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Celiac plexus neurolysis in the management of unresectable pancreatic cancer: When and how?

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Core tip: The efficacy of salvage celiac plexus neurolysis (CPN) either by percutaneous or endoscopic ultrasound (EUS) guided technique has been modest in its ability to reduce pain and narcotic requirements in patients with unresectable pancreatic cancer, and few studies with rigorous methodology exist. Data for early EUS-CPN at time of diagnosis appears to prevent pain escalation while moderating narcotic use and future studies should explore CPN for patients before rescue therapy is needed. Reports of serious and fatal complications of CPN have surfaced in recent years.

Abstract

Pancreatic cancer is the second most common abdominal cancer in North America with an estimated 20% resectability at diagnosis, and overall 5-year survival of 5%. Pain is common in pancreatic cancer patients with 70%-80% suffering substantial pain. Celiac plexus neurolysis (CPN) is a technique that can potentially improve pain control in pancreatic cancer while preventing further escalation of opioid consumption. CPN is performed by injecting absolute alcohol into the celiac plexus neural network of ganglia. This review sets out to explore the current status of CPN in non-resectable pancreatic cancer. We will examine: (1) the efficacy and safety of percutaneous-CPN and endoscopic ultrasound guided-CPN; (2) specific technique modifications including bilateral (*vs* central) injections and celiac ganglia neurolysis; and (3) the issue of CPN timing, early at pancreatic cancer diagnosis *vs* traditional late use as salvage therapy.

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INTRODUCTION

Pancreatic cancer is the second most common abdominal cancer in North America with an estimated number of 45220 new diagnoses and 38460 deaths in the United States in 2013^[1]. The high mortality rate is due in part to the aggressive nature of the tumor and its asymptomatic disease progression leading to delayed diagnosis with an estimated 20% resectability at diagnosis, and overall 5-year survival of 5%^[2,3]. Pain is common in pancreatic cancer patients with 70%-80% suffering substantial pain^[4-6]. As a result, systemic analgesic therapy (SAT)

usually including opioid medication is central to the management of unresectable pancreatic cancer. However, pain can often become intractable and refractory to narcotics leading to dose escalation and opioid associated side effects^[7-9].

Celiac plexus neurolysis (CPN) is a technique that can potentially improve pain control in pancreatic cancer while preventing further escalation of opioid consumption^[6,10]. CPN is most often performed by injecting local anesthetic followed by absolute alcohol into the celiac plexus neural network of ganglia with intention to ablate the tissue transmitting pain from the pancreas and adjacent visceral organs. In current clinical practice, it has been used almost exclusively as salvage therapy when pain control is inadequate with SAT^[11]. CPN modalities include surgical splanchnectomy, percutaneous (PQ)-CPN, and endoscopic ultrasound guided (EUS)-CPN. Surgical splanchnectomy/intra-operative celiac plexus neurolysis can be performed on those not deemed inoperable preoperatively but will not be reviewed in this paper. The two most commonly practiced routes are the posterior PQ-CPN usually under CT or fluoroscopic guidance and EUS-CPN. There has been much controversy as to which route and which specific techniques should be the gold standard based on efficacy and safety. This is partially due to a lack of well-designed randomized controlled trials and lack of studies directly comparing the two modalities. Furthermore, there is recent data to suggest that using CPN as salvage therapy may not be the only or best option and that early CPN, performed at the time of diagnosis, may prevent or slow the spiral of increasing pain and opioid consumption^[12].

This review sets out to explore the current status of CPN in non-resectable pancreatic cancer. We will examine: (1) the efficacy and safety of PQ-CPN and EUS-CPN; (2) specific technique modifications including bilateral (*vs* central) injections and celiac ganglia neurolysis (CGN); and (3) the issue of CPN timing; early at pancreatic cancer diagnosis *vs* traditional late use as salvage therapy.

