Retrospective Study

Impact of Celiac Plexus Neurolysis on Survival in Patients with Unresectable Pancreatic Cancer: A Retrospective, Propensity Score Matching Analysis

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 05-20-2016
Revised manuscript received: 08-01-2016
Accepted for publication: 09-16-2016

Free full manuscript: www.painphysicianjournal.com

Background: Pain caused by pancreatic cancer (PC) is difficult to control. Celiac plexus neurolysis (CPN) can effectively control the pain and reduce the use of opioids. However, the effect of CPN on survival for patients with unresectable PC remains controversial.

Objectives: To determine if CPN is associated with survival benefits for these patients.

Study Design: Retrospective, observational cohort study.

Setting: National Cancer Center in Korea.

Methods: The CPN group included patients who were diagnosed with unresectable PC and underwent fluoroscopically guided bilateral CPN (10 mL dehydrated alcohol each side) once between January 1, 2006, and December 31, 2013. Patients with PC who did not undergo CPN were in the control group; for the final control group, 1:1 propensity score (PS) matching was conducted with the CPN group. The main outcome was median survival (PC diagnosis to death) after PS matching, assessed using Kaplan-Meier curves.

Results: For the primary overall survival analysis, the CPN and control groups included 110 and 258 patients, respectively. The median survival period was not significantly different between the CPN and control groups (278 vs. 203 days, $P = 0.246$), even after PS matching (278 vs. 180 days, $P = 0.127$), or based on time to CPN from diagnosis (≤ 6 vs. > 6 months; 255 vs. 310 days, $P = 0.147$).

Limitations: Retrospective design, small sample size, and inconsistent timing of CPN after the diagnosis date.

Conclusion: CPN did not affect survival for patients with unresectable PC. Considering the limitations of the retrospective design, a well-designed prospective design study should be conducted.

Key words: Celiac plexus, pancreatic neoplasms, survival, neurolysis, pain, propensity score matching, opioids, cancer

-EPain Physician 2017; 20:E357-E365

Pancreatic cancer (PC) is the fourth cancer-related cause of mortality in the US (1). Despite progress in the detection and management of PC, the 5-year survival rate from diagnosis is only 5%, and 80 – 85% of all patients with PC are already unresectable at the time of diagnosis (2). Therefore, the treatment options for 80 – 85% of patients with PC are limited and primarily focused on pain management. For pain

control, physicians usually follow the recommendation of the World Health Organization and use nonsteroidal agents, acetaminophen, or even strong opioids (3). However, this guideline alone has been not sufficient to effectively control the pain, and 55% of patients reportedly complain of insufficient pain control (4). Because opioids also cause various side effects (5), pain control using other modalities is required.

Celiac plexus neurolysis (CPN) is a procedure that is often used to control PC-related pain, opioid requirements, and opioid-related side effects (6-8). While studies have shown positive effects of CPN for pain control in patients with PC, the effect on survival remains controversial. Although a randomized controlled trial found greater survival benefits for a group of patients with pre-existing pain who underwent CPN compared with a control group (9), another randomized controlled trial showed no difference in survival between an experimental group that underwent CPN and a control group that underwent a sham procedure (10). However, these studies were limited by insufficient sample sizes to evaluate survival benefits and the presence of confounding factors because the primary outcome was not survival. Recently, a retrospective study that investigated the impact of CPN on survival as the primary outcome for patients with unresectable PC reported that CPN predicted shorter survival (11). However, the methodological limitations prompted the authors to state that further study was required.

Therefore, we hypothesized that CPN could prolong survival and aimed to determine the effect of CPN on survival in patients with unresectable PC.

Methods

Study Design

This retrospective cohort study was approved by the Institutional Review Board (NCC2015-0251) of the National Cancer Center in Korea. Electronic medical records of patients who were diagnosed with unresectable PC in the National Cancer Center in Korea between January 1, 2006, and December 31, 2013, were reviewed by medical staff with no vested interest in the study. All of the authors who participated in the study were blinded to the data before the statistical analyses were conducted. The medical record technician who extracted the medical records, medical staff who collected the medical records, and the statistician who analyzed the data had no vested interest in the study.

