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Neurolytic Splanchnic Nerve Block and Pain Relief, Survival, and Quality of Life in Unresectable Pancreatic Cancer: A Randomized Controlled Trial

Daosong Dong, M.D., Mingfang Zhao, M.D., Jingmei Zhang, M.D., Ming Huang, M.D., Yanwei Wang, M.D., Liang Qi, M.D., Cheng-fu Wan, M.D., Xue Yu, M.D., Tao Song, M.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Pain arising from pancreatic cancer can be severe and strongly impact quality of life.
- Both opioids and neurolytic blocks are used to control pain from pancreatic cancer, but few studies have directly compared these approaches.

What This Article Tells Us That Is New

- A multicenter study was designed in which patients with unresectable pancreatic cancer and moderate to severe pain were randomized to lytic splanchnic nerve block or block using saline. All patients received opioids according to a set protocol.
- Pain relief was superior for those receiving lytic blocks for 3 months, and opioid use was lower for 5 months. Quality of life was not affected, however.

ABSTRACT

Background: Neurolytic splanchnic nerve block is used to manage pancreatic cancer pain. However, its impact on survival and quality of life remains controversial. The authors' primary hypothesis was that pain relief would be better with a nerve block. Secondarily, they hypothesized that analgesic use, survival, and quality of life might be affected.

Methods: This randomized, double-blind, parallel-armed trial was conducted in five Chinese centers. Eligible patients suffering from moderate to severe pain conditions were randomly assigned to receive splanchnic nerve block with either absolute alcohol (neurolysis) or normal saline (control). The primary outcome was pain relief measured on a visual analogue scale. Opioid consumption, survival, quality of life, and adverse effects were also documented. Analgesics were managed using a protocol common to all centers. Patients were followed up for 8 months or until death.

Results: Ninety-six patients (48 for each group) were included in the analysis. Pain relief with neurolysis was greater for the first 3 months (largest at the first month; mean difference, 0.7 [95% CI, 0.3 to 1.0]; adjusted $P < 0.001$) compared with placebo injection. Opioid consumption with neurolysis was lower for the first 5 months (largest at the first month; mean difference, 95.8 [95% CI, 67.4 to 124.1]; adjusted $P < 0.001$) compared with placebo injection. There was a significant difference in survival (hazard ratio, 1.56 [95% CI, 1.03 to 2.35]; $P = 0.036$) between groups. A significant reduction in survival in neurolysis was found for stage IV patients (hazard ratio, 1.94 [95% CI, 1.29 to 2.93]; $P = 0.001$), but not for stage III patients (hazard ratio, 1.08 [95% CI, 0.59 to 1.97]; $P = 0.809$). No differences in quality of life were observed.

Conclusions: Neurolytic splanchnic nerve block appears to be an effective option for controlling pain and reducing opioid requirements in patients with unresectable pancreatic cancer.

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Pancreatic cancer is the second most common gastrointestinal cancer and the fourth most common cause of cancer-related death in the United States.[1] Early diagnosis and intervention of pancreatic cancer remain a challenge for clinical practitioners.[2] Upper abdominal pain is the most common symptom in patients with pancreatic cancer, and it is also the main reason that patients initially consult a doctor.[3] Approximately 70 to 80% of patients have pain at diagnosis, and over 90% have pain in the advanced stages.[4] Less than 20% of patients can receive surgery, because most patients have local vessel involvement or distant metastases.[5] The prognosis associated with pancreatic cancer is extremely poor, with a median survival time of only 4.4 months, and among patients who undergo pancreatectomy, the median survival time is less than 13 months.[6] Due to the difficulty in early diagnosis and the poor prognosis of this condition, palliative care, including adequate pain relief

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and quality-of-life improvement, has become an increasingly important and integral element of pancreatic cancer treatment. Current international guidelines from the World Health Organization recommend a stepwise dosing strategy to manage cancer pain, where opioids continue to be the most effective and an almost indispensable option in nearly all nonsurgical regimens, with no upper dosing limits. Unfortunately, this approach is still associated with inadequate pain relief in 55% of patients.[7] Furthermore, although high-dose opioids provide some analgesic benefit, they are associated with numerous side effects, such as nausea/vomiting, constipation, poor sleep, and depression. Finally, long-term treatment with high-dose opioids is sometimes accompanied by rapid tolerance, which consequently leads to further dose escalations. Therefore, alternative nonopioid cancer pain treatment options are actively advocated by international consensus,[8] and many studies exploring such options have been conducted.

Currently, neurolytic celiac plexus block (or celiac neurolysis) and splanchnic nerve block are used as alternative nonopioid surgical methods to manage pancreatic cancer pain.[9–12] Although many studies have showed that neurolysis can improve pain relief and slow opioid dose escalation, its impact on quality of life and survival remains controversial. Most current available evidence indicates that celiac neurolysis neither improves nor decreases quality of life or survival.[13] However, in a single-center retrospective study conducted by Fujii-Lau *et al.*,[14] celiac neurolysis was negatively associated with survival, especially among patients with advanced pancreatic cancer. In contrast, Lillemoe *et al.*[11] found that patients who received neurolysis had longer survival times than those who received the saline placebo.

Based on these controversial data, we investigated the efficacy and safety of neurolytic splanchnic nerve block *versus* placebo control in the treatment of pancreatic cancer pain. It is hypothesized that neurolytic splanchnic nerve block would improve pain relief, survival, and quality of life compared with systemic analgesic therapy alone in patients with unresectable pancreatic cancer.

Materials and Methods

Study Design and Protocol Amendments

This trial was a prospective, randomized, double-blind, parallel-armed trial of neurolytic splanchnic nerve block *versus* placebo control in the treatment of pancreatic cancer pain. It was approved by the Human Ethics Committee of The First Affiliated Hospital of China Medical University, Shenyang, China (No. 2016-165-2) and was registered with www.chictr.org.cn in May 2017 (Registration No. ChiCTR-IOR-17011318). The principal investigator was the First Affiliated Hospital of China Medical University. After approval from the Ethics Committee, this trial was conducted from May 2017 to May 2018 at five Chinese centers: The First Affiliated Hospital of China Medical University, The General Hospital of Shenyang Military Region (Shenyang), The Third Hospital of Anshan (Anshan), The Central Hospital of Fuxin City (Fuxin), and Chaoyang Second People's Hospital (Chaoyang). We amended our protocol to extend the study period by 3 months until August 2018 for completion due to the unexpectedly slow recruitment speed. Data collection was carried out between May 2017 and April 2019.

