

Effect of Neurolytic Celiac Plexus Block on Pain Relief, Quality of Life, and Survival in Patients With Unresectable Pancreatic Cancer

A Randomized Controlled Trial

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PANCREATIC ADENOCARCINOMA is an aggressive tumor associated with high mortality. Up to 73% of patients are in pain at the time of diagnosis.¹ Thus, a major treatment focus is to optimize the quality of life (QOL) by managing symptoms, especially by providing adequate pain control.

The recommended approach to manage cancer pain uses systemic medications according to the World Health Organization analgesic ladder.² At times, systemic analgesics do not provide adequate pain relief, or doses are limited by opioid-related adverse effects.³ In these circumstances, celiac plexus or splanchnic nerve blocks with neurolytic solutions may provide analgesia by interrupting visceral afferent pain transmission from the upper abdomen.⁴ However, randomized clinical trials evaluating the efficacy of neurolytic celiac plexus block (NCPB) for pancreatic cancer pain have been limited by small sample sizes, lack of blinding, infrequent pain assessments, or lack of standardized delivery of systemic an-

Context Pancreatic cancer is an aggressive tumor associated with high mortality. Optimal pain control may improve quality of life (QOL) for these patients.

Objective To test the hypothesis that neurolytic celiac plexus block (NCPB) vs opioids alone improves pain relief, QOL, and survival in patients with unresectable pancreatic cancer.

Design, Setting, and Patients Double-blind, randomized clinical trial conducted at Mayo Clinic, Rochester, Minn. Enrolled (October 1997 and January 2001) were 100 eligible patients with unresectable pancreatic cancer experiencing pain. Patients were followed up for at least 1 year or until death.

Intervention Patients were randomly assigned to receive either NCPB or systemic analgesic therapy alone with a sham injection. All patients could receive additional opioids managed by a clinician blinded to the treatment assignment.

Main Outcome Measures Pain intensity (0-10 numerical rating scale), QOL, opioid consumption and related adverse effects, and survival time were assessed weekly by a blinded observer.

Results Mean (SD) baseline pain was 4.4 (1.7) for NCPB vs 4.1 (1.8) for opioids alone. The first week after randomization, pain intensity and QOL scores were improved (pain intensity, $P \leq .01$ for both groups; QOL, $P < .001$ for both groups), with a larger decrease in pain for the NCPB group ($P = .005$). From repeated measures analysis, pain was also lower for NCPB over time ($P = .01$). However, opioid consumption ($P = .93$), frequency of opioid adverse effects (all $P > .10$), and QOL ($P = .46$) were not significantly different between groups. In the first 6 weeks, fewer NCPB patients reported moderate or severe pain (pain intensity rating of $\geq 5/10$) vs opioid-only patients (14% vs 40%, $P = .005$). At 1 year, 16% of NCPB patients and 6% of opioid-only patients were alive. However, survival did not differ significantly between groups ($P = .26$, proportional hazards regression).

Conclusion Although NCPB improves pain relief in patients with pancreatic cancer vs optimized systemic analgesic therapy alone, it does not affect QOL or survival.

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algic medications.⁵⁻⁸ Indeed, the role of neurolytic blocks in the management of any type of cancer pain has not been firmly established by randomized, blinded clinical trials.

Lillemoe and colleagues⁸ showed that patients with unresectable pancreatic cancer randomly assigned to receive in-

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traoperative chemical splanchnicectomy during exploratory laparotomy had significantly decreased pain and opioid consumption vs control patients.⁸ In a subgroup of 34 patients with pain before laparotomy, survival was dramatically improved in those receiving chemical splanchnicectomy. Additional data suggest that pain may be associated with decreased survival in pancreatic cancer patients.⁹ Furthermore, it has been shown that animals with implanted tumors have accelerated tumor growth and increased mortality rates when subjected to pain or stress.^{10,11}

Based on these data, we sought to evaluate the possible association of pain and survival in patients with painful pancreatic cancer. The purpose of our prospective, randomized, double-blinded, placebo-controlled clinical trial was to test the hypothesis that NCPB improves pain relief, QOL, and survival vs optimized systemic analgesic therapy (SAT) alone in patients with unresectable pancreatic cancer.

METHODS

Following Mayo Institutional Review Board approval, this study was conducted at Mayo Clinic in Rochester, Minn. Patients, 18 years or older, with pancreatic cancer were referred from within the institution to the Mayo Division of Pain Medicine. Patients were of either sex, with the diagnosis of histologically proven or radiologically consistent, surgically unresectable pancreatic adenocarcinoma.¹² Patients receiving noncurative pancreatic cancer surgery were eligible for study entry beginning at 5 days following their operation. Pain intensity was assessed for each patient using a numerical rating scale (NRS) from 0 to 10 (0 is no pain and 10 is worst pain imaginable).¹³ To enroll, the pain intensity (average in the last 24 hours) rating had to be an NRS of 3/10 or higher or opioid were required for pancreatic cancer-related pain control and an NRS of lower than 6/10 if already optimized on opioids. An optimized opioid therapy was considered the maximum analgesia achievable without intolerable opioid-

Box 1. Modified Stepwise Analgesic Ladder

Step 1. Mild to Moderate Pain

Give patient nonsteroidal anti-inflammatory drug and/or 5 mg of oxycodone with acetaminophen, 500 mg orally (up to 8 tablets/d)

Step 2. Moderate to Severe Pain

Give patient sustained-release morphine orally. If the patient cannot tolerate morphine or oral and rectal routes are not possible, give transdermal fentanyl patch or oxycodone sustained-release orally

With additional as-needed morphine immediate release pills or elixir orally or 5 mg of oxycodone with acetaminophen, 500 mg orally (up to 8 tablets/d) for breakthrough pain

Box 2. Assessments

Enrollment

Basic demographic data (including any prior radiation therapy and/or chemotherapy) were recorded.