Patient Selection

The CPN group consisted of patients older than 18 years diagnosed with PC based on biopsy, radiologic findings, or clinical course and underwent alcohol-based CPN only once. Patients who underwent a pancreatectomy; had a non-adenocarcinoma cancer type which has a different clinical course and prognosis; underwent CPN more than once; or lacked medical records were excluded. In addition, to reduce immortal time bias, patients who had already been diagnosed with PC in other hospitals were excluded.

The control group consisted of randomly selected patients older than 18 years diagnosed with unresectable PC who had not undergone CPN. The control group included twice as many patients as the CPN group. The random selection was conducted by a medical record technician who was blinded to the purpose of the study. To account for patient differences in cancer and treatment characteristic between the CPN and control groups, 1 to 1 propensity score (PS) matching of the control group to the CPN group was conducted.

Clinical and Survival Data

The following patient characteristics at the time of PC diagnosis in the National Cancer Center were collected from the records: age, gender, body mass index, presence of pain, and opioid use. Cancer characteristics included the site of cancer involvement, stage grouping, tumor TNM stage, and lymph node status. Stage grouping and TNM staging were classified using the American Joint Committee on Cancer, 7th edition, pancreatic cancer staging (12). Treatments of interest, recorded in the medical records as conducted after the PC diagnosis, were chemotherapy, radiotherapy, and palliative surgery. To assess the effect of CPN in the CPN group, the morphine equivalent daily dose (MEDD) was calculated, and pain was rated on a numeric rating scale (NRS) before CPN and one week after CPN.

The survival period was determined as the period between the dates of diagnosis, as confirmed by the center, to the dates of death, based on data from the National Cancer Database of Korea for exact dates of death, including those for out-of-hospital deaths.

The primary outcome was overall survival, compared between the CPN and control groups after PS matching, which was conducted to reduce selection bias. The secondary outcome was overall survival in the CPN group, considering the effect of earlier CPN and therefore compared between $\leq$ 6 months from diagnosis to CPN and > 6 months from diagnosis to CPN.

Celiac Plexus Neurolysis

From January 1, 2006, to December 31, 2013, all CPNs were guided by fluoroscopy and conducted bilaterally by one anaesthesiologist, who was also the principal investigator. All patients were moved to an operating room for CPN, and oxyhaemoglobin, blood pressure, and electrocardiogram were monitored. An intact intravenous fluid line was pre-operatively secured. The patients were in a prone position for sterile disinfection with povidone-iodine (betadine) and draping with a sterile surgical drape. The L1 vertebral body was confirmed with fluoroscopic guidance; the C-arm was rotated 40 degrees from side to side, and the tunnel view was used to determine a 5 – 7 cm lateral entry point at the midline of the L1 vertebral body. The skin was infiltrated with 1% lidocaine, and a 22-gauge Chiba needle (Hakko Co Ltd, Tokyo, Japan) was inserted. The position of the Chiba needle was verified through the fluoroscopic lateral view, and contrast dye (Omnipaque 300; GE Healthcare, Princeton, NJ) was injected. After confirming a linear spread of the contrast dye following the anterior L1 vertebral body, without intravascular, intrathecal, intramuscular, or intradiscal spread, 5 mL of 1.5% lidocaine was injected (Fig. 1). After waiting 15 minutes, pain reduction without neurological adverse events was verified, and 10 mL of sterile dehydrated alcohol was slowly injected. A total 20 mL of neurolytic volume was injected, with 10 mL in each side.

Statistical Analysis

Continuous variables are summarized as mean (standard deviation) or median (25th – 75th interquartile range). Categorical variables are summarized using frequency (%). To compare the characteristics between groups, the Student t-test or Wilcoxon rank sum test was used for continuous variables, and Pearson's chi-squared analysis was used for categorical variables. To reduce the bias, a propensity-based matching approach was used to compare CPN (13). The concept of PS matching is based on counterfactual matching. The PS is defined as the conditional probability of being treated, given the covariates, and can be used to balance the covariates in the 2 groups (treatment and control) to reduce bias. The matching can be conducted

