer can be challenging and often requires a multifaceted approach. The two most common mechanisms leading to pain are pancreatic neuropathy and pancreatic duct obstruction.

Direct effects to nerves in pancreatic tissue can occur because of malignant cell infiltration and resulting inflammation. The phenomenon of perineural invasion, or malignant involvement of the protective sheath that surrounds bundles of axons, occurs in approximately 70% of pancreatic adenocarcinomas, reflecting the disease's neurotropism [16–18]. Malignant involvement of both intrapancreatic and extrapancreatic nerve plexuses, including the celiac plexus, is a common pathologic finding after surgical resection. Another pathologic hallmark of neuropathy is increased nerve density and nerve hypertrophy [19]. Several neurotransmitters, such as glutamate, substance P, nerve growth factor (NGF), and calcitonin gene–related peptide, along with inflammatory cells, have been implicated in the pathophysiology of pain in pancreas cancer [20]. In particular, macrophage infiltration into pancreatic tumors can increase secretion of NGF, leading to activation of pain sensation pathways [21]. Higher levels of NGF have been positively correlated with perineural invasion and pain intensity in pancreas cancer [22]. Afferent neurons respond to the release of neurotransmitters and carry these signals to their ultimate termination in the sensory cortex of the brain [16].

Pancreatic tumors frequently cause occlusion of the main pancreatic duct, which results in an increase in upstream intraductal and interstitial pressure [23]. Pancreatic tumor obstruction of the main pancreatic duct can cause pain via increased intraductal pressures and an ensuing pancreatic exocrine enzyme deficiency leading to malabsorption and postprandial pain [24, 25]. Pancreatic ductal stenting and subsequent lowered interstitial pressure have resulted in relief from obstructive pain in multiple studies [26, 27]. There is a paucity of data in pancreatic cancer, but studies of enzyme replacement treatment in pancreatic insufficiency and malabsorption from other conditions have demonstrated reduced abdominal pain [28–30].

Finally, patients with pancreas cancer can also experience pain related to direct invasion of adjacent organs, distant metastases, and, less commonly, side effects of treatment including chemotherapy, radiation, or surgery. Treatment of these complications, although important, are out of scope for this review.

In summary, most pancreas cancer pain appears attributable to neuropathic mechanisms, although pancreatic insufficiency may play a role.

Systemic Therapy

Pain as a Clinical Trial Endpoint

Chemotherapy plays a crucial role in the management of pain and QOL metrics in patients with advanced pancreatic cancer. Historically, clinical trials with chemotherapy in pancreas cancer have included pain control and QOL as primary or secondary objectives. Burris et al. randomized 126 patients to single agent gemcitabine or fluorouracil (5-FU) [31]. The primary measure of efficacy in the trial was clinical benefit rate, defined as pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight, with an improvement in one parameter without worsening in others. Patients in the gemcitabine arm experienced a significant improvement in alleviation of pain and disease-related symptoms (24% clinical benefit rate vs. 5% for 5-FU). The improvement in clinical benefit rate in addition to the improvement in survival resulted in the approval of gemcitabine for advanced pancreatic cancer. In the PRODIGE 4/ACCORD 11 trial, patients were randomized to mFOLFIRINOX (5-FU, oxaliplatin, irinotecan) or single agent gemcitabine [32]. The patients in both arms had QOL assessed using the European Organization for the Research and Treatment of Cancer QOL Questionnaire C30 (EORTC QLQ-C30) every 2 weeks. After 6 months of therapy, more than twice as many patients experienced a decrease in global health status in the gemcitabine arm compared with the FOLFIRINOX arm ($p < .001$). Patients treated with FOLFIRINOX had significantly increased time until definitive deterioration in their pain scores.

The benefit of chemotherapy in preserving QOL has also been demonstrated with second-line chemotherapy. In the NAPOLI-I trial, fluorouracil + leucovorin + nanoliposomal irinotecan demonstrated a survival benefit in patients pretreated with gemcitabine-based chemotherapy compared with 5-FU + leucovorin [33]. In an analysis of the study's QOL data using the EORTC QLQ-C30, the addition of nanoliposomal irinotecan was associated with maintenance of most health-related QOL metrics, including pain [34].

In summary, effective management of pancreas cancer with multiagent chemotherapy improves survival and QOL and appears to decrease pain levels.

Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs

Most patients present having already taken over-the-counter pain medications such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen (*N*-acetyl-p-aminophenol; APAP; paracetamol) is the most widely used analgesic-antipyretic used in the U.S. [35]. The mechanism of action is not fully understood, and it is

believed to be due to activation of serotonergic inhibitory pathways in the central nervous system (CNS). Interactions with other nociceptive systems may be involved as well [36]. More than 20 different NSAIDs are available and used broadly around the world. The primary effect of NSAIDs is to inhibit cyclooxygenase (prostaglandin synthase), thereby decreasing the production of prostaglandins, prostacyclin, and thromboxanes [37].

The use of these medications is limited in analgesic effects for the treatment of significant and persistent pain. Prolonged use of these medications increases the risk of toxicity. Adverse effects include, but are not limited to, liver damage, the main concern with acetaminophen, gastritis, ulcers, and kidney damage. The medications at correct dosing can be continued if they provide adequate pain relief. However, they are often discontinued secondary to the risks and/or inadequate pain relief [38]. In addition, when administered with chemotherapy, NSAIDs can increase the risk of acute kidney injury in the setting of chemotherapy-induced dehydration, whereas APAP can cause liver function test abnormalities, which may be attributed to or potentiated when administered with chemotherapy.

Opioids

Use of Opioids for Management of Pain

Opioids are the mainstay of pharmacologic options in treating pain in patients with pancreatic cancer. The vast majority of prescribed opioids are pure mu-receptor agonists, which bind to mu-receptors located in the central and peripheral nervous systems. This results in activation of descending inhibitory pathways along with inhibition of afferent pain transmission in the dorsal horn, thalamus, and inflamed peripheral tissues [39]. Some opioids exhibit additional mechanisms for analgesia, such as N-methyl-D-aspartate (NMDA) receptor antagonism (methadone and levorphanol) and/or monoamine reuptake inhibition (tramadol, tapentadol, methadone, and levorphanol) [40, 41]. Currently, the role for buprenorphine, a partial mu-receptor agonist, in managing cancer pain is not well established because of concerns for analgesic ceiling effects [42, 43]. Other mixed agonist/antagonists, such as nalbuphine and pentazocine, are not useful because of activation of kappa-receptors associated with undesired dysesthesia [44–46].

The goal of opioid therapy should be to optimize analgesia and functioning while simultaneously minimizing risks associated with opioid use. This is best achieved by appropriate opioid selection, dosing, and titration, prompt management of common side effects, and consideration of the potential risk for misuse and addiction. Opioid-naïve patients with moderate to severe pain may be started on immediate release (IR) weaker opioids such as tramadol or low doses of stronger opioids such as hydrocodone (available only with acetaminophen), morphine, oxycodone (available with and without acetaminophen), oxymorphone, and hydromorphone. These may initially be prescribed on an as-needed basis to allow for understanding of an individual's medication requirement [47]. Patients requiring several daily doses of IR opioids would benefit from extended release (ER) opioid, providing prolonged and more consistent plasma concentration of drug, thus minimizing fluctuations. IR opioid should be made available for management of breakthrough pain, on an as-needed basis every 3 to 4 hours, at approximately 10%–20% of the basal daily dose of the scheduled ER opioid [48]. Because of the dynamic nature of cancer-associated pain and the substantial variation in individual responsiveness to opioids, there may be a need for ongoing adjustments with close monitoring of outcomes (analgesia, adverse effects, activity, and affect) to achieve an individualized tolerated and effective analgesic response.

