ORIGINAL ARTICLE

The Effectiveness of Repeat Celiac Plexus Neurolysis for Pancreatic Cancer: A Pilot Study

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■ **Abstract**

Background: Celiac plexus neurolysis (CPN) is an effective but temporary management tool for pancreatic cancer pain (PCP). Clinical studies have shown the duration of benefit with initial CPN to be approximately 3 months. When pain recurs, CPN may be repeated, but the outcomes for repeat CPN are not well established. The objective of this study is to determine the success rate and duration of relief following repeat celiac plexus neurolysis (rCPN) for PCP.

Methods: Patients who underwent rCPN were identified from a database and their records reviewed. Responses of rCPN were then compared with iCPN for success rates and duration of relief. Success was defined as ≥ 50% pain relief lasting ≥ 1 month.

Results: Overall, there were 24 rCPN performed. The success rate decreased from 67% after initial CPN to 29% following rCPN ($P = 0.13$). The mean duration of pain relief decreased in parallel from 3.4 months (iCPN) to 1.6 months (rCPN) ($P = 0.03$). Among those who had a successful rCPN, 2.9 months elapsed from iCPN to rCPN, with disease progression noted in 29%. In those who failed rCPN, 7.8 months elapsed, with disease progression appreciated in 71% of cases.

Conclusions: rCPN does not provide as much pain relief as iCPN. Disease progression as detailed on imaging appears to be a major factor in the limitations of rCPN. Further prospective studies are warranted to confirm these results and investigate the utility of rCPN. ■

Key Words: pancreatic cancer, celiac plexus, malignant pain, neurolysis

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and is widely

recognized as one of the most painful malignancies.[1,2] At time of diagnosis, the resectability rate is only 34%.[2] Despite recent advances in medical and surgical therapies for pancreatic cancer, the 1- and 5-year survival rates remain abysmally low at 24% and < 5%, respectively.[1]

Pain is not only a dominant symptom of pancreatic and other upper abdominal cancers at the time of diagnosis, but is nearly ubiquitous at advanced stages. Severe persistent pain from end-stage pancreatic cancer can be emotionally demoralizing and physically incapacitating. Pancreatic cancer pain (PCP) may also impact overall survival.[3] Accordingly, quality of life and palliation become increasingly important in these patients.

Celiac plexus neurolysis (CPN) is a relatively safe and effective treatment for pain secondary to pancreatic and other upper abdominal cancers.[4] By interrupting the afferent transmission of visceral nociception associated with locally invasive pancreatic and other upper abdominal malignancies, it is believed that CPN can reduce visceral abdominal and back pain.[3] CPN has been shown to be superior to systemic analgesic therapy in randomized controlled clinical trials.[5] Many studies support the notion that between half and 3-quarters of patients receive moderate pain relief that can last for many months.[5–9] However, lasting analgesia following CPN is not always achieved.

Refractory PCP has been reported in over 50% of patients following CPN, requiring further therapy.[6] Residual pain may result from technical failure, disease extension outside of the celiac axis, or the concomitant presence of neuropathic pain. In our experience, patient survival often exceeds the benefit of CPN, and with more advanced disease, the likelihood of CPN failure increases. Although rare, there are significant risks associated with CPN, including but not limited to paralysis. Therefore, it is important to determine whether CPN should be repeated, and if so, the factors associated with successful rCPN.

Repeat celiac plexus neurolysis (rCPN) is occasionally performed for refractory PCP; however, there is scant evidence to guide practice. Based on clinical observation, rCPN appears to result in less pain relief than iCPN, a notion supported by Rykowski et al.[8] who found little benefit for rCPN. However, this study was limited by small sample size, and therefore, definitive conclusions could not be drawn. In this study, we retrospectively investigate the utility and effectiveness of rCPN for refractory PCP.

PATIENTS AND METHODS

After permission to conduct this study was granted by the Johns Hopkins Internal Review Board, a prospectively maintained database containing the medical records of 220 consecutive patients who underwent CPN between October 2004 and January 2011 was examined, with 24 identified who underwent rCPN. Inclusion criteria included unresectable pancreatic cancer, moderate or severe abdominal and/or back pain poorly controlled with pharmacotherapy, and the presence of 1-month follow-up data. Exclusion criteria were untreated coagulopathy, unstable medical illness, and cognitive impairment that precluded an accurate response assessment.