The character of the pain, including duration before enrollment, quality, intensity, and location, and its temporal pattern of the pain were obtained.

Weekly Intervals

The following data were obtained by the observer by telephone: Pain intensity rating: a verbal description of least, worst, and average pain intensity in the last 24 hours with a numerical rating scale (NRS) ranging from 0 through 10 (0 is no pain and 10 is worst pain imaginable),¹³ Responses to the NRS were obtained directly from the patient as long as circumstances permitted, with proxy responses from spouse or caregiver noted if necessary.

Quality of life assessments: The Functional Assessment of Cancer Therapy, Pancreatic Cancer (FACT-PA) is a validated, standardized measurement tool to determine QOL, as an outcome measure, in patients with pancreatic cancer.¹⁸ Responses to the FACT-PA questions were obtained directly from the patient as long as circumstances permitted, with proxy responses from spouse or caregiver noted.

Analgesic requirements: The opioid requirements were converted to daily oral morphine equivalents.^{2,19}

Adverse effects assessment: Common opioid-related adverse effects were assessed including nausea, pruritus, constipation, and drowsiness.

Radiation therapy and/or chemotherapy assessment: Any use of radiation and/or chemotherapy (gemcitabine, fluorouracil, or other) was recorded.

Survival time: These determinations were made from both the date of diagnosis and date of randomization until the date of death.

related adverse effects. Patients were excluded if they had received previous NCPB or other neurolytic blocks that could affect pancreatic cancer-related pain or had implanted epidural or intrathecal analgesic therapy. Patients with psychiatric disease affecting assessments, uncorrectable coagulopathy, or allergy to local anesthetics were excluded.

After giving written informed consent, eligible patients were assigned to receive (NCPB) or SAT alone, based on randomization schedules generated by the Mayo Division of Biostatistics. The physician who performed the randomized procedure called a central telephone number to obtain the treatment assignment, which was stratified according to the TNM staging system

(stages III or IV, locally unresectable or metastatic disease, respectively)¹² in blocks of 4 patients to ensure similar numbers in each treatment group. Radiation therapy and chemotherapy were allowed independently. Previous work has shown similar results with different NCPB or splanchnic neurolysis techniques.¹⁴ In this study, patients randomized to NCPB received an alcohol NCPB using a standard needle placement technique.¹⁵ In the prone position, skin and soft tissues of the mid-back were anesthetized with 1% lidocaine at points located 1 cm below the inferior ribs and 7 cm from the midline on each side. A 22-gauge, 5-inch-long needle was inserted and advanced to the anterolateral aspect of the superior portion of the first lumbar vertebral body on each side. Correct bilateral needle placement was confirmed with negative aspiration and fluoroscopic imaging following injection of 1 to 5 mL of iopamidol (radio-

contrast dye). Ten milliliters of 0.5% bupivacaine was injected through each needle. After 10 minutes, a motor and sensory examination of the lower extremities confirmed lack of neurologic deficits. Then, 10 mL of absolute alcohol was injected through each needle.

To control for a placebo response from the NCPB procedure,¹⁶ patients randomized to SAT received a sham procedure using subcutaneous and intramuscular 0.5% bupivacaine injection at typical NCPB sites. This procedure was performed with the identical room and set-up, prone positioning, instruments, fluoroscopy machine movement, personnel, and timing as the actual NCPB. Sham images appeared on the computer screen, but no actual fluoroscopy was used.

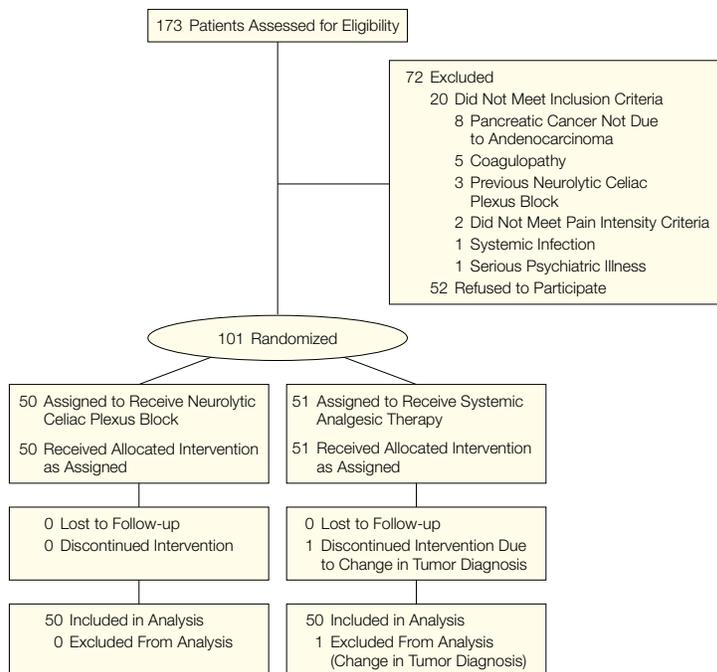
Following the randomized procedure, both treatment groups could receive medications according to a modified analgesic regimen based on World Health