There is no evidence that supports superior efficacy for any one opioid, and selection is typically based on the clinician's experience, the patient's prior experience, and formulary restrictions. However, opioid selection should carefully consider potential concerns that may arise from the opioid's metabolism and/or adverse drug-drug interactions. Concomitant medications including cancer treatment regimens, impairments in organ function, older age, cachexia, and genetics may substantially influence opioid metabolism, resulting in inadequate analgesia or overdosing, especially with repeated doses. Cachexia may modulate response to opioids, especially when using a fentanyl transdermal patch, and decreased analgesic efficacy has been reported [49], although this is clinically managed with appropriate titration. The metabolism of commonly prescribed opioids typically involves two major enzyme systems, cytochrome (CYP) P450 and UDP-glucuronosyltransferases. Accumulation of active metabolites in the presence of renal failure may result in opioid-induced neurotoxicity (OIN). Fentanyl and methadone lack active metabolites, and methadone is excreted fecally through bile salts; thus they are preferred in renal failure. In the presence of liver failure, opioids should be initiated at lower doses and at increased (longer) dosing intervals. Table 1 demonstrates potential concerns that may arise based on the metabolic pathways, as well as with renal or hepatic dysfunction. For example, opioids such as morphine and hydromorphone undergo glucuronidation, with no interaction with CYP enzymes, and are preferable in patients on multiple drug regimens as they have less potential for drug interactions [43, 50, 51].

Management of Opioid Side Effects

Common opioid side effects include opioid-induced bowel dysfunction (OBD), pruritus, and sedation [52]. Serious adverse effects include OIN and respiratory depression. Most patients on opioids experience OBD secondary to opioid-induced increase in gastrointestinal (GI) tone and inhibition of GI peristalsis and secretion. This results in symptoms of bloating, abdominal distention, nausea, anorexia, and constipation [45, 53]. OBD should be anticipated and treated with laxatives and opioid antagonists, and motility agents may be considered in patients with refractory OBD. One randomized controlled trial (RCT) suggested that a fentanyl patch was associated with less constipation than morphine among patients without cancer on opioids [54]. OIN includes a constellation of symptoms such as excessive sedation, cognitive impairment, delirium,

Table 1. Opioid metabolism and recommendations for use [43, 50, 51]

Opioid	Examples of precautions with opioids based on its metabolism
Morphine-like (phenanthrenes)	
Natural opioids	
Morphine	Less potential for drug interactions as morphine does not involve CYP enzymes. Morphine undergoes glucuronidation via UGT2B7 to active metabolites, morphine-3-glucuronide, and morphine-6-glucuronide. Avoid in renal failure; morphine/metabolites may accumulate, causing neurotoxicity.
Codeine	Needs to be metabolized to morphine via the CYP2D6 enzymes to exhibit its analgesic effect. CYP2D6 poor or rapid metabolizers can ↑ or ↓ analgesic/toxic effects.
Semisynthetic opioids	
Hydromorphone	Less potential for drug interactions as hydromorphone does not involve CYP enzymes. It undergoes glucuronidation via UGT2B7 to produce the active metabolite hydromorphone-3-glucuronide. In renal failure, hydromorphone and active metabolites can accumulate causing neurotoxicity.
Oxymorphone	Less potential for drug interactions as oxymorphone does not involve CYP enzymes. Oxymorphone undergoes glucuronidation via UGT2B7 to produce mainly the inactive metabolite oxymorphone-3-glucuronide and minor amounts of the active metabolite 6-OH-oxymorphone, which does not complicate treatment.
Oxycodone	Predominantly metabolized by CYP3A4 (∼80%) to the active metabolite noroxycodone, and via CYP2D6 to oxymorphone. Inhibition of any one enzyme may result in compensation by the other with unexpected outcomes, whereas inhibition of both enzymes significantly increases oxycodone concentrations and associated toxicity.
Hydrocodone	Needs to be metabolized to hydromorphone via the CYP2D6 enzymes to exhibit its analgesic effect. CYP2D6 poor or rapid metabolizers can result in ↑ or ↓ of analgesic/toxic effects. Produces active metabolites that can accumulate in renal failure, causing neurotoxicity. Acetaminophen or NSAID is added to immediate release formulations.
Fentanyl-like (phenylpiperidines)	
Fentanyl	Metabolized by CYP3A4 to the inactive metabolite, norfentanyl. Inhibition or induction of CYP3A4 may increase or decrease fentanyl activity. Renal failure: considered safe, metabolizes to inactive/nontoxic metabolites.
Meperidine	Metabolized via CYP enzymes (2B6, 3A4, and C19) to normeperidine, which can accumulate after multiple doses and in renal failure and may cause neurotoxicity. Is not recommended for management of cancer pain.
Methadone-like (diphenylheptanes)	
Methadone	Several CYP enzymes (especially CYP3A4 and CYP2B6) are involved in its metabolism to mainly inert or weakly active metabolites. Inhibition or induction of CYP3A4 may increase or decrease methadone activity. Renal failure: considered safe; mainly excreted via bile, inert or weakly active metabolites. Potential for qTC* prolongation. Consultation with palliative care or pain specialist is recommended.
Tramadol-like (phenylpropylamines)	
Tramadol	Dual mechanism of action: parent drug inhibits serotonin and epinephrine uptake. Metabolized via CYP2D6 to O-desmethyl tramadol, which has weak mu-agonistic activity. CYP2D6 poor or rapid metabolizers can result in ↑ or ↓ of analgesic/toxic effects. Potential for serotonin syndrome; lower seizure threshold.
Tapenades	Tapentadol has little potential for metabolically based drug interactions as it does not involve CYP metabolism. Tapentadol undergoes glucuronidation via UGT2B7 to produce inactive metabolites. Dual mechanism of action: mu-agonism, along with selective inhibition of norepinephrine reuptake.

Abbreviations: CYP, cytochrome; NSAID, nonsteroidal anti-inflammatory drug; qTC, corrected QT interval; UGT2B7, UDP-Glucuronosyltransferase-2B7.

hallucinations, myoclonus, and opioid-induced hyperalgesia, which may be present alone or in combination [55, 56]. Concurrent use of sedating medications such as benzodiazepines, antihistamines, and gabapentinoids can potentiate opioid toxicity. Such agents must therefore be identified, minimized, or possibly discontinued. Opioid rotation should be considered in patients with inadequate pain relief despite repeated dose escalations, in the presence of OIN, or when side effects preclude dose escalation, using equianalgesic opioid ratios with appropriate initiating dose reductions of 50%–75% to compensate for incomplete cross-tolerance [47, 57].

Assessing Risk and Monitoring for Nonmedical Opioid Use

Opioids are potentially abusable drugs, and although most patients with cancer will likely adhere to prescribed therapy, recent literature suggests that approximately 20% of patients with cancer are at risk for nonmedical opioid use (NMOU) [58]. NMOU is usually detected by observing aberrant behaviors such as early refill requests and doctor shopping, observing felonious behaviors such as stealing or diversion, and assistance of other measures, such as urine drug testing and prescription drug monitoring programs. Universal screening for NMOU risk is recommended for all patients initiated on opioids, with periodic monitoring during the course of opioid therapy [59]. The regulatory requirements vary by state but at minimum should include screening for personal or family history of substance use and/or mental health disorders that have been associated with higher risk [60–62]. Patients who are at high risk for NMOU may require more frequent monitoring with shorter follow-up intervals, periodic urine drug testing, and review of prescription drug monitoring programs, and we recommend referral to pain management specialists. Naloxone injectable or nasal spray should be prescribed at the same time as opioids, to patients and their caregivers, to cover the possibility of opioid overdose for those on high doses.

In summary, opioids continue to be a major class of analgesics in the treatment of pancreatic pain in pancreatic cancer. Analgesic therapy is essential to patient prognosis, to reduce pain intensity and reduce its impact on physical functioning, caloric intake, quality of life, and impediments to tumor reduction therapies. The clinical adverse effects of opioids, especially tolerance, opioid-induced constipation, sleepiness, and confusion, require medical attention to minimize or manage these symptoms. A referral to palliative care or a pain specialist is appropriate for all patients with cancer receiving opioid therapy and should strongly be considered in those with concern for nonmedical use or inappropriate dosing.