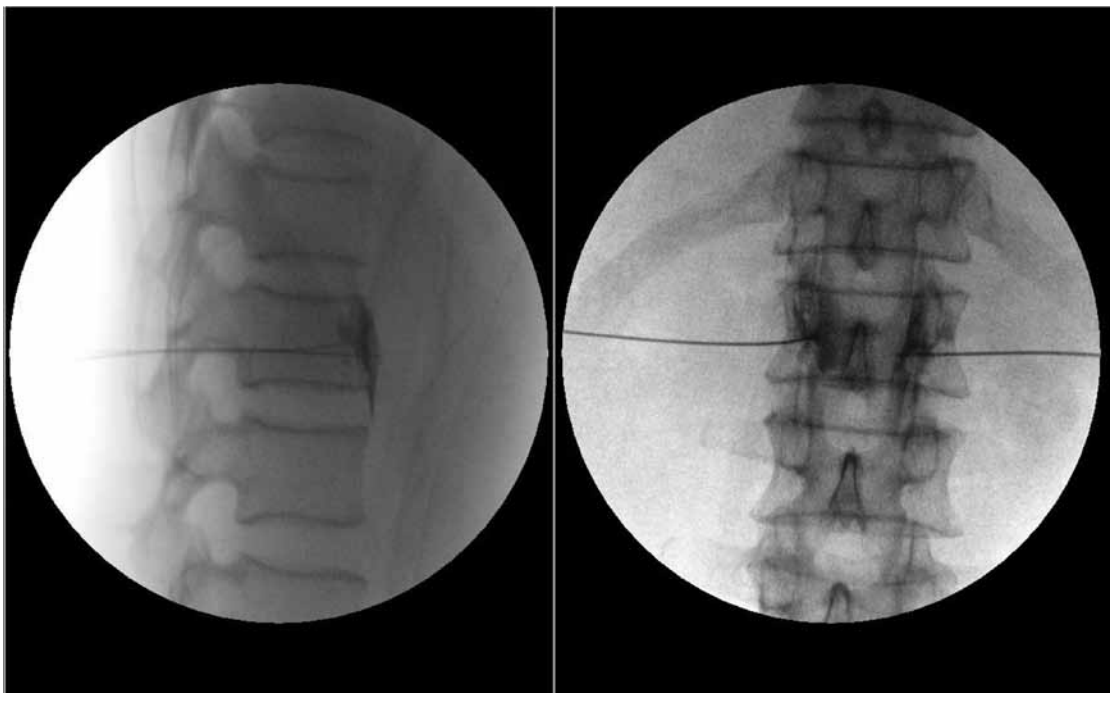


Fig. 1. *(a) Fluoroscopic lateral view of a linear spread of the contrast agent following the anterior L1 vertebral body. (b) Fluoroscopic anterior-posterior view of a linear spread of the contrast agent following the anterior L1 vertebral body.*

Table 1. *Reasons for excluding patients with pancreatic cancer from the analysis.*

Reason for exclusion	CPN group	Control group
Non-adenocarcinoma tumor type	5	2
Multiple CPNs	4	0
Incomplete medical records	7	5
Previous diagnosis in another hospital	8	5
CPN technical failure	1	0
Total	25	12

CPN, celiac plexus neurolysis

Table 2. *Diagnostic techniques for pancreatic cancer.*

Diagnostic Modality	
EUS-guided FNA	29.1%
Pancreatic mass	27.1%
Metastatic site (e.g., liver, lymph node)	2%)
Percutaneous biopsy	35%
Pancreatic mass	11%
Metastatic site (e.g., liver, lymph node)	24%
Surgical biopsy	19%
Brushing biopsy during ERCP	9%
Radiographic and/or EUS imaging and clinical course consistent with pancreatic cancer	7.9%

EUS, endoscopic ultrasound; FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography

Table 3. *Morphine equivalent daily dose and pain scale before CPN and after CPN.*

	Pre-CPN		Post-CPN (1 week)		*P*-value
	Mean	SD	Mean	SD	
Morphine Equivalent Daily Dose (Oral Morphine, mg)	235.36	155.08	184.36	146.77	< 0.0001
Pain scale (NRS)	5.90	1.99	2.60	1.93	< 0.0001

CPN, celiac plexus neurolysis; NRS, numeric rating scale

from the predicted probability from logistic regression analysis [PS = Pr (Z = 1/X = x)]. Median survival was analyzed using Kaplan-Meier curves and compared using log-rank tests for statistical significance. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Among the patients who were diagnosed with unresectable PC between January 1, 2006, and December 31, 2013, 135 patients underwent CPN. After excluding 25 patients (Table 1), 110 patients were included in the analyses. Of the 270 patients who were initially identified for the control group, 12 were excluded (Table 1), resulting in 258 patients for the analyses. After PS matching with the CPN group, 110 patients were included in the final analyses.

