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Outcomes of celiac plexus block and neurolysis, as well as technique in the management of refractory visceral cancer pain

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Abstract
Aim: Assessment of Celiac Plexus Block and Neurolysis Outcomes and Technique in the Management of Refractory Visceral Cancer Pain
Methods: A retrospective study was conducted in the Department of Surgery, & Anesthesiology, Rama medical college hospital & research centre, Hapur, UP, India from September 2019 to August 2020. 80 Patients with non resectable abdominal malignancy, moderate or severe abdominal and/or back pain poorly controlled with pharmacotherapy were included in this study. The age, gender, duration of pain, origin of tumor, opioid dosage, type of radiological guidance (i.e., fluoroscopic Vs computed tomography [CT]), single- vs double- needle technique, type of block (i.e., anterocrural, retrocrural, or mixed), immediate vs delayed neurolysis, volume of local anesthetic employed for diagnostic block, use and type of sedation, and volume of alcohol used for neurolysis were examined.
Results: A total of 80 patients underwent CPB with CPN over the period of the study. Mean age was 55.8 years (range 35–77). There were 45 male patients (56.25%) and 35 female patients (43.75%). Duration of pain was equally split, with 40 patients (50%) having pain for less than 6 months and the same number with pain for greater than 6 months. Our sample consisted primarily of patients with pancreatic cancer (70, 87.5%) with the remainder (10, 12.5%) of other visceral origin. 41 tumors were located in the pancreatic head (58.57%), 22 in the body (31.43%), 8 in the tail (11.43%), and 12 in the neck (17.14%). The majority of patients had metastatic disease detected (65, 81.25%), while 5 patients (6.25%) did not have metastatic disease and in 10 patients (15%) this variable was undocumented. The average daily morphine equivalent dose was 248.2 mg (range 0–1165 mg). There were 30 procedures (37.5%) done under fluoroscopic guidance and 50(62.5%) done under CT guidance. Those variables that were clearly associated with a positive outcome included morphine equivalent dose per day below 250 mg and the absence of sedation for the procedure (both $P>0.05$). Strongly associated with positive outcome but falling just short of statistical significance were the use of CT guidance for the procedure and the use of less than 20 cc volume of local anesthetic for the diagnostic block prior to neurolysis ($P< 0.07$ and $P<0.08$, respectively). Logistic regression for those not having sedation predicting a positive outcome revealed an OR of 4.17 (95% CI = 1.12– 15.19). Logistic regression for those on preprocedural morphine equivalent dose below that for the mean for the study sample (248.2 mg/day) predicting a positive outcome yielded an OR of 9.34 (95% CI = 1.62–52.49) Although falling short of statistical significance, there was a trend toward significance found in positive procedural outcomes associated with pain duration less than 6 months (P = 0.17), single rather than double needle technique (P = 0.17), and lesions found in the tail of the pancreas (P = 0.13).
Conclusion: CPN may provide intermediate pain relief to a significant percentage of patients suffering from pancreatic cancer. Candidates likely to experience a positive outcome include those who are on lower doses of opioid analgesics, and have a shorter duration of disease.

Keywords: Outcome, celiac plexus block, neurolysis, pain

Introduction
Pancreatic cancer is an extremely fatal primary malignant neoplasm and its incidence has increased over the past few decades. Fewer than 30% of patients are diagnosed at the surgically respectable stage because of the high malignancy, invasive growth, and propensity of early metastasis, with the overall 5-year survival rate<5% [1, 2]. Visceral pain is present in over 70% of pancreatic cancer patients at the time of diagnosis and gradually deteriorates to a level that is difficult to be controlled by administration of pain relief medicine, which represents the most important and challenging palliative care for patients with advanced pancreatic cancers [3, 4].

