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
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 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 hydrocodeone (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,
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].

### 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.  
Tapentadones | 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.
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 Clinical 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.
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 reductions 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.

| 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 |
| Lilleeoe 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 compared 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 |

Table 2. Selected trials in pancreas cancer pain management

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.

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.
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 \((decrease\ in\ the\ pain\ score\ by\ \geq 2\ points)\), 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.
**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 micropuncture 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 neurotransmitters 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.

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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PANCANCER-ASSOCIATED PAIN MANAGEMENT

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