Celiac Plexus Diagnostic and Neurolytic Procedures

All procedures were performed under sterile conditions with IV sedation provided ''as needed'' at the discretion of the attending physician. The decision to use fluoroscopy or computed tomography (CT) was based on several factors including patient condition, resource availability, and radiological demonstration of tumor distribution. All procedures were performed in the prone position using a posterior approach.

Fluoroscopically Guided. Following local anesthetic infiltration, 7-inch, 22-gauge spinal needles were inserted in a superomedial direction to between T12 and L1 using a co-axial view. Blocks were designated as anterocrural on the left when the needle either traversed the aorta or was positioned lateral to it (as determined by contrast spread), and on the right when it was advanced to a similar depth. Retrocrural blocks were designated as such when the needle was positioned adjacent to the anterior edge of the vertebral body or just past it but proximal to the aorta. These were generally done for cases of more advanced disease, where the tumor burden could interfere with the injectate dispersion (Figures 1–3). In all cases, the injection of contrast was used to confirm needle position in relation to the diaphragmatic crura.

CT-Guided. Helically acquired 2.5-mm axial CT images were obtained from the top of T12 to the bottom of L1. Following local anesthetic infiltration, 7-inch, 22-gauge spinal needles were inserted in the anteroposterior plane using skin markers. Following

radiologic confirmation of appropriate needle placement, contrast was administered through each needle. Retrocrural positioning was defined as contrast spread confined entirely posterior to the diaphragmatic crura on axial CT image. Anterocrural spread was defined as the presence of radiopaque contrast anterior to the diaphragmatic crura (Figure 4).

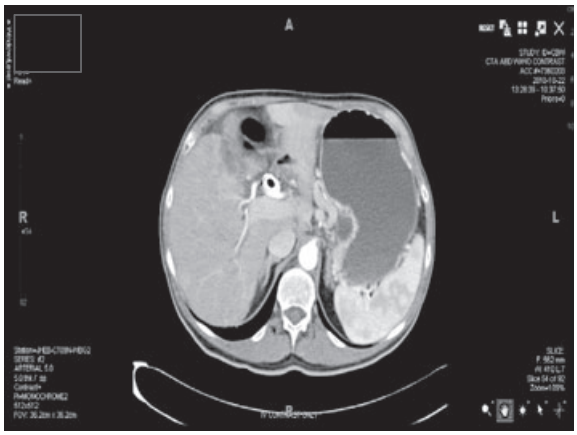

Figure 1. Abdominal CT scan of 64 year-old male showing normal liver.

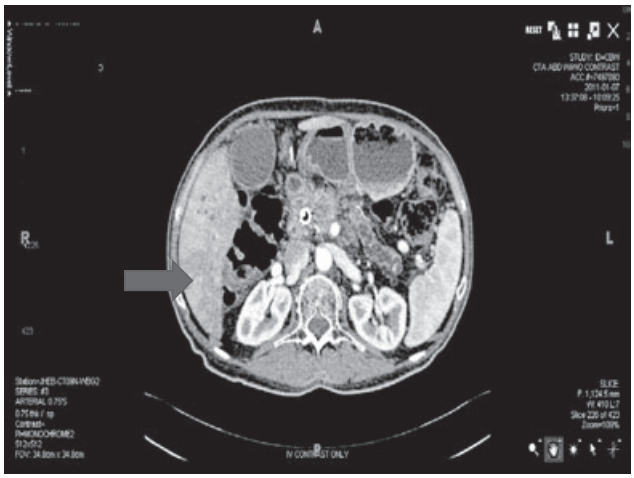

Figure 2. Abdominal CT in the same 64 year-old male showing metastatic lesions present in liver.

Neurolysis. The diagnostic/prognostic block with local anesthetic agents (a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine) was considered positive if the patient reported ≥ 50% pain relief based on a 6-hour pain diary and activity log, or if logistical circumstances precluded 2 separate visits, 10 to 15 minutes after the injection of local anesthetic. All patients who obtained significant pain relief after their block underwent subsequent neurolysis with 80% to 100% ethanol, the volume of which was determined based on clinical circumstances, contrast spread, and the volume administered for the diagnostic block. Following neurolysis, the patient was kept prone for at least 30″ to minimize the possibility of posterior spread to spinal nerves.

