

REVIEW ARTICLE

Endoscopic Management of Pain in Pancreatic Cancer

Parit Mekaroonkamol, Field F Willingham, Saurabh Chawla

Division of Digestive Diseases, Department of Medicine, Emory University School of Medicine, USA

ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and one of the leading causes of cancer mortality in the United States. Due to its aggressive behavior and lack of effective therapies, palliation plays a critical role in the management of the disease.

Most patients with pancreatic cancer suffer from severe pain, which adversely predicts prognosis and significantly impacts the quality of life. Therefore pain management plays a central role in palliation. Non-steroidal anti-inflammatory drugs and opioid agents are often first line medications in pain management, but they do not target the underlying pathophysiology of pain and their use is limited by adverse effects and dependence.

The proposed mechanisms of pain development in pancreatic cancer include neurogenic inflammation and ductal hypertension which may be targeted by endoscopic therapies. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) and pancreatic duct stent placement are the two primary endoscopic modalities for palliative management in pancreatic cancer patients with refractory pain. Other endoscopic treatments such as biliary stent placement and enteral stent placement for biliary and duodenal obstruction may also help palliate pain in addition to their role in decompression. This article reviews the existing evidence for these endoscopic interventions for pain management in pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States with an incidence of 22.1 cases per 100,000 per year during 2006 – 2010 [1]. It is estimated that there will be 46,420 new cases and 39,590 deaths in 2014 [1]. Due to the aggressive behavior and lack of effective therapies, it is predicted that pancreatic cancer may become the second leading cause of cancer mortality in the United States by 2020 [2]. The majority of patients with pancreatic cancer have an unresectable tumor at the initial presentation [3], making the 5-year survival rate as low as 6.7% [4] and the median survival approximately 12 months [5, 6]. With its poor prognosis, palliation plays a critical role in the management of the disease.

Up to 80% of patients with pancreatic cancer report abdominal pain [7, 8] and 44-70% suffer from severe pain [9, 10]. Difficult-to-control pain is reported in more than 90% of patients with advanced disease [11, 12]. The presence of pain on initial diagnosis not only impacts the quality of life, but also predicts the prognosis of the

disease. Pain in pancreatic cancer is believed to represent extrapancreatic perineural invasion and is associated with a higher recurrence rate and poorer prognosis, even in operable patients [13-15]. Pain critically impacts patients' quality of life, and pain management plays a central role in palliation.

According to World Health Organization and European Society of Medical Oncology guidelines on cancer pain relief, non-steroidal anti-inflammatory drugs and opioid agents are first line medications in pain management [16, 17]. However, their use is often limited by numerous adverse effects including constipation, somnolence, nausea, pruritus, tolerance, and addiction [18, 19]. Even though endoscopic interventions for pain control have been more extensively studied in chronic pancreatitis than in pancreatic cancer [20], the proposed mechanisms for pain development in both conditions share some common pathways, including ductal hypertension and neurogenic inflammation theories [13]. Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) and pancreatic duct stent placement are the two primary endoscopic modalities for palliative management in pancreatic cancer patients with refractory pain. Other endoscopic treatments such as biliary stent placement and enteral stent placement for biliary and duodenal obstruction may have palliative effects in addition to their role in decompression. This article reviews the existing evidence for these endoscopic interventions for pain management in pancreatic cancer.

Pathophysiology of Pain in Pancreatic Cancer

The etiologies of pain in pancreatic cancer are multifactorial. Glandular inflammation, increased pancreatic ductal pressure, infiltration of nerve sheaths, and neural ganglia

Received November 21st, 2014 – **Accepted** December 30th, 2014

Key words Celiac Plexus; Duodenum; Endoscopy; Pain; Palliative Care; Pancreatic Ducts; Pancreatic Neoplasms

Correspondence Saurabh Chawla
Department of Medicine and Digestive Diseases
Emory University School of Medicine
Faculty Office Building, 49 Jesse Hill Jr. Drive
Suite 431, Atlanta, GA 30303
USA

Phone + 404-778-1684

Fax + 404-778-1681

E-mail schawla2@gmail.com

invasion are believed to play important roles in the pathophysiology [21, 22]. Similar to other abdominal visceral pain, pancreatic pain is transmitted to the higher cortex via the spinothalamic tract, spinoreticular tract, spinoparabrachial tract, and post-synaptic dorsal column pathway [23-27]. Nociceptive signals in pancreatic cancer are believed to be generated by three main mechanisms: neurogenic inflammation, perineural invasion, and pancreatic ductal hypertension.

Neurogenic Inflammation

Neurogenic inflammation is an inflammatory reaction induced by neurogenic transmitters released from sensory nerve terminals. This inflammation not only stimulates nociceptors and causes pain, but can also cause tissue damage via arteriolar vasodilation, mast cell degranulation, histamine release and plasma extravasation [27].

A pain model in chronic pancreatitis demonstrates a direct correlation between pain intensity and increased pain neurotransmitter (substance P and calcitonin gene-related peptide (CGRP)), and the degree of perineural inflammatory cell infiltrates [28, 29]. The release of these pain neurotransmitters is induced by an activation of a sensory nerve receptor called potential vanilloid receptor subtype1 (TRPV1) [30, 31]. The level of TRPV1 gene expression is also found to be high in patients with pancreatic cancer [31]. Substance P can trigger a cascade of proinflammatory mediators, including interleukin-1, interleukin-6, and prostaglandin E2 [32, 33], causing mast cell degradation, plasma extravasation, and neutrophil attraction [27, 34, 35]. CGRP by itself is a potent vasodilator and can cause tissue edema [36, 37].