Organization guidelines (BOX 1).¹⁷ When an opioid in combination with a nonopioid analgesic drug (step 1) failed to relieve mild to moderate pain, an appropriate opioid was used to treat severe pain (step 2). These analgesics were dosed in a manner blinded to the patients' randomized treatment group.

If patients had a 6/10 or higher rating of pain intensity despite optimized opioid medications or experienced intolerable adverse effects to opioid medications, rescue treatment could occur. The rescue consisted of an alcohol NCPB and was performed by a qualified member of the study team, usually the clinical manager, with the initial treatment assignment remaining blinded.

The study team consisted of members with unique roles to maintain the study blinding: the clinical manager was a physician blinded to the randomized intervention who was responsible for all pain management decisions including dosing of analgesic medications; the observer was a clinical research nurse blinded to the randomized intervention who performed all patient assessments (BOX 2); the operator was a physician not blinded to the randomized intervention who performed the NCPB or sham procedure. Following the randomized procedure, the operator was not actively involved in the care of that patient. Other medical decisions for each patient were made by the patient's primary physician.

Figure 1. Flow Diagram of Patient Progress Through the Phases of the Randomized Trial



The number of patients with data available diminished over time due to death, intermittently missed follow-up contacts, and occasional failure to respond to individual follow-up questions. From a repeated measures analysis performed using data from weeks 1 through 24 after randomization, pain intensity was found to decrease gradually with time ($P=.002$) and was significantly lower for neurolytic celiac plexus block than for systemic analgesic therapy. The numeric rating scale ranges from 0, no pain to 10, the worst pain imaginable.

Statistical Analysis

The sample size of 50 per group was chosen to provide statistical power (2-tailed $\alpha = .05$) of more than 90% to detect a difference in pain intensity of 2 or more units and power of 90% to detect a doubling of survival for NCPB compared with SAT. All analyses were performed using an intention-to-treat approach based on initial randomization. Cumulative survival probabilities were estimated using the Kaplan-Meier method. The Cox proportional hazards model compared survival between groups after adjusting for stage of disease (III or IV). Pain intensity (11-point scale), opioid consumption (de-

defined as daily oral morphine equivalents in milligrams), and QOL (Functional Assessment of Cancer Therapy—Pancreatic Cancer [FACT-PA] short form) were collected weekly. The FACT-PA total score was calculated and expressed as a percentage of the maximum possible score, as were the subscale scores for physical well-being, functional well-being, and additional concerns specific to pancreatic cancer. To satisfy model fitting assumptions, opioid consumption was analyzed using a logarithmic transformation ($y = \log_{10} [\text{daily oral morphine equivalents} + 1]$). Data following randomization for these end points were analyzed by repeated measures analysis using general linear models that allow for a varying number of observations and take into account the correlation of data within subjects.²⁰ Study week was included in the model as a regression variable. The treatment \times study week interaction term was included in initial analyses to evaluate whether the NCPB effect may diminish over time. Given the absence of a significant interaction, subsequent analyses were performed with only main effect terms for treatment and study week. The number of patients with data available diminished over time due to patient death, intermittent missed follow-up contacts, and occasional failure to respond to individual follow-up questions. Due to diminishing sample sizes, data beyond 24 weeks following randomization were not included in any repeated measures analysis. To examine the potential influence of missing data, analyses were repeated with intermittent missing data imputed using linear interpolation and missing data due to patient death imputed using the last observed data value. The percentage of patients' rating a given opioid based on adverse effect as moderate or any time during the first 6 weeks following randomization was compared between treatment groups using the Fisher exact test. Time-to-rescue therapy was compared between groups using the log-rank test. In all cases, 2-sided tests

were used with $P \leq .05$ considered statistically significant. All analyses were performed using SAS statistical software (Version 8.2 of the SAS System for Unix, SAS Institute Inc, Cary, NC).

RESULTS

Between October 1997 and January 2001, 173 patients were screened for enrollment (FIGURE 1). Of these, 153 (88%) met study inclusion criteria and 20 were excluded. Of the 153 eligible study patients, 101 (66%) agreed to participate. One patient was withdrawn because the diagnosis changed from pancreatic adenocarcinoma to a less aggressive tumor. The remaining 100 patients were followed up weekly for at least a year (through March 2002) or until their death, forming the study cohort. To evaluate for the possible presence of inclusion biases, we reviewed available medical records of patients who met study inclusion criteria for variables including age, sex, presence of significant pain or requirement of opioid use for pain, and disease stage. In all cases, there were no significant differences for those enrolled in the study vs those not enrolled using a 2-sample *t* test or χ^2 test, as appropriate.