Outcome Measures

A successful procedure was defined as ≥ 50% pain relief persisting for ≥ 1 month after rCPN. The following variables were also examined: age, gender, predominant location of pain, duration of pain, origin of tumor, time from diagnosis to initial and repeat CPN, opioid use, type of radiological guidance employed (ie, fluoroscopic vs. CT), single vs. double needle technique, type of block (ie, anterocrural, retrocrural, or mixed), volume of alcohol used for neurolysis, and radiologic evidence of metastasis, encasement of the celiac axis, and evidence of disease progression on repeat imaging.

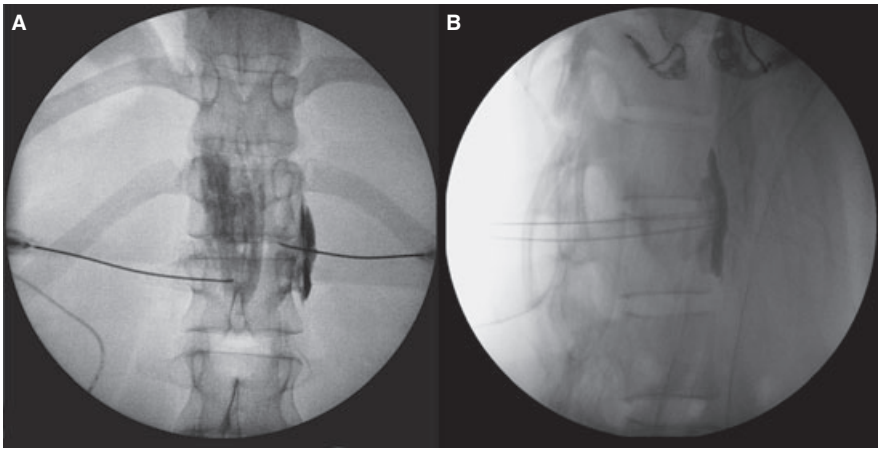

Figure 3. Antero-posterior (A) and lateral (B) fluoroscopic images showing bilateral retrocrural contrast distribution. The retrocrural approach was used when the disease burden around the celiac axis was expected to interfere with diffusion of the injectate.

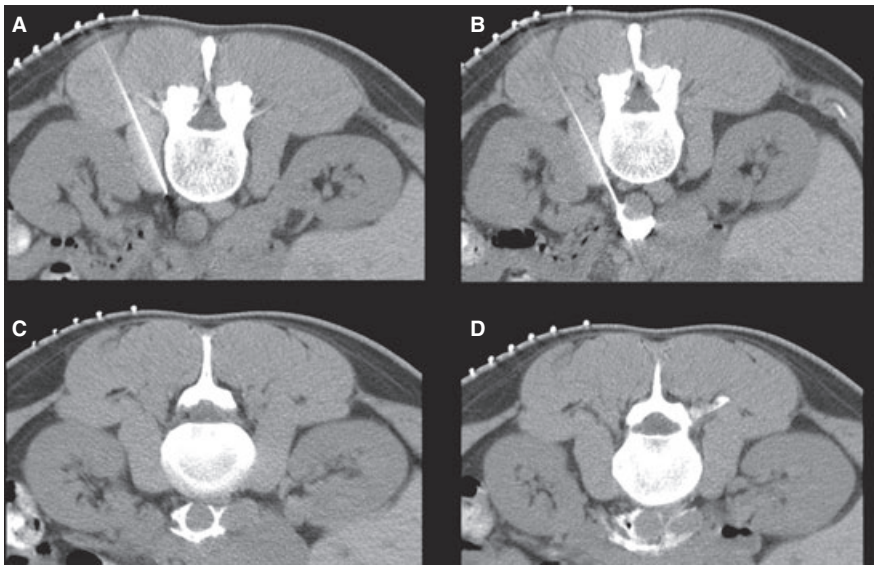

Figure 4. Sequential images demonstrating a left-sided anterocrural approach for a celiac plexus blockade. Note the contrast spread encompassing the celiac axis. The anterocrural approach was generally used when patients did not have extensive tumor spread around the celiac axis.