Another important pathway of neurogenic inflammation is the expression of nerve growth factor (NGF), a cytokine-like neurotrophin peptide that can induce neuroblast formation, neuronal maturation, and inflammatory cell migration [13, 38]. When NGF binds to its receptor, Tyrosine kinase receptor-A (TrkA), it initiates the mitogen-activated protein (MAP) kinase pathway which results in up-regulation and synthesis of substance P, CGRP, and other neuropeptides [13, 39, 40]. NGF is expressed in pancreatic cancer cells, while TrkA is located on sensory and sympathetic nerve sheaths. The level of NGF/TrkA expression is found to correlate with perineural invasion and the severity of clinical pain [38].

These pathways suggest that neuro-immune interaction, similar to that found in chronic pancreatitis, also plays an important role in pain generation in pancreatic cancer. Other pain-associated neurogenic markers such as Interleukin-8 and growth-associated protein-43 are found to interact closely with substance P and other receptors in pain models in chronic pancreatitis [41, 42]. However, their roles in pain generation in pancreatic cancer are less clear.

Perineural Invasion

The pancreas is a richly innervated organ. Pancreatic pain is believed to be primarily transmitted via the celiac plexus as first proposed by Kappis et al. in 1914 [43, 44]. Loose

connective tissue with low resistance in the perineural spaces makes perineural invasion and the extrapancreatic nerve plexus a common site for local spread of pancreatic cancer cells [13, 45]. In addition, the pancreatic perineural space is rich in neural-cell adhesion molecules, transforming growth factor α , and epidermal growth factor receptors, providing a suitable environment for the local spread and growth of the cancer cells [46, 47]. This spread of tumor cells via the perineural space to the retropancreatic region can cause pain, and is also associated with a higher local recurrence rate, decreased chance of curative resection, and a poorer prognosis [45]. Chemotaxis of cancer cells is believed to involve certain neuroendocrine mediators as demonstrated by increased NGF/TrkA expression in pancreatic cancer cells [13, 46]. However, these complex interactions are still poorly understood. In addition, up to 25% of patients with perineural invasion experience no pain [38], consistent with the multi-factorial nature of pain in this disease.

Pancreatic Ductal Hypertension

Pancreatic duct obstruction is commonly seen in pancreatic cancer, particularly when the tumor is located in the pancreatic head, causing pancreatic duct dilation and "obstructive type" pain [44]. Increased pancreatic ductal pressure has shown to be directly correlated with pain intensity in chronic pancreatitis [48]. Previous studies have demonstrated that decompression of pancreatic ductal hypertension in pancreatic cancer patients can alleviate the pain, supporting the theory of pancreatic ductal hypertension as one of the mechanisms mediating pain in pancreatic cancer [3, 49, 50].

The other hypothesis involves an ischemic effect wherein pancreatic intraparenchymal hypertension leads to a compartment-like physiology. This model is based on animal studies showing decreased blood flow to the pancreas when pancreatic interstitial pressure is increased [51-53]. However, other research found no correlation between intraoperative pancreatic intraparenchymal pressure and preoperative pain severity in a small study involving 12 patients [54].

Pancreatic cancer may also result in biliary and duodenal obstruction, which may occur with or without pancreatic ductal obstruction, depending on the location and the spread of the tumor [55, 56]. Pain, nausea, vomiting, and obstructive jaundice are major symptoms resulting from increased intraductal and intraluminal pressure [56]. However, the mechanism of the pain in this setting would be similar to the pain produced by non-malignant etiologies, and not necessarily related to an invasive process as described above.

Clinical Manifestations of Pain Associated with Pancreatic Cancer:

While pain from pancreatic cancer has been characteristically described as a chronic progressive epigastric pain radiating to the back [44], pain from pancreatic cancer can be broadly categorized into 2 types:

visceral (neuropathic) pain and obstructive pain [49]. Neuropathic pain is described as chronic, fairly continuous, dull, epigastric or upper back pain that is not related to a meal, while obstructive pain is described as episodic post-prandial epigastric or left hypochondrial pain that typically radiates to the back, similar to the pain in chronic pancreatitis [49]. Obstructive pain is believed to be related to pancreatic ductal hypertension, while neuropathic pain is believed to be the result of perineural invasion and neurogenic inflammation [3, 49, 57].

Endoscopic Therapies for Alleviating Pain Associated with Pancreatic Cancer:

Endoscopic Ultrasound-Guided Celiac Plexus Neurolysis (EUS-CPN)

Celiac plexus ganglia receive visceral afferent signals from the pancreatic nerves and transmit them centrally. They play an important role in pain perception in pancreatic cancer. Neuromodulatory pain control in unresectable pancreatic cancer was first described in the setting of intraoperative injection of phenol around the celiac ganglia [58]. Since then, celiac plexus neurolysis (CPN) techniques have evolved and CPN can be performed intraoperatively, percutaneously (anteriorly or posteriorly with radiologic guidance such as fluoroscopy, computed tomography, or ultrasound) or via an EUS-guided approach [59].

Several meta-analyses and systematic reviews underscore the efficacy and safety of CPN using percutaneous and intraoperative approaches [10, 11, 60]. Though the procedure does not improve survival, it can significantly reduce pain scores, decrease narcotic usage, and alleviate constipation in up to 90% of the patients with a long-lasting benefit up to 3 months [11, 60].

Since the introduction of EUS-guided CPN [61], it has gained popularity as a minimally-invasive approach to improve pain control in pancreatic cancer and is recommended in many current guidelines for the management of refractory cancer-related pain [17, 22, 62-65].