The majority of patients were diagnosed using a percutaneous biopsy (35%; Table 2). Compared with before CPN, the MEDD (235.36 ± 155.08 mg to 184.36 ± 146.77 mg; $P < 0.0001$) and NRS decreased (5.90 ± 1.99 to 2.60 ± 1.93; $P < 0.0001$) one week after CPN (Table 3). Before PS matching, age ($P = 0.002$), opioid use ($P = 0.019$), site of involvement ($P = 0.04$), stage grouping ($P = 0.002$), TNM stage ($P = 0.003$), lymph node status ($P = 0.024$), chemotherapy ($P = 0.001$), and palliative surgery ($P = 0.001$) were significantly different between the groups at diagnosis (Table 4). After the PS matching, these differences were no longer significant (Table 4). There were no differences in patient, cancer, and treatment characteristics between the groups based on the duration from diagnosis to CPN (≤ 6 months vs. > 6 months; Table 5).

Survival Outcome

The median overall lengths of survival of the CPN and control groups before matching were 278 (95% CI, 228 – 327) and 203 (95% CI, 171 – 235) days, respectively ($P = 0.246$; Fig. 2). The difference in median overall length of survival between the CPN and control groups was not statistically significantly different after PS matching (278 [95% CI, 228 – 327] vs. 180 [95% CI, 137 – 222] days, $P = 0.127$; Fig. 3).

Median survival based on the duration from diagnosis to CPN was also not significantly different (≤ 6 months from diagnosis, 255 [95% CI, 198 – 312] days vs. > 6 months from diagnosis, 310 [95% CI, 218 – 402] days, $P = 0.147$; Fig. 4).

Discussion

Effective pain control for cancer patients is closely related with mood, functional ability, and stress, all of which affect survival (14). Our hypothesis was based on reports that better pain control, as part of early palliative care, prolonged survival for those who underwent

Table 4. *Baseline characteristics of patients with pancreatic cancer at diagnosis in the National Cancer Center in Korea, before and after propensity score matching for the controls.*

Variables		CPN (n = 110)	Controls (Pre-matched, n = 258)	*P*-value	Controls (Matched, n = 110)	*P*-value
Patient characteristics						
Age, years		65.7 (9.15)	69 (9.65)	0.002	67 (9.57)	0.441
Gender	Male	65.1	61.6	0.535	60.2	0.449
	Female	34.9	38.4		40.8	
BMI, kg/m^2		23 (3.12)	22.6 (3.12)	0.28	22.7 (3.3)	0.35
Presence of pain		86.8	82.2	0.28	87	0.903
Opioid use		77.4	64.7	0.019	74	0.461
Cancer characteristics						
Site of involvement	Head	40	37	0.04	41	0.595
	Neck	5	8		5	
	Body	16	12		21	
	Tail	33	35		23	
	2 sites	6	8		10	
Stage grouping	I	1.9	5.8	0.002	0.0	0.802
	II	15.1	20.5		25.0	
	III	33.0	15.9		36.2	
	IV	50.0	57.8		56.6	
TNM stage	0	0	0	0.003	0	0.244
	1	1.9	2.7		0	
	2	2.8	7.4		1	
	3	29.2	45.0		35	
	4	66.0	45.0		64	
Lymph node status, positive		64.2	51.2	0.024	62	0.907
Treatment Characteristics						
Chemotherapy		84.9	58.9	0.001	90.2	0.25
Radiation therapy		35.8	35.7	0.973	37	0.579
Palliative surgery		12.3	31.0	0.001	19	0.100

Values are reported as mean (standard deviation) or %.
CPN, celiac plexus neurolysis; BMI, body mass index

CPN, compared with those who did not (15). Also, opioid use would likely be lower in the CPN group, resulting in fewer side effects, less tumor growth, and lower likelihood of recurrence (16,17). In contrast, in the present study, there was no difference in survival between the CPN and control groups; however, owing to the retrospective nature, mood and quality of life (QOL) were not evaluated.