Inclusion and Exclusion Criteria

Patients presenting to the emergency room or the pain clinic with pancreatic cancer–related pain were first identified by a member of the pain medicine department staff. Once a potential research subject was identified, the subject was seen and examined by a pain management physician (the research assistant) who was a member of the research team and asked to participate in the study. This research assistant evaluated eligibility, obtained informed consent, and enrolled the participants. Written informed consent was obtained from all study participants. The main eligibility criteria were as follows: (1) patients diagnosed with advanced pancreatic cancer (stage III or IV, as determined according to the American Joint Commission on Cancer 6th Edition Staging System for Patients with Pancreatic Adenocarcinoma[6]); (2) patients with self-reported moderate to severe pain related to pancreatic cancer (visual analogue scale [VAS], 4 or greater); and (3) patients in palliative care who would not receive any anticancer treatments, including radiation therapy, chemotherapy, or targeted therapies. No changes to the eligibility criteria occurred during the trial. The main exclusion criteria were as follows: (1) patients who underwent pancreatic resection or noncurative pancreatic cancer surgery, (2) patients who previously underwent any kind of neurolysis that could affect pancreatic cancer pain, (3) patients previously diagnosed with severe psychiatric diseases, and (4) patients with systemic or local infection.

Randomization and Patient Assignment

After enrollment and consent, eligible patients were randomly divided into the neurolytic splanchnic nerve block (true block, neurolysis) group and systemic analgesic therapy alone (sham injection, control) group. A randomization sequence was created by a study statistician using SAS version 9.0 statistical software (SAS Institute, USA) and was stratified by center with a 1:1 allocation ratio using a fixed block size of 2. The allocation sequence was concealed from relevant research assistant physicians and patients following a planned double-blind design using numbered, opaque, and sealed office envelopes. Additional layers of thick black paper within both sides of the envelope were used to assure that envelopes were impermeable to intense light. Envelopes containing participant allocation information were opened by a research nurse only after baseline assessments and

immediately before allocating participants to either one of two intervention groups. All the subjects were followed up for 8 months or until death, and all the outcome measurements were collected and documented monthly (visits 1 to 8). All authors had access to the study data and reviewed and approved the final manuscript.

Description of Splanchnic Nerve Block Procedures

The splanchnic nerve block procedures were performed bilaterally under computed tomography guidance according to previously described methods with minor modifications.[12,15] Briefly, the patient was positioned in a prone position. A computed tomography scan was performed, and two needles were introduced bilaterally at the angle parallel to the T12–L1 intervertebral disc (between the 12th thoracic vertebra and the 1st lumbar vertebra, T12–L1). After the needle tips penetrated the intervertebral disc and advanced to the posterolateral aspect of the aorta, 2 ml of iopamidol (contrast agent) was injected to confirm the correct placement under fluoroscopic imaging. Then, 5 ml of 0.5% bupivacaine was injected through the needles, and after confirming that there were no neurologic deficits in the lower extremities, 12 to 18 ml of either absolute alcohol (neurolysis) or normal saline (control) was injected. Systemic analgesic therapy with opioids was given in both groups to control cancer pain. Analgesics were managed using a protocol common to all centers, and rules for dose modification are provided in Supplemental Digital Content 1 (http://links.lww.com/ALN/C669).

Outcome Measurement

The primary outcome was pain relief on the basis of the VAS numeric scores. Secondary outcomes were overall survival, total opioid consumption in morphine equivalence, and quality-of-life scores. Adverse events were recorded throughout the study period and reported. No changes made to the definition of study outcomes occurred during the trial.

Demographics. Demographic information was collected after enrollment by a research assistant who was also responsible for follow-up of patients regarding their pain levels, survival status, and quality of life, among other features. Both the research assistant and enrolled patients were blinded to the treatment assignment.

Pain Relief. Study participants' pain was assessed using the VAS scoring system. It is a standard and verified 10-point scale for pain self-report, where a score of 0 represents no pain at all and a score of 10 represents the highest pain level that an individual can imagine. After enrollment, patients were asked to report their average VAS within the last 24 h as the baseline measurement. For all follow-up visits, VAS scores were collected using the averaged self-reported pain within the past 7 days.

Survival. The survival data were determined by measuring the length of time from the date of randomization to the end of the observation period or the date of death.

Opioid Consumption. The level of opioid consumption of each follow-up visit was derived from the mean consumption of the preceding 7 days, and the data were translated into daily oral dose of morphine equivalent measured in milligrams for analysis.

Quality of Life. Patients' quality of life was evaluated with the 36-item version of the Short Form Health Survey, which is comprised of two components: a physical component summary and a mental component summary.[16,17] Both components are normalized scores ranging from 0 to 100 points, and a score less than 50 indicates a below-average status. Both scores were recorded and calculated at each follow-up visit.

Adverse Events. Procedure-related adverse events and opioid-related side effects were monitored and documented during the entire follow-up period. All the related adverse events were ascertained by a questionnaire with direct questioning, if applicable.

Interim Analysis

No changes in methods occurred after trial commencement, and no interim analysis was conducted.

Power Analysis

Sample size calculation was completed using SAS version 9.0. Assuming a two-tailed alpha = 0.05, a total sample of N = 96 patients (n = 48 patients for each group) would achieve 90% power to detect a minimal effect size of Cohen's D = 0.7 utilizing a two independent sample Student's *t* test. This effect size equates to a 1.4-point difference in the VAS score between two groups assuming a SD = 2.

Statistical Analysis

For descriptive statistics, continuous variables were summarized using the mean and SD or median and 25th/75th percentiles, depending on the data distribution. Categorical variables were summarized using frequencies and percentages. Standardized mean differences were reported for comparisons of demographic variables and outcome measures at each time point. A standardized mean difference of more than 0.1 was considered statistically significant.