A similar procedure known as celiac plexus block (CPB) has primarily been used for the control of pain in benign pancreatic disease. Even though the endoscopic techniques in CPB and CPN are identical, their principle difference is the injectate used. Celiac plexus block uses anesthetic agents such as bupivacaine with anti-inflammatory agents such as triamcinolone and depo-medrol for temporary neuronal inhibition, while CPN involves permanent ablation of nervous tissue using sclerosing or neurolytic agents such as 5% phenol and absolute alcohol (0.25% bupivacaine is usually used preceding the neurolytic agent) [59, 62, 64]. Due to its shorter duration of pain relief, CPB is used in benign disease, primarily for chronic pancreatitis, while EUS-CPN may be the first line therapy for cancer-related pain [19, 22, 66]. CPN performed for pancreatic cancer may have a longer lasting pain relief with a median response of 20 weeks [22, 67]. CPN can however lead to significant retroperitoneal fibrosis and may potentially preclude patients from future surgery. Therefore it is primarily

recommended for palliative pain relief with unresectable malignant disease [19, 62].

The endosonographic anatomic landmark of the celiac ganglia is typically located at the posterior gastric wall, just below the gastroesophageal junction, approximately 40 cm from the incisors. By EUS, the ganglia may be seen as two small (2-3 mm) elongated hypoechoic structures with hyperechoic central foci anterolateral to the aorta, adjacent to the celiac trunk, just distal to the take-off of celiac artery from the aorta [19, 59, 62]. In some cases, small nerve fibers can be seen as thin hypoechoic structures arising from the edges of the ganglia. Delivering the neurolytic agent directly to the ganglia with endosonographic confirmation is believed to be the most accurate and most effective technique, yielding a 5-fold higher chance of clinical response compared to blind injection using anatomical landmarks alone [12]. However, direct visualization of the ganglia by EUS is not always possible [12]. If the ganglia cannot be visualized, blind injection may be performed using single-puncture (cephalad to the celiac trunk) or double-puncture (left and right of the celiac trunk) techniques. Compared to percutaneous techniques, an EUS-guided approach, with or without direct visualization of the ganglia, is more effective in pain reduction, with a longer lasting effect, and fewer complications [59, 68, 69].

A prospective study found that EUS-CPN can relieve pain in 78% of unresectable pancreatic cancer patients with an effect lasting up to 24 weeks [70]. A recent meta-analysis of 119 patients from 3 studies and a meta-analysis of 236 patients from 6 studies confirmed these results and found overall pain reduction of 73-80% with this approach [22, 66]. Better efficacy has also been reported with bilateral injection compared to single site injection in subgroup analysis [66].

In spite of its proven efficacy, there are a significant number of patients that do not respond, or only partially respond to EUS-CPN and continue to have refractory pain. There are conflicting data on significant changes in the opioid use [11, 70, 71] and reports of increased consumption of opioids following the procedure [72]. Certain tumor characteristics such as involvement of the pancreatic head and a locally advanced presentation are also known to have less response to the intervention [72, 73]. The varying clinical outcomes may involve the operator dependent nature of the procedure and lack of a standardized technique. Attempts should be made to directly visualize the ganglion before the injection and when possible, bilateral injection is preferred over single site injection [12, 66].

The concept of EUS-CPN involves ablation of the celiac ganglia, which carry sympathetic nervous transmission, therefore, sympatholytic reactions are expected. Transient hypotension (1-38%) and diarrhea (4-44%) may be observed post-procedure but are usually self-limited and typically resolve within 48 hours [19, 22, 62, 66, 68]. They may require a short course of anti-diarrheal medication or intravenous fluids [60, 68, 69]. Persistent diarrhea

requiring octreotide injection and persistent orthostatic hypotension requiring oral vasopressors have rarely been observed [74]. A paradoxical increase in abdominal pain may be observed in 9% of the patients and can last for a mean of 2.2 days [22, 62, 71]. Though rare, major complications such as pneumothorax, empyema, peripancreatic abscess, retroperitoneal bleeding, impotence, and paraplegia have been reported with CPN performed by percutaneous techniques [22, 59, 60]. Such major complications have not been reported with EUS-CPN [12, 22, 75]. Antibiotic prophylaxis with levofloxacin or ciprofloxacin intravenously before the procedure is warranted in CPB but its benefit in CPN is controversial given the presumed bactericidal effect of the absolute alcohol used in CPN [62, 69, 71].

Pancreatic Duct Stent Placement

Pancreatic duct stent placement (PDSP) effectively decompresses the pancreatic duct and is known to be an effective treatment for pain in chronic obstructive pancreatitis [20, 76, 77]. Since pancreatic ductal hypertension is one of the likely mechanisms of pain in pancreatic cancer, decompression by stenting may alleviate pain in patients with pancreatic cancer. This approach may be particularly suited to patients with tumor located at the head of pancreas causing ductal obstruction and obstructive pain, which may be less likely to respond to CPN [72, 73].

The indications and the use of PDSP have evolved over the past decade. It is commonly used in the treatment of chronic pancreatitis, pancreatic pseudocysts, pancreas divisum, pancreatic duct injuries, pancreatic duct stricture, pancreatic fistulae, and prophylactically to prevent post-ERCP pancreatitis [20, 76, 78]. Despite its established capacity to reduce intraductal hypertension, to bypass obstructive lesions, to restore luminal patency, and in pain reduction in chronic pancreatitis [20, 79, 80], the role of PDSP in pain management in pancreatic cancer is less well established.