At enrollment, the treatment groups had similar treatment history: radiation therapy (16% NCPB vs 10% SAT, $P = .37$) or chemotherapy (22% NCPB vs 18% SAT, $P = .62$ for any chemotherapy [gemcitabine, fluorouracil, or other] or 6% NCPB vs 8% SAT, $P = .70$ for gemcitabine). During the first 6 weeks following randomization, 8 patients (16%) in each treatment group received radiation treatment. During this initial 6-week period, the percentage of patients who received some form of chemotherapy was similar between treatment groups (60% NCPB vs 56% SAT, $P = .69$) as was the percentage of patients who received gemcitabine (46% NCPB vs 38% SAT, $P = .42$). Since the possible use and timing of radiation therapy and/or chemotherapy were not controlled for in our study cohort, further analyses evaluating their potential

Table 1. Baseline Characteristics

Characteristic	SAT (n = 50)	NCPB (n = 50)
Age, y		
Mean (SD)	63.4 (11.5)	62.6 (11.3)
Median	62.5	63.0
Range	38-89	38-90
Sex, No. (%)		
Men	29 (58)	24 (48)
Women	21 (42)	26 (52)
Stage, No. (%)		
III	17 (34)	17 (34)
IV	33 (66)	33 (66)
Time since diagnosis, mo		
Mean (SD)	1.2 (2.8)	2.7 (7.5)
Median	0	0
Range	0-14	0-45
Prior treatment, No. (%)		
Chemotherapy	9 (18)	11 (22)
Radiation	5 (10)	8 (16)
Pain location, No. (%)*		
Abdominal		
None	2 (4)	1 (2)
Supraumbilical	26 (53)	24 (48)
Infraumbilical	4 (8)	4 (8)
Both	17 (35)	21 (42)
Temporal pattern		
None	2 (4)	1 (2)
Intermittent	9 (18)	10 (20)
Constant	39 (78)	39 (78)
Back pain		
Temporal pattern		
None	4 (8)	8 (16)
Intermittent	22 (44)	19 (38)
Constant	24 (48)	23 (46)

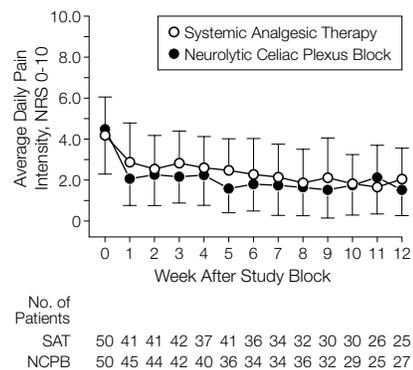
Abbreviations: NCPB, neurolytic celiac plexus block; SAT, systemic analgesic therapy.
*Data were missing for 1 patient in the SAT group.

effects would be subject to bias and were therefore not performed.

Baseline characteristics were similar between groups (TABLE 1). Seventy-eight percent of patients reported constant abdominal pain and 47% reported constant back pain. There were no significant mean (SD) differences in baseline pain intensity (4.4 [1.7] NCPB vs 4.1 [1.8] SAT, $P = .41$), QOL (50.5 [15.0] NCPB vs 51.2 [16.1] SAT, percentage of maximum FACT-PA total score, $P = .82$), or the percentage of patients using opioid medications (26% NCPB vs 42% SAT, $P = .09$).

At week 1, the mean pain intensity significantly decreased for each group from baseline. For the NCPB group, the mean (SD) pain intensity at week 1 in-

Figure 2. Average Pain Intensity From Baseline Through Week 12



NCPB, neurolytic celiac plexus block; NRS, numerical rating scale; SAT, systemic analgesic therapy. Curves were calculated using the Kaplan-Meier method with patients who died without receiving rescue censored at the time of death. From a repeated measures analysis performed using data from weeks 1 through 24 after randomization, pain intensity was found to decrease gradually with time ($P = .002$) and was significantly lower for NCPB than for SAT ($P = .01$). The NRS ranges from 0, no pain, to 10, the worst pain imaginable. Error bars indicate standard deviation.

indicates a 53% reduction from baseline (4.5 [1.7] vs 2.1 [1.4], $n = 45$, $P < .001$), which was significantly larger ($P = .005$) than the 27% reduction observed in the SAT group (3.7 [1.6] vs 2.7 [2.1], $n = 41$, $P = .01$). The QOL score at 1 week improved from baseline for both treatment groups ($P < .001$ for each) without significant difference between treatment groups ($P = .77$). Most patients (93% in each group) used opioids during the first week with similar amounts of opioid used between groups.

After week 1, pain intensity decreased gradually ($\beta = -0.03$, $SE = 0.01$, $P = .002$) and was significantly lower for NCPB than for SAT ($\beta = -0.51$, $SE = 0.20$, $P = .01$, FIGURE 2 and TABLE 2). The percentage of patients reporting pain intensity of 5/10 or higher (equivalent to “moderate” to “severe” pain²¹) at 1 or more follow-up contacts during the first 6 weeks was sig-

nificantly higher for patients in the SAT group vs those in the NCPB group (40% vs 14%, $P = .005$).