Differences in outcomes of VAS, daily oral dose of the morphine equivalent, the physical component summary scores, and the mental component summary scores between two groups were compared using a random intercept linear mixed effects model. The fixed effects included baseline values of these two outcomes as covariates, group (neurolysis or control), center name (The First Affiliated Hospital of China Medical University, Shenyang, Anshan, Fuxin, Chaoyang) and time points (visits 1 to 8), and the random intercepts were patients' research identifiers. Whether to

include the interaction term of the group and time point (group × time point) in the final model was determined by comparing the interaction model fitness with the model without the interaction term utilizing a likelihood ratio test. *Post hoc* pairwise comparisons were conducted, and estimated marginal means of the adjusted mean differences accompanied by their CIs were calculated. Missing data involving the VAS scores, daily oral dose of the morphine equivalent, the physical component summary scores, and the mental component summary scores due to attrition (*e.g.*, death, loss to follow-up) were further examined and addressed in several *post hoc* sensitivity analyses. These analyses included the following: we (1) refitted our linear mixed effects models by adding adjusting terms of disease severity of the length of survival or the clinical stage, and (2) performed single imputations of all study outcomes using the last observation carried forward method. All sensitivity models were compared to the original linear mixed effects models using likelihood ratio tests, and results were reported in Supplemental Digital Content 2 (http://links.lww.com/ALN/C670).

Differences in survival between the two groups were compared using the log-rank test, and survival trends were visualized using Kaplan–Meier curves. After the proportional hazards assumption was carefully assessed, the Cox proportional hazard regression model was used to estimate the hazard ratio between the two study groups. *Post hoc* subgroup analyses were conducted by clinical stage (III *vs.* IV) and location of pain. Analyses of adverse events were conducted using the chi-square or Fisher exact test. All statistical tests were two-sided. Alpha was set to 0.05. *Post hoc* adjustments for *P* values were conducted using the Bonferroni method (number of comparisons = 8 for all outcomes). Statistical analysis was performed using Rstudio and R statistical programming software (RStudio Inc., USA). R packages including "tidyverse," "lmer," "lmerTest," and "emmeans" were used for modeling and parameter estimation.

Results

Trial Information

A total of 96 patients was eligible and enrolled in the study. The analysis was conducted using the intention-to-treat method, and the date of randomization was utilized as the initial time point to calculate survival. The Consolidated Standards of Reporting Trials diagram is provided in figure 1.

Patient Characteristics

Patients' demographic characteristics are summarized and reported in table 1. There were no statistically significant differences between the two groups in terms of age (standardized mean difference = 0.09), sex (standardized mean difference = 0.08), and body mass index (standardized mean difference = 0.08). There were small but statistically significant differences in cancer disease condition variables including tumor node metastasis staging (standardized mean difference = 0.13) and location of pain (standardized mean difference = 0.10) but not in the location of the tumor (standardized mean difference = 0.04) between study groups.

Study Follow-up

A total of 93 patients (93/96, 96.9%) completed the trial. One patient from the control group was lost to follow-up at month 7 after enrollment, and two patients from the neurolysis group were lost to follow-up at month 6 and month 7. This satisfactory low dropout rate (3 of 96, 3.1%) was attributed to the strict national regulations regarding the usage of opioid drugs required by the Chinese government.

VAS

Descriptive summary and inferential statistics of VAS are reported in table 2 and illustrated in figure 2. Both study groups showed significant decrease in VAS after analgesic treatment compared to the baseline (all $P < 0.001$). We found statistically significant differences in group ($P < 0.001$) and time ($P < 0.001$), and the group-by-time interaction was also statistically significant (both likelihood ratio test and interaction $P = 0.008$). We found that the treatment effect of neurolysis compared with the control group in pain relief, despite being statistically significant for the first 3 months, had a small effect size (largest at the first month visit; mean difference, 0.7 [95% CI, 0.3 to 1.0]; adjusted $P < 0.001$), and this treatment effect gradually declined to similar levels in the control group at the fourth month (mean difference, 0.4 [95% CI, 0.1 to 0.6]; adjusted $P = 0.120$). This result was consistent with our sensitivity analyses using imputed data (only group main effect; mean difference, 0.5 [95% CI, 0.1 to 0.8]; adjusted $P = 0.006$), and when adding patients' survival status (largest effect at first month; mean difference, 0.7 [95% CI, 0.3 to 1.0]; adjusted $P < 0.001$) and clinical stage into the primary model (largest effect at first month, 0.7 [95% CI, 0.3 to 1.0]; adjusted $P < 0.001$).

Survival

We found a significant difference in overall survival between the neurolysis group (median survival = 102.5 days) and the control (median survival = 151.0 days) based on the univariate Cox proportional hazards regression (hazard ratio, 1.56 [95% CI, 1.03 to 2.35]; $P = 0.036$, clustered by research centers). Kaplan–Meier survival curves and cumulative risk tables are presented in figure 3. Corresponding log-rank test is presented in Supplemental Digital Content 2 (http://links.lww.com/ALN/C670).

We then tested several candidate multivariable Cox regression models by including potential confounding

