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Clinical efficacy of EUS-guided celiac plexus neurolysis *versus* EUS-guided celiac ganglion irradiation with iodine-125 seeds for pain relief in advanced pancreatic cancer: A long-term retrospective study

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ABSTRACT

Background and Objective: To compare the efficacy of EUS–guided celiac plexus neurolysis (CPN) and celiac plexus irradiation with iodine-125 (^{125}I) seeds with absolute ethanol for relieving pain in patients with advanced pancreatic cancer.

Methods: We retrospectively analyzed data of 81 patients with advanced pancreatic cancer who underwent EUS-CPN or EUS-^{125}I implantation between January 2017 and December 2020. Postoperative pain was assessed using visual analog scale (VAS) scores; self-assessments of quality of life and the median survival time were compared between the 2 groups.

Results: EUS-CPN and ^{125}I implantation were performed in 43 and 38 patients, respectively. Postoperative VAS scores were significantly lower than the preoperative levels in both groups. One week after the operation, 26 patients (60.5%) in the EUS-CPN group achieved partial pain relief, whereas no patients in the EUS-^{125}I seed group experienced pain relief. However, after 4 weeks postoperatively, VAS scores had decreased, and the rate of partial pain relief was higher for EUS-^{125}I seeds than for EUS-CPN. Self-assessments of quality of life were similar in both groups during the first 1 month after the procedure.

Conclusions: Both EUS-CPN and EUS-^{125}I seeds can safely and effectively relieve pain in patients with advanced pancreatic cancer. Although EUS-^{125}I seeds take additional time to show effects, the extent and duration of pain relief are better compared with CPN, and interestingly, the median survival time was different.

Key words: Advanced pancreatic cancer pain; Celiac plexus neurolysis; EUS; EUS-guided implantation of iodine-125 (^{125}I seeds); Visual analog scale

INTRODUCTION

Seventy percent of patients with pancreatic cancer (PC) have abdominal pain as a presenting complaint, and as the disease progresses, almost 90% of patients develop abdominal pain.[1] Persistent and intractable pain can seriously affect the quality of life (QoL) of these PC patients. Therefore, pain management is one of the major goals of palliative care in PC.

With the availability of a new generation of painkillers such as oxycodone and fentanyl, there have been substantial improvements in pain management.[2,3]

However, there are still many patients whose pain relief is not obvious. Other methods to provide pain relief include radiation-based therapies, which are partially effective in relieving pain, but they have definite deleterious effects on neural tissues and adjoining structures.

Pain arising from the visceral organs of the abdomen, such as the pancreas, is transmitted to the brain by afferent nerve fibers via the celiac plexus located around the origin of the celiac trunk. Injecting a neurolytic agent such as ethanol or phenol into the celiac plexus causes ablation of the nerve fibers and reduces the transmission of pain signals. This procedure is called celiac plexus neurolysis (CPN). CPN has been used as an adjunct to analgesic medications for providing pain relief to PC patients.[4] CPN can be performed by surgical, percutaneous, and endoscopic techniques. Computed tomography–guided CPN has been found to achieve pain relief in 58% of cases.[5] In addition, CPN reduced daily requirements of oral morphine in the first 5 months. On the other hand, a recent meta-analysis found that EUS–guided CPN was effective in up to 71% of cases. Studies have reported that

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EUS-guided CPN is safer compared with surgical or percutaneous CPN.[6,7]

Ablation of the celiac plexus can also be performed by targeted irradiation using external radiation or iodine-125 (^{125}I) seeds. In our previous preliminary study, we observed that EUS-^{125}I seeds around the celiac ganglia could safely and effectively induce apoptosis of local neurons in porcine PC models.[8] We also demonstrated that EUS-guided celiac ganglia irradiation with ^{125}I seeds was safe, feasible, and effective in patients who have abdominal pain due to PC, because ^{125}I seeds released low-dose gamma rays continuously, which inflicted significant damage on celiac ganglia, demonstrated by the increase in apoptosis from the surface to the depth of the ganglia.[9–10] However, it remains unclear whether the effectiveness and safety of EUS-CPN are superior to that of EUS-^{125}I seeds. Therefore, the purpose of this study was to compare the safety and efficacy of EUS-CPN and EUS-^{125}I seeds in providing pain relief to patients with advanced PC.