Despite the availability of improved nonsteroidal anti-inflammatory drugs and opioid analgesics, a high dose of such drugs still cannot provide adequate analgesia, and on the other hand, the dosage of analgesia drugs cannot be unlimitedly increased due to the intolerable adverse effects [5]. Thus, a more effective pain-relieving approach is highly demanded for the patients with medication-resistant pain. Celiac plexus neurolysis (CPN) is a technique that can potentially improve pain control in patients with pancreatic cancer while reducing the dosage of opioid drugs and the drug-related side effects accordingly. Since its establishment, CPN has been performed percutaneously under the guidance of fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI) [6-8]. Interventional MRI takes advantage of the multiple unique features of MRI, such as good temporal resolution, excellent issue contrast, spatial resolution, and real- or near real-time imaging, enabling the excellent identification of critical structures, such as vessels and nerves, without contrast injection [9-11]. In addition, both patient and doctor avoid exposure to ionizing radiation during the whole procedure of the treatment [12]. The development of magnetic resonance (MR) hardware and software makes MRI scan much faster and more flexible in accessing the target. An easy-to-use optical navigation system has been used in operation. It could facilitate the fast and accurate determination of the skin entry point, precise needle trajectory planning, and the lesion targeting in one step, which simplified MRI-guided procedures [13].

Materials and methods

A retrospective study was conducted in the Department of Surgery & Anesthesiology, Rama medical college hospital & research centre, Hapur, UP, India from September 2019 to August 2020, after taking the approval of the protocol review committee and institutional ethics committee. After taking informed consent detailed history was taken from the patient or the relatives. The technique, risks, benefits, results and associated complications of the procedure were discussed with all patients.

Inclusion criteria

80 Patients with unresectable abdominal malignancy, moderate or severe abdominal and/or back pain poorly controlled with pharmacotherapy were included in this study.

Exclusion criteria

Patients with untreated coagulopathy, unstable medical illness, and cognitive impairment that precluded an accurate response assessment were excluded from this study.

The following variables were examined via retrospective study: age, gender, duration of pain, origin of tumor, opioid dosage, type of radiological guidance (i.e., fluoro- scopic vs computed tomography [CT]), single- vs double- needle technique, type of block (i.e., anterocrural, retrocrural, or mixed), immediate vs delayed neurolysis, volume of local anesthetic employed for diagnostic block, use and type of sedation, and volume of alcohol used for neurolysis.

All procedures were done in an outpatient setting with peripheral intravenous access and standard monitoring. Patients were prehydrated with crystalloid solution, and sedation with midazolam and fentanyl was administered “as needed” at the discretion of the attending physician. Factors considered with respect to the decision to sedate patients included preprocedure pain, anxiety, patient wishes, and the subject’s ability to tolerate the prone position for prolonged time periods.

Fluoroscopically Guided

The decision to use fluoroscopy or 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. For fluoroscopically guided procedures, 22-gauge 7-inch spinal needles were inserted in a super medial 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 vertebral body or just past it but proximal to the aorta. In all cases, the injection of contrast was used to confirm needle position in relation to the diaphragmatic crura.

Computed Tomography

The patient was positioned prone on the CT or fluoroscopy table and scout images were obtained. Helically acquired 2.5-mm axial CT images were obtained from the top of T12 to the bottom of L1. Seven-inch, 22-gauge needles were inserted in the anteroposterior plane after administration of subcutaneous local anesthesia with 1% lidocaine with bicarbonate. Skin markers were placed in order to place needles optimally to reach either antero- or retrocrurally while avoiding structures such as the pleural space, lung parenchyma, and kidneys. Needle angles and needle depths on the optimal scout image were calculated and employed to facilitate needle placement. Retrocrural placement of needles was most often precipitated by significant tumor burden in the vicinity of the celiac axis, thereby presumptively inhibiting potential spread of medication in the anterocrural area. Following radiographic confirmation of appropriate needle placement, several cubic centimeters of radiographic contrast was administered through each needle and another image was taken to ensure appropriate spread. Gadolinium was used in patients who had an allergy to intravenous contrast material. 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 radiographic contrast anterior to the diaphragmatic crura. Needles were repositioned as needed to achieve appropriate placement as decided by the attending physician. Following this, a test dose of 2% lidocaine with epinephrine was given, 3 cc sequentially through each needle, and the patient’s vital signs were observed for indices of intravascular injection for 60 seconds. Diagnostic block was subsequently performed with the local anesthetic agents (a 50:50 mixture of 2% lidocaine and 0.5% bupivacaine). Approximately 10–15 minutes after instillation of the local anesthetic, the patient was queried as to the level of pain that was appreciated. Neurolysis All patients who underwent “immediate” neurolysis received prognostic blocks done with either lidocaine 2% or a lidocaine–bupivacaine mixture. A block was considered positive if the patient reported greater or equal to 50% pain relief 10 minutes after the local anesthetic was injected. In those patients who underwent delayed neurolysis, either bupivacaine 0.5% or a bupivacaine–lidocaine combination was used for the prognostic block. A “delayed” block was deemed positive if the patient reported greater or equal to 50% sustained pain relief lasting at least 3 hours. The decision regarding whether to perform immediate or delayed neurolysis was made at the discretion of the attending physician, subject to patientrelated factors and resource availability. All patients who obtained significant pain relief after their local anesthetic block