Previous studies have demonstrated that PDSP using either 5 Fr or 7 Fr stents can reduce the pain intensity and opioid consumption in 75% and 70% of the pancreatic cancer patients, respectively [50, 57, 81]. The pain reduction lasted for a mean of 5.5 months [50]. The studies included only patients with cancer at the pancreatic head and radiographic evidence of pancreatic ductal obstruction in the studies. Plastic stents and metallic stents have been employed. In one study, failure to respond seemed to be related to the type of pain patients experienced, irrespective of the type of stent used [57]. All patients with obstructive type of pain (N=7) responded to PDSP, while those with chronic unremitting pain (N=3) did not show a response despite evidence of pancreatic duct stenosis [57]. The authors concluded that PDSP may be preferable for pancreatic cancer patients with obstructive type pain. A subsequent larger prospective study found that PDSP is a valid and safe palliative option. This trial enrolled patients with cancer at pancreatic head, evidence of pancreatic

ductal stenosis, and obstructive type pain. They found that PDSP could not only reduce pain, but also decrease opioid consumption, and improve quality of life [3]. The response rate to the procedure was 82%, similar to previous studies and a long-lasting effect of up to 12 weeks was seen in 62%. Of note, there was no increase in efficacy when a 10 Fr stent was used instead of a 7 Fr stent, suggesting that an increased diameter was not required for efficacy in pain reduction. There is no data available from a randomized controlled trial, however, other small studies using stents ranging from 5 Fr to 11.5 Fr in size yielded similar results [57, 81-83].

A systematic review of 7 studies demonstrated a technical success in deploying a stent in 83% of patients. Pain alleviation was observed in 60-88% [49]. No serious complications were reported in any study [3, 50, 57]. 2 out of 107 patients had stent migration and required a repeat endoscopy to retrieve the stent and replace a new one [3, 57]. In one study, one case of post-sphincterotomy bleeding occurred but hemostasis was achieved endoscopically without the need for blood transfusion [3].

The British Society of Gastroenterology has endorsed PDSP as an adjunctive approach for pain palliation [64]. It has been postulated that PDSP may be more effective for obstructive pain in patients with pancreatic ductal obstruction. However, the available studies are small with a non-randomized design. Larger high-quality controlled studies are needed to evaluate PDSP and EUS-CPN, given the different pain relieving mechanisms these two procedures can offer.

Endoscopic Management for Peri-Pancreatic Luminal Obstruction

Approximately 70% of pancreatic adenocarcinoma involves the pancreatic head, predisposing patients to biliary and gastroduodenal obstruction [84]. Pain, pruritus, jaundice, nausea, vomiting, and fever are common presenting obstructive symptoms [7]. Endoscopic retrograde cholangiopancreatography (ERCP) with endobiliary stent placement remains the first line palliative option for malignant biliary stenosis [85]. Surgical decompression should be reserved for patients undergoing curative resection or when stenting is not possible [84]. Expandable metal stent placement is associated with less migration and occlusion relative to plastic stents. It is the preferred type of stent for palliation in a patient with a life expectancy greater than a few months due to its durable patency and reduced need for scheduled stent exchanges [84].

Gastroduodenal obstruction usually occurs at the peripyloric and duodenal regions late in the course of the disease. 20% of pancreatic cancer patients who present with duodenal obstruction are in the terminal stage [55, 86]. Surgical gastrojejunostomy and percutaneous endoscopic gastro-jejunal tube placements were once the only options for these patients. However, considering the poor prognosis and morbidity associated with a surgical

bypass, operative intervention may not be ideal [87, 88]. With the introduction of self-expandable metallic enteral stents, endoscopic gastroduodenal stenting has proven to be a safe and effective non-surgical minimally-invasive option [86].

When concomitant biliary obstruction is found (23-61% of the cases), biliary stents can be placed before, simultaneously, or after the placement of the duodenal stent. The stents may be deployed using fluoroscopic and endoscopic guidance, by fluoroscopy alone, or via a through-the-scope technique. The use of interlocking metal stents, stent-in-stent techniques, and EUS-guided biliary drainage followed by combined stent placement in patients who have both biliary and duodenal obstruction have been reported in patients with advanced loco-regional disease [56, 86, 89-93].

In a systematic review of 606 patients [86] undergoing gastroduodenal stenting, there was a 97% technical success rate of stent deployment and significant clinical improvement in 87% of the patients. The majority of the technical failures were due to complex anatomy and severe obstruction (53%), while clinical failures primarily involved progression of disease (61%) and early stent migration (15%). The gastric outlet score increased significantly from 0.4 (no oral intake or liquid diet only) to 2.4 (soft solid to full diet). Complications included stent obstruction (17.2%), stent migration (5.1%), pain (2.5%), biliary obstruction (1.3%), perforation (0.7%) and bleeding (0.5%). The major causes of obstruction were in-stent tumor growth, stent fracture, stent collapse, insufficient stent coverage, new stenotic sites, stent migration, and food impaction. 79% of these obstructions were successfully treated by additional stent placement. No procedure-related deaths were reported. The authors concluded that gastroduodenal stent placement is a viable palliative option in select patients with unresectable tumors, symptomatic gastric outlet obstruction without multiple stenotic lesions, metastatic disease (but not carcinomatosis peritonei) with anticipated short survival time, and no symptomatic improvement after medical treatment.

Though the survival period of patients with unresectable pancreatic adenocarcinoma has improved due to more effective chemotherapy [86, 94], long term data on duodenal and biliary metallic stents placed for palliation is limited. A retrospective review of 100 patients [94] found a median metallic biliary stent patency of 7 months (0.4-21 months) and a median metallic duodenal patency of 6 months (0.5-15 months). Clinical success rate (symptomatic improvement after stent placement) was 96% for biliary stenting and 92% for duodenal stent placement. Combined endoscopic stenting had technical success rate of 91%. This study suggests that despite longer periods of survival, endoscopic stenting remains a viable palliative option for both biliary and duodenal obstructions [94].

Other endoscopic modalities such as balloon dilation, laser ablation, and radiotherapy have shown transient symptomatic relief, and long-term adequate oral intake

is rarely obtained with these approaches therefore, they are not considered first line therapy [88]. EUS-guided biliary drainage is a novel technique for complicated cases after ERCP has failed. With a curvilinear echoendoscope, a needle can be safely and accurately deployed from the antrum, duodenal bulb, or second portion of duodenum to the dilated biliary tree, allowing cholangiography and stent placement, creating a bilio-enteric anastomosis. EUS-guided choledochoduodenostomy, hepaticogastrostomy, and choledochostomy are novel techniques developed from this concept. Data from small studies has shown promise [56, 90, 93, 95-100] however, larger studies are warranted to evaluate their safety and efficacy and standardize the techniques.