MATERIALS AND METHODS

Patient selection

The dataset used in this study was collected from our PC database. The clinical data of biopsy-proven, advanced unresectable PC patients having cancerous pain on a visual analog scale (VAS) score four or more and who underwent EUS-guided CPN with absolute alcohol or EUS-^{125}I seeds at Changhai Hospital from January 2017 to December 2020 were collected retrospectively. A doctor who charged clinical research confirmed VAS scores before and after EUS-CPN. A tumor was considered unresectable if (1) the superior mesenteric artery involvement was greater than 180 degrees, (2) the involved segment of superior mesenteric vein or portal vein could not be repaired, and/or (3) there were metastases to distant lymph nodes beyond the area of resection. An EUS-guided procedure was not performed in patients who had (1) coagulation disorders (international normalized ratio >1.5), (2) thrombocytopenia (platelet count <50,000/L), (3) altered anatomy (eg, gastric bypass, extensive mass, or lymphadenopathy prohibiting visualization or access; massive ascites), (4) previous surgical resection, (5) VAS score <4, (6) pregnancy, and (7) allergic or intolerant to the drugs used (including alcohol). This study was approved by the ethics committee of Changhai Hospital (Shanghai, China, CHEC2019-055). All patients signed a consent form.

Patients were excluded from the analysis, including VAS score missing before and after EUS-CPN and the Short-Form 36-item health survey questionnaire (SF-36) missing. A doctor who charged clinical research confirmed VAS scores.

Both EUS-guided procedures were performed by 2 expert endosonographers who had performed >1000 EUS examinations, >500 EUS-FNA/FNB procedures, and >30 EUS-CPN procedures.

Procedure of EUS-^{125}I seeds

The procedure was performed using a linear-array echo endoscope (GF-UC240 P-AL5; Olympus, Tokyo, Japan), EUS biopsy needles (ECHO-3-22), 19-gauge EUS needles (Wilson-Cook Medical, Winston-Salem, NC), a seed gun (Mick Radio-Nuclear Instruments, Mount Vernon, NY), and a seed-releasing device for unfolding. The ^{125}I seeds were obtained from Xinke Pharmaceutical Co, Ltd (Shanghai, China; Supplementary Figure 1, http://links.lww.com/ENUS/A356). The length of each seed source was 4.5 mm, and the diameter was 0.8 mm. The seeds emitted gamma rays with a radioactivity of 2.59×10^6 Bq, had a radioactive half-life of 60.1 days, and had a penetration depth of 1.7 cm for human tissue. If the diameter of celiac ganglion is less than 0.8 cm, we will implant 2 seeds, and if the diameter of celiac ganglion is more than 0.8 cm, four seeds will be placed.

The procedure was performed under conscious sedation or general anesthesia using intravenous propofol in all patients. By observing the anatomical landmarks of the aorta, the celiac plexus was identified by locating the celiac artery and diaphragmatic crus on EUS. A single puncture was performed to release the seeds [Figure 1A]. X-ray of the abdomen was performed after EUS-guided seed implantation if it was required to confirm the location of the seeds.

Procedure for EUS-CPN

A 22- or 25-gauge EUS–fine needle aspiration needle (EZ Shot, Olympus; EchoTip, Cook Japan Inc, Tokyo, Japan; or Expect, Boston Scientific Japan K.K., Tokyo, Japan) was used to inject 0.25% bupivacaine on either side of the origin of the celiac artery. After the injection of bupivacaine (2–3 mL), absolute ethanol (95%) was injected (10 mL), and bilateral celiac ganglion injections were performed [Figure 1B]. The needle was withdrawn, and the diffusion of ethanol was observed by EUS.