underwent subsequent neurolysis within 2 weeks using 80–100% alcohol. Following neurolysis, the patient was kept prone for at least 30 minutes to minimize the possibility of posterior spread to spinal nerves. There was no increase in the volume of either local or neurolytic injectate in response to patient effect. This volume was determined a priori based on both practitioner preference as well as needle location.

The duration of pain was calculated based on time of presentation. Opioid dose was calculated from the average consumption at the time of the local anesthetic block based on conversion to oral morphine equivalents [14]. The remainder of the data was obtained directly from medical records or saved radiological images (i.e., designation of antero- or retrocrural). A positive outcome was predesignated as greater or equal to 50% pain relief lasting more than 1 month in duration. Opioid Equivalency Calculations an equianalgesic opioid equivalency chart was used as detailed in Table 1.

Statistical Analysis

Demographic and block characteristics were analyzed using t-tests and 2-sample tests of proportions as applicable. The odds ratio (OR) for sedation and morphine dose predicting the main outcome were calculated using logistic regression. Multivariable logistic regression models were used to determine the cumulative effect of significant variables. Analysis was performed using intercooled Stata 8.2 (Statacorp, College Station, TX)

Results

A total of 80 patients underwent CPB with CPN over the period of the study. Demographics are detailed in Table 2. Mean age was 55.8 years (range 35–77). There were 45 male patients (56.25%) and 35 female patients (43.75%). Duration of pain was equally split, with 40 patients (50%) having pain for less than 6 months and the same number with pain for greater than 6 months. Our sample consisted primarily of patients with pancreatic cancer (70, 87.5%) with the remainder (10, 12.5%) of other visceral origin. 41 tumors were located in the pancreatic head (58.57%), 22 in the body (31.43%), 8 in the tail (11.43%), and 12 in the neck (17.14%). The majority of patients had metastatic disease detected (65, 81.25%), while 5 patients (6.25%) did not have metastatic disease and in 10 patients (15%) this variable was undocumented. The average daily morphine equivalent dose was 248.2 mg (range 0–1165 mg). There were 30 procedures (37.5%) done under fluoroscopic guidance and 50(62.5%) done under CT guidance. As in Figure 1 and, Table 3 details patient characteristics by outcome. As mentioned above, 10 procedures (15%) did not have documentation of the presence or absence of metastatic disease. Only 60 of 80 procedures documented opioid analgesic intake (75%). In 4 of 80 cases (5%), the duration of pain prior to the procedure was unknown. The volume of local anesthetic employed for diagnostic block was undocumented in 10 cases (15%), while the volume of alcohol used for neurolysis was undocumented in 1 case (1.25%). Those variables that were clearly associated with a positive outcome included morphine equivalent dose per day below 250 mg and the absence of sedation for the procedure (both $P>0.05$). Strongly associated with positive outcome but falling just short of statistical significance were the use of CT guidance for the procedure and the use of less than 20 cc volume of local anesthetic for the diagnostic block prior to neurolysis ($P< 0.07$ and $P<0.08$, respectively). Logistic regression for those not having sedation predicting a positive outcome revealed an OR of 4.17 (95% CI = 1.12– 15.19). Logistic regression for those on preprocedural morphine equivalent dose below that for the mean for the study sample (248.2 mg/day) predicting a positive outcome yielded an OR of 9.34 (95% CI = 1.62–52.49) Although falling short of statistical significance, there was a trend toward significance found in positive procedural outcomes associated with pain duration less than 6 months (P = 0.17), single rather than double needle technique (P = 0.17), and lesions found in the tail of the pancreas (P = 0.13). Those factors found not to be associated with outcome from CPN in this study included patient age, patient sex, location of tumor in the pancreas, presence of metastatic disease, duration of pain prior to the procedure, antero- Vs retrocrural approach, immediate vs delayed neurolysis, single- vs. double-needle approach, percent pain relief with diagnostic block, presence of neuropathic pain descriptors, and volume of alcohol employed for neurolysis.

