Review Article

Pain management of pancreatic head adenocarcinomas that are unresectable: celiac plexus neurolysis and splanchnicectomy

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Background: Pancreatic adenocarcinoma is often incurable at the time of diagnosis. For patients with unresectable or recurrent disease, palliation of pain is a key component of care. Medical management with narcotics has numerous side effects and may be ineffective. Interventions for pain control include celiac plexus neurolysis (CPN) and splanchnicectomy. The purpose of this review is to outline pertinent anatomy, techniques, side effects, complications, and efficacy of interventions for palliation of pain from pancreatic cancer.

Methods: We reviewed current literature, as well as our own patients, to assess the role and outcomes of CPN and splanchnicectomy. Short descriptions of procedural techniques and functional illustrations are provided.

Results: Both CPN and splanchnicectomy have excellent outcomes with regard to pain control. Quality of life and survival, however, have not been conclusively demonstrated to improve with either technique. Data regarding head-to-head comparisons of the two interventions is lacking.

Conclusions: Patients with incurable pancreatic carcinoma should be offered either CPN or splanchnicectomy when medical management with narcotics has failed.

Keywords: Splanchnic nerves; celiac plexus; ganglia sympathetic; pancreatic cancer; palliative care

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Introduction

Adenocarcinoma of the pancreas is the fifth leading cause of cancer death in the world (1). Because patients often present with locally advanced or metastatic disease, curative resection is rarely an option. As a result, intervention for these unfortunate patients is often limited to palliation. The primary goal of palliation is ensuring that patients do not suffer painful effects of cancer progression, like obstruction of the common bile duct and/or duodenum and abdominal pain from malignant infiltration into the celiac plexus.

Up to 90% of patients with pancreatic cancer experience pain (1). Narcotics may be given initially, but significant side effects, such as a reduction in quality of life, have been reported. Because of this, attention has been given to two palliative interventions: celiac neurolysis and splanchnic neurectomy. Both celiac plexus neurolysis (CPN) and splanchnicectomy have been examined and described in the literature for a number of years. The purpose of this paper is to outline pertinent anatomy, techniques, side effects, complications, and the efficacy of CPN and splanchnicectomy for palliation of pain from pancreatic cancer.

Anatomy

Pain from pancreatic cancer is believed to stem from malignant neural invasion and the stimulation of visceral afferent neural fibers which travel from the celiac plexus through the splanchnics (2). A majority of patients report pain in the epigastrium and over half of these same patients complain of associated back pain. Only a minority of patients, however, report back pain without epigastric discomfort (3).

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Neurolytic treatment is directed at the celiac plexus, while a neurectomy is performed on the splanchnic nerves, either unilaterally or bilaterally. The celiac plexus is made up of the right and left ganglia, surrounding the aorta at the level of the celiac artery. It consists of visceral afferent, as well as sympathetic, and parasympathetic efferent fibers (4), and is located in the peri-aortic fat pads at the level of the diaphragmatic hiatus and celiac artery. There are commonly two to five celiac ganglia lying between T12 and L2 (5). Sympathetic nerve fibers run from the spinal cord to the sympathetic chain and then synapse in the celiac ganglia. In turn, pain from the foregut and midgut travels retrograde via parasympathetic visceral afferent nerve impulses from the celiac plexus through the splanchnic nerves to the central nervous system.

The splanchnic nerves are easily recognized as neural branches from the sympathetic trunk running anterior and inferiorly toward the diaphragmatic hiatus overlying the thoracic vertebral column. There are three classically described splanchnic nerves: the Greater, Lesser, and Least. Branches at levels T5-T9 most commonly form the greater splanchnic nerves, while the lesser splanchnics are formed from ganglia associated with T8-T12 and the least splanchnic nerves are formed by T10-L1. After being relayed from the splanchnics, stimuli reach the thalamus and cortex of the brain; this information is perceived as pain (6).

Celiac plexus neurolysis (CPN)

Originally described in 1914, modern CPN may be performed percutaneously, at the time of laparotomy, or under the direction of endoscopic ultrasound (EUS) (7). Alcohol is typically injected into the plexus but it may also be injected into the ganglia proper. Although steroid injections have been described for CPN, they are more commonly used for pain associated with chronic pancreatitis than for pain with pancreatic cancer.