Radiation Therapy

Radiation therapy is another strategy that could be used to successfully address pain associated with locally advanced peripancreatic cancer, as both conventional and more technologically advanced palliative courses of radiation therapy have been shown to be effective.

Multiple single institution retrospective studies have demonstrated that moderately dosed hypofractionated courses could be used for pain palliation [63, 64]. Doses of 6–30 Gy given in 1–10 fractions have been shown to be well tolerated with no severe toxicities. Response rates measured as stable or decreased analgesic requirements have been shown to be between 60% and 100% with about half of patients achieving complete pain resolution [64–66]. Short courses of palliative radiation therapy have also been shown to be highly effective for pain reduction. Ebrahimi et al. analyzed patients treated with one, two, or three fractions of 8 Gy once a week for 1–3 weeks [65]. Sixty percent of the treated patients noted pain relief, and 7% had complete pain resolution with benefit noted a week after the last radiation treatment. Additionally, older, frailer adults and patients with metastatic disease also benefited [65]. Based on these findings, a prospective clinical trial aiming to assess the pain relief after palliative radiation therapy of 24 Gy in 3-weekly fractions is currently recruiting patients in The Netherlands (Netherlands Trial Register, Trial NL4896 [NTR5143]).

Given the immediate proximity of the pancreas to vital organs, more technologically advanced radiation therapy approaches, such as stereotactic body radiation therapy (SBRT), have been developed to deliver higher doses of radiation in a more conformal fashion. Although SBRT is more frequently used in the definitive setting, it has also been used for pain palliation. Different fractionation schemes have been used with high response rates. A recent systematic review of SBRT usage for palliation of abdominal pain associated with pancreas cancer revealed that doses between 16.5 Gy and 45 Gy in one to six fractions resulted in pain response rates of over 80%, with 54% of patients reporting complete pain resolution [67]. SBRT was also associated with a low to moderate rate of grade 3 toxicities (3.3%–18%), including duodenal bleeding, ulcerations, and bowel obstruction [67]. In addition to providing high rates of pain relief, SBRT can also improve nausea (100%), anorexia (58%), weight loss (80%), and fatigue (20%) in patients with medically inoperable disease [68].

Although the exact mechanisms by which radiation therapy alleviates pain in patients with pancreas cancer is not entirely clear, it is thought that radiation therapy may help with pain attributable to both tumor-related ductal obstruction and perineural invasion by decreasing the overall amount of disease, thus lessening the ductal obstruction, and decreasing the negative effects of perineural invasion by disruption of the inflammatory pathways [7, 19]. The latter is supported by a recent study that demonstrated that ablative doses of radiation targeting the celiac plexus alone could lead to significant pain relief [69]. This prospective phase I study demonstrated that abdominal pain decreased significantly in all treated patients with 17% reporting complete pain resolution. Treatment was well tolerated with no grade 3 or higher toxicities and is the basis for an ongoing phase II clinical trial (NCT02356406). In patients with poor prognosis, pain relief from palliative radiation alone has been shown to be comparable to concurrent chemoradiation [70]. Furthermore, the addition of radiation therapy further prolonged pain medication–free survival when combined with plexus block, demonstrating that radiation therapy could be used either on its own or in combination with other modalities [66].

In summary, both SBRT and conformal radiotherapy are associated with effective pain control and may also provide a noninvasive means to decrease dependence on opioids to adequately manage tumor-related pain. Given the clinical evidence, palliative radiation therapy to either the primary or select metastatic sites for symptom management was also strongly recommended by the recent ASTRO clinical guidelines for the treatment of pancreas cancer [71]. SBRT is associated with a low rate of grade 3 toxicities, so performance status and extent of disease should be considered when selecting a suitable palliative radiotherapy approach.

Table 2. Selected trials in pancreas cancer pain management

Authors	Intervention	Study type (number of patients)	Outcome
Staats et al. [12]	CPN vs. placebo	Randomized trial ($n = 130$)	CPN reduced pain and improved mood and survival compared with placebo
Lillemoe et al. [123]	CPN vs. placebo	Randomized trial ($n = 117$)	CPN reduced pain compared with placebo
Wong et al. [74]	CPN vs. medical management	Randomized trial ($n = 100$)	CPN reduce pain but not QOL or survival compared with medical management
Jain et al. [124]	CPN vs. medial management	Randomized trial ($n = 100$)	CPN reduced pain and reduced opioid requirement; no difference in QOL
Wyse et al. [125]	CPN vs. medical management	Randomized trial ($n = 98$)	CPN reduced pain but did not improve QOL or survival compared with medical management
Chen et al. [126]	Electroacupuncture vs. placebo	Randomized trial ($n = 60$)	Electroacupuncture reduced pain compared with placebo
Stefaniak et al. [127]	CPN vs. TS	Case series ($n = 59$)	Significant reduction in pain and fatigue with both interventions
Johnson et al. [128]	CPN vs. TS vs. medical management	Randomized trial ($n = 58$)	No differences between groups in pain or opioid consumption
Zhang et al. [73]	CPN vs. medical management	Randomized trial ($n = 56$)	CPN decreased pain and opioid requirement compared with medical management; no difference in QOL

Most of these studies were able to show significant reduction in pain levels with an analgesic intervention compared with placebo, sham procedure, or medical treatment, usually opioids.
Abbreviations: CPN, celiac plexus neurolysis; QOL, quality of life; TS, thoracoscopic splanchnicectomy.

Non–Radiation-Focused Therapies

Neurolysis

Celiac plexus neurolytic block, or celiac plexus neurolysis (CPN), and thoracoscopic splanchnicectomy (TS) are invasive neurolytic procedures that may decrease the need for opioids in managing pain originating from an upper abdominal malignancy, particularly pancreas cancer [66, 72]. Application of chemical agents or physical injury results in a permanent or temporary degeneration of targeted nerve fibers to interrupt neuronal transmission. Neurolytic procedures are usually performed in patients with advanced cancer who have not responded adequately to pharmacologic options. The relevant innervating neuroanatomy of the plexus, pancreas, and local tumor spread is important when considering such procedures.

Recent studies support that neurolytic procedure use and efficacy earlier in patient management, for example, after one or two trials of opioid therapy, have been inadequate for pain control. The neurolytic injectate is usually 50%–100% ethyl alcohol. For CPN, several techniques may be used to approach the celiac plexus, such as percutaneous (aided by fluoroscopy or computed tomographic imaging), surgical placement, or endoscopic ultrasound. Historically, the majority of RCTs demonstrating benefit from CPN for pancreas cancer pain in adults have been performed percutaneously. Table 2 includes selected RCTs reporting reduced pain levels in patients with pancreatic cancer. Individually, a majority of CPN studies have demonstrated significant improvements in pain at 2, 4, or 8 weeks, [73, 74], and in some studies, this was associated with lower opioid usage [75]. The 2011 Cochrane review (six RCTs, published 1993–2008) [76] demonstrated significantly lower pain scores at 4 weeks (−0.43; 95% confidence interval [CI], −0.73, −0.14; $p = .004$], with a trend toward lower pain at 8 weeks (−0.44; 95% CI, −0.89, −0.23; $p = .06$]. In subsequent reviews by Nagels et al. (2013, five RCTs) and Zhong et al. (2014, eight RCTs), statistical improvements in pain scores with CPN were found at 4 but not at 8 weeks [77, 78]. Thus, current evidence suggests that percutaneous CPN improves pain scores at 4 weeks, which may not be sustained over time. However, all three meta-analyses demonstrated significant reductions in opioid consumption at 4 and 8 weeks or last report.

More recent studies have provided evidence of the benefits of the endoscopic approach, with lower reported comorbid risks CPN [72, 79]. CPN and TS are reported to have at least 50% reduction in pain levels, usually lasting several weeks. The procedure can be repeated and given while the patient is still eligible for chemotherapy or radiation therapy.