PQ-CPN

Pain control

Initial meta-analyses regarding the use of PQ-CPN in controlling pain due pancreatic cancer showed conflicting results and are limited to mostly retrospective and uncontrolled studies^[10,13,14]. Since then, several RCTs have been published of which 5 (265 patients) from 1993-2008 were analyzed in a recent systematic review^[5,15-19]. They demonstrated statistically significant improved pain level in the PQ-CPN group compared to SAT at 1-2 wk by -0.87 [95%CI: -1.47-(-0.28), $P = 0.004$], and at 4 wk by -0.47 [95%CI: -0.71-(-0.23), $P = 0.0001$]. At 8 wk however, the statistical difference was lost -0.31 (95%CI: -0.74-0.12) and similarly no study showed benefit at 12 wk^[18]. A previous meta-analysis, by Yan *et al*^[6], also comprised of 5 RCTs (302 patients, 3 studies over-

lap with Nagels *et al*^[18]) including one intra-operative neurolysis^[5,6,16,17,20,21]. This analysis found pain improvement at 2, 4 and 8 wk of -0.34 (95%CI: -1.03-0.34, $P = 0.33$), -0.50 [95%CI: -0.85-(-0.15), $P = 0.005$], and -0.60 [95%CI: -0.82-(-0.37), $P < 0.00001$] respectively^[6].

Regardless of the statistical significance found at different time points between these often heterogeneous studies within 2 meta-analyses, it is striking that all of the point estimates are less than one. A decrease of less than one point on a pain scale is unlikely to be clinically significant and questions whether the procedure is beneficial at all. The difficulty in interpreting the true clinical significance lies in the fact that opioid consumption (see below) is a direct confounder of pain and both pain and opioid use are routinely analyzed with univariate statistical models. If opioid consumption were to simultaneously decrease or even remain unchanged relative to the SAT groups then the difference in pain corrected for opioid use may become clinically significant (data unavailable).

Opioid consumption

To allow for some comparison, data from the 2 above meta-analyses will be used. Nagels *et al*^[18] found an absolute reduction in opioid use compared to SAT at 2 wk of -44.64 mg [95%CI: -72.74-(-16.54), $P = 0.002$], 4 wk -72.41 mg [95%CI: -86.14-(-58.68), $P < 0.00001$], 8 wk -70.02 mg [95%CI: -104.05-(-36.00), $P < 0.0001$] and one study at 12 wk (105 ± 65 mg *vs* 169 ± 71 mg, $P < 0.01$)^[18]. Yan *et al*^[6] found similar findings of decreased opioid use with PQ-CPN at 2 wk -39.99 mg [95%CI: -60.08-(-19.91), $P < 0.0001$], 4 wk -53.69 mg [95%CI: -79.65-(-27.73), $P < 0.0001$] and 8 wk -80.45 mg [95%CI: -134.66-(-26.24), $P = 0.004$].

Some of the above differences in opioid requirements do seem clinically significant, but as mentioned, to measure their true benefit a bivariate or multi-variate analysis would be necessary. These studies also did not convincingly show a decrease benefit in opioid related side effects. However, as discussed below this patient population has symptoms impacted by numerous factors including multiple medications, psycho-social stressors, and mobility. Therefore, to isolate constipation (for example) as strictly a narcotic induced side-effect is likely inappropriate.

Quality of life

Finally, when assessing the effect of PQ-CPN on quality of life (QOL), the data is inconclusive with some studies suggesting an improvement while others failing to demonstrate a significant difference^[5,6,15,16,18,19].

It is important to note that the patient population being dealt with are palliative patients at the end of their life. Pain is an extremely complex entity at baseline, and its complexity is only enhanced in patients with a growing and spreading tumor who are facing their own mortality. Although the overall impact on QOL remains controversial, a modest pain reduction in the context of

clinically significant opioid reduction may still be very meaningful. Furthermore, the QOL scales used varied widely and could not be easily combined in any meta-analysis, and the QOL categories themselves within these scales would not be expected to improve by better pain control alone. A simple question such as “did this procedure improve your life in a meaningful way?” may have more appropriately assessed its worthiness. Nevertheless, these concepts and issues still bring into question whether PQ-CPN as a last resort in salvage therapy should be recommended to these patients.