CONCLUSION

EUS-CPN, pancreatic ductal decompression, biliary stent placement, duodenal stent placement, and EUS-guided biliary drainage are useful endoscopic interventions for pain management in pancreatic cancer. They may spare terminal patients with pancreatic cancer a laparotomy and the associated operative morbidity. EUS-CPN has been studied most extensively for intractable pancreatic pain. Its role for palliation in pancreatic cancer is well established [17, 64, 65]. PDSP can be considered for patients with malignant obstruction and may be especially suited to patients presenting with obstructive type of pain [3, 49, 64]. The appeal of PDSP involves management of the underlying obstructive physiology, rather than treatment of the symptom alone. More studies are needed to define the role of these modalities in the palliation of pain in the large population of patients with unresectable pancreatic cancer. There are also no data on combination therapy in those that have failed standard treatment and continue to have refractory pain. When pain is associated with jaundice and gastric outlet obstruction, ERCP with biliary stenting, enteral stenting, or double stenting techniques can be offered. When conventional transpapillary approaches fail to provide decompression, the novel EUS guided approaches may be considered if available. Further studies to compare the efficacy among these interventions, to evaluate selection criteria, and to determine the proper timing of these procedures are needed. Hopefully, concurrent with advances in palliation, novel treatment modalities will continue to improve on the overall survival and quality of life for patients presenting with late or advanced stage disease.

Conflicting Interest

Authors have no conflicts of interest

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: a cancer journal for clinicians. 2014; 64(1): 9-29.
2. Muniraj T, Jamidar PA, Aslanian HR. Pancreatic cancer: a comprehensive review and update. Dis Mon. 2013; 59(11): 368-402. [PMID: 24183261]