High-Intensity Focused Ultrasound

High-intensity focused ultrasound (HIFU), also called focused ultrasound surgery, has demonstrated its therapeutic potential in disorders of the central nervous system since the 1950s [80]. Directed ultrasound waves cause both thermal and nonthermal effects in biological tissues. Absorption of HIFU results in elevated tissue temperatures and ablates tissues at specific thresholds. Bubbles form and may boil, resulting in mechanical tissue disruption and collapse, sometimes causing cavitation [81]. To achieve these effects, a transducer generates a pulse of ultrasound energy that propagates via a coupling medium (typically oil or degassed water) into the body, converging on a focal region. Within the focal region a small volume of tissue is exposed to high-amplitude pressure waves. HIFU has been used for ablation of primary and secondary liver tumors and breast tumors

[81]. The mechanism of pain relief with this procedure is not fully understood, but hypotheses include the following: (a) nerve fibers in the tumor are damaged or undergo apoptosis by the thermal effects, (b) the targeted celiac plexus is inactivated from transmitting the pain signal to the brain, and (c) the resultant tumor shrinkage reduces the mechanical pressure on the innervating nerve fibers, decreasing the neurotransmission that signals pain intensity and tissue source [82].

A retrospective study of HIFU in China demonstrated limited clinical effectiveness in tumor reduction in patients with pancreas cancer with 15% achieving partial responses, 57% stable disease, and 38% progressive disease ($n = 83$). Despite this, 80% of the patients reported moderate to severe pancreatic pain at baseline and significant pain reduction after treatment [83]. Twenty-one patients (31.3%) had complete remission of pain (no pain and no need of opioid analgesics), 33 patients (49.3%), had a partial remission of pain (decrease in the pain score by ≥2 points), and 13 patients (19.4%) had no improvement of pain. Pain relief was observed in 88% (22/25) of patients who had an objective tumor response and in 76.2% (32/42) who did not. Another Chinese trial combined gemcitabine with HIFU demonstrating, again, that approximately 80% responded with decreased pain scores [84].

A 2017 meta-analysis assessing palliative treatments of pancreatic cancer–related pain using HIFU included 23 studies with a total number of 865 patients; 729 had pancreatic cancer, of whom 639 underwent HIFU treatment [80]. Among the 639 patients with pancreatic cancer, 567 reported abdominal pain before HIFU treatment, and 459 experienced partial to complete resolution of pain (81% response rate to treatment; 95% CI, 0.76–86). Reported complications were few or minor including superficial skin burns (3.4%), subcutaneous fat sclerosis (6.7%), and an asymptomatic pancreatic pseudocyst (1.1%).

Case series of HIFU from Germany, Bulgaria, and Spain have demonstrated improvement in pain, potentially with a survival benefit [85–88]. Between 2008 and 2013, 29 patients with locally advanced pancreas cancer and 14 patients with metastatic pancreas cancer underwent HIFU tissue ablation at least 4 weeks after chemotherapy was discontinued [88]. Clinical response, a decrease in pain, was achieved 82% of the time with confirmation and sustainment at 8 weeks after the procedure. The researchers also obtained complete responses in 11 patients (25%) at the end of the combined treatment of HIFU plus systemic chemotherapy, 9 with stage III and 2 with stage IV pancreatic cancer. The median overall survival for this group was 16 months, which in 2013 was longer than expected. Most reported studies focus on improved pain levels from single-center experiences. A randomized trial would be the most efficacious way to definitively answer the question regarding the benefit of HIFU.

Intrathecal Drug Delivery

The first report of a fully implantable device with continuous delivery of intrathecal opioids for cancer pain was published in 1981 [89]. Intrathecal drug delivery systems (IDDSs) consist of a small "pain pump" with a reservoir for opioid medication storage placed under the skin in the abdominal area; via a tunneled catheter, this delivery system doses medication directly into the intrathecal space surrounding the spinal cord. Reductions in pain levels are noted in some patients as early as the first administered dose. Pain pumps offer several advantages. Intrathecal opioid delivery reduces pain intensity scores using lower opioid doses than what is needed with peripheral or oral administration and thus results in fewer side effects. The main risks are bleeding and infection, and cerebrospinal fluid leakages are rare [90].

An observational study designed to evaluate the 11-year results (2006–2017) of IDDSs for refractory pancreas cancer pain [91, 92] demonstrated that IDDS-treated patients experienced 50%–75% reductions in mean pain levels. Ropivacaine was usually added as a first- or second-line therapy. Clonidine was used until 2011, then gradually replaced by ziconotide, for use in first line combined with either morphine or ropivacaine, or as a second-line monotherapy. During this period, 453 patients were diagnosed with pancreas cancer at Institut de Cancérologie de L'Ouest, of whom 93 were treated with IDDS for severe refractory pancreas cancer pain. The median presurgical numerical rating scale (NRS) was 8 (interquartile range, 7–9). The IDDS infusions resulted in significant reductions in mean pain levels (50%–75%) between baseline preimplantation and after surgery. Most patients maintained reduced pain scores from the first postsurgery week of testing through 3 months. Minor complications such as postdural puncture headache occurred in 30 patients (32.3%). Severe nonlethal complications were noted in 10.7% of the patients: one case of surgical wound dehiscence and two cases of infection after pump refill requiring intravenous antibiotics. Most patients (83%) resumed chemotherapy during the first 30 days after IDDS surgery [93].

An RCT of IDDS versus comprehensive medical management (CMM) was undertaken and reported in 2002 [94]. Two hundred and two patients were enrolled with 146 evaluable patients at 4 weeks. The main outcome measure was pain control combined with change of toxicity (Common Terminology Criteria for Adverse Events version 4). Clinical success was higher for IDDS versus CMM at 85% versus 71% ($p = .05$). The mean visual analog scale scores decreased from 7.57 to 3.67 for a 50% reduction in pain for IDDS and 7.81 to 4.76 for a 40% reduction in pain with CMM ($p = .055$). The toxicity scores were 17% and 50% ($p = .004$) for IDDS and CMM, respectively, reflecting fewer opioid-induced side effects with the doses needed with IDDS. Survival was even improved at the 6-month mark of 54% versus 37% for IDDS and CMM, respectively ($p = .06$). Overall, IDDS treatment improved clinical success, when used in patients with the appropriate functional status and prognosis, in pain control with fewer side effects.

In summary, neurolytic procedures (such as celiac plexus block), HIFU, and intrathecal administration of opiates may be appropriate therapies to consider for those whose oral medications do not provide adequate relief. Interventional gastroenterologists and pain management specialists are usually able to provide nerve blocks, and the latter, intrathecal pumps and management when needed.

Integrative Therapies

Herbal Medicines or Nutraceuticals

The National Center for Complementary and Integrative Health estimated that 40% of adult Americans self-report the use at least one form of complementary and alternative medicine (CAM), most often for alleviation of pain, fatigue, and insomnia [95]. Similarly, at least 30%–40% of surveyed patients with cancer under active therapy self-report that they have tried at least one CAM therapy, and Buckner et al. reported that CAM use increased after the diagnosis of cancer was made [96]. An estimated 20% of patients do not report their CAM use to HCPs, assuming either that CAM is safe or that their HCP will chastise this use [97]. Treating physicians need to specifically query patients regarding CAM use. Most of the medical claims of CAM therapies in visceral pain have not been adequately researched to confidently recommend their safe and effective use. There are reported interactions of herbal therapies with medications that could affect efficacy or side effect profiles of prescribed medications, including chemotherapeutic agents, acetaminophen, hypoglycemic agents, anticoagulants, and opioids, or impair host immunocompetence or organ function [98–100]. The safest recommendation is to stop CAM, nutraceutical, or herbal therapies while on chemotherapy. Acupuncture, transcutaneous electrical nerve stimulation, and cannabis, frequently used by patients for pain reduction, are briefly discussed below.