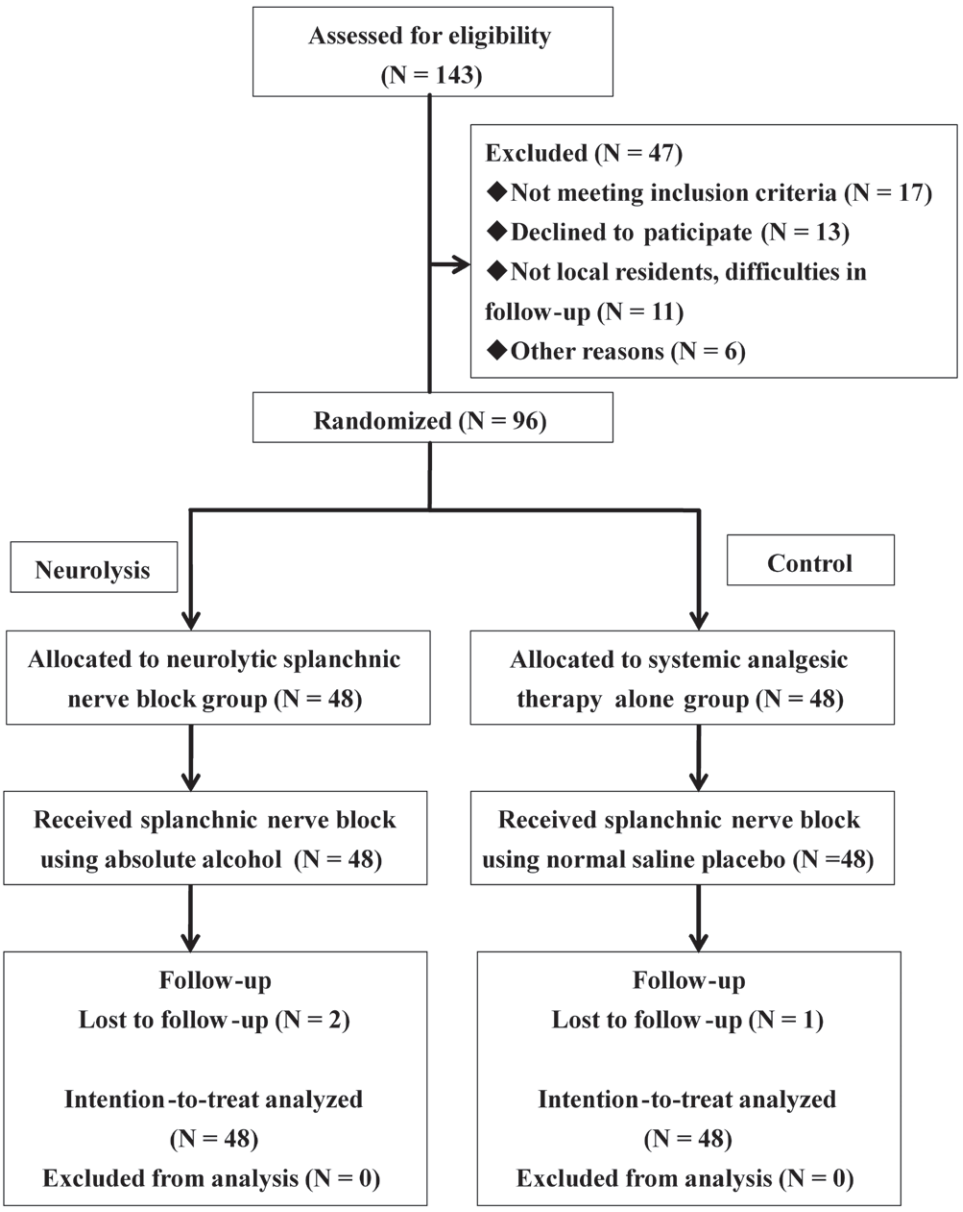

Fig. 1. Patient flow diagram. Time from randomization to study endpoint (8 months).

terms (standardized mean difference greater than 0.1 at the baseline visit), including tumor node metastasis stage, location of pain, and their interaction terms with group. We found no statistically significant main effect and interaction effect with group for location of pain (all corresponding $P > 0.05$). We found a statistically significant main effect of stage ($P = 0.012$) when we included it in a confounder model and a potential interaction effect of clinical stage with group ($P = 0.088$) in a subsequent interaction model. We conducted a subsequent subgroup analysis to explore the between-study-group difference in survival by clinical stage. We found a statistically significant reduction in survival in the neurolysis group compared with the control group for stage IV patients (hazard ratio, 1.94 [95% CI, 1.29 to 2.93]; $P = 0.001$) but no difference for stage III patients (hazard ratio, 1.08 [95% CI, 0.59 to 1.97]; $P = 0.809$). The median survival times for patients with stage III disease were 197.0 and 169.0 days for the neurolysis and control groups, respectively. For patients with stage IV disease, the median survival times were 69.0 and 146.0 days for the neurolysis and control groups, respectively. Multivariable Cox regression model–adjusted survival curves by different stages are presented in figure 4. Proportional hazard assumptions were met for all Cox models.

Table 1. Descriptive Statistics of Participants' Demographic Characteristics

Characteristic	Systemic Analgesic Therapy Alone n = 48	Neurolytic Splanchnic Nerve Block n = 48	Standardized Mean Difference*
Age, yr	60.2 ± 10.8	61.2 ± 11.5	0.090
Sex (%)			0.084
Male	28 (58)	26 (54)	
Female	20 (42)	22 (46)	
Body mass index (median [interquartile range]), kg/m^2	19.7 [18.3, 22.2]	19.10 [17.6, 22.1]	0.081
Stage (%)			0.132
III	15 (31)	18 (38)	
IV	33 (69)	30 (62)	
Tumor location (%)			0.042
Body or tail	27 (56)	28 (58)	
Head	21 (44)	20 (42)	
Location of pain (%)			0.102
Abdominal pain	13 (27)	11 (23)	
Back pain	7 (15)	8 (17)	
Both	28 (58)	29 (60)	
Metastasis in stage IV disease (%)			< 0.001
Liver	17 (52)	14 (47)	
Bone	6 (18)	8 (27)	
Pelvic organs	3 (9)	1 (3)	
Lung	2 (6)	3 (10)	
Other	5 (15)	4 (13)	
Total	33 (100)	30 (100)	
Center (%)			< 0.001
The First Affiliated Hospital of China Medical University	22 (46)	22 (46)	
Anshan	14 (29)	14 (29)	
Chaoyang	5 (11)	5 (11)	
Shenyang	4 (8)	4 (8)	
Fuxin	3 (6)	3 (6)	

Data are presented as the mean ± SD or n (%), unless otherwise indicated.

*Standardized mean difference > 0.1 was considered to indicate a statistically significant difference.

Anshan, The Third Hospital of Anshan; Chaoyang, Chaoyang Second People's Hospital; Fuxin, The Central Hospital of Fuxin City; Shenyang, The General Hospital of Shenyang Military Region.