The present finding is also different from that of a previous retrospective study conducted with a large sample (11), which reported CPN as a predictor of shorter survival. However, as mentioned by the author, the limitations included statistically significant differences between the CPN and control groups in patient, cancer, and treatment characteristics, which can influence survival. Therefore, selection bias was highly likely. Moreover, both CPN and celiac ganglia neurolysis were performed by various operators using different techniques and injected neurolytic volumes. For the patients who were transferred to hospice care, the exact date of death was often unknown as part of the data collection. In addition, because many of the patients had al-

Table 5. *Baseline characteristics of patients with pancreatic cancer at diagnosis in the National Cancer Center in Korea, based on the length from diagnosis to celiac plexus neurolysis (CPN).*

		From diagnosis to CPN (n = 110)		*P*-value
		≤ 6 months (n = 55)	> 6 months (n = 55)	
Age (years)		66.7 (9.1)	65.7 (9.8)	0.573
Body weight (kg)		61.7 (10.1)	58.8 (9.7)	0.132
Height (cm)		162.2 (9.2)	161.8 (8.6)	0.821
Gender (Male/Female)		50.7/48.8	49.3/51.2	0.884
Presence of pain		51.6	48.4	0.405
Opioid use		52.9	47.1	0.255
Cancer characteristics				
Site of involvement	Head	55.8	44.2	0.777
	Neck	50.0	50.0	
	Body	41.2	58.8	
	Tail	50.0	50.0	
	2 sites	33.3	66.7	
Stage grouping	I	33.3	66.7	0.727
	II	41.2	58.8	
	III	55.6	44.4	
	IV	50.0	50.0	
TNM stage	I	50.0	50.0	0.718
	II	25.0	75.0	
	III	46.9	53.1	
	IV	52.8	47.2	
Treatment characteristics				
Chemotherapy		48.9	51.1	0.589
Radiation therapy		43.6	56.4	0.319
Palliative surgery		47.0	53.0	0.781

Values are reported as mean (standard deviation) or %.

ready been diagnosed with PC in another hospital, the survival period was determined from the presentation date, not the diagnosis date (11).

The present study has 4 advantages compared with this previous study. First, PS matching was used to prevent differences in patient, cancer, and treatment characteristics, which were present in the previous study, and the subsequent selection bias. PS matching reduces bias, which is a disadvantage of a retrospective cohort study (13,18). Second, operator-related confounding factors were minimized. CPN was conducted by many physicians using various techniques, over a long period of time, in the previous study (11). However, only one experienced pain physician who used the same techniques (fluoroscopic guidance, bilateral, 10 mL neurolytic volume for each side) was involved in the present study, which was conducted over a shorter period of time, minimizing potential confounding factors. Third, because the previous study involved a number of patients who were already diagnosed with PC, the ability to determine survival from the time of diagnosis was limited. In the present study, patients with suspected cancer at the primary health care center were transferred directly to the center and were therefore diagnosed with PC at the center. As a result, survival was determined from the time of diagnosis, without immortal bias. Last, the dates of death of all the patients were acquired from the National Cancer Database of Korea. Therefore, those who received hospice care in other hospitals or who died outside the hospital were also included, allowing accurate comparison analysis without missing patients.

There are 3 possible reasons for the lack of different survival outcomes between the 2 groups, despite the PS matching. First, the duration from diagnosis to CPN differed in each patient. Earlier, active palliative management that includes pain control for cancer patients has long been discussed for its effects on mood, QOL (19), and survival (15). There was no difference in overall survival between CPN performed within 6 months from diagnosis and CPN performed more than 6 months after diagnosis. Similarly, in the study by Wyse et al (20), CPN performed at diagnosis did not result in better survival, but was beneficial for pain outcomes at one month and 3 months after diagnosis.

Second, the sample size, with a significance set at $P < 0.05$, limited the ability to detect significant clinical efficacy (e.g., survival) with CPN, because PC has a very poor prognosis. Although proper pain control temporarily improves the performance status of patients with PC, CPN does not necessarily lead to better survival outcomes. Prospective studies have also failed to demonstrate the benefits of CPN in terms of QOL and survival, although they showed a benefit of CPN for pain outcomes (10,20).