Acupuncture

Acupuncture-based therapies (e.g., acupuncture, acupressure, and electroacupuncture) are nonpharmacologic therapies reported to reduce nociceptive and neuropathic pain in animal models and clinical trials including patients with visceral pain and cancer [101–103]. Generally, with acupuncture a sterile needle is applied by micropunctate insertions along specific physiologic landmarks, called meridian points, purported to affect the differential release of neurotransmitters [104, 105]. In electroacupuncture, electrical leads are applied to placed acupuncture needles to increase the stimulation directed to the acupuncture point [106]. The most accepted mechanism of action is stimulation of the sympathetic and parasympathetic nervous systems to blunt excessive sympathetic discharge and rebalance the sympathetic to parasympathetic activity ratios. Subsequent release of mediators from the spinal cord is also antinociceptive and anti-inflammatory [107].Acupuncture and electroacupuncture studies in animal models have supported that the analgesic effect is mediated via the sympathetic nervous system and spinal cord via neurotropic mediators such as enkephalin, dynorphin, 5-hydroxytryptophan, epinephrine, somatostatin, and endogenous opioid pathways [105, 108]. Animal studies have shown resultant decreases in blood pressure in naturally hypertensive rats, lasting over 24 hours [109, 110], and reductions in nociceptive behaviors in pain models [111].

Clinical trials of acupuncture for reduction of visceral pain are of variable quality and bias. A few studies report its efficacy in reducing mild to moderate severe pain levels (baseline levels NRS score of 3–7) by 30%–50%, usually starting by 24 hours after the procedure and lasting several hours to several days [101]. A recent study of RCT of daily acupuncture for 3 days on patients with pancreas cancer with moderate pancreatic pain levels reported significantly decreased pain intensity (40%), compared with the study group treated with sham acupuncture. Patients wishing to try these modalities should be referred to a qualified and experienced practitioner and be prepared to comply with acupuncture practices and treatment schedules.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a drug-free, noninvasive, and low-risk alternative for managing pain. The TENS device generates a low-intensity electrical current that travels through the lead wires to the adhesive pads placed on or near the area of pain on the body. The current is carried through the skin to muscles involved in the painful areas, to engage the local nociceptive fibers and modulate release of neurotransmitters. Generally, pain scores are reduced by 20%–50% within 30 minutes of electrical stimulation and can last one to several hours. Studies of TENS application include a range of low to high electrical stimulation. Generally, the most effective pain reduction is reported with high frequency and sufficiently high intensity at which current conduction is slightly uncomfortable but not painful [107, 112]. TENS and electroacupuncture applications to the visceral acupuncture points PC6 and ST36 have also been shown to rebalance the gastric waves and decrease abdominal pain related to gastric hypomotility in small studies of patients with scleroderma and diabetes [107, 108, 113, 114]. TENS treatment is a safe option for most patients, and is considered low risk for injury, side effects, or addiction but is not recommended with for patients with an open abdominal wound, cardiac pacemaker, or pregnancy. Patients should remain awake during TENS application and use caution when operating heavy machinery or driving. There is one report of TENS application decreasing opioid efficacy in an animal model [115]. Analgesic tolerance to continued TENS use has also been described [112]. More studies are needed and will determine the usefulness of TENS for targeted patient symptoms in pancreatic cancer.

The Endocannabinoid System: Marijuana and Synthetic Cannabinoids

The endocannabinoid system comprises cannabinoid (CB) receptors, their endogenous ligands (endocannabinoids), and proteins responsible for metabolism. It is an extensive network of cannabinoid receptors and endogenous mediators throughout the brain, nervous system, and GI tract that regulate neural, digestive, and immunologic systems [116–118]. Cannabis in ingested or inhaled form can modulate several central and peripheral cannabinoid receptors, including CB1 and CB2. Cannabidiol (CBD), a CB2 agonist, and Δ9-tetrahydrocannabinol (THC), a CB1 agonist, are the two main chemical components of cannabis. There are several approved synthetic cannabinoids. Dronabinol and nabilone are both synthetic versions of THC and are approved by the U.S. Food and Drug Administration for

Table 3. Summary of current pain treatment modalities and barriers for use in patients with pancreatic cancer

Treatment modalities	Barriers
Systemic chemotherapy	Performance status of patients at presentation.
Opioids	Side effects, concern for abuse, provider comfort on required dosing.
Radiation therapy	Performance status, minimal barriers outside of locations of radiation therapy centers.
Neurolysis/HIFU	Interventional gastroenterologists, although available at academic centers, may not be available in the general community.
Intrathecal drug delivery	Limited availability of pain specialists. Resource intensive. Unclear benefit and cost effectiveness in those expected to live less than 6 months.
CAM (CBD, cannabis, acupuncture)	Lack of data and lack of coverage.

Abbreviations: CAM, complementary and alternative medicine; CBD, cannabidiol; HIFU, high-intensity focused ultrasound.

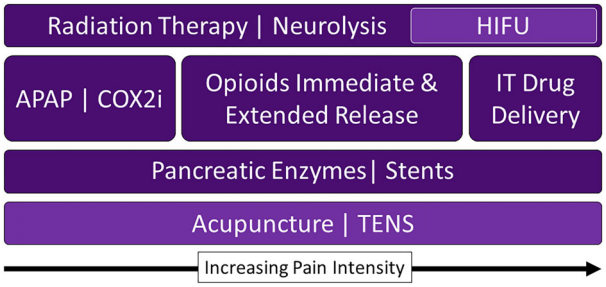

Figure 1. Available modalities for management of pancreas cancer pain are stacked in boxes along the *x*-axis, which depicts increasing pain intensity from left to right. The boxes are "stacked" to show that pain management modalities can be used throughout the patient's clinical course and that to achieve optimal relief, pain treatment can be switched or continued as a modality is added, usually from a higher box, or one listed to the right. The dark purple boxes contain pain treatment modalities that are considered standards of care. The light purple boxes contain pain treatment modalities that are currently considered experimental. Neurolysis includes celiac and splanchnic plexus or nerve blocks.
Abbreviations: APAP, acetaminophen; COX-2i, cyclooxygenase-2 inhibitor; HIFU, high-intensity focused ultrasound; IT, intrathecal; TENS, transcutaneous electrical nerve stimulation.

nausea and vomiting associated with cancer chemotherapy in patients with refractory nausea. They have a generally lackluster record in analgesia. Olorinab is a highly selective CB2 receptor agonist currently in phase IIb clinical trials for the treatment of visceral gastrointestinal pain (NCT04043455).

Marijuana or cannabis is currently legalized (or decriminalized) for adult medical and/or recreational use in close to 70% of the U.S. Cannabis plants have traditionally been promoted for putative analgesic, sedative, anti-inflammatory, antispasmodic, appetite stimulant, and anticonvulsant activities and mood improvement [119]. Historically the major routes of cannabis ingestion have been by inhalation and by mouth. Both routes have reported analgesic efficacy in the chronic pain setting, best reported in the setting of neuropathic or arthritic pain [120]. In patients with impaired GI absorption, orally ingested compounds might have reduced efficacy. Ingestion by inhalation may provide more rapid and better analgesic effect [121]. Emerging studies have reported a decrease in reported opioid use in patients with chronic pain using transdermal or vaping delivery modalities [120]. Inhalation is the most widespread recreational form of administration and has all the risks expected with smoking. Vaporizers remove much of this risk and have a rapid onset of effect; however, there is significant variability in bioavailability and dosing. Oral, oromucosal, or sublingual administration has a slower onset but also lasts longer. There are no major differences between the oral, sublingual, and oromucosal routes [122]. More studies will be needed to assess marijuana's potential efficacy and optimal route of delivery for patients with pancreatic cancer.

