EUS-guided celiac ganglion irradiation with iodine-125 seeds for pain control in pancreatic carcinoma: a prospective pilot study CME

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Background: Celiac plexus neurolysis for the palliative reduction of pain in unresectable pancreatic carcinoma (PC) is safe but provides limited relief. In a previous study, we found that EUS-guided implantation of iodine-125 (^{125}I) around the celiac ganglia is a safe procedure and can induce apoptosis of local neurons in a porcine model.

Objective: To evaluate the safety and efficacy of direct celiac ganglion irradiation with ^{125}I seeds for the relief of moderate to severe pain secondary to unresectable PC.

Design: Prospective study.

Setting: Single, tertiary care referral center.

Patients: This study enrolled consecutive patients who had moderate to severe pain resulting from biopsy-proven unresectable PC.

Intervention: All patients underwent EUS-guided direct celiac ganglion irradiation with ^{125}I seeds. Follow-up was conducted at least once weekly until death.

Main Outcome Measurements: Blood parameters, Visual Analog Scale (VAS) score, mean analgesic (MS Contin [morphine sulfate]) consumption, and complications were evaluated during follow-up.

Results: Twenty-three patients with unresectable PC underwent the procedure. The mean number of seeds implanted in the celiac ganglion per patient was 4 (range 2-6). Immediately after the procedure, pain relief and analgesic consumption showed no significant changes compared with preoperative values. Six patients (26%) reported pain exacerbation. Two weeks later, the VAS score and mean analgesic consumption were significantly less than preoperative values. No procedure-related deaths or major complications occurred.

Limitations: Uncontrolled study.

Conclusions: EUS-guided direct celiac ganglion irradiation with ^{125}I seeds can reduce the VAS score and analgesic drug consumption in patients with unresectable PC. (Gastrointest Endosc 2012;76:945-52.)

Pancreatic carcinoma (PC) is an aggressive malignancy with increasing incidence. Because of retroperitoneal growth and invasion of the celiac ganglia, PC often causes refractory abdominal pain, and this pain is the chief symptom of PC patients. Approximately 75% of these patients have pain at diagnosis and more than 90% in advanced stages.[1] Thus, pain is a significant detriment to the quality of life of PC patients, and consequently pain management is 1 of the major goals of palliative treatment.

Management of PC pain is a clinical challenge and often requires large doses of opioid analgesics. However, adverse reactions are often intolerable and limit their use.

Abbreviations: CGN, celiac ganglion neurolysis; CPN, celiac plexus neurolysis; EUS-CGN, EUS-guided celiac ganglion neurolysis; NCPB, neurolytic celiac plexus blockade; PC, pancreatic carcinoma; SD, standard deviation; VAS, Visual Analog Scale; WHO, World Health Organization.

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Nonpharmacological therapies have been developed to achieve pain control and avoid drug-related side effects. Such therapies include celiac plexus neurolysis (CPN), which involves the injection of a neurolytic agent (eg, absolute alcohol) in and around the celiac ganglion. Although CPN is considered safe, it provides limited benefit in terms of degree and duration of pain relief; the greater the extent of invasion of the celiac ganglia is, the less the analgesic effect achieved by CPN is.[2-5] Such limited efficacy may be at least partially attributed, until recently, to the lack of an imaging technique for the celiac ganglia, affecting the accuracy of the neurolytic agent delivery. The recognition that the celiac ganglia can be visualized and accessed by EUS allows the direct injection of neurolytic agents into individual celiac ganglia.[6-8]

Radioactive rays have a definite injurious effect on neural tissues.[9,10] In a previous preliminary study, we found that EUS-guided implantation of iodine-125 (^{125}I) around the celiac ganglia is a safe procedure and can induce apoptosis of local neurons in a porcine model.[11] We therefore hypothesize that direct implantation of ^{125}I seeds into the celiac ganglia may offer enhanced pain relief safely. To test this hypothesis, we conducted a pilot study to determine the feasibility and safety of EUS-guided direct celiac ganglion irradiation with ^{125}I seeds in 23 patients with moderate to severe pain secondary to unresectable PC.

Take-home Message

- To the best of the authors' knowledge, this is the first study to evaluate the efficacy and safety of direct celiac ganglion irradiation with iodine-125 (^{125}I) seeds in the treatment of pain resulting from advanced pancreatic carcinoma.
- The results suggest that EUS-guided celiac ganglion irradiation with ^{125}I seeds is safe, feasible, and effective.