Third, another study reported median survival of 8.5 months for patients with PC (21); therefore, if CPN is conducted after diagnosis, it might already be too late to realize a survival benefit. In addition, severe pain in the abdomen and back, which is a major reason for CPN, is an independent factor of poor prognosis and shortened survival (22). Considering these 3 reasons, a prospective study with a large sample size is needed,

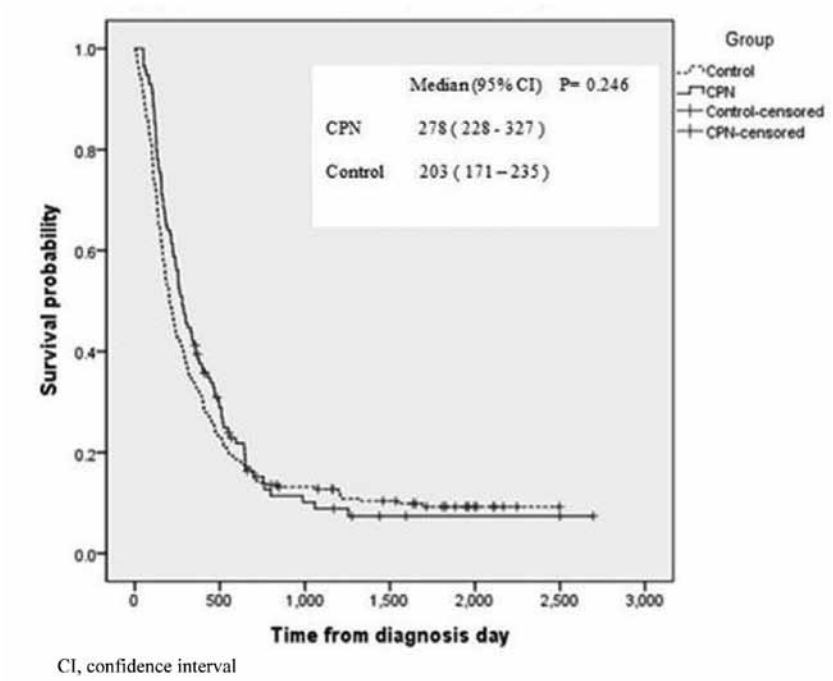
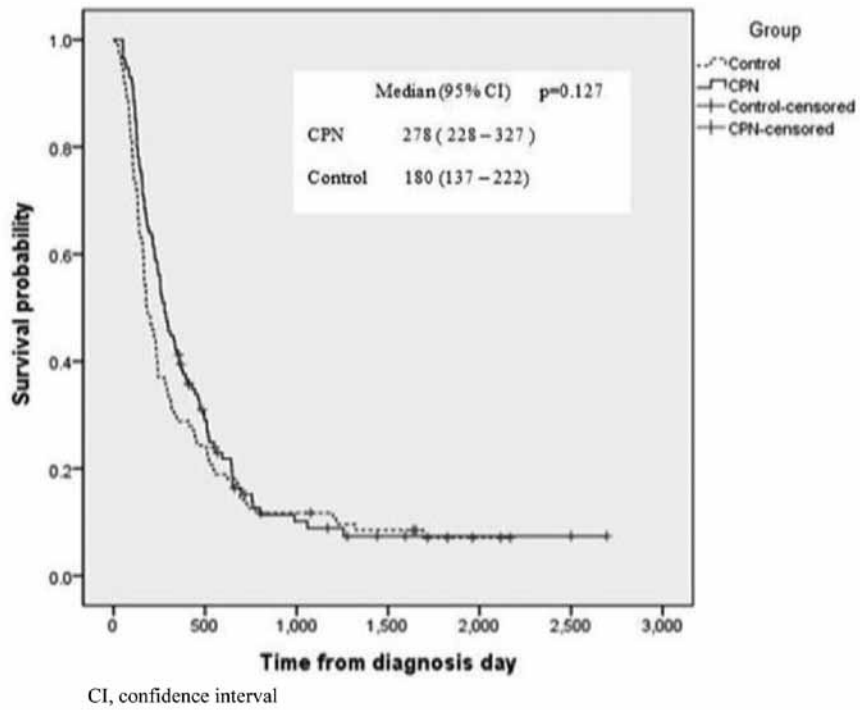