Statistical Methods

Statistical analyses were performed using STATA version 10.1 (Statacorp, College Station, TX, U.S.A.). The Shapiro–Wilk W test for normal data was performed on continuous outcome measures. The distribution of categorical variables in each group was compared using Fisher's exact test. Continuous variables are reported as mean and standard. Categorical data are reported by number of subjects and percentage. Comparisons between the initial CPN treatment and the repeat CPN treatment were made with paired *t*-tests or Fisher's exact test. As the continuous data in each group had a normal distribution, comparisons between treatment groups were made with 2-way analysis of variance (ANOVA). For multiple significance testing, post hoc Bonferroni correction was used. Regression analysis was used to quantify the association between the many possible predictive variables and clinical outcome of the repeat CPN. Because the outcome variable was binary (either positive or negative), a logistic statistical model was chosen. Unadjusted univariable analyses were performed, followed by multivariable logistic regression. Those variables with $P < 0.25$ in univariable analysis were included in multivariable logistic regression.

Table 1. Baseline Demographic and Clinical Characteristics of Study Subjects

Variable	"Failed" Initial Celiac Plexus Neurolysis *N* = 8	"Successful" Initial Celiac Plexus Neurolysis *N* = 16	*P* value
Age, mean (SD)	53.8 (11.3)	54.6 (10)	0.85
Gender			
Male	4	11	0.41
Female	4	6	
Baseline 0 to 10 NRS Pain Score, mean (SD)	6.1 (1.5)	5 .5 (1.5)	0.39
Location of pain[1]			
Abdomen	5	5	0.002
Back	3	0	
Abdomen and back	0	11	
Interval from diagnosis to 1st block in months, mean (SD)	13.4 (16.4)	4.2 (2.5)	0.04
Location of tumor			
Head	2	7	0.83
Body	2	4	
Tail	0	1	
Body–tail	3	3	
Head–body	0	1	
Location of tumor			
Head	3	7	0.56
Nonhead	5	9	
Proportion with metastases, n (%)	7 (88)	14 (88)	1.00
Prior to 1st block	6	11	
Prior to 2nd block (or shortly thereafter)	1	3	
Proportion with encasement of celiac axis, n (%)	6 (75)	8 (50)	0.56
Prior to 1st block	3	5	
Prior to 2nd block (or shortly thereafter)	3	3	

RESULTS

Baseline demographic and clinical characteristics of those patients who had a failed initial CPN as compared to those who had a successful initial CPN are presented in Table 1. Those patients with a successful response to iCPN were more likely to have pain symptoms in the back and abdomen, and have a shorter time interval from diagnosis of pancreatic cancer to iCPN (mean, 13.4 months; SD, 16.4 vs. 4.2; SD, 2.5;

$P = 0.04$). There were no differences between groups for age, sex, baseline NRS, location of tumor, proportion of patients with metastases, radiological technique used, antecrural vs. retrocural approach, and the proportion of patients with tumor encasement of the celiac axis.

Clinical characteristics of those patients who had a successful repeat neurolysis compared to those who did not are presented in Tables 2 and 3. A total of 24 rCPN were performed. The overall success rate decreased from 67% after the iCPN to 29% following the rCPN ($P = 0.13$). The mean duration of pain relief also decreased from 3.4 months after the iCPN to 1.7 months after rCPN ($P = 0.03$). The proportion of subjects with a positive rCPN after an unsuccessful iCPN was 50% (4/8), which favorably compared to the 19% (3/16) success rate in those individuals who had a successful iCPN ($P = 0.13$). In those individuals who experienced a successful rCPN, a shorter interval from iCPN to rCPN elapsed than in those who failed rCPN (mean, 2.9 months; SD, 3.2 vs. 7.8; SD, 12.1; $P = 0.31$). On a similar note, subjects who failed rCPN were significantly more likely to have interval disease progression on repeat imaging than in those who obtained benefit from their repeat procedure (93% vs. 50%; OR, 0.07; 95% CI, 0.0 to 0.9; $P = 0.05$). The 2 groups differed in the location of pain symptoms, with a higher proportion of abdominal and combination abdominal/back pain in the unsuccessful rCPN group ($P = 0.04$). Patients who had a successful rCPN also tended to have a higher volume of EtOH injected for neurolysis (mean, 22.9; SD, 4.9 vs. 17.6; SD, 5.8; OR, 1.1; 95% CI, 0.9 to 1.4; $P = 0.14$).