PATIENTS AND METHODS

Patients

Patients were eligible for EUS-guided direct celiac ganglion irradiation if they had moderate to severe narcotic-dependent pain resulting from biopsy-proven unresectable PC. Tumors were deemed unresectable if there was superior mesenteric artery or celiac encasement greater than 180 degrees, unreconstructable superior mesenteric vein/portal occlusion or metastases to lymph nodes beyond the field of resection.[12] Patients were excluded from the study if they had (1) uncorrectable coagulopathy (international normalized ratio >1.5), (2) thrombocytopenia (platelet count <50,000/L), (3) inadequate sedation, or (4) altered anatomy (eg, gastric bypass or an extensive mass or lymphadenopathy prohibiting visualization or access). The Ethical Institutional Review Board of Changhai Hospital approved the study protocol. Written informed consent was obtained from each subject before enrollment in the study.

^{125}I seeds and equipment

^{125}I seeds were obtained commercially (Xinke Pharmaceutical, Shanghai, China). The core source was silver-containing Na^{125}I, packaged in a laser-sealed titanium alloy tube. Each seed source was 4.5 mm in length and 0.8 mm in diameter. The seeds had a radioactive half-life of 60.1 days, a mean ± standard deviation photon energy of 27 ± 35 KeV in gamma rays, and a penetration depth of 1.7 cm for human tissue. The equipment used included a linear-array echoendoscope (GF-UC240P-AL5; Olympus, Tokyo, Japan), 19-gauge EUS needles (Wilson-Cook Medical, Winston-Salem, NC), a seed gun (Mick Radio-Nuclear Instruments, Mount Vernon, NY), and a seed-releasing instrument for deployment.

Procedure and postoperative treatment

Patients were initially prehydrated with 500 to 1000 mL of normal saline solution. An intravenous infusion of 400 mg ciprofloxacin was given during the procedure, followed by 500 mg ciprofloxacin administered postoperatively for 3 days. Immediately before the procedure, patients were placed in the left lateral decubitus position and underwent anesthesia-assisted sedation by using intravenous propofol (2.0-2.5 mg/kg for initialization, then 8-10 mg/kg/h for maintenance). During the procedure, patients were continuously monitored with automated noninvasive blood pressure and pulse oximeter devices.

Linear array EUS imaging was performed from the posterior lesser curve of the gastric fundus to visualize the aorta in the longitudinal plane. The aorta was traced distally to the celiac trunk. The celiac ganglia were identified, numbered, and measured in the same manner as previously described by Levy et al.[6] Because the optimal dose of irradiation has not yet been determined, we planned to insert 2 seeds into ganglia less than 0.8 cm in diameter, and 4 seeds for those 0.8 cm or larger. The puncture distance was measured, and the aspiration needle was inserted via the biopsy channel. Doppler flowmetry was used to avoid puncturing blood vessels. Aspiration was performed continuously under negative pressure. When the needle reached the target site, the stylet was retracted and the seeds were released through the stylet by using the Mick seed gun. Finally, the needle was withdrawn (Fig. 1). We performed single puncturing to release the seeds, and implantation in ganglia was successful at the first puncturing in all 23 patients.

After the procedure, vital signs were monitored for 2 hours. Patients were questioned as to the presence or absence of procedure-related complications. Enhanced CT scans and abdominal radiography were performed the day after surgery to check whether the aspiration site was correct. Blood was drawn for evaluation of white blood cell count, serum amylase, liver and kidney function, and immune function before and 14 days after the procedure.