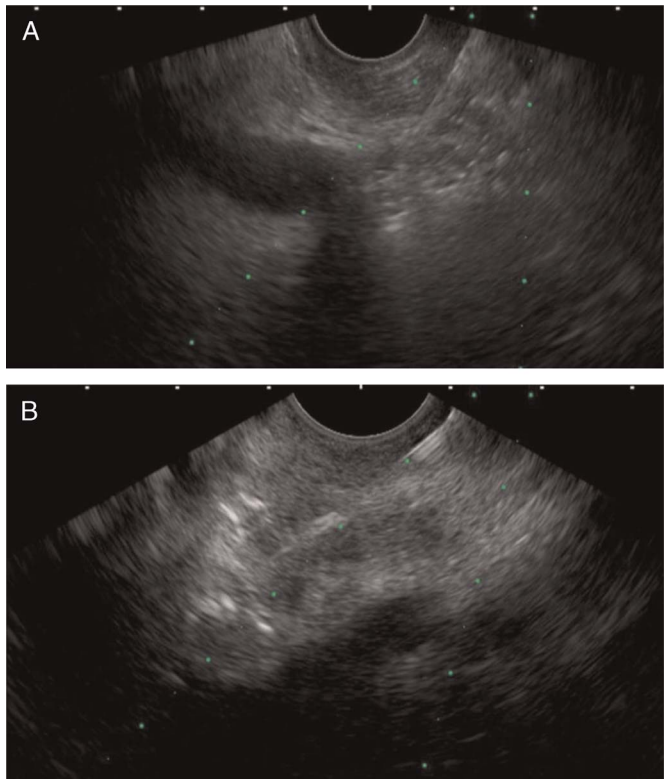

Figure 1. Schematic diagram of puncture. A, EUS-guided implantation of ^{125}I seeds near the celiac ganglia, the yellow arrow is pointing to ^{125}I seed. B, EUS-guided CPN: a 22- or 25-gauge EUS–fine needle aspiration needle was inserted on either side of the origin of the CA, and 0.25% bupivacaine (2–3 mL) was injected followed by 95% absolute ethanol (10 mL). CA: celiac artery; CPN: celiac plexus neurolysis; ^{125}I: iodine-125.

Outcome measurements

Subjective criteria

The self-reported Scott-Huskisson VAS was used to assess pain relief.[11] The baseline VAS score for pain was recorded in all patients before operation (range, 0–10). According to the National Comprehensive Cancer Network on Adult Cancer Pain (Version 2.2005), VAS scores were classified as mild (1–3), moderate (4–6), and severe pain (7–10).

Objective criteria

The SF-36 was also used to assess QoL. Questionnaire responses were collected before intervention and at weeks 1 and 2 after intervention. The survival time of patients was also recorded.

Protection from radiation

To protect the operators and assistants from radiation exposure, lead clothing, gloves, and glasses were used. All seeds were placed in protective devices before their release in a special area of the Nuclear Medicine Department. A radiation dose meter (Shanghai Institute of Radiation Medicine, Shanghai, People's Republic of China) was set up on site for timely detection of radiation leakage.

Statistical analysis

Statistical analysis was conducted using SPSS software version 22 (IBM Corp, Armonk, NY). Student *t* test was used to compare continuous data between the 2 groups. χ^2 or Fisher exact test was used when appropriate to compare the categorical data. Cumulative survival was analyzed by using the Kaplan-Meier method and Cox regression analysis. Statistical significance was set at *P* value <0.05.

RESULTS

Patient demographics and clinical characteristics

Ninety-eight patients were collected from our PC database, 9 patients did not filled in SF-36 scores, and 8 patients who lost the VAS score were excluded from the analysis. Of the 81 patients included in this study, 43 were in the EUS-CPN group (29 men, 14 women; median age, 62 years), and 38 were in the EUS-^{125}I seed group (25 men, 13 women; median age, 64 years). The exclusion criteria are shown in Figure 2. In the EUS-CPN group, 20 patients (47.37%) had a tumor in the pancreatic head and body, whereas 23 patients (52.63%) had a tumor in the pancreatic tail. Seventeen and 26 patients in the EUS-CPN group had TNM stage III and IV disease, respectively. In the EUS-^{125}I seed group, the tumor was located in the pancreatic head and tail in 13 (34.6%) and 25 (65.4%) patients, respectively. Fifteen and 23 patients had TNM stage III and IV disease, respectively. There were no statistically significant differences in age, sex, tumor location, or TNM stage between the 2 groups (Table 1).