Fig. 2. *Overall survival before propensity score matching of control patients with pancreatic cancer with patients with pancreatic cancer who underwent celiac plexus neurolysis (CPN).*



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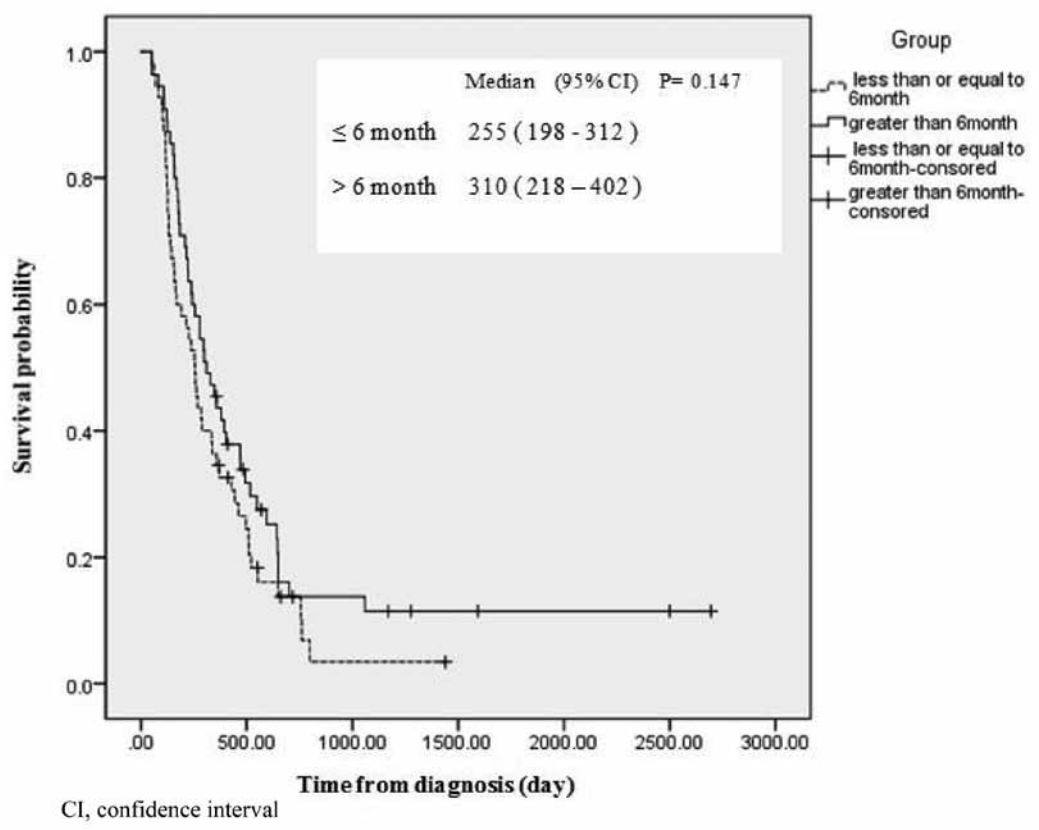

Fig. 4. *Overall survival of patients with pancreatic cancer who underwent celiac plexus neurolysis (CPN) (≤ 6 months from diagnosis vs. > 6 months from diagnosis).*

in which CPN is conducted at an early stage and the results are compared with those from a control group.

There are some limitations in the present study. First, the pain score and performance status were hard to determine owing to the retrospective cohort design. In addition, 12 patients were excluded because of insufficient medical records. Second, because the actual timing of CPN after the diagnosis date was not consistent for each patient, it was impossible to demonstrate a causative relationship between CPN and survival. Despite these limitations, this study is the first, to our knowledge, to use a PS matching approach to evaluate the effect of CPN on survival. Moreover, the study results provide reliable information about the outcomes and effectiveness of CPN, as conducted in a consistent manner by one experienced pain technician over a relatively short period of time.

Conclusion

In conclusion, CPN did not affect survival for patients with unresectable PC in the present study. However, a well-designed prospective study with a large sample size should be conducted in the future.

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