Table 1: Equianalgesic opioid conversion chart

Equianalgesic opioid conversion chart
Morphine 30 mg
Oxycodone 20 mg
Hydrocodone 30 mg
Hydromorphone 6 mg
Methadone 4 mg
Meperidine 300 mg
Codeine 200 mg
Propoxyphene 200 mg
Oxymorphone 10 mg
Transdermal fentanyl (12.5 mcg/h) Oral transmucosal fentanyl 800 mcg Intrathecal morphine 0.1 mg

Table 2: Demographic and clinical characteristics of study subjects, N = 50

Characteristic		
Age, mean (range)	55.78	%
Gender		
Male	45	56.25
Female	35	43.75
Pancreatic cancer, count (%)	70	87.5
Location		
Head	41	58.57
Neck	12	17.14
Body	22	31.43
Tail	8	11.43
Presence of metastases, count (%)=70		
Yes	65	81.25
No	5	6.25
Morphine equivalent dose/day	248.2	

Pain duration		
<6 months	40	50
>6 months	40	50
Imaging technique, count (%)		
Fluoroscopy guided	30	37.5
Computed tomography guided	50 Technical approaches, count (%)	62.5
Antecrural	42	52.5
Retrocrural	33	41.25
Both	5	6.25
Time of neurolysis, count (%)		
Immediate	70	87.5
Delayed	10	12.5
Needles		
Single	10	12.5
Double	70	87.5
Pain relief with diagnostic block, count (%)		
≥50%, ≤80% relief	50	62.5
≥80% relief	30	37.5
Local anesthetic volume for diagnostic block, count (%)		
≤20 mL	40	50
≥20 mL	30	37.5
Sedation, count (%)		
Versed	16	20
Versed and fentanyl	14	17.5
No sedation	50	62.5
Volume of alcohol neurolysis, count (%)		
<20 mL	25	31.25
≥20 mL	55	68.75

Table 3: Patient characteristics by outcome, N = 80

Characteristic	**Negative Outcome N = 30**	**Positive Outcome N = 50**	***P*-value**
Age, mean (standard deviation)	56.7 (10.6)	55.4 (8.2)	0.57
Sex			
Female, count (%)	17 (48.57)	18 (51.43)	0.41
Male, count (%)	13 (28.89)	32 (71.11)	
Pancreatic cancer, count (%)	30 (42.86)	40 (57.14)	0.62
Location, N = 70			
Head	19 (46.34)	22 (53.66)	0.87
Neck	7 (58.33)	5 (41.67)	0.38
Body	10 (45.45)	12 (54.55)	0.74
Tail	2 (25)	6 (75)	0.13
Presence of metastases=70			
Yes	25(35.71)	40 (57.14)	0.62
No	2 (40)	3 (60)	
Morphine equivalent dose/day, mean (standard deviation)	347.2 (344.1)	142.5 (132.8)	0.03
Pain duration, count (%)			
<6 months	8 (20)	32 (80)	0.11
>6 months	22 (55)	18 (45)	
Imaging technique, count (%)			
Fluoroscopy guided	17 (56.67)	13(43.33)	0.07
Computed tomography guided	13 (25)	37 (74)	
Technical approach, count (%)			
Antecrural	18(42.86)	24 (57.14)	0.45
Retrocrural	11 (33.33)	22 (66.67)	
Both	1 (20)	4 (80)	
Time of neurolysis, count (%)			
Immediate	26 (52)	44 (48)	0.85
Delayed	4 (40)	6 (60)	
Needles			
Single	1 (10)	9 (90)	0.17
Double	29 (41.43)	41 (58.57)	
Pain relief with diagnostic block, count (%)			
≥80% relief	20 (40)	30 (60)	0.55
≥50% but ≤80% relief	10 (50)	10 (50)	
Local anesthetic volume for diagnostic block, count (%)			
≤20 mL	10 (25)	30 (75)	0.08