Pain intensity and opioid consumption

As shown in Table 2, the mean preoperative VAS scores in the CPN and EUS-^{125}I seed groups were similar (5.95 [4–10] *vs.* 5.88 [4–8]). One week after the procedure, 26 patients in the CPN group and none of the patients in EUS-^{125}I seed group experienced relief of abdominal pain. Two weeks after the operation, the VAS score in the CPN and EUS-^{125}I seed groups had decreased to 3.95 (1–9) and 4.46 (3–7), respectively [Figure 3]. Four weeks after the operation, the VAS score in the CPN group had increased to 4.53 (2–7), but in the EUS-^{125}I seed group, the VAS score had decreased to 3.25 (1–5).

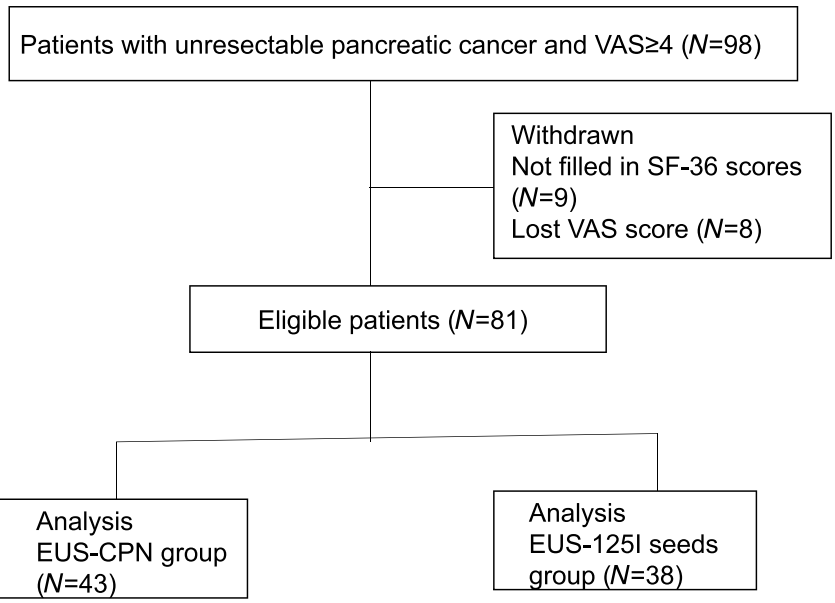

Figure 2. Patient flowchart. Forty-three patients in the EUS-guided celiac plexus neurolysis group and 38 patients in the EUS-^{125}I seed group were used in the analysis. EUS-CPN: EUS–guided celiac plexus neurolysis.

Table 1

Clinical characteristics of the study patients

	EUS-CPN (n = 43)	EUS-^{125}I Seeds (n = 38)	P
Sex, male	29	25	0.87
Age, mean (range), y	62 (36–74)	64 (38–77)	0.48
Location of the main tumor			
Pancreatic head	20	13	0.26
Pancreatic body + tail	23	25	
UICC stage			0.99
III	17	15	
IV	26	23	
Operation time, mean (range), min	17 (10–23)	16 (8–25)	0.89
Opioid usage, mean (range), mg	52 (20–220)	68 (40–90)	0.06
Overall survival, mean (range), d	80 (43–182)	89 (68–196)	0.04
Previous therapies			
None	31	24	0.39
Radiotherapy	2	2	
Chemotherapy	7	6	
Biliary stent placement	3	6	
Surgical operation	0	0	

EUS-CPN: EUS–guided celiac plexus neurolysis; ^{125}I: iodine-125; UICC: Union for International Cancer Control.

In the CPN group, 2 weeks after the operation, daily consumption dose of opioids had decreased to 46.89 (0–220) mg, and at 4 weeks, daily consumption dose of opioids had increased to 50.4 (0–220) mg; however, in the EUS-^{125}I seed group at 2 and 4 weeks after the operation, daily consumption dose of opioids had decreased to 46.89 (0–220) and 42.16 (10–70) mg, respectively (Table 2).

QoL self-assessment using the Turkish version of the SF-36

The mean preoperative SF-36 scores of the EUS-CPN and EUS-^{125}I seed groups were similar (71.27 *vs.* 70.26, P = 0.82). At 1 and 4 weeks postoperatively, the mean SF-36 scores in the EUS-CPN and EUS-^{125}I seed groups were similar. In addition, there was no significant difference between the SF-36 scores before and after the procedure in both groups (Table 3).