Technique

Historically, percutaneous and surgical neurolysis was considered the mainstay treatment. Percutaneous CPN is generally approached posteriorly with imaging guidance, while surgical neurolysis, which was originally performed during staging laparotomy, has been replaced by laparoscopy (4,8). Over time, however, both treatments seem to have yielded to the EUS approach. EUS CPN offers several advantages over radiologic and surgical techniques, including enhanced needle precision, the ability to inject the neurolytic agent into a larger area, and the ability to perform CPN at the time of tumor biopsy and staging (9). Regardless of which technique is chosen, alcohol is injected bilaterally into the peri-aortic fat pad at the level of celiac artery and diaphragmatic hiatus.

EUS-guided CPN is currently the most common technique used today. Consistent with other endoscopic procedures, traditional preoperative questioning and positioning is performed. Next, adequate hydration is ensured and anticoagulants are held as indicated. Pulse oximetry and non-invasive blood pressure monitoring are obtained while the patient is sedated and recovering. Antibiotics are administered for those on proton pump inhibitors due to the risk of post-operative abscess from bacterial overgrowth of the upper GI tract. EUS may be performed using linear-array endosonographic imaging by way of a GF-UC30P (Olympus Corporation, Center Valley, PA, USA), GF UC140P-AL5, or GF UC 160 PAT8 (Pentax Precision Instruments, Orangeburg, NY, USA).

Visualization of the celiac plexus is best seen from the posterior lesser curve of the stomach. The aorta is seen longitudinally, and the first arterial branch below the diaphragm is identified (*Figure 1*). With experience, the celiac plexus and ganglia can be readily identified. Traditionally, a 22-guage needle is advanced through the scope after being purged of air in anticipation of injection. There are larger specialty needles for CPN, including needles with multiple side-holes, to allow for a larger injection field (EUSN-20-CPN: Cook Endoscopy, Winston-Salem, NC, USA). The needle is advanced near the lateral anterior aorta, flushed, and aspirated. For CPN in pancreatic cancer patients, 10 mL (0.25%) of bupivacaine is injected, followed by 10 mL of dehydrated (98%) alcohol. The needle is then flushed and directed to the contralateral side of the aorta where the injection sequence is repeated. Impediments to visualization include lymphadenopathy or direct tumor encasement of the plexus and/or ganglia. In these cases, unilateral injection may be the only possibility, which could result in an associated decrease in efficacy (10). This procedure typically takes well under an hour. Afterwards, the patient is monitored and then discharged home in the absence of unstable vital signs as appropriate.

Literature

Multiple studies have compared CPN to medical pain management. In 1995, Eisenberg *et al.* reported pain relief

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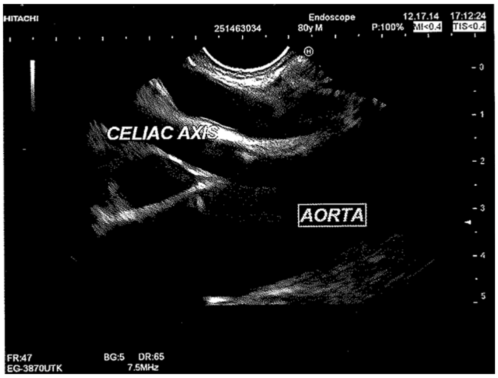

Figure 1 Endosonographic view of aorta and celiac artery origin (Image furnished by Dr. D Palma).

in 90% of their patients at 3 months from CPN, with a majority of those having significant relief until death (11). Lillemoe *et al.* and Wong *et al.* both reported pain control beyond 6 months to be common (8,12). In 2004, JAMA published a randomized control trial (RCT) that compared patients who underwent percutaneous CPN using a posterior approach with patients given systemic analgesic medications (12). Their results showed a significant difference in pain scores between the two groups, with the CPN patients reporting less severe pain (14% *vs.* 40%; P=0.005). This same study, however, did not show CPN to improve patient quality of life or survival. In 2007, Yan *et al.* performed a meta-analysis of five randomized trials comparing CPN to medical management (13). A significant difference was found between groups in visual analog scores and opioid usage, the results favored CPN. A second meta-analysis of nine RCT's performed by Puli *et al.* in 2009, showed an 80% decrease in pain with CPN compared to non-interventional management (14). In a RCT by Wyse *et al.* [2011], patients were randomized to CPN had significantly less pain than those who did not have intra-operative neurolysis (15).