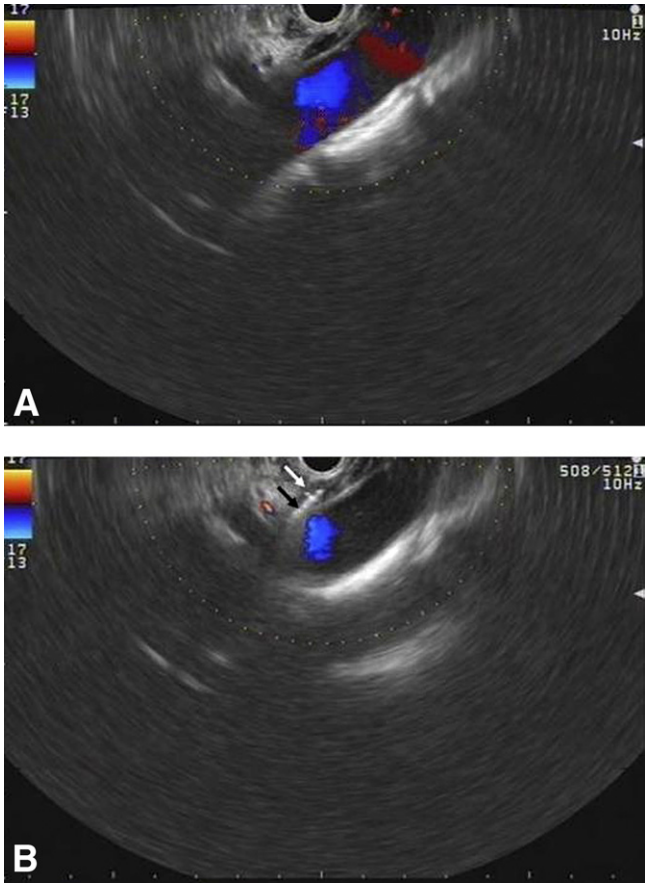

Figure 1. EUS-guided seed implantation in the celiac ganglia. **A**, EUS shows a celiac ganglion before implantation. **B**, EUS shows a celiac ganglion after implantation. The *white arrow* indicates the location of the seeds in celiac ganglion, the *black arrow* indicates the location of air.

Postoperative drug therapy was administered according to the guidelines of the World Health Organization (WHO) for cancer pain relief.[13] Opioid administration was conducted according to the WHO criteria for opioid dose escalation until adequate analgesia was achieved or intolerable side effects were experienced. Because external irradiation may also reduce pain definitely which will make the results complicated, therefore, none of patients in this study received radiotherapy.

Chemotherapy

All enrolled PC patients were required to receive standard chemotherapy[12] 1 week after the procedure to control tumor progression, starting with gemcitabine 1.0 g/m^2 over 30 minutes weekly for 3 weeks every 28 days. The chemotherapy was repeated for up to 6 cycles if tolerated.

Criteria for evaluation of pain relief

The degree of pain relief was evaluated by using subjective and objective criteria. The self-reported Scott-Huskisson Visual Analog Scale (VAS) was used as a subjective evaluation of pain relief.[14,15] All patients were interviewed before the procedure to obtain a baseline pain score based on the VAS (range 0-10) with 0 corresponding to no pain and 10 corresponding to the worst pain. According to the National Comprehensive Cancer Network on Adult Cancer Pain (Version 2.2005), we determined that VAS scores of 1 to 3 correspond to mild pain, 4 to 6 to moderate pain, and 7 to 10 to severe pain. Complete pain relief was the total absence of pain (VAS score = 0), partial pain relief was reduction in pain intensity of at least 3 points on the VAS score, and no pain relief was the persistence of unmodified pain. The objective criterion for pain relief was the mean consumption of analgesic drugs (defined as daily oral morphine equivalents in milligrams).[14,16] To make an easy exchange between different analgesic doses and good compliance of the patients, the researchers decided to choose MS Contin (morphine sulfate) as the standard analgesic agent in this study.

Follow-up

Follow-up was conducted until death. The following parameters were monitored: (1) the VAS score; (2) mean analgesic consumption; (3) occurrence, severity, and means of therapy for initial pain exacerbation after the procedure; and (4) complications related to the procedure, including minor complications such as fever, infection, breathing difficulty, bleeding, and diarrhea, and the major ones such as bleeding need surgery, paralysis, and death.[17] There was a special physician who was blinded to the study who collected the patients' opinions. When the patients were admitted to the hospital, he would explain the detailed evaluation method of VAS scale. After the patients were discharged from the hospital, the physician would make regular assessments by telephone or by outpatient clinic visit at least once weekly and suggested that the patients alter the dose of MS Contin according to the effect.

Radiation protection

To protect the operating physicians and assistants from radioactive exposure, they were asked to wear lead clothing and gloves and glasses. All seeds should be located inside the protective gear before released, which is performed in special area of the nuclear medicine department. A radiation dose meter (Shanghai Institute of Radiation Medicine, Shanghai, People's Republic of China) is set on-site to guarantee that there is no leakage of radiation.

Statistical analysis

Statistical analysis was performed by using SPSS version 18.0 (SPSS, Inc, Chicago, Ill). Continuous variables are expressed as mean ± standard deviation or mean (range). Comparisons of serum parameters before and after the operation were performed by using the paired Student *t* test. Comparison of VAS score and MS Contin consumption before and after seed implantation was performed by using the general linear model. *P* values $<.05$ were considered statistically significant.