Patient survival

The median overall survival was 80 days (95% confidence interval, 75–85 days) in the EUS-CPN group and 89 days (95% confidence interval, 79–93 days) in the EUS-^{125}I seed group; the difference was significant (P < 0.05) [Figure 4]. There were no adverse events in both groups, the seeds did not migrate during the follow-up period. Cox regression analysis showed that therapeutic method was an independent risk factor for prognosis (P = 0.041), and the hazard ratio was 0.616, which means that the patient's risk of death is lower in the EUS-^{125}I seed group compared with the EUS-CPN group (Supplementary Table 1, http://links.lww.com/ENUS/A357).

DISCUSSION

In this study, we found that both EUS-CPN and EUS-^{125}I seeds were effective in relieving pain and reducing the requirements of analgesics in patients with advanced PC. Furthermore, the QoL was similar in the 2 groups. To the best of our knowledge, this is the first study to compare the outcomes of EUS-CPN and EUS-^{125}I seeds for pain management in PC patients.

CPN relieves pain by blocking the transmission of pain signals from the afferent nerve to the spinal cord. Studies have shown that the analgesic effect of EUS-CPN lasts for only 8 to 12 weeks.[12] An autopsy study found that anhydrous ethanol mainly causes dehydration and degeneration of nerve cells, cell coagulation, and pathological changes such as lipoprotein and mucin precipitation through extraction of cholesterol and phospholipid in nerve membrane. It will certainly greatly affect the permeability of ethanol, resulting in its destructive power to the deep nerve tissue, which

Table 2

Comparison of VAS scores and MS Contin consumption between the EUS-CPN and EUS-^{125}I seed groups

	Groups	VAS Score	P	MS Contin Consumption	P Value CPN *vs.* ^{125}I Seed
Before	CPN	5.95 (4–10)	0.06	51.94 (20–220)	0.06
	^{125}I seed	5.88 (4–8)		69.26 (40–90)	
After week 1	CPN	4.16 (2–9)	0.025	49.89 (10–220)	0.03
	^{125}I seed	6.15 (4–8)		71.78 (40–120)	
After week 2	CPN	3.95 (1–9)	0.34	46.89 (0–220)	0.34
	^{125}I seed	4.46 (3–7)		55.02 (30–90)	
After week 4	CPN	4.53 (2–7)	0.04	58 (0–140)	0.04
	^{125}I seed	3.25 (1–5)		42.16 (10–70)	

EUS-CPN: EUS–guided celiac plexus neurolysis; ^{125}I: iodine-125; VAS: visual analog scale.

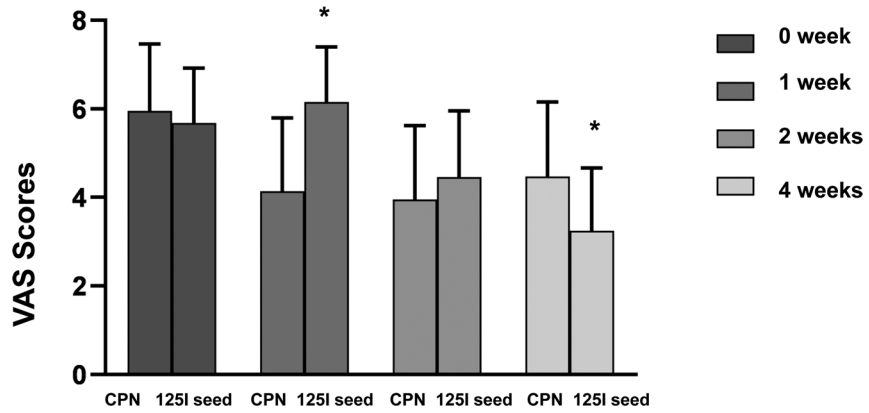

Figure 3. Changes in the VAS scores before and after the operation in the EUS-CPN and EUS-^{125}I seed groups. In the CPN group (red rectangle shown), the mean VAS score was 5.95 (4–10) before the operation, which gradually reduced to 3.95 (1–9) at 2 weeks after the operation. Four weeks after the operation, the VAS score in the CPN group had increased to 4.53 (2–7). In the EUS-^{125}I seed group (green rectangle shown), the mean VAS score was 5.88 (4–8) before the operation, which increased to 6.15 (4–8) at 1 week after the operation. Subsequently, VAS score reduced to 4.46 (3–7) 2 weeks after the operation. Four weeks after the operation, in the EUS-^{125}I seed group, the VAS score had decreased to 3.25 (1–5). The VAS score showed statistically significant differences between the 2 groups in 1 and 4 weeks. *There is a significant statistical difference between the two groups (P<0.05). EUS-CPN: EUS–guided celiac plexus neurolysis; VAS: visual analog scale.