Predictive factors for failure of CPN include direct tumor invasion of the plexus and unilateral injection (10). To date, there have been no head-to-head comparisons between CPN techniques. As a result, endoscopic, percutaneous, and surgical approaches to CPN are considered equally effective.

Complications

Complications of CPN are rare, occurring in approximately 1.5-2% of patients. Possible complications, however, do include transient, usually asymptomatic hypotension, retroperitoneal abscess, and severe self-limited post-procedural pain. Transient complications include post-procedural diarrhea and hypotension due to sympathetic blockade. Permanent, unremitting diarrhea has been reported in very rare cases (16). There is also a risk of cephalic spread of the neurolytic agent, which may result in involvement of the cardiac nerves and plexus (17). Spinal complications have also been reported, particularly with posterior approaches; fortunately, these are rare, occurring in less than 1% of patients. Lower extremity weakness, paresthesias, paraplegia have all been reported. This is likely due to the alcohol injection causing spasm or thrombosis of the Artery of Adamkiewicz, which supplies the inferior spinal cord (18,19). At least one fatality has been reported from associated complications (20).

Thoracoscopic splanchnicectomy

The first description of palliative chemical splanchnicectomy dates back to 1969. The first description of bilateral splanchnicectomy for pain secondary to pancreatic cancer was described by Sadar *et al.* in 1974 (21,22). Splanchnicectomy was initially performed under direct vision at the time of thoracotomy and combined with sympathectomy (22). The use of the thoracoscope to aid in the performance of splanchnicectomy for palliation of pain associated with pancreatic cancer was later described in 1993 in the *British Journal of Surgery* (23). Since then, several short case series have been published as techniques continue to be refined. Today, thoracoscopic splanchnicectomy may be performed either unilaterally or bilaterally.

Prior to consideration for splanchnicectomy, we ensure patients have failed medical management. Failure of medical managements is a subjective opinion, but if a patient's pain is able to be controlled by fewer than three daily doses of moderate strength narcotics, and they are able to maintain a productive life, surgical management may be avoided or at least delayed. We define pain control as a patient rating his or her pain as ≤3/10 on a visual analog score, and a productive life as being able to leave one's home and/or accomplish activities of daily living in line with the expectations of the patient. If these criteria are not met, consideration for bilateral thoracoscopic splanchnicectomy (BTS) is given.

When interviewing the patient, special attention should be given to his or her pulmonary reserve as well as to previous thoracic disease and/or interventions. Clues to possible thoracic adhesions should be explored. These

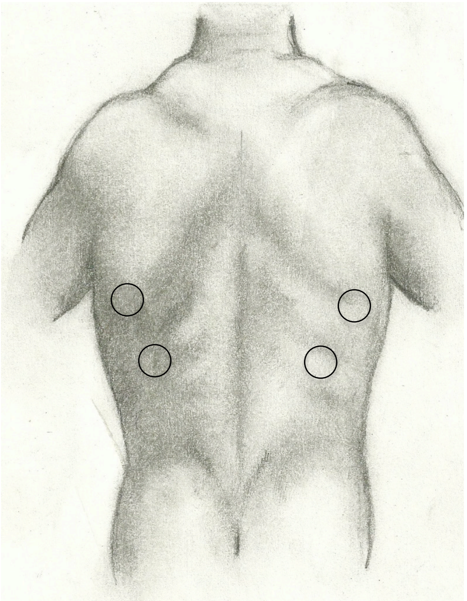

Figure 2 Author's illustration of the posterior thorax: trochar placement sites are denoted by circles placed at the inferior apex of the scapula and two intercostal spaces inferior and 2 cm medially.