Opioid Consumption

Descriptive statistics regarding opioid consumption (daily oral dose of the morphine equivalent measured in milligrams) are reported in table 2. The preexisting opioid consumption was significantly decreased in the first 3 months compared with its baseline in the neurolysis group (mean difference, 54.8 [95% CI, 29.9 to 79.7]; $P < 0.001$; mean difference, 45.3 [95% CI, 18.5 to 72.1]; $P < 0.001$; mean difference, 22.3 [95% CI, 4.2 to 40.4]; $P = 0.016$ at the first, second, and third months, respectively). We found statistically significant differences in opioid consumption between the two study groups ($P < 0.001$), by time ($P < 0.001$) and the interaction term of group by time point was also statistically significant (both likelihood ratio test and interaction $P < 0.001$). We found that the reduction effect of opioid consumption with neurolysis lasted and slowly declined until the sixth month (mean difference, 33.2 [95% CI, 3.0 to 63.4]; adjusted $P = 0.136$; largest at the first month visit, 95.8 [95% CI, 67.4 to 124.1]; adjusted $P < 0.001$) compared with the control. This result was similar to our sensitivity analyses using imputed data (largest mean difference at month 1, 95.1 [95% CI, 76.1 to 114.1]; and minimal at month 8, 60.5 [95% CI, 41.5 to 79.5]; all $P < 0.001$), and patients' survival status and clinical stage did not bias our inferences of exposure–outcome relationship (likelihood ratio test $P = 0.796$ and $P = 0.098$).

Quality of Life

Descriptive statistics of the physical component summary and mental component summary scores are reported in table 2. The multivariable linear mixed effects model indicated that there were statistically significant differences in the physical component summary scores between the two study groups ($P = 0.003$), by time ($P = 0.001$), and the interaction term of group and time was also statistically significant (likelihood ratio test $P = 0.029$ and interaction $P = 0.031$). We conducted *post hoc* pairwise

Table 2. VAS, Daily Oral Dose of Morphine Equivalent, and Quality of Life

Visit	Neurolytic Splanchnic Nerve Block (Neurolysis) (n = 48)		Systemic Analgesic Therapy Alone (Control) (n = 48)		Difference between Groups, Mean (95% CI) Control – Neurolysis	*P* Value	Adjusted *P* Value
	n (%)	Mean ± SD	n (%)	Mean ± SD			
VAS							
Baseline	48 (100)	6.7 ± 1.3	48 (100)	6.7 ± 1.2			
Month 1	40 (83)	2.8 ± 1.2	45 (94)	3.5 ± 1.0	0.7 (0.3 to 1.0)	< 0.001*	< 0.001*
Month 2	32 (67)	2.9 ± 0.7	39 (81	3.4 ± 0.9	0.6 (0.3 to 0.8)	< 0.001*	< 0.001*
Month 3	25 (52)	3.0 ± 0.6	33 (69)	3.4 ± 0.8	0.5 (0.2 to 0.7)	0.002*	0.016*
Month 4	22 (46)	3.1 ± 0.8	29 (60)	3.4 ± 0.8	0.4 (0.1 to 0.6)	0.015*	0.120
Month 5	20 (42)	3.2 ± 0.8	24 (50)	3.4 ± 0.9	0.3 (–0.1 to 0.6)	0.103	0.824
Month 6	15 (31)	3.3 ± 0.8	20 (42)	3.4 ± 0.9	0.2 (–0.2 to 0.5)	0.366	> 0.999
Month 7	10 (21)	3.3 ± 0.8	17 (35)	3.5 ± 0.9	0.1 (–0.3 to 0.5)	0.757	> 0.999
Month 8	7 (15)	3.3 ± 0.5	15 (31)	3.5 ± 0.9	0.0 (–0.5 to 0.4)	0.878	> 0.999
Daily oral dose of morphine equivalent, mg							
Baseline	48 (100)	127.1 ± 49.4	48 (100)	126.6 ± 44.8			
Month 1	40 (83)	71.0 ± 63.5	45 (94)	162.3 ± 50.5	95.8 (67.4 to 124.1)	< 0.001*	< 0.001*
Month 2	32 (67)	76.4 ± 41.0	39 (81	171.0 ± 54.9	83.3 (55.8 to 110.8)	< 0.001*	< 0.001*
Month 3	25 (52)	97.4 ± 47.2	33 (69)	180.5 ± 59.4	70.8 (43.5 to 98.0)	< 0.001*	< 0.001*
Month 4	22 (46)	123.6 ± 39.7	29 (60)	192.6 ± 54.3	58.2 (30.6 to 85.9)	< 0.001*	< 0.001*
Month 5	20 (42)	146.5 ± 32.6	24 (50)	197.7 ± 55.8	45.7 (17.1 to 74.4)	< 0.001*	< 0.001*
Month 6	15 (31)	165.0 ± 39.0	20 (42)	206.2 ± 48.3	33.2 (3.0 to 63.4)	0.017*	0.136
Month 7	10 (21)	174.5 ± 43.4	17 (35)	212.4 ± 50.6	20.7 (–11.6 to 53.0)	0.671	> 0.999
Month 8	7 (15)	186.4 ± 56.8	15 (31)	216.7 ± 53.8	8.2 (–26.6 to 42.9)	> 0.999	> 0.999
Physical component summary†							
Baseline	48 (100)	26.7 ± 16.7	48 (100)	26.2 ± 16.2			
Month 1	40 (83)	36.0 ± 12.8	45 (94)	29.7 ± 14.8	–5.7 (–9.6 to –1.9)	0.004*	0.032*
Month 2	32 (67)	34.0 ± 11.1	39 (81	28.6 ± 11.8	–4.7 (–8.2 to –1.2)	0.008*	0.064
Month 3	25 (52)	31.4 ± 7.8	33 (69)	28.0 ± 11.0	–3.7 (–7.1 to –0.4)	0.030*	0.240
Month 4	22 (46)	30.7 ± 9.1	29 (60)	28.0 ± 14.5	–2.7 (–6.2 to 0.7)	0.122	0.976
Month 5	20 (42)	29.7 ± 9.1	24 (50)	28.8 ± 11.9	–1.7 (–5.5 to 2.1)	0.371	> 0.999
Month 6	15 (31)	27.7 ± 9.2	20 (42)	28.9 ± 12.6	–0.7 (–5.0 to 3.6)	0.745	> 0.999
Month 7	10 (21)	28.4 ± 8.3	17 (35)	27.6 ± 12.9	0.3 (–4.6 to 5.2)	0.903	> 0.999
Month 8	7 (15)	28.0 ± 9.0	15 (31)	26.8 ± 13.2	1.3 (–4.3 to 6.9)	0.646	> 0.999
Mental component summary†							
Baseline	48 (100)	30.9 ± 16.1	48 (100)	30.5 ± 17.1			
Month 1	40 (83)	32.6 ± 13.3	45 (94)	30.9 ± 14.5	–1.0 (–6.5 to 4.5)	> 0.999	> 0.999
Month 2	32 (67)	31.2 ± 9.2	39 (81	29.2 ± 11.5	–0.8 (–5.4 to 3.6)	> 0.999	> 0.999
Month 3	25 (52)	29.7 ± 7.9	33 (69)	28.7 ± 10.5	–0.5 (–4.9 to 3.6)	> 0.999	> 0.999
Month 4	22 (46)	28.7 ± 8.2	29 (60)	27.7 ± 14.3	–0.3 (–3.9 to 4.4)	> 0.999	> 0.999
Month 5	20 (42)	28.2 ± 9.1	24 (50)	27.9 ± 12.2	–0.1 (–4.0 to 5.1)	> 0.999	> 0.999
Month 6	15 (31)	27.1 ± 8.6	20 (42)	27.0 ± 11.3	0.1 (–4.5 to 6.3)	> 0.999	> 0.999
Month 7	10 (21)	26.8 ± 7.0	17 (35)	25.5 ± 11.6	0.2 (–4.7 to 8.1)	> 0.999	> 0.999
Month 8	7 (15)	27.6 ± 6.0	15 (31)	24.7 ± 12.3	0.4 (–5.8 to 8.4)	> 0.999	> 0.999