Opioid consumption increased with time ($\beta = 0.06$, $SE = 0.005$, $P = .002$, analyzed using \log_{10} transformation) with no evidence of a difference between groups ($\beta = -0.01$, $SE = 0.141$, $P = .93$). During the first 6 weeks after randomization, the percentage of patients reporting moderate or severe opioid adverse effects did not differ significantly between treatment groups (nausea 50% vs 38%, pruritus 16% vs 10%, sedation 46% vs 30%, and constipation 40% vs 52% for NCPB vs SAT; $P \geq .10$ for all, TABLE 3).

Following week 1, QOL (FACT-PA total score) gradually declined with time ($\beta = -0.35$, $SE = 0.15$, $P = .02$) and did not differ between groups ($\beta = -2.11$, $SE = 2.81$, $P = .46$). The physical and functional well-being subscales of the FACT-PA each decreased with time (physical $\beta = -0.67$, $SE = 0.24$, $P = .007$;

Table 2. Pain Intensity and Quality of Life

	Observed Values*						Carry-Forward Values*			
	SAT			NCPB			SAT		NCPB	
	No. of Patients	Mean (SD)	Median (IQR)	No. of Patients	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
	Pain, 1-10									
Baseline	50	4.1 (1.8)	4.2 (3-5)	50	4.4 (1.7)	4.2 (3-6)				
Week										
1	41	2.7 (2.1)	3 (1.3-4)	45	2.1 (1.4)	2 (1-3)	3.1 (2.1)	3 (2-5)	2.2 (1.4)	2 (1-3)
4	37	2.5 (1.6)	2 (1.3-4)	40	2.2 (1.5)	2 (1-3)	2.7 (1.8)	2.2 (1.4-4)	2.2 (1.4)	2 (1-3)
8	32	1.8 (1.7)	1 (0-3)	36	1.6 (1.5)	1 (0.2-3)	2.2 (2.1)	2 (0.7-3.3)	1.7 (1.5)	1 (0-3)
12	25	2.0 (1.5)	2 (1-3.3)	27	1.5 (1.3)	1 (0-2)	2.2 (1.8)	2 (1-3.3)	1.7 (1.5)	2 (0-3)
16	21	1.7 (1.5)	2 (0-3)	24	1.2 (1.2)	1 (0-2)	2.4 (1.8)	2 (1-3)	1.6 (1.5)	1.5 (0-3)
20	17	2.4 (2.4)	2 (0.2-4)	19	1.7 (1.3)	1 (1-3)	2.6 (2.1)	2.2 (1-4)	1.8 (1.5)	2 (0.4-3)
24	13	2.0 (2.2)	1 (0-3)	14	0.8 (1.1)	0 (0-1.3)	2.4 (2.1)	2 (0.7-4)	1.5 (1.5)	1 (0-3)
	Quality of Life†									
Baseline	47	51.2 (16.1)	51.1 (38.0-63.0)	47	50.5 (15.0)	50.0 (38.4-62.0)				
Week										
1	41	64.2 (17.1)	64.1 (49.3-76.6)	45	61.4 (14.9)	63.0 (53.1-73.0)	60.7 (18.7)	63.0 (45.7-75.3)	60.7 (14.7)	62.0 (51.8-72.8)
4	34	63.6 (16.2)	60.3 (51.6-77.2)	38	58.5 (14.6)	59.2 (46.5-70.4)	59.3 (18.8)	59.4 (47.8-71.6)	56.9 (13.7)	58.7 (46.7-66.8)
8	32	61.6 (18.8)	61.4 (42.7-78.0)	36	56.8 (17.7)	53.3 (43.5-70.4)	55.4 (20.5)	53.1 (39.9-66.3)	55.4 (16.3)	52.2 (42.4-65.2)
12	26	60.9 (17.5)	57.1 (47.3-73.1)	24	58.5 (18.8)	60.3 (44.6-69.3)	54.7 (19.7)	51.1 (39.1-69.4)	53.3 (16.1)	51.1 (40.8-63.2)
16	21	62.1 (18.6)	62.9 (49.0-75.0)	21	61.7 (17.0)	62.0 (46.8-73.4)	51.8 (18.5)	48.7 (38.9-64.4)	52.2 (16.1)	47.8 (40.2-62.5)
20	16	62.7 (18.2)	60.6 (49.5-76.1)	19	61.7 (18.5)	57.6 (47.8-73.9)	50.4 (17.4)	48.4 (38.0-62.0)	51.9 (16.6)	47.8 (40.2-62.5)
24	12	59.7 (25.5)	54.8 (42.5-88.9)	14	70.4 (15.5)	73.4 (61.9-80.4)	48.7 (18.2)	45.8 (38.0-57.6)	52.5 (17.8)	47.8 (39.9-65.5)

Abbreviations: IQR, interquartile range; NCPB, neurolytic celiac plexus block; SAT, systemic analgesic therapy.

*Patients were followed up weekly until death. Data are presented for selected weeks. Declining sample sizes for the observed data reflect attrition due to patient death, intermittent missed follow-up contacts, and occasional failure to respond to individual follow-up questions. For the carry-forward technique, missing data due to patient death are imputed using the last observed data value and intermittent missing data are imputed using linear interpolation. Using this approach, 50 patients were used for both groups at all periods with the exception of quality of life for patients in the NCPB group, for which 49 patients were used for each period.