EUS-CPN

EUS-CPN has emerged as a promising approach to CPN that has the potential for better visualization of the celiac plexus through close proximity and real-time high-resolution ultrasound, possibly allowing for more precise and safer injections. However, the data supporting this approach once again in the context of salvage therapy are limited to uncontrolled retrospective studies. Wiersema and Wiersema^[22] were the first to describe EUS-CPN in 58 patients and showed modest improvement in pain control up to 12 wk following therapy. More specifically, 45 patients (78%) experienced a decrease in pain score independently of narcotic use. Since then, there have been several other observational studies (with no control group) examining EUS-CPN in relieving pain due to pancreatic cancer^[23-26]. In a systematic review of these studies, a significant pain reduction was noted at weeks 2, 4, 8, and 12 with a mean difference in pain score of -4.26 [95%CI: -5.53-(-3.00)], -4.21 [95%CI: -5.29-(-3.13)], -4.13 [95%CI: -4.84-(-3.43)], -4.28 [95%CI: -5.63-(-2.94)] respectively^[18]. This is consistent with a meta-analysis, which showed a pain reduction in 80% of the patients following EUS-CPN for pancreatic cancer^[27]. EUS-CPN studies showed relatively stable or slightly lower opioid requirements that paralleled this pain reduction^[16,17,19]; however, there is no randomized controlled study for EUS-CPN used specifically as salvage therapy despite these promising data.

ADVERSE EVENTS ASSOCIATED WITH CPN

PQ-CPN

It is important to distinguish common or even expected side effects from CPN complications. Frequent minor adverse events associated with PQ-CPN are believed to be due to disturbances of the autonomic system resulting from ablation of the celiac plexus and sympathetic blockade leading to unopposed parasympathetic activity. One study estimated diarrhea (9%), hypotension (8%), constipation (40%), nausea and vomiting (41%), and lethargy (49%)^[6]. Pain at the site of injection (96%) has also been frequently reported^[10]. Rare complications are described in case reports and include lower neurological deficit (weakness and paresthesia), pneumothorax, and

hematuria; and are estimated to occur at 2%^[10]. Paraplegia itself is believed to occur secondary to needle trauma or vasospasm induced by the injection of alcohol into the artery of Adamkiewicz leading to ischemic cord injury *via* the anterior spinal artery. Paraplegia has been reported in the literature and is estimated to occur in less than 0.15% of the cases^[28].

EUS-CPN

Data on adverse events of EUS-CPN are limited to small retrospective studies and case reports. Similar minor periprocedural events such as transient hypotension were described in 3 case series and estimated at 11%^[23,25,26]. Diarrhea was noted in 4 studies in approximately 18%^[23,24,26,29]. Transient abdominal pain was described in case series at rates varying from 1.5% to 8%^[22,23,25,26]. Theoretically, EUS might be the safer modality. Its anterior approach through the gastric wall allows for direct passage of the needle into the target area while visualizing and avoiding vascular structures, without having to traverse the retrocrural space near other vital organs. Although initial reports (prior to 2012) of serious adverse events were lacking, there have been a number of severe complications recently reported in the literature. Gimeno-Garcia *et al.*^[30] reported the first fatal complication with EUS-CPN in the context of chronic pancreatitis leading to celiac artery thrombosis and vasospasm resulting in multi-organ ischemic injury and death. Subsequently, 2 additional reports of ischemic injury and death following EUS-CPN, were also believed to be due to injection of ethanol into the celiac artery leading to vasospasm^[31,32]. Other reported complications include retroperitoneal bleeding, and 2 cases of paraplegia^[30,33,34].

Overall, although EUS may potentially enhance precision of injections, no conclusions can be made regarding the safer modality without head to head studies with PQ-CPN. Furthermore, serious fatal complications although rare are not unavoidable with EUS-guided therapy.

PQ-CPN VS EUS-GUIDED CPN

There are no studies directly comparing EUS-CPN and PQ-CPN in the management of pancreatic cancer. Efficacy of celiac plexus block (CPB) for chronic pancreatitis pain (using an anesthetic agent \pm steroids as opposed to ethanol in neurolysis for pancreas cancer) remains controversial. However, two RCTs comparing EUS and PQ-CPN in CPB for chronic pancreatitis have suggested greater efficacy with EUS-CPB than PQ-CPB^[35,36]. Gress *et al.*^[35] studied 20 patients showing greater and more persistent pain relief up to 12 wk post-treatment favoring EUS-CPB. Major weaknesses in this study; however, include its small sample size and unblinded methodology. Santosh *et al.*^[36] performed a larger, single-blinded RCT involving 56 patients favoring EUS-CPB over PQ-CPB for initial pain relief with 70% *vs* 30% responding to treatment respectively. Pain relief was also shown to be

more persistent with 38% *vs* 10% having significant pain relief at 12 wk. Although data from these RCTs of CPB in chronic pancreatitis are not directly applicable to CPN in pancreatic cancer, they do suggest a potential superior efficacy with they do suggest a potential superior efficacy with EUS in terms of drug delivery. Trials comparing PQ and EUS-CPN are certainly needed.