3. Wehrmann T, Riphaus A, Frenz MB, Martchenko K, Stergiou N. Endoscopic pancreatic duct stenting for relief of pancreatic cancer pain. *European journal of gastroenterology & hepatology*. 2005; 17(12): 395-400. [PMID: 10464348]
4. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W, et al. SEER cancer statistics review, 1975–2008. Bethesda, MD: National Cancer Institute. 2011; 19.
5. Oberstein PE, Olive KP. Pancreatic cancer: why is it so hard to treat? *Therap Adv Gastroenterol*. 2013; 6(4): 321-37. [PMID: 23999170]
6. Bilimoria KY, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer*. 2007; 110(4): 738-44. [PMID: 17580363]
7. Molinari M, Helton W, Espat NJ. Palliative strategies for locally advanced unresectable and metastatic pancreatic cancer. *Surgical Clinics of North America*. 2001; 81(3): 651-66. [PMID: 11459279]
8. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia I. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *British Journal of Surgery*. 1998; 85(2): 199-201. [PMID: 9501815]
9. Brescia FJ, Portenoy RK, Ryan M, Krasnoff L, Gray G. Pain, opioid use, and survival in hospitalized patients with advanced cancer. *Journal of Clinical Oncology*. 1992; 10(1): 149-55. [PMID: 1345797]
10. Arcidiacono PG, Calori G, Carrara S, McNicol ED, Testoni PA. Celiac plexus block for pancreatic cancer pain in adults. *Cochrane Database Syst Rev*. 2011; 3. [PMID: 21412903]
11. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. *The American journal of gastroenterology*. 2007; 102(2): 430-8. [PMID: 17100960]
12. Ascunze G, Ribeiro A, Reis I, Rocha-Lima C, Sleeman D, Merchan J, et al. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). *Gastrointestinal endoscopy*. 2011; 73(2): 267-74. [PMID: 21295640]
13. di Mola FF, di Sebastiano P. Pain and pain generation in pancreatic cancer. *Langenbeck's Archives of Surgery*. 2008; 393(6): 919-22. [PMID: 18193269]
14. Larson D, Rodin A, Roberts D, O'Steen W, Rapperport A, Lewis S. Perineural lymphatics: myth or fact. *The American Journal of Surgery*. 1966; 112(4): 488-92. [PMID: 5915292]
15. Bockman D, Büchler M, Beger H. Interaction of pancreatic ductal carcinoma with nerves leads to nerve damage. *Gastroenterology*. 1994; 107(1): 219-30. [PMID: 8020665]
16. Organization WH. Cancer pain relief: with a guide to opioid availability: World Health Organization; 1996. [PMID:]
17. Ripamonti C, Bandieri E, Roila F. Management of cancer pain: ESMO clinical practice guidelines. *Annals of oncology*. 2011; 22(suppl 6): vi69-vi77. [PMID: 22997447]
18. Levy MJ, Wiersema MJ. EUS-guided celiac plexus neurolysis and celiac plexus block. *Gastrointestinal endoscopy*. 2003; 57(7): 923-30. [PMID: 12776048]
19. Michaels AJ, Draganov PV. Endoscopic ultrasonography guided celiac plexus neurolysis and celiac plexus block in the management of pain due to pancreatic cancer and chronic pancreatitis. *World Journal of Gastroenterology*. 2007; 13(26): 3575.
20. Adler DG, Lichtenstein D, Baron TH, Davila R, Egan JV, Gan S-I, et al. The role of endoscopy in patients with chronic pancreatitis. *Gastrointestinal endoscopy*. 2006; 63(7): 933-7.
21. Staats PS, Hekmat H, Sauter P, Lillemoe K. 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 Medicine*. 2001; 2(1): 28-34. [PMID: 15102315]
22. Kaufman M, Singh G, Das S, Concha-Parra R, Erber J, Micames C, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. *Journal of clinical gastroenterology*. 2010; 44(2): 127-34. [PMID: 19826273]
23. Hobbs SF, Chandler MJ, Bolser DC, Foreman RD. Segmental Organization of Visceral and Somatic Input Onto C,-T, Spinothalamic Tract Cells of the Monkey. 1992. [PMID: 1479431]
24. Lima D. A spinomedullary projection terminating in the dorsal reticular nucleus of the rat. *Neuroscience*. 1990; 34(3): 577-89. [PMID: 1693758]
25. Bernard J, Huang G, Besson J-M. The parabrachial area: electrophysiological evidence for an involvement in visceral nociceptive processes. *Journal of neurophysiology*. 1994; 71(5): 1646-60. [PMID: 8064340]
26. Brown A, Fyffe R. Form and function of dorsal horn neurones with axons ascending the dorsal columns in cat. *The Journal of physiology*. 1981; 321(1): 31-47. [PMID: 7338813]
27. Vera-Portocarrero L, Westlund KN. Role of neurogenic inflammation in pancreatitis and pancreatic pain. *Neurosignals*. 2005; 14(4): 158-65. [PMID: 16215298]
28. Büchler M, Weihe E, Fries H, Malfertheiner P, Bockman E, Müller S, et al. Changes in peptidergic innervation in chronic pancreatitis. *Pancreas*. 1992; 7(2): 183-92. [PMID: 1372738]
29. Keith R, Keshavjee S, Kerenyi N. Neuropathology of chronic pancreatitis in humans. *Canadian journal of surgery. Journal canadien de chirurgie*. 1985; 28(3): 207-11. [PMID: 3995416]
30. Wick EC, Hoge SG, Grahn SW, Kim E, Divino LA, Grady EF, et al. Transient receptor potential vanilloid 1, calcitonin gene-related peptide, and substance P mediate nociception in acute pancreatitis. *American Journal of Physiology-Gastrointestinal and Liver Physiology*. 2006; 290(5): G959-G69. [PMID: 16399878]
31. Hartel M, Di Mola FF, Selvaggi F, Mascetta G, Wente MN, Felix K, et al. Vanilloids in pancreatic cancer: potential for chemotherapy and pain management. *Gut*. 2006; 55(4): 519-28. [PMID: 16174661]
32. Lotz M, Carson DA, Vaughan JH. Substance P activation of rheumatoid synoviocytes: neural pathway in pathogenesis of arthritis. *Science*. 1987; 235(4791): 893-5. [PMID: 2433770]
33. Lotz M, Vaughan JH, Carson DA. Effect of neuropeptides on production of inflammatory cytokines by human monocytes. *Science*. 1988; 241(4870): 1218-21. [PMID: 2457950]
34. Lembeck F, Holzer P. Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. *Naunyn-Schmiedeberg's archives of pharmacology*. 1979; 310(2): 175-83. [PMID: 93706]
35. Jacques L, Couture R, Drapeau G, Regoli D. Capillary permeability induced by intravenous neurokinins. *Naunyn-Schmiedeberg's archives of pharmacology*. 1989; 340(2): 170-9. [PMID: 2478892]
36. Brain S, Williams T, Tippins J, Morris H, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. 1985. [PMID: 3917554]
37. Escott KJ, Brain SD. Effect of a calcitonin gene-related peptide antagonist (CGRP8-37) on skin vasodilatation and oedema induced by stimulation of the rat saphenous nerve. *British journal of pharmacology*. 1993; 110(2): 772-6. [PMID: 8242250]
38. Friess H, Zhu Z-W, di Mola FF, Kulli C, Graber HU, Andren-Sandberg Å, et al. Nerve growth factor and its high-affinity receptor in chronic pancreatitis. *Annals of surgery*. 1999; 230(5): 615. [PMID: 10561084]
39. Zhu Z-W, Friess H, Wang L, Zimmermann A, Büchler MW. Brain-derived neurotrophic factor (BDNF) is upregulated and associated with pain in chronic pancreatitis. *Digestive diseases and sciences*. 2001; 46(8): 1633-9. [PMID: 11508661]
40. Ganju P, O'Bryan JP, Der C, Winter J, James IF. Differential regulation of SHC proteins by nerve growth factor in sensory neurons and PC12 cells. *European Journal of Neuroscience*. 1998; 10(6): 1995-2008. [PMID: 9753087]
41. Di Sebastiano P, Fink T, Weihe E, Friess H, Innocenti P, Beger H, et al. Immune cell infiltration and growth-associated protein 43 expression correlate with pain in chronic pancreatitis. *Gastroenterology*. 1997; 112(5): 1648-55. [PMID: 9136844]
42. Di Sebastiano P, Di Mola F, Di Febbo C, Baccante G, Porreca E, Innocenti P, et al. Expression of interleukin 8 (IL-8) and substance P in human chronic pancreatitis. *Gut*. 2000; 47(3): 423-8. [PMID: 10940282]