Data are presented as the mean ± SD or n (%), unless otherwise indicated. VAS scores range from 0 to 10, with higher scores indicating worse pain. The level of opioid consumption at each follow-up visit was translated into the daily oral dose of morphine equivalent for analysis. Patient quality of life was evaluated with the 36-item version of the Short Form Health Survey, which is comprised of two components: a physical component summary and mental component summary.

*$P < 0.05$ was considered to indicate a statistically significant difference. †Score range: 0 to 100. Higher scores represent better quality of life, and a score less than 50 indicates the below-average status.

VAS, visual analogue scale.

comparisons, and the results showed that the effect size of physical component summary score improvement in neurolysis compared with that in the control group was small and only statistically significant for the first month (mean difference, 5.7 [95% CI, 1.9 to 9.6]; adjusted $P = 0.032$ for the first month; largest at the first month visit and declined by time). We did not find a statistically significant difference in the mental component summary scores between the two groups (likelihood ratio test $P = 0.501$ and interaction $P = 0.506$). Patients' survival status and clinical stage did not bias our inferences of exposure–outcome relationship for physical component summary (likelihood ratio test $P = 0.380$ and $P = 0.059$) and mental component summary (likelihood ratio test $P = 0.376$ and $P = 0.185$).

Side Effects

There was no operative mortality or severe complication. In the neurolysis group, the most common complications related to the block were transient orthostatic hypotension

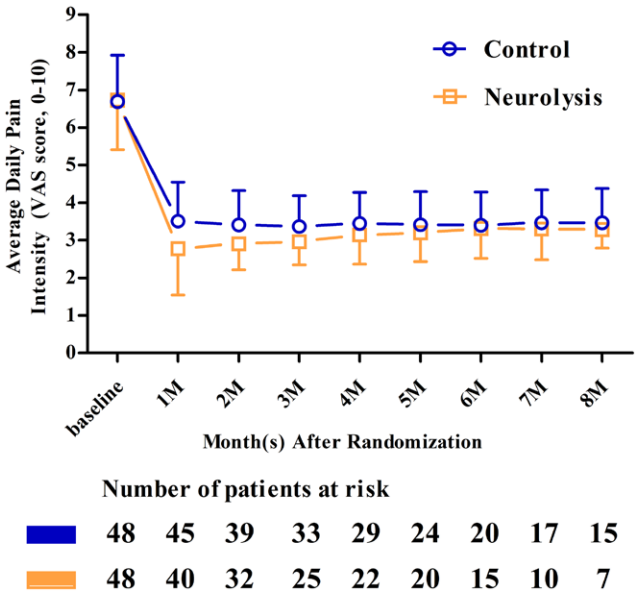

Fig. 2. Average pain intensity during the entire follow-up period. Pain intensity was assessed with visual analogue scale (VAS) scores. The pain reduction effect of neurolysis compared with the control was statistically significant for the first 3 months (largest at the first month visit; mean difference, 0.7 [95% CI, 0.3 to 1.0]; adjusted $P < 0.001$), and this treatment effect gradually declined to levels similar to those in the control group starting from the fourth month (mean difference, 0.4 [95% CI, 0.1 to 0.6]; adjusted $P = 0.120$). The VAS ranges from 0, no pain, to 10, the worst pain imaginable. *Error bars* indicate the SD.

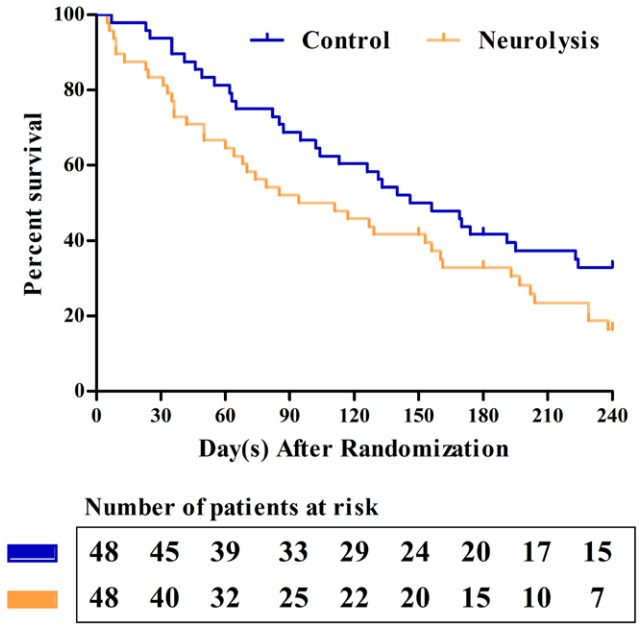

Fig. 3. Survival curves of patients from the time of randomization based on Kaplan–Meier estimates. There was a significant difference between the neurolysis (median survival = 102.5 days) and control groups (median survival = 151.0 days) based on the univariate Cox proportional hazards regression (hazard ratio, 1.56 [95% CI, 1.03 to 2.35]; $P = 0.036$, clustered by research center). This figure shows the Kaplan–Meier survival curves and cumulative risk tables.