BILATERAL OR UNILATERAL CPN AND CGN

Bilateral vs unilateral/central neurolysis

Unilateral neurolysis is accomplished by a single injection into the base of the celiac artery takeoff. This technique may not adequately expose celiac ganglia to ethanol as it is now appreciated that the majority of ganglia are between the celiac artery and left adrenal gland^[37].

Bilateral injection, is performed by injecting into both sides of the celiac plexus by torquing the echoendoscope to each side of the celiac artery and advancing the injection needle parallel to its trajectory. Although there is potential for more adverse events due to greater needle movement, the bilateral approach has been shown by some to be more effective in providing pain relief. In a prospective cohort study comparing unilateral *vs* bilateral CPN or CPB, the bilateral technique achieved significantly more pain relief *vs* unilateral (mean percent pain reduction) 70.4% (61.0, 80.0) *vs* 45.9% (32.7, 57.4), $P = 0.0016$, at day 7 post treatment. Although this is a short-term study the onset of neurolysis effect begins soon after the nerve ablation, therefore a comparison between two techniques at 7 d can still be revealing. The only predictor of a $> 50\%$ pain reduction was bilateral injection [odds ratio 3.55, (95%CI: 1.72-7.34)]^[38]. Furthermore a meta-analysis also suggested superiority of pain reduction with bilateral injection over central injection, 85.54% *vs* 45.99% respectively^[27]. A subsequent RCT comparing the two approaches in pancreatic cancer in 50 patients did not suggest a significant difference in terms of pain control or adverse events. However, there was a trend to nearly a 30% increase in duration of effect (11 wk *vs* 14 wk) in favor of bilateral, a result, which may have been limited by sample size^[39]. Furthermore, the point estimate for central/unilateral seemed high at 69% (compared to approximately 45% in other studies) and may have prevented a difference from being detected. One must keep in mind that meta-analyses of the highest quality studies for both PQ-CPN and EUS-CPN included almost only the bilateral technique^[6,27]. The bilateral technique also requires significant advancement on either side of the celiac artery and may be operator dependent. Finally, two other studies also support the notion that injection deeper^[40] and along both sides of the celiac axis provide better pain relief^[41]. Although there is no definitively proven superior technique, we favor the bilateral technique given the sum of the above evidence as well as the concept of wider distribution of the ethanol near areas where ganglia are most commonly found.

Central ganglia neurolysis

Recent developments in EUS equipment have improved resolution such that injection directly into celiac ganglia is possible in certain patients. One prospective study in 200 patients undergoing diagnostic EUS demonstrated a rate of celiac ganglia detection of 81%, Figure 1^[42]. Another study demonstrated a ganglia visualization rate of 89% in 57 patients^[43]. These percentages seem high in our experience nevertheless exemplify the real possibility of visualizing ganglia. Since ganglia are collections of nerve bodies and glial cells, injections into these structures have the potential to obliterate more neurons successfully, possibly leading to greater pain suppression. Levy *et al*^[44] provided preliminary data on EUS-CGN demonstrating its safety and effectiveness in achieving significant pain relief in 94% of the subjects with pancreatic cancer. In addition, a retrospective analysis of EUS-CPN and CGN found that visualization of celiac ganglia was the best predictor of response to therapy^[26]. Recently, an RCT comparing EUS-CGN *vs* EUS unilateral CPN showed substantial greater pain relief in the CGN group (73.5% *vs* 45.5%, $P = 0.026$) with similar adverse events^[37]. However, the comparison was not against bilateral injection and the response rate with CGN *vs* unilateral was remarkably similar to the bilateral *vs* unilateral technique referenced above 70.4% (61.0, 80.0) *vs* 45.9% (32.7, 57.4), $P = 0.0016$ ^[38].