Individual patient trials using cannabis as an analgesic for pancreatic pain or chemotherapy-induced peripheral neuropathy might be considered and discussed, depending on the willingness of HCP and the patient and on local laws. Some points to consider if the patient requests cannabis for pain relief are as follows: (a) Patients should be educated regarding cannabis and the inconclusive status of cannabinoids in visceral and neuropathic pain. (b) THC and CBD content in many available cannabis plants are many times higher than what was available even 10 years ago. Patients should be advised to try lower content THC and enhanced CBD content mixtures to have fewer CNS effects, to proceed with caution, and to avoid driving and operating heavy machinery. (c) Cannabis can enhance sedation when combined with other sedatives, such as opioids.

Conclusion

Patients with pancreas cancer often have pain and at an increased intensity when compared with other patients. The optimal approach of pain management is not known (Table 3), but despite usual care patients continue to have pain that is suboptimally managed. Pancreatic enzyme insufficiency causes postprandial pain and bloating; we recommend determining the role of pancreatic enzyme insufficiency in causing pain and managing it with pancreatic enzyme replacement therapy at early time points [2]. Most patients will already have tried acetaminophen and nonsteroidal anti-inflammatory drug at presentation, but if not, these should be used early. Appropriate counseling and initiating of opiates will most likely be indicated with the need for frequent re-evaluation over the course of treatment. The exact timings of CPN, radiation therapy, and HIFU are hard to define, but these should be considered as appropriate options. CPN has shown benefit early, whereas the latter will likely be used after the initiation of chemotherapy. Intrathecal delivery of pain medicines is usually used in the refractory setting (Fig. 1).

Efficacious analgesic regimens will lead to improved QOL, eligibility for treatment, and functional outcomes and longer survival. Analgesic therapies should effectively and efficiently cover ongoing and breakthrough pain. Early referral to a pain or palliative care specialist can be helpful to determine the best analgesic plan for the patient and, if needed, assist in locating the accessible interventional expertise for any analgesic procedures. Analgesia needs to be effective, safe, and accessible, be coadministered with cancer treatment, have minimal or tolerable side effects, and blunt weight loss and sarcopenia. Finally, clinical trials in pain management of newer therapies including cannabinoids are warranted.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clinic 2020;70:7–30.

2. Hendifar AE, Petzel MQB, Zimmers TA et al. Pancreas cancer-associated weight loss. ***The Oncologist*** 2019;24:691–701.

3. Wolfgang CL, Herman JM, Laheru DA et al. Recent progress in pancreatic cancer. CA Cancer J Clin 2013;63:318–348.

4. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605–1617.

5. So WK, Marsh G, Ling WM et al. The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: A multicenter study. Oncol Nurs Forum 2009;36: E205–E214.

6. Westermann A, Matrisian LM, Rahib L. The need for improvement in the management of fatigue, depression and pain in pancreatic cancer. J Clin Oncol 2019;37(suppl 4):429a.

7. Koulouris AI, Banim P, Hart AR. Pain in patients with pancreatic cancer: Prevalence, mechanisms, management and future developments. Dig Dis Sci 2017;62:861–870.

8. Michalski CW, Oti FE, Erkan M et al. Cannabinoids in pancreatic cancer: Correlation with survival and pain. Int J Cancer 2008;122:742–750.

9. Muller MW, Friess H, Koninger J et al. Factors influencing survival after bypass procedures in patients with advanced pancreatic adenocarcinomas. Am J Surg 2008;195:221–228.

10. Scarborough BM, Smith CB. Optimal pain management for patients with cancer in the modern era. CA Cancer J Clin 2018;68:182–196.

11. D'Haese JG, Hartel M, Demir IE et al. Pain sensation in pancreatic diseases is not uniform: The different facets of pancreatic pain. World J Gastroenterol 2014;20:9154–9161.

12. Staats PS, Hekmat H, Sauter P et al. The effects of alcohol celiac plexus block, pain, and mood on longevity in patients with unresectable pancreatic cancer: A double-blind, randomized, placebo-controlled study. Pain Med 2001;2: 28–34.

13. Hameed M, Hameed H, Erdek M. Pain management in pancreatic cancer. Cancers (Basel) 2010;3:43–60.

14. van den Beuken-van Everdingen MHJ, van Kuijk SMJ, Janssen DJA et al. Treatment of pain in cancer: Towards personalised medicine. Cancers (Basel) 2018;10:502.

15. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG et al. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Ann Oncol 2007;18:1437–1449.

16. Barreto SG, Saccone GT. Pancreatic nociception–revisiting the physiology and pathophysiology. Pancreatology 2012;12:104–112.

17. Hirai I, Kimura W, Ozawa K et al. Perineural invasion in pancreatic cancer. Pancreas 2002;24: 15–25.

18. Dobosz L, Kaczor M, Stefaniak TJ. Pain in pancreatic cancer: Review of medical and surgical remedies. ANZ J Surg 2016;86:756–761.

19. Ceyhan GO, Bergmann F, Kadihasanoglu M et al. Pancreatic neuropathy and neuropathic pain–a comprehensive pathomorphological study of 546 cases. Gastroenterology 2009;136:177–186.e171.

20. Demir IE, Schorn S, Schremmer-Danninger E et al. Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. PLoS One 2013;8:e60529.

21. Lahoud MJ, Kourie HR, Antoun J et al. Road map for pain management in pancreatic cancer: A review. World J Gastrointest Oncol 2016;8: 599–606.

22. Zhu Z, Kleeff J, Kayed H et al. Nerve growth factor and enhancement of proliferation, invasion, and tumorigenicity of pancreatic cancer cells. Mol Carcinog 2002;35:138–147.

23. Koulouris AI, Banim P, Hart AR. Pain in patients with pancreatic cancer: Prevalence, mechanisms, management and future developments. Dig Dis Sci 2017;62:861–870.

24. Warshaw AL, Banks PA, Fernandez-Del Castillo C. Aga technical review: Treatment of pain in chronic pancreatitis. Gastroenterology 1998;115:765–776.

25. Drewes AM, Bouwense SAW, Campbell CM et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology 2017;17:720–731.

26. Costamagna G, Alevras P, Palladino F et al. Endoscopic pancreatic stenting in pancreatic cancer. Can J Gastroenterol 1999;13:481–487.

27. Wehrmann T, Riphaus A, Frenz MB et al. Endoscopic pancreatic duct stenting for relief of pancreatic cancer pain. Eur J Gastroenterol Hepatol 2005;17:1395–1400.

28. Whitcomb DC, Lehman GA, Vasileva G et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol 2010;105:2276–2286.

29. Trapnell BC, Maguiness K, Graff GR et al. Efficacy and safety of Creon 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370–377.

30. Gubergrits N, Malecka-Panas E, Lehman GA et al. A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Aliment Pharmacol Ther 2011;33:1152–1161.

31. Burris HA 3rd, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J Clin Oncol 1997;15:2403–2413.

32. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol 2013;31:23–29.

33. Wang-Gillam A, Li CP, Bodoky G et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1):

A global, randomised, open-label, phase 3 trial. Lancet 2016;387:545–557.

34. Hubner RA, Cubillo A, Blanc JF et al. Quality of life in metastatic pancreatic cancer patients receiving liposomal irinotecan plus 5-fluorouracil and leucovorin. Eur J Cancer 2019;106:24–33.

35. Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. Clin Liver Dis 2013; 17:587–607, viii.

36. Smith HS. Potential analgesic mechanisms of acetaminophen. Pain Physician 2009;12: 269–280.

37. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971;231:232–235.

38. Magee DJ, Jhanji S, Poulogiannis G et al. Nonsteroidal anti-inflammatory drugs and pain in cancer patients: A systematic review and reappraisal of the evidence. Br J Anaesth 2019; 123:e412–e423.

39. Corder G, Castro DC, Bruchas MR et al. Endogenous and exogenous opioids in pain. Annu Rev Neurosci 2018;41:453–473.

40. Knezevic NN, Yekkirala A, Yaksh TL. Basic/translational development of forthcoming opioid- and nonopioid-targeted pain therapeutics. Anesth Analg 2017;125:1714–1732.

41. Morrone LA, Scuteri D, Rombola L et al. Opioids resistance in chronic pain management. Curr Neuropharmacol 2017;15:444–456.