†Quality of life was assessed using the Functional Assessment of Cancer Therapy scale for Pancreatic Cancer (FACT-PA). Data represent the FACT-PA total score expressed as a percentage of the maximum possible score.

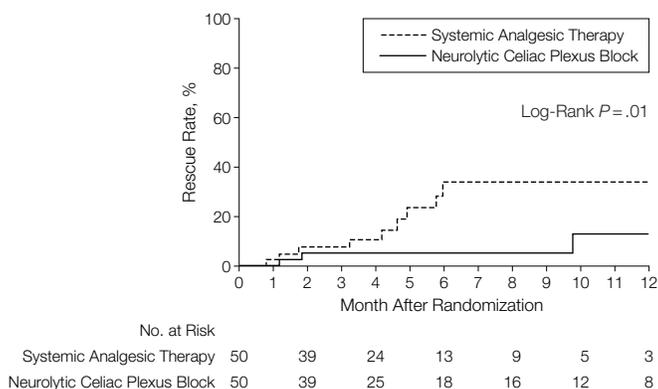
Table 3. Opioid Use*

	Observed Values†						Carry-Forward Values†			
	SAT			NCPB			SAT		NCPB	
	No. of Patients	Median (IQR)	Patients Using Opioids, %	No. of Patients	Median (IQR)	Patients Using Opioids, %	Median (IQR)	Patients Using Opioids, %	Median (IQR)	Patients Using Opioids, %
Baseline	50	0 (0-11)	42	50	0 (0-5)	26				
Week										
1	44	80 (30-274)	93	46	66 (33-208)	93	73 (30-204)	92	58 (32-208)	92
4	44	155 (31-628)	91	44	128 (48-238)	95	151 (30-585)	90	112 (45-259)	92
8	39	127 (44-554)	92	39	180 (62-384)	97	130 (41-555)	90	168 (46-364)	90
12	34	231 (30-555)	94	33	249 (62-643)	94	181 (38-555)	94	182 (34-456)	88
16	27	165 (30-760)	93	25	223 (48-571)	92	178 (45-676)	94	199 (30-556)	86
20	20	229 (19-750)	85	22	243 (49-549)	95	181 (45-810)	92	194 (27-549)	88
24	16	182 (31-530)	88	19	161 (30-654)	95	181 (42-690)	92	204 (30-742)	88

Abbreviations: IQR, interquartile range; NCPB, neurolytic celiac plexus block; SAT, systemic analgesic therapy.
 *Opioid use is expressed as milligrams per day oral morphine equivalents and summarized using median (IQR). At each follow-up contact data regarding opioid consumption and dosing changes were documented from the time of the previous contact. Thus if a patient could not be contacted on a given week the data for that week were obtained at the next follow-up contact.
 †Patients were followed up weekly until death. Data are presented for selected weeks. Declining sample sizes for the observed data reflect attrition due to patient death, intermittent missed follow-up contacts, and occasional failure to respond to individual follow-up questions. For the carry-forward technique, missing data due to patient death are imputed using the last observed data value and intermittent missing data are imputed using linear interpolation. Using this approach, 50 patients were used for both groups at all periods.

functional $\beta = -0.66$, $SE = 0.24$, $P = .008$) with no difference between groups (physical $\beta = -4.14$, $SE = 3.30$, $P = .21$; functional $\beta = -3.42$, $SE = 4.06$, $P = .40$; Table 2). The additional subscale for concerns specific to pancreatic cancer did not change significantly over time ($\beta = -0.09$, $SE = 0.17$, $P = .59$) and did not differ between groups ($\beta = -1.36$, $SE = 2.48$, $P = .59$). An additional analysis was performed for the FACT-PA item that asks patients to rate the truth of the statement, "I have pain" using the following responses: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; or 4, very much. From this analysis, pain was found to decrease gradually with time ($P = .003$) and was significantly lower for the NCPB than for the SAT group ($P = .02$). A total of 13 patients (3 NCPB, 10 SAT) received rescue NCPB for pain relief following randomization. Time to rescue was significantly longer for those in the NCPB than for those in SAT groups ($P = .01$, log-rank test; FIGURE 3). In all cases, similar findings were obtained when the analyses of pain intensity, opioid consumption, and QOL were repeated using only data collected prior to rescue. Findings were also consistent when intermittent missing data were imputed using linear interpolation and missing data due to patient death imputed using the last observed data value.

Figure 3. Cumulative Percentage of Patients Who Received Rescue Neurolytic Celiac Plexus Block



Curved were calculated using Kaplan-Meier method with patients who died without receiving rescue treatment censored at the time of death.