In multivariable analysis, the presence of metastases was associated with a 90% decrease in success rate; however, the small numbers involved failed to reach (OR, 0.1; 95% CI, 0.01 to 1.3; $P = 0.08$). No statistically significant differences between rCPN success and failure groups were observed for age, sex, baseline pain score, location of tumor, presence of metastasis, encasement of celiac axis, opioid use, peritoneal tumor involvement, use of repeat diagnostic block, radiologic guidance employed, needle approach or technique used, or the use of sedation for the procedure (Table 4).

Table 2. Demographic and Clinical Characteristics Stratified by Outcome of Repeat Neurolysis

Variable	Negative Outcome *N* = 17	Positive Outcome *N* = 7	*P* value
Age, mean (SD)	52.4 (10.5)	59 (8.2)	0.15
Gender			
Male	11	4	1.0
Female	6	3	
Baseline 0 to 10 NRS pain score, mean (SD)	5.8 (1.6)	5.7 (1.4)	0.86
Location of pain			
Abdomen	8	2	0.04
Back	0	3	
Abdomen and back	9	2	
Interval from diagnosis to 1st block (months), mean (SD)	7.4 (10.9)	7.0 (9.4)	0.94
Interval from 1st block to 2nd block (months), mean (SD)	7.8 (12.1)	2.9 (3.2)	0.31
Location of tumor	*N* = 16	*N* = 7	
Head	6	3	0.74
Body	3	1	
Tail	1	0	
Body–tail	5	3	
Head–body	1	0	
Location of tumor			
Head	6	3	0.64
Nonhead	10	4	
Proportion with metastases, n (%)	16 (94)	5 (71)	0.17
Prior to 1st block	12	5	
Prior to 2nd block (or shortly thereafter)	4	0	
Proportion with encasement of celiac axis, n (%)	10 (59)	4 (57)	1.0
Prior to 1st block	6	2	
Prior to 2nd block (or shortly thereafter)	4	2	
Proportion with interval disease progression on imaging, n (%)	14/15 (93)	3/6 (50)	0.05

Table 3. Procedural Characteristics Stratified by Outcome

Variable	Negative Outcome	Positive Outcome	*P* value
Image guidance	*N* = 17	*N* = 7	1.0
CT to CT	5	2	
CT to fluoro	2	0	
Fluoro to fluoro	6	2	
Fluoro to CT	2	2	
Intraop to fluoro	1	0	
EUS to fluoro	0	1	
Fluoro to EUS	1	0	
Approach	*N* = 16	*N* = 7	1.0
Retro to retro	9	2	
Retro to ante	2	1	
Ante to ante	1	1	
Ante to retro	2	2	
Intraop to retro	1	0	
EUS to retro	0	1	
Retro to EUS	1	0	
Technique	*N* = 15	*N* = 6	1.0
Single–single	1	0	
Double–double	12	6	
Single–double	1	0	
Double–single	1	0	
Volume of injectate (mL), mean (SD)	17.6 (5.8)	22.9 (4.9)	0.05

CT, computed tomography; EUS, endoscopic ultrasound-guided.

Table 4. Factors Associated with Successful Outcome of Repeat Celiac Plexus Neurolysis (rCPN)