42. Schmidt-Hansen M, Bromham N, Taubert M et al. Buprenorphine for treating cancer pain. Cochrane Database Syst Rev 2015(3):CD009596.

43. Trescot AM, Datta S, Lee M et al. Opioid pharmacology. Pain Physician 2008;11(suppl 2): S133–S153.

44. Gear RW, Gordon NC, Hossaini-Zadeh M et al. A subanalgesic dose of morphine eliminates nalbuphine anti-analgesia in postoperative pain. J Pain 2008;9:337–341.

45. Gendron L, Cahill CM, von Zastrow M et al. Molecular pharmacology of delta-opioid receptors. Pharmacol Rev 2016;68:631–700.

46. Land BB, Bruchas MR, Lemos JC et al. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. J Neurosci 2008;28:407–414.

47. Nersesyan H, Slavin KV. Current aproach to cancer pain management: Availability and implications of different treatment options. Ther Clin Risk Manag 2007;3:381–400.

48. Perez-Hernandez C, Blasco A, Gandara A et al. Prevalence and characterization of breakthrough pain in patients with cancer in Spain: The CARPE-DIO study. Sci Rep 2019;9:17701.

49. Chiba T, Takahashi H, Tairabune T et al. Cancer cachexia may hinder pain control when using fentanyl patch. Biol Pharm Bull 2020;43: 873–878.

50. Mercadante S. Opioid metabolism and clinical aspects. Eur J Pharmacol 2015;769:71–78.

51. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613–624.

52. O'Brien T, Christrup LL, Drewes AM et al. European Pain Federation position paper on appropriate opioid use in chronic pain management. Eur J Pain 2017;21:3–19.

53. Leppert W. Emerging therapies for patients with symptoms of opioid-induced bowel dysfunction. Drug Des Devel Ther 2015;9:2215–2231.

54. Allan L, Hays H, Jensen NH et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322: 1154–1158.

55. Sivanesan E, Gitlin MC, Candiotti KA. Opioid-induced hallucinations: A review of the literature, pathophysiology, diagnosis, and treatment. Anesth Analg 2016;123:836–843.

56. Vella-Brincat J, Macleod AD. Adverse effects of opioids on the central nervous systems of palliative care patients. J Pain Palliat Care Pharmacother 2007;21:15–25.

57. Lohse I, Brothers SP. Pathogenesis and treatment of pancreatic cancer related pain. Anticancer Res 2020;40:1789–1796.

58. Carmichael AN, Morgan L, Del Fabbro E. Identifying and assessing the risk of opioid abuse in patients with cancer: An integrative review. Subst Abuse Rehabil 2016;7:71–79.

59. Dalal S, Bruera E. Pain management for patients with advanced cancer in the opioid epidemic era. Am Soc Clin Oncol Educ Book 2019; 39:24–35.

60. Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. Clin J Pain 2008;24:497–508.

61. Kim YJ, Dev R, Reddy A et al. Association between tobacco use, symptom expression, and alcohol and illicit drug use in advanced cancer patients. J Pain Symptom Manage 2016;51: 762–768.

62. Edlund MJ, Martin BC, Fan MY et al. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: Results from the TROUP study. Drug Alcohol Depend 2010;112: 90–98.

63. Wolny-Rokicka E, Sutkowski K, Grzadziel A et al. Tolerance and efficacy of palliative radiotherapy for advanced pancreatic cancer: A retrospective analysis of single-institutional experiences. Mol Clin Oncol 2016;4:1088–1092.

64. Morganti AG, Trodella L, Valentini V et al. Pain relief with short-term irradiation in locally advanced carcinoma of the pancreas. J Palliat Care 2003;19:258–262.

65. Ebrahimi G, Rasch CRN, van Tienhoven G. Pain relief after a short course of palliative radiotherapy in pancreatic cancer, the Academic Medical Center (AMC) experience. Acta Oncol 2018; 57:697–700.

66. van Geenen RC, Keyzer-Dekker CM, van Tienhoven G et al. Pain management of patients with unresectable peripancreatic carcinoma. World J Surg 2002;26:715–720.

67. Buwenge M, Macchia G, Arcelli A et al. Stereotactic radiotherapy of pancreatic cancer: A systematic review on pain relief. J Pain Res 2018; 11:2169–2178.

68. Ryan JF, Rosati LM, Groot VP et al. Stereotactic body radiation therapy for palliative management of pancreatic adenocarcinoma in elderly and medically inoperable patients. Oncotarget 2018;9:16427–16436.

69. Lawrence YR, Hammer L, Morag O et al. Celiac plexus radiosurgery: A new palliative modality for upper gastrointestinal malignancies—final results of a proof-of-concept clinical trial. J Clin Oncol 2018;36(suppl 15): 10098a.

70. Wong AA, Delclos ME, Wolff RA et al. Radiation dose considerations in the palliative treatment of locally advanced adenocarcinoma of the pancreas. Am J Clin Oncol 2005;28:227–233.

71. Palta M, Godfrey D, Goodman KA et al. Radiation therapy for pancreatic cancer: Executive summary of an ASTRO clinical practice guideline. Pract Radiat Oncol 2019;9:322–332.

72. Cornman-Homonoff J, Holzwanger DJ, Lee KS et al. Celiac plexus block and neurolysis in the management of chronic upper abdominal pain. Semin Intervent Radiol 2017;34:376–386.

73. Zhang CL, Zhang TJ, Guo YN et al. Effect of neurolytic celiac plexus block guided by computerized tomography on pancreatic cancer pain. Dig Dis Sci 2008;53:856–860.

74. Wong GY, Schroeder DR, Carns PE et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: A randomized controlled trial. JAMA 2004;291:1092–1099.

75. Mercadante S. Celiac plexus block versus analgesics in pancreatic cancer pain. Pain 1993; 52:187–192.

76. Arcidiacono PG, Calori G, Carrara S et al. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev 2011(3): CD007519.

77. Nagels W, Pease N, Bekkering G et al. Celiac plexus neurolysis for abdominal cancer pain: A systematic review. Pain Med 2013;14:1140–1163.

78. Zhong W, Yu Z, Zeng JX et al. Celiac plexus block for treatment of pain associated with pancreatic cancer: A meta-analysis. Pain Pract 2014; 14:43–51.

79. Si-Jie H, Wei-Jia X, Yang D et al. How to improve the efficacy of endoscopic ultrasound-guided celiac plexus neurolysis in pain management in patients with pancreatic cancer: Analysis in a single center. Surg Laparosc Endosc Percutan Tech 2014;24:31–35.

80. Dababou S, Marrocchio C, Rosenberg J et al. A meta-analysis of palliative treatment of pancreatic cancer with high intensity focused ultrasound. J Ther Ultrasound 2017;5:9.

81. Maloney E, Hwang JH. Emerging HIFU applications in cancer therapy. Int J Hyperthermia 2015;31:302–309.

82. Zhou Y. High-intensity focused ultrasound treatment for advanced pancreatic cancer. Gastroenterol Res Pract 2014;2014:205325.

83. Xiong LL, Hwang JH, Huang XB et al. Early clinical experience using high intensity focused ultrasound for palliation of inoperable pancreatic cancer. JOP 2009;10:123–129.

84. Zhao H, Yang G, Wang D et al. Concurrent gemcitabine and high-intensity focused ultrasound therapy in patients with locally advanced pancreatic cancer. Anticancer Drugs 2010;21: 447–452.

85. Marinova M, Wilhelm-Buchstab T, Strunk H. Advanced pancreatic cancer: High-intensity focused ultrasound (HIFU) and other local ablative therapies. Rofo 2019;191:216–227.

86. Strunk HM, Henseler J, Rauch M et al. Clinical use of high-intensity focused ultrasound

(HIFU) for tumor and pain reduction in advanced pancreatic cancer. Rofo 2016;188:662–670.