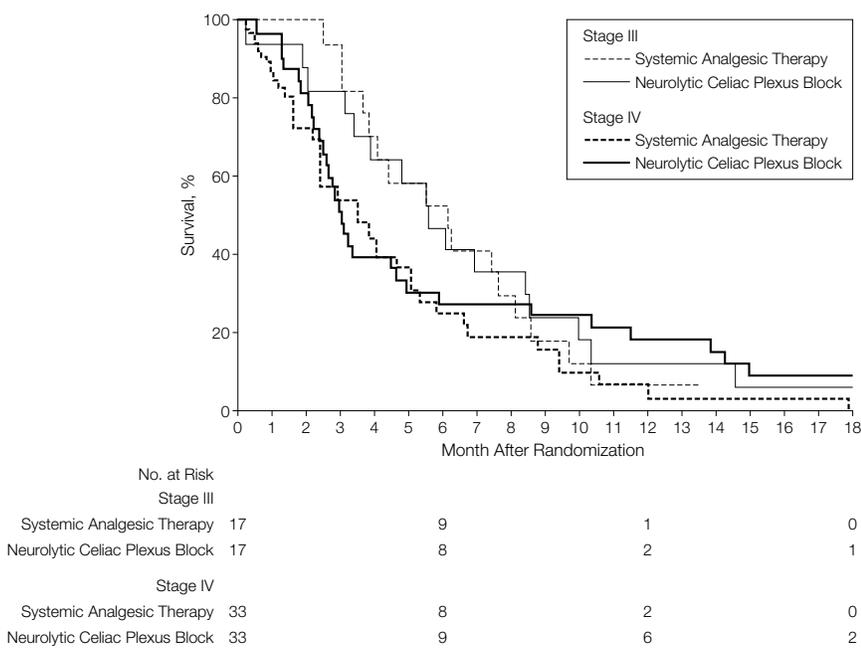
At the time of last follow-up, 96 (47 NCPB, 49 SAT) patients were deceased. Survival following randomization did not differ significantly between treatment groups ($P = .26$; hazard ratio, 0.8; 95% confidence interval [CI], 0.5-1.2; proportional hazards regression adjusting for stage of disease; FIGURE 4). Median survival for patients with stage III disease was 5.5 months for NCPB and 6.1 months for SAT. For patients with stage IV disease, the median survival was 2.9 months for NCPB and 3.4 months for

SAT. The percentage of patients alive a year after randomization was 16% (12% stage III, 18% stage IV) for NCPB patients and 6% (6% stage III, 6% stage IV) for SAT patients.

COMMENT

A recent National Institutes of Health State-of-the Science Conference Statement on Symptom Management in Cancer (July 15-17, 2002) highlighted the lack of properly designed comparative analgesic trials for cancer patients such as NCPB vs SAT in the

Figure 4. Survival After Randomization by Cancer Stage



Survival after randomization did not differ significantly between treatment groups ($P = .26$); proportional hazards regression adjusting for stage of disease.

management of pancreatic cancer pain. Our major finding is that NCPB significantly improves pain relief in patients with pancreatic cancer compared with optimized SAT alone but does not affect QOL or survival.

Both NCPB and SAT were able to provide a clinically meaningful reduction in pain intensity from baseline,²² which is similar to previous findings.^{5,7} Opioid therapy was implemented or intensified in both groups. During the first week after intervention, NCPB provided analgesia with a mean pain rating similar to other studies,^{5,6} which was significantly better than SAT alone, demonstrating that our block technique was effective. Furthermore, the analgesic benefit of NCPB over SAT alone was sustained over the longer term until death. This finding is similar to the larger study of chemical splanchnicectomy during surgery ($n=137$) by Lillemoe et al⁸ but different from previous smaller unblinded studies (20 to 24 total patients) primarily showing short-term analgesic benefit over weeks with NCPB compared with SAT.⁵⁻⁷ The efficacy of the

NCPB is also suggested by our finding that more patients randomly assigned to SAT required NCPB rescue (Figure 3).

A previous study found that up to 85% of patients with advanced pancreatic cancer experience severe pain with advanced disease.²³ Our results suggest that application of a pain management protocol, with or without NCPB, can maintain pain intensity in the “mild”²¹ category over time in most patients, even those with advanced disease. Our interpretation is that NCPB is an efficacious adjunctive analgesic therapy, but a key intervention is the implementation of an aggressive pain management protocol with opioids used throughout the course of disease. It is possible that the treatment effect size provided by the NCPB would have been larger if the SAT were not as optimized, as might occur in certain clinical practice settings.

In clinical practice, opioid doses required for adequate analgesia in cancer patients, even among those with similar tumors, are extremely variable as observed in our study. Opioids were fre-

quently required even in those receiving NCPB, as previously observed by Ischia et al,¹⁴ with no difference between groups. This result is different from the findings of Lillemoe et al,⁸ which did not control for delivery of opioids according to need, approach, or provider.⁸ Other smaller studies⁵⁻⁷ of between 20 and 24 patients were not double blinded, thereby, potentially biasing those not receiving the active treatment with NCPB to requiring increased opioids.¹⁶

At week 1, QOL improved as pain relief improved but without difference between groups. As expected, QOL estimated by the FACT-PA declined over time but without difference between groups. A previous small study showed decreased deterioration of QOL estimated by functional status in those with NCPB.⁵ It is possible that the relatively smaller difference in pain scores between groups in our study was insufficient to affect the more global assessment of QOL estimated by the FACT-PA.