is not enough. PC, on the other hand, has a retroperitoneal growth characteristic and tends to invade the tissues surrounding the abdominal trunk, which further impedes the osmosis of ethanol and leads to limited analgesic effects. Moreover, the analgesic effect of different parts of the tumor would also be different.

Kanno et al.[13] reported that EUS-CPN reduced the mean VAS scores when compared with medication use alone (1.3 ± 1.3 in the CPN group *vs.* 2.3 ± 2.3 in the medication group). Wyse et al.[14] also compared the pain relief using EUS-CPN and medication alone using the 7-point Likert scale and found that the mean % change in the pain was +11% *versus* –18% at 1 month and +12% *versus* –49% at 3 months, respectively. Consistent with these findings, we also observed that VAS score was declined from baseline at 1 week after EUS-CPN.

Studies have demonstrated that external radiation may play a role in controlling pain in patients with PC.[15,16] Our previous study indicated that EUS-guided interstitial implantation of ^{125}I seeds in the human celiac ganglia can aid in managing pain.[17] The length of each seed source was 4.5 mm, and the diameter was 0.8 mm. The seeds emitted gamma rays with a radioactivity of 2.59×10^6 Bq, had a radioactive half-life of 60.1 days, and had a penetration depth of 1.7 cm for human tissue. Our previous animal experiment had revealed that direct irradiation by implanting ^{125}I seeds near the celiac plexus could induce neuronal apoptosis, which is positively correlated with the time and dose of irradiation. In the present study, we observed significant decreases in VAS scores after operation in the EUS-^{125}I seed group at 1 month, and the score was less than EUS-CPN. These findings may be related to these 2 treatments' different modes of action. Moreover, the neuronal damage caused by direct irradiation of ^{125}I seeds was more obvious than that of absolute ethanol.

The duration of pain relief is important for enhancing QoL.[18] A study reported that standard EUS-CPN was superior to EUS-guided celiac ganglia neurolysis in pain reduction and QoL improvement.[19] In our study, 26 patients (60.5%) in the EUS-CPN group experienced pain relief 1 week after the operation, whereas 2 patients had aggravation of abdominal pain for 3 days (1–5 days). By contrast, no patients in the EUS-^{125}I seed group experienced pain relief 1 week after the operation, and 3 experienced an aggravation of abdominal pain for 8.5 (7–10) days. Consistent with our report, another study also reported that, despite treatment with bupivacaine before CPN, transient aggravation of abdominal pain occurred in the postoperative period.[20] However, no patients had aggravation of abdominal pain for the first week in the EUS-^{125}I seed group. In addition, the difference in the analgesic effect of the 2 groups did not correlate with QoL scores. Moreover, the postoperative QoL scores did not differ from baseline in either of the groups.

Patients with advanced PC usually have a shorter survival time. According to the Union for International Cancer Control (UICC), stage IV indicates the presence of distal metastases.[21] In our study, the median survival was 80 and 89 days in the EUS-CPN and EUS-^{125}I seed groups, respectively. Previous studies have reported a median survival of 10.46 months and 174 days, respectively, in patients undergoing EUS-CPN, which was longer than those observed in the current study. This may be because the present study had more patients with UICC stage IV disease (60.5% and 61.5% in the EUS-CPN and EUS-^{125}I seed groups, respectively) than previous studies, and most of our patients had not received chemotherapy or other therapies. The length of each seed source was 4.5 mm and the diameter was 0.8 mm, which had a

Table 3

Comparison of quality-of-life self-assessment using the SF-36 score between the 2 groups

	Groups	SF-36 Score*	*P* Value CPN *vs.* ^{125}I Seed
Before the procedure	CPN	71.27 (32–94)	0.82
	^{125}I seed	70.26 (46–98)	
After week 1	CPN	76.01 (50–99)	0.43
	^{125}I seed	72.74 (44–99)	
After week 4	CPN	77.29 (46–99)	0.33
	^{125}I seed	72.95 (46–99)	

* means: There is a significant statistical difference between the two groups (P< 0.05).