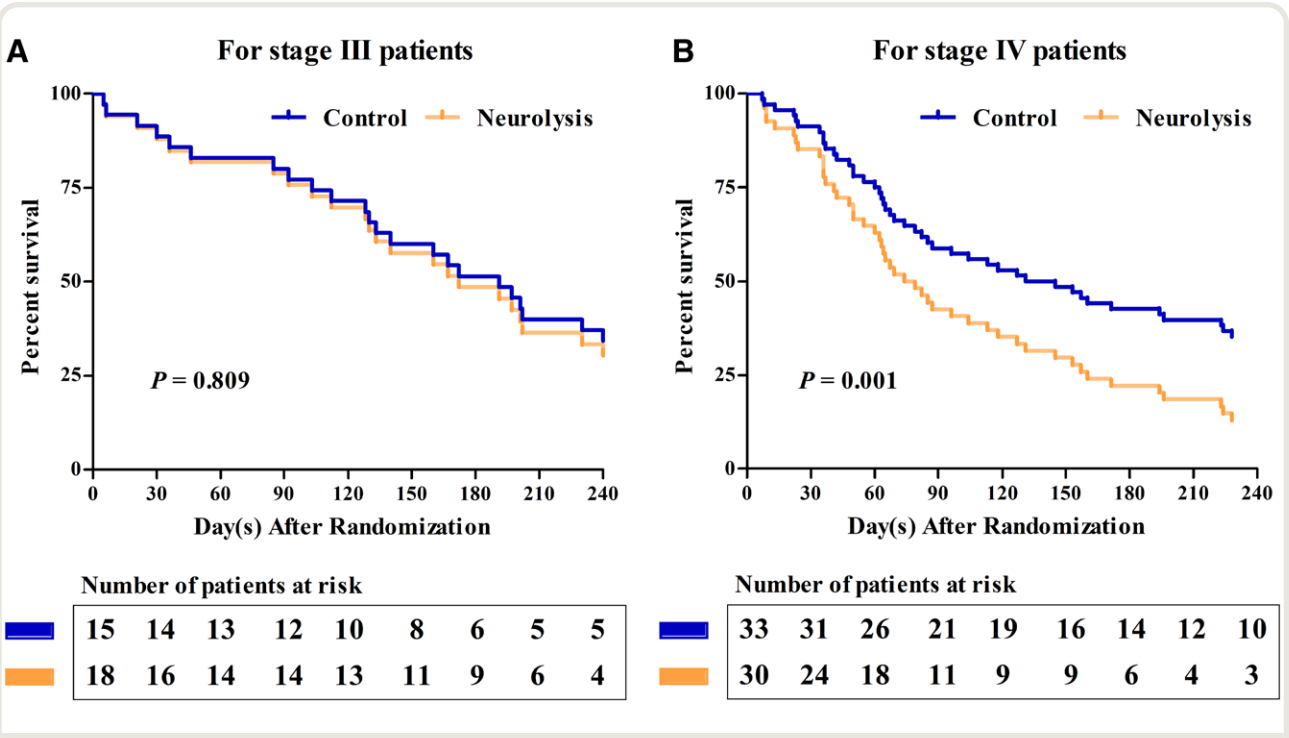

Fig. 4. Multivariable Cox regression model with survival curves adjusted for cancer stage. Survival data calculated based on the tumor node metastasis staging system for stage III (*A*) and stage IV (*B*). There was a statistically significant reduction in survival in the neurolysis group compared with the control group for stage IV patients (hazard ratio, 1.94 [95% CI, 1.29 to 2.93]; $P = 0.001$), but there was no difference for stage III patients (hazard ratio, 1.08 [95% CI, 0.59 to 1.97]; $P = 0.809$). The median survival times for patients with stage III disease were 197.0 and 169.0 days for the neurolysis and control groups, respectively. For patients with stage IV disease, the median survival times were 69.0 and 146.0 days for the neurolysis and control groups, respectively.

(29 of 48, 60.4%), lethargy (27 of 48, 56.3%), exhaustion (25 of 48, 52.1%), transient diarrhea (1 to 3 days, 14 of 48, 29.2%), prolonged orthostatic hypotension (more than 3 days, 6 of 48, 12.5%), diarrhea (more than 3 days, 5 of 48, 10.4%), and numbness in the front of the thigh (2 of 48, 4.2%). The most common adverse reactions in all patients treated with narcotics were nausea, vomiting, inappetence, constipation, and sedation. The incidence of constipation was significantly lower in the neurolysis group than in the control group in the first 2 months ($P = 0.004$ and 0.020 at the first and second months, respectively). There were no significant differences between the two study groups with regard to nausea, vomiting, or inappetence.

Discussion

The results of this trial demonstrated that neurolytic splanchnic nerve block significantly improves pain relief and reduces quick dose escalation of opioids in patients with unresectable pancreatic cancer compared with systemic analgesic therapy alone. Moreover, neurolysis did not improve quality of life but could result in stage-specific survival discrimination and shorten survival among late-stage patients.

Both groups of patients treated with neurolysis or systemic analgesic therapy alone had a reduction in pain intensity, which was similar to previous findings,[9,10,13,18] while neurolysis generated a quicker pain reduction at the beginning of treatment (for the first 2 months in this study). This quick pain relief effect declined quickly to similar levels in the control group starting from the third month, which indicated that our block technique was effective. Opioid therapy was implemented in both groups. Many previous studies[10,13,19,20] have confirmed that reduced amounts of analgesics result from neurolysis, and our clinical results are consistent with these results. From our data, the analgesic benefit of neurolysis over systemic analgesic therapy alone lasted for almost the whole follow-up period. However, some trials[11,21] failed to detect the effect of a reduction in opioid consumption. Our interpretation was that neurolysis was an efficacious alternative option that may play a crucial role in patients with moderate to severe pain conditions. Based on our study, opioid doses required for satisfactory pain relief in patients with pancreatic cancer–related pain were extremely variable. Opioids are frequently required even in patients who undergo neurolysis procedures.