Overall, superior efficacy of EUS-CGN is possible but unproven, especially compared to bilateral injection. This also lends biologic plausibility to bilateral injection being more efficacious than central since the ganglia frequently “and remove” as very are located lateral to the celiac artery and may be injected with the bilateral technique even when not visualized. CGN is also not possible *via* PQ-CPN. With EUS-guided CGN, although the drug is injected into the ganglia, it is conceivable that drug also diffuses beyond the targeted ganglia and destroys adjacent, invisible ganglia. Also, variation in equipment, make and model significantly impact ability to visualize ganglia and so success rates cannot be generalized. At this time we do not recommend CGN as a standard for CPN technique as it does not provide a wider distribution of the ethanol over the bilateral technique, but does add a degree of technical complexity and dependence on quality of equipment.

TIMING OF CPN: EARLY (NEAR TIME OF DIAGNOSIS) VS TRADITIONAL SALVAGE THERAPY

We hypothesize that one of the primary reasons why the magnitude of effect shown for salvage CPN is often seen as marginal and not clearly clinically meaningful is that it is offered “too late”. Once pancreatic cancer has progressed causing increasing pain and tolerance to narcotics, a true rescue is unlikely to occur. The postulated advantage of early therapy therefore is to prevent

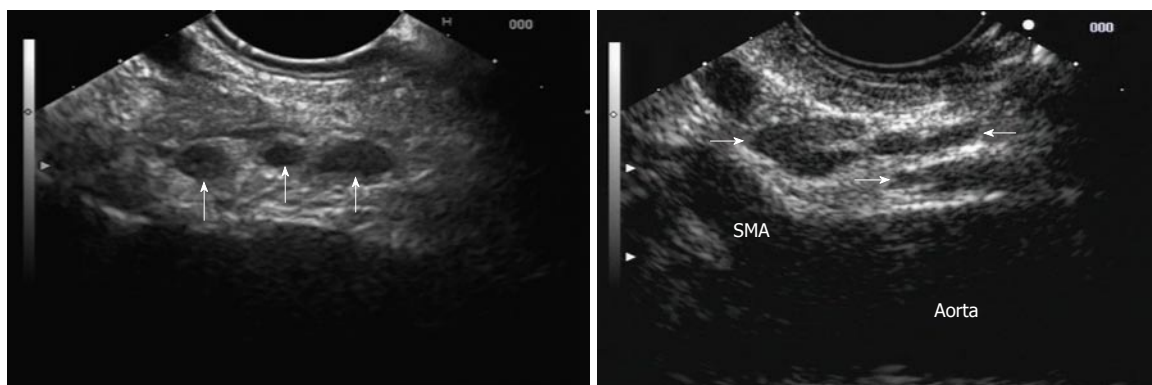


Figure 1 Three celiac ganglia are demonstrated in each image (arrows). SMA: Superior mesenteric artery.

or minimize both pain progression and narcotic dose escalation and tolerance. We addressed this issue in the first sham controlled RCT comparing early EUS-CPN (at the time of diagnosis) for unresectable pancreatic cancer *vs* standard SAT^[12]. The difference in absolute mean change in pain between the early and salvage therapies were -1.0 [95%CI: -1.7-(-0.1)] at 1 mo and -2.2 [95%CI: -3.1-(-1.4)] at 3 mo favoring the early CPN group. Despite starting with a lower pain level than salvage therapy trials the absolute decrease in pain was greater than those found in the PQ-CPN RCTs above, and statistically significant at 3 mo. For difference in mean percent change in pain score the EUS-CPN group trended at 1 mo and was significantly greater at 3 mo as well, -28.9% (95%CI: -67.0-2.8, $P = 0.09$), and -60.7% [95%CI: -86.6-(-25.5), $P = 0.01$] respectively. In the SAT group, morphine use increased compared with baseline at both 1 mo (mean absolute change in MEQ consumption +54 mg [95%CI: +20-(+96)] and particularly at 3 mo (mean absolute change in MEQ consumption +100 mg [95%CI: +49-(+180)]). In the EUS-CPN group, morphine use also increased at 1 mo (mean change in MEQ consumption +53 mg [95%CI: +28-(+89)]), but plateaued by 3 mo (mean change in MEQ consumption +50 mg [95%CI: +28-(+79)]). Comparing groups, EUS-CPN did not significantly reduce narcotic use at 1 mo, however, at 3 mo post-procedure there was a strong trend towards lower opioid consumption in the CPN group -49.5 mg (95%CI: -127.5-7.0, $P = 0.10$). Importantly, patients who did not receive subsequent radiation or chemotherapy demonstrated greater difference between groups. For example, a significant reduction in narcotic consumption was noted at 3 mo -144.5 mg [95%CI: -290.0-(-30.0)] (Table 1). The stronger results in patients who did not undergo adjuvant therapy underlies that this therapy with its inherent benefit to the patient, diluted the magnitude of effect of CPN alone. Therefore, data from this RCT suggest that early EUS-CPN prevents pain escalation while moderating narcotic use. Compared to all of the studies using salvage therapy, both PQ and EUS-CPN, these results seem very favorable.