≥20 mL	20 (66.67)	10 (33.33)	
Sedation, count (%)			
Versed	11 (68.75)	5 (31.25)	0.08
Versed and fentanyl	8(57.14)	6 (42.86)	0.47
No sedation	15 (30)	35 (70)	0.03
Volume of alcohol neurolysis, count (%)			
≤20 mL	10 (40)	15 (60)	0.22
≥20 mL	28 (50.10)	27(49.90)	

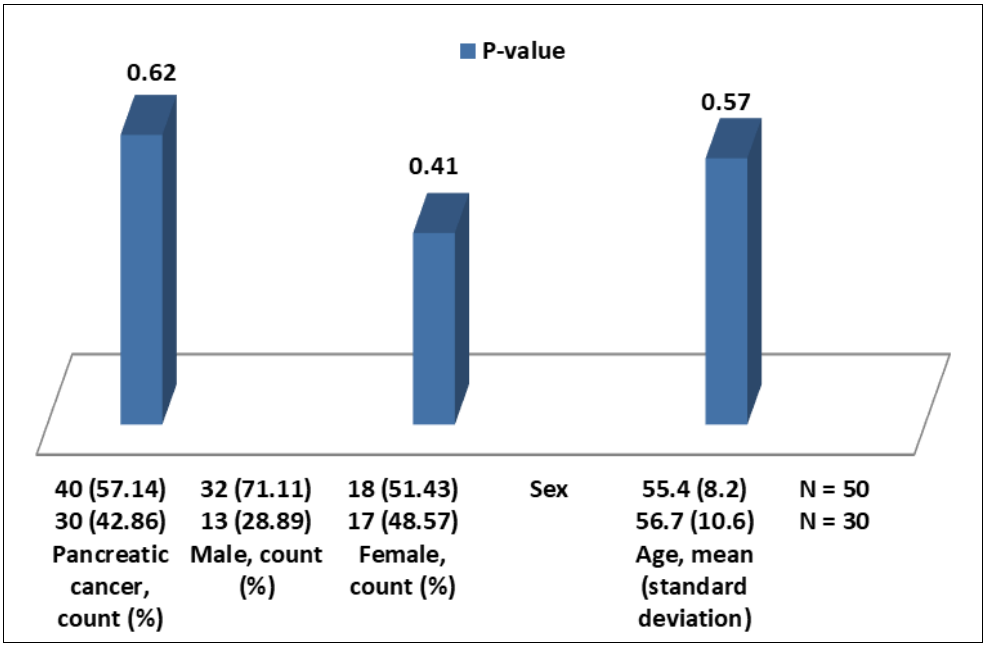

Fig 1: Patient characteristics by outcome along with its p-value.

Discussion

The few high-quality studies published on CPN have yielded mixed results. In a randomized study by Wong *et al*. [15] conducted in 100 patients with unresectable pancreatic cancer, the authors found that whereas repeated pain scores recorded over a 6-week period were significantly lower in the CPN group than the group that received a sham block plus systemic therapy, no differences were observed regarding opioid consumption, opioid-related side effects, and quality of life. However, a similar randomized study by Polati *et al*. [16] found contrasting results. No long-term differences in pain relief were observed between 24 patients allocated to either CPN or pharmacotherapy, but those who underwent CPN required less opioid medications and experienced fewer side effects. An older, randomized study by Kawamata *et al*. [17] comparing conventional pharmacotherapy to pharmaco therapy plus CPN in 21 patients with advanced pancreatic cancer did demonstrate good results. The patients who underwent CPN had significantly lower VAS pain scores in the first 4 weeks postprocedure despite less opioid consumption than those who received only analgesic therapy. Yet, both groups experienced a comparable deterioration in quality of life. The mixed results of this study underscore the need for refining selection criteria.