43. Kappis M. Erfahrungen mit local anasthesie bie bauchoperationen. *Vehr Dtsch Gesellsch Chir.* 1914; 43: 87-9.
44. Lebovits AH, Lefkowitz M. Pain management of pancreatic carcinoma: a review. *Pain.* 1989; 36(1): 1-11. [PMID: 2465529]
45. Bockman D, Büchler M, Beger H. Morphology of pancreatic cancer: Involvement of nerves. *Cancer of pancreas.* Ulm Germany, Universitätsverlag Ulm GmbH. 1996: 99-108.
46. Kenmotsu M. Relationship between perineural invasion and expression of neuro-endocrine markers and neural cell adhesion molecule in human pancreatic carcinoma. *Jpn J Gastroenterol Surg.* 1990; 23(11): 2580-5.
47. Seki H, Tanaka JI, Sato Y, Kato Y, Umezawa A, Koyama K. Neural cell adhesion molecule (NCAM) and perineural invasion in bile duct cancer. *Journal of surgical oncology.* 1993; 53(2): 78-83. [PMID: 8501910]
48. Ebbehøj N, Borly L, Bülow J, Rasmussen S, Madsen P. Evaluation of pancreatic tissue fluid pressure and pain in chronic pancreatitis: a longitudinal study. *Scandinavian journal of gastroenterology.* 1990; 25(5): 462-6. [PMID: 2359973]
49. Costamagna G, Mutignani M. Pancreatic stenting for malignant ductal obstruction. *Digestive and liver disease.* 2004; 36(9): 635-8. [PMID: 15460850]
50. Costamagna G, Gabrielli A, Mutignani M, Perri V, Crucitti F. Treatment of "obstructive" pain by endoscopic drainage in patients with pancreatic head carcinoma. *Gastrointestinal endoscopy.* 1993; 39(6): 774-7. [PMID: 7507450]
51. Toyama M, Lewis M, Kusske A, Reber P, Ashley S, Reber H. Ischaemia-reperfusion mechanisms in acute pancreatitis. *Scandinavian Journal of Gastroenterology.* 1996; 31(S219): 20-3. [PMID: 8865466]
52. Reber P, Patel A, Toyama M, Ashley S, Reber H. Feline model of chronic obstructive pancreatitis: effects of acute pancreatic duct decompression on blood flow and interstitial pH. *Scandinavian journal of gastroenterology.* 1999; 34(4): 439-44. [PMID: 10365907]
53. Karanjia N, Widdison A, Leung F, Alvarez C, Lutrin F, Reber H. Compartment syndrome in experimental chronic obstructive pancreatitis: effect of decompressing the main pancreatic duct. *British journal of surgery.* 1994; 81(2): 259-64. [PMID: 8156353]
54. Manes G, Büchler M, Piemmicco O, Di Sebastiano P, Malfertheiner P. Is increased pancreatic pressure related to pain in chronic pancreatitis? *International journal of pancreatology.* 1994; 15(2): 113-7. [PMID: 8071569]
55. Conio M, Demarquay J-F, De Luca L, Marchi S, Dumas R. Endoscopic treatment of pancreatico-biliary malignancies. *Critical reviews in oncology/hematology.* 2001; 37(2): 127-35. [PMID: 11166586]
56. Tonozuka R, Itoi T, Sofuni A, Itokawa F, Moriyasu F. Endoscopic double stenting for the treatment of malignant biliary and duodenal obstruction due to pancreatic cancer. *Digestive Endoscopy.* 2013; 25(S2): 100-8. [PMID:]
57. Tham T, Lichtenstein D, Vandervoort J, Wong R, Slivka A, Banks P, et al. Pancreatic duct stents for "obstructive type" pain in pancreatic malignancy. *The American journal of gastroenterology.* 2000;95(4):956-60. [PMID: 10763944]
58. Copping J, Willix R, Kraft R. Palliative chemical splanchnicectomy. *Arch Surg.* 1969;98(4):418-20. [PMID: 4180408]
59. Snady H. Interventional endoscopy, and neoadjuvant therapy and the gastroenterologist. *Hematology/oncology clinics of North America.* 2002; 16(1): 53-79. [PMID: 12063829]
60. Eisenberg E, Carr D, Chalmers T. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. *Anesthesia & Analgesia.* 1995; 80(2): 290-5. [PMID: 7818115]
61. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. *Gastrointestinal endoscopy.* 1996; 44(6): 656-62. [PMID: 8979053]
62. Collins D, Penman I, Mishra G, Draganov P. EUS-guided celiac block and neurolysis. *Endoscopy.* 2006; 38(9): 935-9. [PMID: 16981114]
63. Amr YM, Makharita MY. Comparative study between 2 protocols for management of severe pain in patients with unresectable pancreatic cancer: one-year follow-up. *The Clinical journal of pain.* 2013; 29(9): 807-13. [PMID: 23917696]
64. Pancreatic S. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut.* 2005; 54(Suppl 5): v1. [PMID: 15888770]
65. Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson AB, Casper ES, et al. Pancreatic adenocarcinoma, Version 2.2012 featured updates to the NCCN Guidelines. *Journal of the National Comprehensive Cancer Network.* 2012; 10(6): 703-13. [PMID: 22679115]
66. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. *Digestive diseases and sciences.* 2009; 54(11): 2330-7. [PMID: 19137428]
67. Harada N, Wiersema M, Wiersema L. Endosonography-guided celiac plexus neurolysis. *Gastrointestinal endoscopy clinics of North America.* 1997; 7(2): 237-45. [PMID: 9101264]
68. Gunaratnam N, Norton I, Sarma A, Wiersema M. Endosonography guided celiac plaxus neurolysis (EUS CPN) for pancreatic cancer (PCA) pain: Indications, efficacy, complications and patient outcomes. *Gastrointestinal endoscopy,* 1999. Mosby-year book inc 11830 westline industrial dr, st louis, mo 63146-3318 usa: ab91-ab. [PMID:]
69. Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. A prospective randomized comparison of endoscopic ultrasound-and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. *The American journal of gastroenterology.* 1999; 94(4): 900-5. [PMID:]
70. Gunaratnam NT, Sarma AV, Norton ID, Wiersema MJ. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. *Gastrointestinal endoscopy.* 2001; 54(3): 316-24. [PMID:]
71. Levy MJ, Topazian MD, Wiersema MJ, Clain JE, Rajan E, Wang KK, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. *The American journal of gastroenterology.* 2008; 103(1): 98-103. [PMID: 17970834]
72. Mercadante S, Catala E, Arcuri E, Casuccio A. Celiac plexus block for pancreatic cancer pain: factors influencing pain, symptoms and quality of life. *Journal of pain and symptom management.* 2003; 26(6): 1140-7. [PMID: 14654266]
73. Catalano MF, Ahmed U, Chauhan SS, Patel SN, Geenen JE. Celiac plexus neurolysis (CPN) in the treatment of refractory pain of pancreatic cancer (PCA): site specific response to therapy. *Gastrointestinal Endoscopy.* 2005; 61(5): AB273. [PMID:]
74. Mercadante S. Celiac plexus block versus analgesics in pancreatic cancer pain. *Pain.* 1993; 52(2): 187-92. [PMID: 8455966]
75. Wiechowska-Kozłowska A, Boer K, Wojcicki M, Milkiewicz P. The efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis for treatment of pain in patients with pancreatic cancer. *Gastroenterology research and practice.* 2012; 2012.
76. Lehman GA. Role of ERCP and other endoscopic modalities in chronic pancreatitis. *Gastrointestinal endoscopy.* 2002; 56(6): S237-S40. [PMID: 12447274]
77. Rösch T, Daniel S, Scholz M. i wsp.; European Society of Gastrointestinal Endoscopy Research Group. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long-term follow-up. *Endoscopy.* 2002; 34: 765-71. [PMID: 12244496]
78. Warshaw AL, Banks PA, Fernández-del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. *Gastroenterology.* 1998; 115(3): 765-76. [PMID: 9721175]
79. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *New England Journal of Medicine.* 2007; 356(7): 676-84. [PMID: 17301298]
80. Dite P, Ružicka M, Zboril V, Novotný I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. *Endoscopy.* 2003; 35(07): 553-8. [PMID: 12822088]