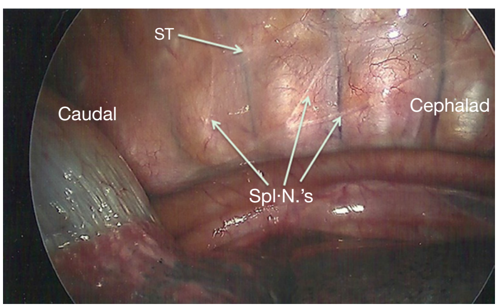

Figure 3 A thoracoscopic view of the right hemithorax is shown. Sympathetic trunk (ST) and splanchnic nerves (Spl N.'s) are labeled.

include previous severe pulmonary infections with associated empyema or parapneumonic effusions, the need for previous thoracostomy drainage or thoracentesis, thoracic trauma with associated hemothorax, previous pneumothorax, and previous thoracoscopy or thoracotomy. If any of these situations apply, the patient should be informed that it may be challenging to visualize the splanchnic nerves on the affected side without extensive dissection and/or thoracotomy. In a palliative operation, these patients should be largely avoided because of increased morbidity. Counseling should also be provided on the limited but distinct possibility of continued pain despite a technically successful operation. Following appropriate preoperative discussions, the patient is consented for the procedure.

Technique

At our institution, we perform BTS. Although this has not been compared head-to-head with unilateral splanchnicectomy, we are of the opinion that pain control is better with a bilateral neurectomy. This procedure can be easily executed with a single-lumen endotracheal tube; there is no need for continuous arterial blood pressure monitoring or central venous access. We prefer a posterior approach as described by Cuschieri *et al.* (24). The patient is placed in the prone position with the arms abducted and flexed at the elbow. To perform a BTS, we use two 5 mm trochars. We start initially on the left side, as it has been our experience that the left pleura is often thicker with more retro pleural fat, which can make visualization of the nerves on the left side often harder than the right. Despite that, the nerves are typically easy to find if one is familiar with their normal position, a skill that is acquired after only a few operations. The first trochar is placed at the inferior apex of the scapula while the anesthetist suspends respirations. Once placed, carbon dioxide (CO_2) insufflation is instilled at a pressure of 12 mmHg. A 5 mm, 30-degree angled scope is used to assess for successful trochar placement. Once the surgeon is satisfied, respirations can be resumed. In all, this initial step generally takes less than 1 minute. Next, the second trochar is placed two intercostal spaces inferior to the first and about 2 cm medially (*Figure 2*). It may also be placed two intercostal spaces superior to the first in the event there is elevation of the hemi-diaphragm. A third trochar may be used if needed, but this is rarely the case. The surgeon will then turn his or her attention to the posterior thorax to identify the sympathetic trunk. The arch of the aorta is used as a landmark, above which the splanchnics do not lie. The costophrenic angle is seen as well, below which the splanchnics are never found. The splanchnic nerves are seen running in an inferior and medial position from the sympathetic trunk (*Figure 3*). Once the splanchnics are identified, a small opening is made in the pleura on either side of the nerve with a right angle cautery. To avoid the risk of bleeding, the nerve is divided on the corpora of the vertebral body between the intercostal vessels. We recommend lifting the nerve with the right angle cautery so that division is obvious once the nerve recedes into the pleura (*Figure 4*). There are typically two to five nerves easily found on each side. After searching for

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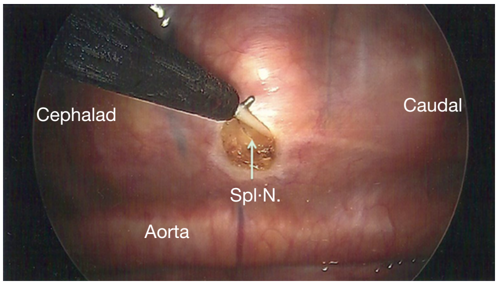

Figure 4 Thoracoscopic view of left-sided splanchnic nerve (Spl N.) lifted from pleura prior to division with hook cautery is demonstrated.