We sought to further evaluate the possible association between pain and survival. A higher percentage of patients were alive a year after randomization to NCPB (16%, $n=8$) vs SAT (6%, $n=3$), but this difference was not significant. Lillemoe et al had a different finding with improvement in survival and in pain relief, but only in a small subgroup with significant preoperative pain ($\geq 3/10$) randomly assigned to receive chemical splanchnicectomy ($n=20$) vs controls ($n=14$). Compared with our study, there are distinct differences in the Lillemoe et al study including a different celiac block technique using chemical splanchnicectomy during surgery, a different study population consisting entirely of surgically operated patients, a relatively small sample size when considering only patients with significant pain ($n=34$), much less frequent pain assessments occurring every 2 months, and lack of a standardized approach to providing analgesic therapy that would be difficult to optimize. Also, the pain ratings in the study by Lillemoe et al were higher in both chemical splanchnicectomy and controls with larger absolute

mean differences between groups compared with our study at similar time points. It is possible these factors may have contributed to the difference in findings between the Lillemoe et al study and our study. Furthermore, although the current investigation was designed to provide 90% power to detect a difference in survival based on the results of Lillemoe et al (ie, doubling of survival for NCPB vs SAT), the sample-size for the current investigation may not provide adequate statistical power to make definitive conclusions regarding smaller differences in survival that still may be clinically relevant.

In conclusion, we found that both NCPB and optimized SAT alone can provide effective analgesia, though NCPB

can provide significantly better analgesia than optimized SAT alone. However, the NCPB had no effect on opioid consumption, QOL, or survival.

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Study concept and design: Wong, Schroeder, Warner.
Acquisition of data: Wong, Carns, Wilson, Martin, Kinney, Mantilla.

Analysis and interpretation of data: Wong, Schroeder, Warner.

Drafting of the manuscript: Wong, Schroeder, Warner.
Critical revision of the manuscript for important intellectual content: Wong, Schroeder, Carns, Wilson, Martin, Kinney, Mantilla, Warner.

Statistical expertise: Wong, Schroeder.

Obtained funding: Wong, Warner.

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REFERENCES

1. Grahm AL, Andren-Sandberg A. Prospective evaluation of pain in exocrine pancreatic cancer. *Digestion*. 1997;58:542-549.
2. Jacox A, Carr DB, Payne R, et al, eds. *Management of Cancer Pain*. Rockville, Md: Agency for Health Care Policy and Research, March; 1994. AHCPR Publication 94-0592.
3. Ventrafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer*. 1987;59:850-856.
4. Goudas L, Carr DB, Bloch R, et al. *Management of Cancer Pain*. Rockville, Md: Agency for Healthcare Research and Quality; 2001. AHCPR Publication 02-E002.
5. Kawamata M, Ishitani K, Ishikawa K, et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. *Pain*. 1996;64:597-602.
6. Polati E, Finco G, Gottin L, Bassi C, Pederzoli P, Ischia S. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. *Br J Surg*. 1998;85:199-201.
7. Mercadante S. Celiac plexus block vs analgesics in pancreatic cancer pain. *Pain*. 1993;52:187-192.
8. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial. *Ann Surg*. 1993;217:447-457.
9. Kelsen DP, Portenoy R, Thaler H, Tao Y, Brennan M. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. *Surgery*. 1997;122:53-59.
10. Lewis JW, Shavit Y, Terman GW, Gale RP, Liebeskind JC. Stress and morphine affect survival of rats challenged with a mammary ascites tumor (MAT 13762B). *Nat Immun Cell Growth Regul*. 1983;3:43-50.
11. Page GG, Ben-Eliyahu S, Yirmiya R, Liebeskind JC. Morphine attenuates surgery-induced enhancement of metastatic colonization in rats. *Pain*. 1993;54:21-28.
12. *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer-Verlag; 2002.
13. Anderson KO, Syrjala KL, Cleeland CS. How to assess cancer pain. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment*. New York, NY: Guilford Press; 2001.
14. Ischia S, Ischia A, Polati E, Finco G. Three posterior percutaneous celiac plexus block techniques. *Anesthesiology*. 1992;76:534-540.
15. Moore DC. Intercostal nerve block combined with celiac plexus (splanchnic) block. In: Moore DC, ed. *Regional Block*. 4th ed. Springfield, Ill: Charles C Thomas Publisher; 1981.
16. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? *N Engl J Med*. 2001;344:1594-1602.
17. *Cancer Pain Relief*. 2nd ed. Geneva, Switzerland: World Health Organization; 1996.
18. Cella DF, Bonomi AE. Measuring quality of life: 1995 update. *Oncology*. 1995;9(suppl 11):47-60.
19. Levy MH. Pharmacologic treatment of cancer pain. *N Engl J Med*. 1996;335:1124-1132.
20. Littell RC, Milliken GA, Stroup WW, Wolfinger RD. *SAS System for Mixed Models*. Cary, NC: SAS Institute Inc; 1996.
21. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? *Pain*. 1995;61:277-284.
22. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149-158.
23. Kalsner MH, Barkin J, MacIntyre JM. Pancreatic cancer. *Cancer*. 1985;56:397-402.