CPN: celiac plexus neurolysis; ^{125}I: iodine-125; SF-36: Short-Form 36-item health survey questionnaire.

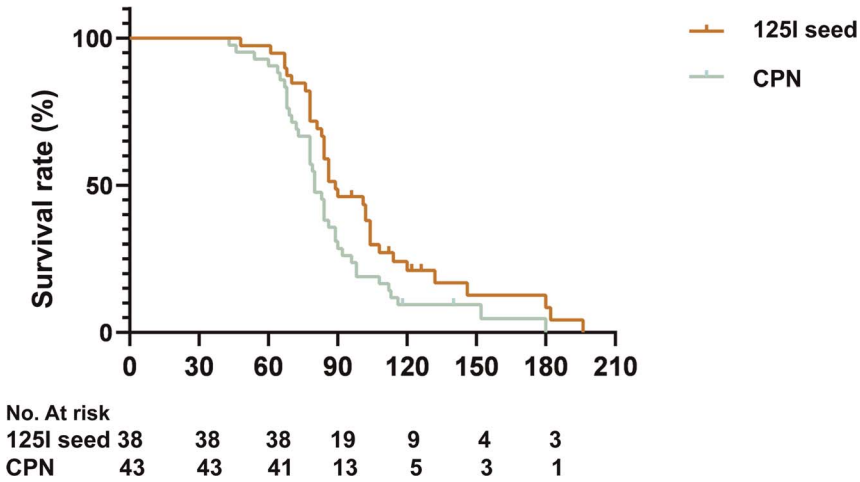

Figure 4. Median patient survival was 80 days in the EUS-CPN group and 89 days in the EUS-^{125}I seed group, and the difference was significant ($P < 0.05$). EUS-CPN: EUS–guided celiac plexus neurolysis.

penetration depth of 1.7 cm for human tissue, so the EUS-^{125}I seed group did not show a decrease in tumor size. It is worth noticing that therapeutic method was an independent risk factor for prognosis ($P = 0.041$) in our study; the hazard ratio was 0.616.

There are some limitations of this study. First, it was a retrospective single-center study; there may be selection bias. Second, patients with advanced PC often have enlarged celiac lymph nodes due to metastases, which makes it difficult to distinguish from the celiac ganglion. Also, the celiac ganglion cannot be clearly displayed in every patient.[22,23] Many studies have reported that, when the celiac ganglion can be identified, direct injection into the ganglion can achieve a higher rate of pain relief. However, the technical success rates of EUS-CPN and EUS-CGN were 100% and 80.4%, respectively, and those who received EUS-CPN had longer survival compared with CGN. Therefore, in our study, we choose EUS-CPN to relieve patients' pain.

In conclusion, the findings of this study indicate that both EUS-CPN and EUS-^{125}I seeds are safe and effective in alleviating abdominal pain in patients with advanced PC. EUS-CPN with absolute ethanol provides faster pain relief than EUS-^{125}I seeds in patients with advanced PC. However, EUS-^{125}I seeds provide a higher degree of pain relief and last for a longer duration compared with EUS-CPN, and the EUS-^{125}I seed group had the long median survival time. In our study, we did not observe the displacement of seeds. Randomized, prospective, controlled, and comparative clinical trials are needed to confirm the safety and long-term effectiveness of pain management between the 2 groups in the future.

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Conflicts of Interest

Zhen-Dong Jin is an Associate Editor of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

Authors Contributions

Ping-Ping Zhang drafted and edited the manuscript. Xiao-Ju Su oversaw statistical analyses. Li Li acquired the data. Yu-ling Wang and Ting Yang analyzed and interpreted the data. Teng Wang and Dong-Qing Zhu revised the manuscript for important intellectual content. Kai-Xuan Wang and Zhen-Dong Jin conceptualized the study.

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