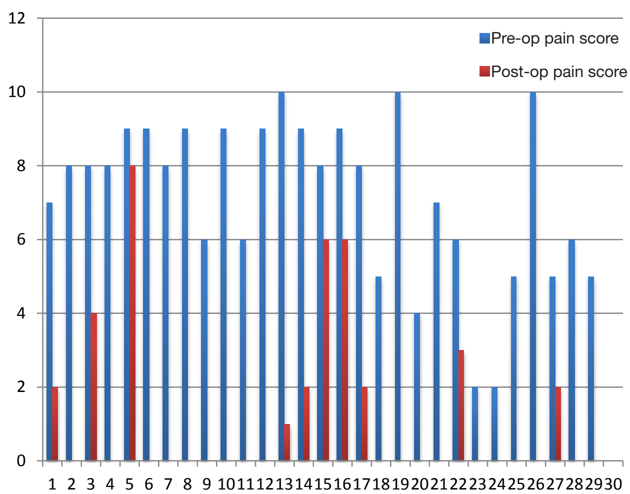

Figure 5 Histogram of pre-operative and post-operative visual analog pain scores of patients who underwent bilateral thoracoscopic splanchnicectomy at Greenville Health system.

and dividing all of the nerves, the insufflation is released, a rubber catheter is placed into the hemithorax, and large tidal volumes are given by the anesthetist. The exterior end of the rubber catheter is placed under water at the level of the skin, creating a water seal. Once the lungs are fully re-inflated, the trochars and catheter are removed, the skin incisions closed, and the procedure is repeated on the right side.

At this point, the patient is awakened and a chest X-ray is performed in the recovery room to assess for retained CO_2. If the patient is stable, even in the presence of pneumothorax, observation is safe and an X-ray should be repeated on post-operative day 1. In the event the patient is unstable during or after emergence from anesthesia, urgent X-ray in the operating room (if possible, quickly) and auscultation of the chest are used to assess for tension pneumothorax. A chest thoracostomy tube is then placed on the affected side. We admit our patients for overnight observation in a non-telemetry room; however, outpatient procedures have been reported without complication. Operative time is usually less than 1 hour and the total hospital length of stay rarely exceeds 1 post-operative day.

Literature

Outcomes of splanchnicectomy for palliation of pain associated with pancreas cancer are encouraging. Results of this procedure for chronic pancreatitis are more readily available in the literature but remain sparse for the treatment of malignant pancreatic disease. Pietrabissa *et al.* reported on 20 patients who experienced significant improvement in visual analog scores for at least 3 months post-operatively (25). In a study by Lică *et al.*, similar outcomes on another 15 patients were demonstrated (26). At the 2010 Asian Pacific Hepato-Pancreato-Biliary meeting. Vitale *et al.* presented data on 36 patients who underwent BTS for pancreatic cancer. In that study, mean survival was 229 days and average pain scores dropped from 8.3 to 2.0 on a 0-10 scale. The quality of life survey on these same patients, however, only demonstrated a limited improvement. At our institution we internally reviewed the first 29 patients who underwent BTS. We too found a significant decrease in patient pain scores post-operatively (4.1 to 1.1; P value =0.004) (*Figure 5*).

Complications

Complications of splanchnicectomy are rare, occurring in less than 2% of patients. Similar to other thoracoscopic procedures, specific complications include pneumothorax, chylothorax, hemothorax, need for thoracotomy, persistent pain, transient hypotension, and diarrhea (3). Pneumothorax was the most commonly reported complication, as two out of the 92 patients reviewed required an unplanned thoracostomy tube.

Conclusions

Pancreatic cancer is a pervasive disease that is often incurable. As a result, pain control is a key component of palliation of this disease. Given the side effects of high-dose narcotics, interventional approaches focused on neurolysis and/or neurectomy are attractive options. This can be

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done using a variety of approaches, each of which has been shown to be efficacious with minimal morbidity. Currently published data is heterogeneous, and head-to-head comparisons of each is lacking. Regardless, each approach appears to be safe, effective, and technically easy to perform. There is little reason any patient with this disease should suffer from abdominal pain without an attempt at either celiac plexus block or splanchnicectomy.

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