81. Costamagna G, Alevras P, Palladino F, Rainoldi F, Mutignani M, Morganti A. Endoscopic pancreatic stenting in pancreatic cancer. *Canadian journal of gastroenterology* 1998; 13(6): 481-7. [PMID: 10464348]
82. Catalano M, Alcocer E, Raijman I, Lahoti S, Hogan W, Geenen J. Palliative endoscopic therapy in patients with pancreatic cancer and obstruction of the pancreatic duct using pancreatic stenting. *Gastrointestinal endoscopy*, 1998. Mosby-year book inc 11830 westline industrial dr, st louis, mo 63146-3318 usa: ab133-ab.
83. Lichtenstein D, Slivka A, Banks P, Carr-Locke D. Pancreatic stent placement for palliation of "Obstructive" pain in pancreatic malignancy. *Gastrointestinal Endoscopy*. 1995; 41(4): 425.
84. El Kamar FG, Grossbard ML, Kozuch PS. Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. *The Oncologist*. 2003; 8(1): 18-34. [PMID: 12604729]
85. Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Leighton JA, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. *Gastrointestinal endoscopy*. 2005; 62(1): 1-8. [PMID: 15990812]
86. Dormann A, Meisner S, Verin N, Lang AW. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. *Endoscopy*. 2004; 36(06): 543-50. [PMID: 15202052]
87. Van Heek N, Van Geenen R, Busch O, Gouma D. Palliative treatment in "peri"-pancreatic carcinoma: stenting or surgical therapy? *Acta gastroenterologica Belgica*. 2001; 65(3): 171-5.
88. Tendler DA. Malignant gastric outlet obstruction: bridging another divide. *The American journal of gastroenterology*. 2002; 97(1): 4-6. [PMID: 11808968]
89. Freeman ML, Cass OW. Interlocking expandable metal stents for simultaneous treatment of malignant biliary and duodenal obstruction. *Gastrointestinal endoscopy*. 1996; 44(1): 98-9. [PMID: 8836730]
90. Iwamuro M, Kawamoto H, Harada R, Kato H, Hirao K, Mizuno O, et al. Combined duodenal stent placement and endoscopic ultrasonography-guided biliary drainage for malignant duodenal obstruction with biliary stricture. *Digestive Endoscopy*. 2010; 22(3): 236-40. [PMID: 20642617]
91. Moon JH, Choi HJ, Ko BM, Koo HC, Hong SJ, Cheon YK, et al. Combined endoscopic stent-in-stent placement for malignant biliary and duodenal obstruction by using a new duodenal metal stent (with videos). *Gastrointestinal endoscopy*. 2009; 70(4): 772-7. [PMID: 19595319]
92. Mutignani M, Tringali A, Shah S, Perri V, Familiari P, Iacopini F, et al. Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. *Endoscopy*. 2007; 39(05): 440-7. [PMID: 17516351]
93. Itoi T, Yamao K. EUS 2008 Working Group document: evaluation of EUS-guided choledochoduodenostomy (with video). *Gastrointestinal endoscopy*. 2009;69(2):S8-S12. [PMID: 19179177]
94. Maire F, Hammel P, Ponsot P, Aubert A, O'Toole D, Hentic O, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. *The American journal of gastroenterology*. 2006;101(4):735-42. [PMID: 16635221]
95. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delperio J. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy*. 2001;33(10):898-900. [PMID: 11571690]
96. Burmester E, Niehaus J, Leinweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: report of 4 cases. *Gastrointestinal endoscopy*. 2003; 57(2): 246-51. [PMID:]
97. Puspok A, Lomoschitz F, Dejaco C, Hejna M, Sautner T, Gangl A. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. *American Journal of Gastroenterology*. 2005; 100(8): 1743-7. [PMID: 16086710]
98. Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. *Gastrointestinal endoscopy*. 2006; 64(1): 52-9. [PMID: 16813803]
99. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. *JOP*. 2007; 8(4): 438-43. [PMID: 17625296]
100. Yamao K, Bhatia V, Mizuno N, Sawaki A, Ishikawa H, Tajika M, et al. EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: results of long-term follow-up. *Endoscopy*. 2008; 40(04): 340-2. [PMID: 18389451]