There are several interesting findings in our study. The one variable that was most clearly associated with a successful CPN outcome was pre-block opioid dose. Those subjects who experienced a positive outcome from neurolysis were on a mean oral morphine equivalent dose of 148.2 mg/day, which was less than half the average dose (355.2 mg/day) of those who obtained a negative outcome. There are several possible explanations for this finding. The first is that those patients on higher doses of opioids might have been faced with a more significant tumor burden and less favorable disease state. The evidence supporting this premise is mixed. Although the presence of metastases was not associated with outcome, a trend was observed whereby patients with a positive outcome were noted to have a shorter duration of pain. A second hypothesis is that opioid-induced hyperalgesia may have contributed to the negative influence opioid use appeared to have on outcome. Nociceptor sensitization is a well-documented consequence of highdose opioid consumption [14, 18] and previous studies have found a negative outcome between opioid use and pain treatment outcomes [19-21]. A third explanation is that an undocumented third variable was responsible for the correlation between opioid dose and treatment failure. Previous studies have demonstrated an association between opioid use and poor coping skills, depression, and catastrophization [22, 23]. In epidemiological studies evaluating outcome predictors for chronic pain, all of these have been shown to negatively influence treatment results [24-26]. The absence of sedative administration was significantly associated with a positive outcome. Among the 50 procedures performed without intravenous sedation, almost three quarters (N = 35) were associated with a positive outcome (P = 0.03). This remained significant after confounding variables were controlled for by logistic regression analysis (4.17 (95% CI = 1.12– 15.19), and regardless of whether midazolam was mixed with an opioid. There is evidence in the literature to both support and oppose the use of sedation during diagnostic procedures. The most common reason cited for foregoing sedation during prognostic blocks is that it might confound the results of the diagnostic procedure. Possible reasons for this include reducing anxiolysis [27] limiting the patient's ability to engage in normal

postblock activities of daily living, the muscle relaxant properties of benzodiazepines [28, 29] and for those who received opioids, the persisting analgesic effects. In a study evaluating the effect of periprocedure sedation before cervical facet joint blocks, Manchikanti and colleagues [30] found that administration of fentanyl for periprocedural anxiolysis served as a confounding factor when >50% but not >80% pain relief was used as the cutoff point. Minimal confounding effects were observed when midazolam was administered regardless of the reference standard, or for either drug when the same group performed a similar trial assessing the diagnostic validity of lumbar facet joint injections [31]. In this study [31] raising the threshold from 50% to 80% had little impact on the confounding effect of sedation. Although the effects of both variables fell just shy of statistical significance, strong trends were found whereby the use of lower local anesthetic volumes and CT imaging were associated with positive outcomes. Procedures in which 20 cc of injectate was used (P = 0.08). Whereas it seems intuitive that lower volumes would be associated with a higher degree of specificity than when more liberal dosages are injected, this has never been evaluated for neurolytic procedures. However, this finding has been confirmed for numerous other diagnostic injections, including stellate ganglion blocks [32] lumbar facet blocks [33], and selective nerve root blocks [34, 35]. Those subjects undergoing CPN under CT guidance were more likely to obtain a positive outcome than those whose procedure was performed under fluoroscopic guidance (P = 0.07). This point may seem intuitive, as CT provides a clearer picture of anatomy and tumor burden, and allows for more precise needle placement and better delineation of injectate spread. In a meta-analysis by Eisenberg *et al*. [36] the authors found similar rates of success for fluoroscopic and CT-guided procedures, although significantly fewer fluoroscopically guided procedures were included in this review. There are several limitations to our study, which mostly revolve around the retrospective nature. First, different physicians performed each procedures using slightly different techniques, and in different contexts. Whereas this might enhance the external validity of the study, the lack of standardization also limits the conclusions one can draw. The data for the procedures reviewed were also not uniformly charted, and in some instances were absent. For example, in some cases the relative position of the needle(s) had to be gleaned from saved images to determine whether it was retrocrural or antecrural. Finally, although statistical significance was detected for many variables, the power for detecting other differences may not have been sufficient. Future study might consist of a prospective study which would allow for a more complete gathering of some of the missing variables unable to be captured in our retrospective analysis. Ideally, such a study would be powered to obtain statistical significance from major variables of interest.

Conclusion

The present study concluded that CPN may provide intermediate pain relief to a significant percentage of patients suffering from pancreatic cancer. Candidates likely to experience a positive outcome include those who are on lower doses of opioid analgesics, and have a shorter duration of disease. Technical factors that may improve outcomes include the judicious (i.e., lower) use of sedation and local anesthetic for the diagnostic block, and if feasible, performing the procedure using CT guidance.

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