CONCLUSION

Severe and intractable pain refractory to traditional SAT is a common occurrence of non-resectable pancreatic cancer. Pain control is crucial in the management of this population with several retrospective studies and a handful of RCTs demonstrating greater pain relief with equal and/or decreased opioid requirements with CPN (PQ or EUS). Although there are no head to head trials comparing EUS to PQ-CPN, data comparing the two modalities for CPB in chronic pancreatitis suggests EUS may be superior. Despite no conclusive data suggesting superiority, EUS does offer the potential for enhanced visualization of important vital structures and of celiac ganglia should CGN studies become more robust. Given the sum of the evidence and with wider distribution of ethanol in areas where ganglia are known to reside, we favor bilateral CPN over central injection. However this superiority is still controversial and central injections are certainly acceptable if the echoendoscopist is more comfortable with the latter. CGN cannot yet be recommended given inconsistent visualization of ganglia and the lack of trials compared to the bilateral technique which itself can be reproduced consistently in patients using only the celiac artery as a landmark. Perhaps most importantly, we feel there should be an emphasis of future studies on performing CPN early (at or near diagnosis) and the only existing EUS-CPN RCT did examine this approach with results comparable and seemingly superior to existing PQ-CPN RCTs done exclusively for salvage therapy. Preventing the escalation of pain and narcotic use should be the purpose of CPN in patients with unresectable pancreatic cancer. One must note, however, that pain due to pancreatic cancer is multifactorial not only including celiac plexus pathways but also from, for example, intestinal obstruction and liver capsule distention from metastases. CPN will only target some of these pain mechanisms and may play less of a role as disease progresses and other pain etiologies become more pronounced.

Given the totality of existing evidence, it appears that in 2013, the optimal patient for successful and meaningful CPN would be undergoing diagnostic and staging

Table 1 Early endoscopic ultrasound-celiac plexus neurolysis *vs* systemic analgesic therapy: Pain relief and narcotic consumption with or without chemo-XRT^[12]

EUS-CPN <i>vs</i> control	After 1 mo (95%CI)	After 3 mo (95%CI)
Difference in mean % change in pain relief:		
No chemo-XRT ¹	-59.6% (-95.4 to -27.6) ¹	-85.8% (-127.6 to -51.3) ¹
Chemo-XRT	31.0% (-34.3 to 106.2)	-45.6% (-72.6 to -23.3) ¹
Difference in mean change in MEQ consumption:		
No chemo-XRT	-2.4 mg (-58.4 to 60.8)	-144.5 mg (-291 to -30) ¹
Chemo-XRT	11.4 mg (-23.7 to 39.4)	26.1 mg (-12.2 to 56.5)

¹Statistically significant $P < 0.05$. EUS-CPN: Endoscopic ultrasound-celiac plexus neurolysis; Chemo-XRT: Chemotherapy and radiation therapy; MEQ: Morphine equivalent.

EUS for pancreas cancer. CPN in this instance may be more impactful if the patient happens to not undergo subsequent chemotherapy/radiotherapy. Rare, serious, and even life threatening complications regardless of timing and route have to be disclosed and discussed with the patient in detail. Future studies should focus on early CPN in this unfortunate patient population.

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