87. Marinova M, Strunk HM, Rauch M et al. High-intensity focused ultrasound (HIFU) for tumor pain relief in inoperable pancreatic cancer: Evaluation with the pain sensation scale (SES) [in German]. Schmerz 2017;31:31–39.

88. Vidal-Jove J, Perich E, Del Castillo MA. Ultrasound guided high intensity focused ultrasound for malignant tumors: The Spanish experience of survival advantage in stage III and IV pancreatic cancer. Ultrason Sonochem 2015;27:703–706.

89. Onofrio BM, Yaksh TL, Arnold PG. Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin. Mayo Clin Proc 1981;56: 516–520.

90. Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. J Neurosurg 1996;85:458–467.

91. Dupoiron D, Leblanc D, Demelliez-Merceron S et al. Optimizing initial intrathecal drug ratio for refractory cancer-related pain for early pain relief. A retrospective monocentric study. Pain Med 2019;20:2033–2042.

92. Carvajal G, Dupoiron D, Seegers V et al. Intrathecal drug delivery systems for refractory pancreatic cancer pain: Observational follow-up study over an 11-year period in a comprehensive cancer center. Anesth Analg 2018;126:2038–2046.

93. Dupoiron D. Intrathecal therapy for pain in cancer patients. Curr Opin Support Palliat Care 2019;13:75–80.

94. Smith TJ, Staats PS, Deer T et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: Impact on pain, drug-related toxicity, and survival. J Clin Oncol 2002;20:4040–4049.

95. John GM, Hershman DL, Falci L et al. Complementary and alternative medicine use among US cancer survivors. J Cancer Surviv 2016;10: 850–864.

96. Buckner CA, Lafrenie RM, Denommee JA et al. Complementary and alternative medicine use in patients before and after a cancer diagnosis. Curr Oncol 2018;25:e275–e281.

97. Stub T, Quandt SA, Arcury TA et al. Perception of risk and communication among conventional and complementary health care providers involving cancer patients' use of complementary therapies: A literature review. BMC Complement Altern Med 2016;16:353.

98. Jermini M, Dubois J, Rodondi PY et al. Complementary medicine use during cancer treatment and potential herb-drug interactions from a cross-sectional study in an academic centre. Sci Rep 2019;9:5078.

99. Zhou X, Li CG, Chang D et al. Current status and major challenges to the safety and efficacy presented by Chinese herbal medicine. Medicines (Basel) 2019;6:14.

100. Choi S, Oh DS, Jerng UM. A systematic review of the pharmacokinetic and pharmacodynamic interactions of herbal medicine with warfarin. PLoS One 2017;12:e0182794.

101. Lee IS, Cheon S, Park JY. Central and peripheral mechanism of acupuncture analgesia on visceral pain: A systematic review. Evid Based Complement Alternat Med 2019;2019:1304152.

102. Chen S, Wang S, Rong P et al. Acupuncture for visceral pain: Neural substrates and potential mechanisms. Evid Based Complement Alternat Med 2014;2014:609594.

103. Lau CH, Wu X, Chung VC et al. Acupuncture and related therapies for symptom management in palliative cancer care: Systematic review and meta-analysis. Medicine (Baltimore) 2016; 95:e2901.

104. Zhang R, Lao L, Ren K et al. Mechanisms of acupuncture-electroacupuncture on persistent pain. Anesthesiology 2014;120:482–503.

105. Han JS. Acupuncture: Neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci 2003;26: 17–22.

106. Chen JDZ, Ni M, Yin J. Electroacupuncture treatments for gut motility disorders. Neurogastroenterol Motil 2018;30:e13393.

107. Sallam H, McNearney TA, Doshi D et al. Transcutaneous electrical nerve stimulation (TENS) improves upper GI symptoms and balances the sympathovagal activity in scleroderma patients. Dig Dis Sci 2007;52:1329–1337.

108. Wang CP, Kao CH, Chen WK et al. A single-blinded, randomized pilot study evaluating effects of electroacupuncture in diabetic patients with symptoms suggestive of gastroparesis. J Altern Complement Med 2008;14:833–839.

109. Xin JJ, Gao JH, Wang YY et al. Antihypertensive and antihypertrophic effects of acupuncture at PC6 acupoints in spontaneously hypertensive rats and the underlying mechanisms. Evid Based Complement Alternat Med 2017;2017:9708094.

110. Huo ZJ, Li Q, Tian GH et al. The ameliorating effects of long-term electroacupuncture on cardiovascular remodeling in spontaneously hypertensive rats. BMC Complement Altern Med 2014;14:118.

111. Liao HY, Hsieh CL, Huang CP et al. Electroacupuncture attenuates induction of inflammatory pain by regulating opioid and adenosine pathways in mice. Sci Rep 2017;7: 15679.

112. Vance CG, Dailey DL, Rakel BA et al. Using TENS for pain control: The state of the evidence. Pain Manag 2014;4:197–209.

113. McNearney TA, Sallam HS, Hunnicutt SE et al. Prolonged treatment with transcutaneous electrical nerve stimulation (TENS) modulates neuro-gastric motility and plasma levels of vasoactive intestinal peptide (VIP), motilin and interleukin-6 (IL-6) in systemic sclerosis. Clin Exp Rheumatol 2013;31:140–150.

114. Sarosiek I, Song G, Sun Y et al. Central and peripheral effects of transcutaneous acupuncture treatment for nausea in patients with diabetic gastroparesis. J Neurogastroenterol Motil 2017;23:245–253.

115. Chandran P, Sluka KA. Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration. Pain 2003;102:195–201.

116. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets 2009;8:403–421.

117. Starowicz K, Przewlocka B. Modulation of neuropathic-pain-related behaviour by the spinal endocannabinoid/endovanilloid system. Philos Trans R Soc Lond B Biol Sci 2012;367:3286–3299.

118. Starowicz K, Finn DP. Cannabinoids and pain: Sites and mechanisms of action. In: Kendall D, Alexander SPH eds. Advances in Pharmacology. Vol. 80: Cannabinoid Pharmacology. New York: Elsevier, 2017:437–475.

119. Abrams DI. Integrating cannabis into clinical cancer care. Curr Oncol 2016;23:S8–S14.

120. Lake S, Walsh Z, Kerr T et al. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: A longitudinal analysis. PLoS Med 2019;16:e1002967.

121. Cranford JA, Bohnert KM, Perron BE et al. Prevalence and correlates of "vaping" as a route of cannabis administration in medical cannabis patients. Drug Alcohol Depend 2016;169:41–47.

122. Sánchez C. Routes of Administration and Cannabis Products with Therapeutic Purposes. Barcelona, Spain: Fundación CANNA, 2021. Available at https://www.fundacion-canna.es/en/routes-administration-and-cannabis-products-therapeutic-purposes.

123. Lillemoe KD, Cameron JL, Kaufman HS et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. Ann Surg 1993;217:447–455; discussion 456–447.

124. Jain PN, Shrikhande SV, Myatra SN et al. Neurolytic celiac plexus block: A better alternative to opioid treatment in upper abdominal malignancies: An Indian experience. J Pain Palliat Care Pharmacother 2005;19:15–20.

125. Wyse JM, Carone M, Paquin SC et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 2011;29: 3541–3546.

126. Chen H, Liu TY, Kuai L et al. Electroacupuncture treatment for pancreatic cancer pain: A randomized controlled trial. Pancreatology 2013;13:594–597.

127. Stefaniak T, Basinski A, Vingerhoets A et al. A comparison of two invasive techniques in the management of intractable pain due to inoperable pancreatic cancer: Neurolytic celiac plexus block and videothoracoscopic splanchnicectomy. Eur J Surg Oncol 2005;31:768–773.

128. Johnson CD, Berry DP, Harris S et al. An open randomized comparison of clinical effectiveness of protocol-driven opioid analgesia, celiac plexus block or thoracoscopic splanchnicectomy for pain management in patients with pancreatic and other abdominal malignancies. Pancreatology 2009;9:755–763.