	Unadjusted Univariate Analysis (OR, 95% CI)	Adjusted Multivariate Analysis (OR, 95% CI)	*P* value
Age	1.1 (1.0 to 1.2)		
Sex	0.7 (0.1 to 4.4)		
Location of pain symptoms	0.9 (0.4 to 2.4)		
NRS at rCPN	0.9 (0.5 to 1.4)		
Opioids at rCPN	1 (0.99 to 1.0)		
Time interval between iCPN and rCPN	0.9 (0.7 to 1.1)		
Total disease duration at time of rCPN	1 (0.9 to 1.1)		
Location of tumor	1.1 (0.6 to 2.1)		
Presence of metastasis	0.1 (0.1 to 1.3)	0.1 (0.01 to 1.3)	0.08
Encasement of CP by tumor	1.1 (0.4 to 3.2)		
Peritoneal involvement	0.8 (0.1 to 9.1)		
Progression of tumor between iCPN and rCPN	0.07 (0.0 to 0.9)		0.045
Method radiologic guidance	0.9 (0.2 to 4.4)		
Ante vs. retrocrural approach	1 (0.1 to 6.7)		
Vertebral level of needle tip	0.8 (0.1 to 4.5)		
Volume of EtOH on rCPN	1.2 (1 to 1.4)	1.1 (0.9 to 1.4)	0.14
Presence of diagnostic block (rDx) before rCPN	2 (0.2 to 22)		
Pain reduction after rDx block	0.2 (0.03 to 1.3)	0.15 (0.08 to 2.5)	0.19
Volume of rDx block	0.8 (0.6 to 1.1)	0.7 (0.5 to 1.1)	0.15

**P* value determined from univariable logistic regression analysis.

Complications were all minor and self-limiting and included 2 cases of temporary orthostatic hypotension and 1 patient who experienced diarrhea. All resolved within 7 days.

DISCUSSION

Several studies have documented the benefit of CPN for PCP. Most studies suggest that up to 3-quarters of patients experience moderate pain relief in the intermediate term after CPN,[5–9] although many are fraught with methodological limitations. A recent study found that little demographic or clinical differences between CPN responders and nonresponders except that those with a successful outcome were on lower doses of opioids requirements and received less sedation during their diagnostic block.[10] Whereas these results augur for the use of liberal selection criteria, no patient in this series underwent rCPN.

As novel medical and surgical treatments are employed for pancreatic cancer, a subset of patients may survive longer and outlast the benefits conferred by CPN. Refractory PCP has been reported to affect greater than 50% of patients following CPN.[6] The etiology of residual pain is often multifactorial and may include 1 or more of the following: (1) technical failure, (2) disease progression, (3) neuropathic pain, as such invasion may involve the celiac plexus and associated neural networks, and (4) somatic pain from peritoneal carcinomatosis. In such cases, an important question frequently arises: should we repeat CPN? Based on our clinical experience, rCPN may not be as effective as iCPN. This notion was previously postulated in an earlier study, but the numbers were too small to draw definitive conclusions.[8]

The current study demonstrated that both the magnitude and duration of pain relief following rCPN were significantly less than after the initial procedure. Few factors were found to be associated with rCPN outcome, which might be expected considering our small sample size. However, similar to previous research demonstrating the importance of tumor location[8] and tumor burden,[11] our study confirms that anatomical factors such as disease progression and metastases play an important role in determining outcomes following rCPN. This observation can explain why those subjects who failed to obtain relief from rCPN tended to "endure" a longer time interval between procedures. Another possible contributing factor is that as the adverse effects of disease progression are realized and expectations decline, the placebo effect may be weaker. The placebo effect is extremely powerful for pain-alleviating interventions, but mood disorders and declining doctor and patient expectations in late-stage cancer can result in diminished response.[12,13]

The generalizability of this study is limited by the small sample size and uncontrolled methodology. Nevertheless, our results suggest that there is still a subset of patients who can benefit from rCPN. For the 30% of individuals who positively responded to rCPN, the improved function and quality of life associated with pain relief during terminal cancer can be rewarding and meaningful. Further analysis is therefore warranted to identify the subgroup of responders who may benefit from repeat neurolysis.

Several flaws in this study need to be addressed. First, because data were collected from a database, some of the clinical variables analyzed were selected *post hoc*. Yet, because of the infrequency with which rCPN is performed and the patient population involved, a randomized study would not be practical

in this setting. Second, this series contained no objective documentation of functional improvement or quality of life. Our modest results should therefore be viewed cautiously, given the high expectation bias that accompanies any invasive procedure, especially one that was previously deemed successful.

In conclusion, the results of this study show that pain reduction following rCPN may be less pronounced and shorter-lived than after initial CPN. Although a small subset of patients may benefit from rCPN, the data also suggest that disease progression as identified on imaging, and a longer interval between blocks, may be important factors in treatment failures. Prospective studies are necessary to confirm our results and to identify the best candidates for rCPN.

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