Although most previous studies advocated that neurolysis prolonged survival, or at least had no impact on it,[11,21,22]

our study showed that neurolysis could shorten survival among patients with late-stage disease. Similarly, in a retrospective study by Fujii-Lau *et al.*,[14] neurolysis was found to result in a shortened survival time, especially among patients with advanced disease. Previous data have shown that in contrast to patients in advanced disease stages, patients in early disease stages (stages I and II) who undergo neurolysis seem to have prolonged survival compared with those receiving pharmacologic therapy.[11,23] Moreover, a double-blind, randomized, placebo-controlled study from Staats *et al.*[21] confirmed that neurolysis could prolong life expectancy, even among patients with unresectable pancreatic cancer. Based on the controversial views mentioned above, there are insufficient clinical data to support the theory that neurolysis has different effects on patient survival at different stages of pancreatic cancer. However, regarding the clinical effects on quality of life based on stage, a study by Crippa *et al.*[24] demonstrated that surgical and/or medical interventions can provide improvements in quality of life for patients with early-stage pancreatic cancer, while for patients with advanced disease, quality of life decreases at follow-up. Unfortunately, their data could not determine the impact on survival based on stage.

In current clinical practice, neurolysis is often used as salvage therapy when pain control is inadequate with analgesics.[25,26] A prospective study conducted by de Oliveira *et al.*[20] suggested that neurolysis should be considered earlier for the management of cancer pain. The results from several reports[11,27,28] also demonstrated that early neurolysis may have advantages over late use. With the development of endoscopic ultrasonography, endoscopic ultrasound-guided celiac neurolysis, which makes early neurolysis possible, has gained popularity as a minimally invasive approach and is currently widely used to manage pancreatic cancer–related pain.[29,30] Recent data collected by Wyse *et al.*[29,31] suggested that the earlier neurolysis is performed, such as at the time of diagnosis, the more the patient will benefit from it, and they advocated early neurolysis performed at disease diagnosis rather than late use as a final resort. Currently, it is still difficult to clarify the impact of neurolysis on life expectancy for several reasons. First, effective pain control resulting from neurolysis is associated with changes in mood, functional ability, and stress, all of which affect survival.[32] Another factor related to neurolysis that is associated with survival is the dosage of opioid medications, which may directly or indirectly affect tumor growth.[33] Previous studies reporting the effect of opioids on tumor growth have presented some controversies regarding whether morphine may either promote or inhibit tumor growth, and the impacts of opioids on the invasiveness and metastasis of tumors are conflicting.[34] Furthermore, the relationship between immunity and survival is also worth studying. Patients will obtain pain relief and need decreased amounts of analgesics after neurolysis. Both changes may result in improved immune function, which could contribute to improved life expectancy.[35–37] Importantly, the decreased sympathetic excitability resulting from neurolysis may also affect survival. The sensation of pain arising from upper abdominal organs involves the celiac plexus.[38] The splanchnic nerve (issued from the thoracic sympathetic nerve), which is an integral part of the celiac plexus, is considered to be the crucial factor in pancreatic cancer pain.[39] When neurolysis is conducted, ablation of the celiac plexus, especially of the thoracic sympathetic nerve, results in sympathetic disorders and unopposed parasympathetic activity.[14] Thus, we believe that disturbances in the autonomic nervous system play a major role in the impact of neurolysis on survival. In this study, more than half of the patients in the neurolysis group experienced lethargy (27 of 48, 56.3%) or exhaustion (25 of 48, 52.1%). We hypothesized that these phenomena resulting from the procedure could be explained by decreased sympathetic excitability, which may accelerate death. However, this hypothesis cannot explain the different mortality rates according to tumor node metastasis stages. Although many studies have focused on the impact of the autonomic nervous system on heart failure[40,41] and stroke,[42,43] limited data can be found to elucidate the relationship between life expectancy and sympathetic disorders of the visceral nerve. Based on current evidence, it is difficult to address whether neurolysis provides a prolonged life expectancy among patients with early-stage pancreatic cancer or if it shortens survival among patients with advanced disease. It is equally difficult to elucidate how neurolysis can affect survival.

Although our study showed that neurolysis resulted in stage-specific survival discrimination, this current investigation was originally designed to provide 90% power to detect a difference in VAS, not in survival. The sample size for the analysis of subgroup survival may not provide adequate statistical power to make definitive conclusions that may still be clinically relevant. Our study was not powered *a priori* for subgroup analyses of survival by different clinical stages; hence, the nonsignificant findings for stage III patients can be due to lack of study power. Additionally, potential selection biases due to patients' death during the observation period may have emerged to confound our inferential results, but the direction is likely to be toward null. This is because end-stage cancer patients with higher mortality generally would require more opioids, suffer from more severe pain, and report lower physical scores. More clinical trials are needed to verify these findings and clarify the relationship between neurolysis and survival.

In summary, we found that neurolytic splanchnic nerve block improved pain relief and reduced quick dose escalation of opioids compared with the placebo control in patients with unresectable pancreatic cancer. Neurolysis resulted in stage-specific survival discrimination and could shorten the survival of patients, especially in those with stage IV disease. Neurolysis did not improve quality of life. Even based on the *post hoc* exploratory subgroup analysis,

the role of neurolysis should be carefully reconsidered for all late-stage patients, especially for stage IV patients. Rather than its late use as a final resort, neurolysis should be recommended early, such as at the time of pancreatic cancer diagnosis. Neurolysis appears to be less risky when performed on patients with stage III disease, but further studies should be conducted regarding its survival impact and clinical utility. Patients with stage IV pancreatic cancer and their relatives should be fully informed before the neurolysis procedure is conducted. Consequently, we expect our findings to have considerable implications for clinical practice.

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Competing Interests

The authors declare no competing interests.

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Correspondence

Address correspondence to Dr. Song: Department of Pain Medicine, The First Affiliated Hospital of China Medical University, No. 155 Nanjing North Street, Shenyang, 110001, China. tao_song0608@163.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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