TABLE 1. Demographic and clinical characteristics of patients

Parameter	
Age, y, no.	
Median (range)	64 (38-77)
<50	1
50-65	16
>65	6
Sex, M/F	14/9
Tumor location, no.	
Pancreatic head	8
Pancreatic body/tail	15
Tumor stage, no.	
III	7
IV	16
Previous therapy, no.	
None	11
Radiotherapy	3
Chemotherapy	5
Biliary stent placement	8
Time from diagnosis to enrollment, mo, no.	
Within 2 mo	12
2-6 mo	8
>6	3
Survival from referral, d (range)	79 (43-156)

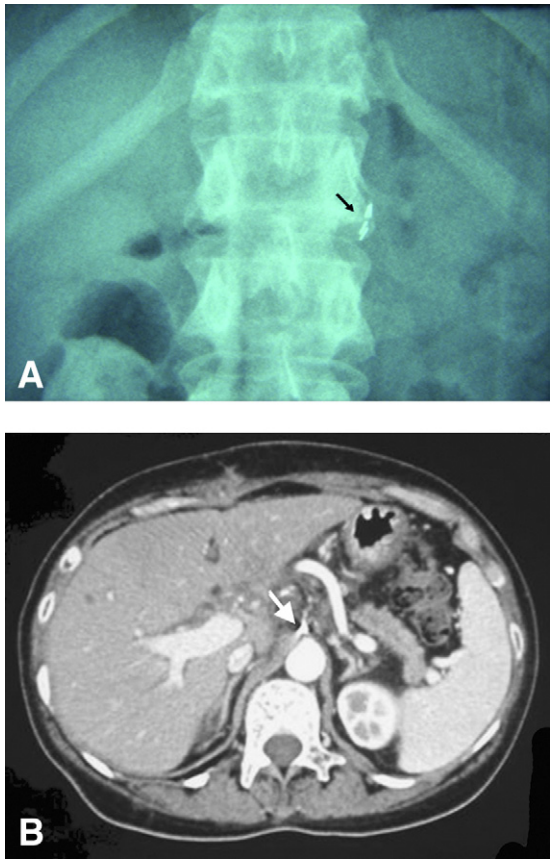

Figure 2. (**A**), A radiograph and (**B**) CT scan of a patient after EUS-guided seed implantation in the celiac ganglia. The *arrow* indicates the location of the seeds.

RESULTS

Twenty-seven patients were initially enrolled in the study from January 2009 to December 2011. Four patients underwent the standard CPN procedure because the celiac ganglia could not be clearly identified. The celiac ganglia could be seen and accessed in 85.2% (23/27) of patients. As a result, a total of 23 patients underwent direct ganglion implantation with ^{125}I seeds. The patients (14 men and 9 women) were between 38 and 77 years of age, with an average age of 64 years. Of all patients undergoing direct ganglion implantation with ^{125}I seeds, 8 had carcinoma of the pancreatic head and 15 of the pancreatic body or tail, 7 had stage III carcinoma, 16 had stage IV carcinoma; 11 had received no previous therapy, 3 had previous radiotherapy, 5 had previous chemotherapy(gemcitabine 1.0 g/m^2), and 8 had received biliary stent placement. Table 1 shows the demographic and clinical characteristics of these patients. At least 1 cycle of chemotherapy was administrated for all 23 patients 1 week after the procedure.

A median of 1.8 ganglia were identified (range 1-3), and all visible ganglia implanted. The mean number of radioactive seeds implanted in the celiac ganglion per patient was 4 (range 2-6). CT scans and radiographs after aspirations revealed that the implantation was successful the first time in all patients (Fig. 2). Neither major complications such as death and paraplegia nor minor ones such as diarrhea and orthostatic hypotension occurred. No significant differences were noted between the before and after surgery blood parameters ($P > .05$ for all; Table 2).

Table 3 shows the VAS score and MS Contin controlled-release tablet (Mundipharma Pharmaceutical Co, Ltd, Beijing, People's Republic of China) consumption before and after seed implantation. Before treatment, the mean VAS score was 5.78 (range 4-8), and all patients received MS Contin; the mean consumption of this drug was 68.26 mg (range 40-90 mg). Immediately after the procedure, no patient reported pain relief. Conversely, 6 patients (26.1%) experienced pain exacerbation lasting a mean duration of 8.5 days (range 7-10 days), and MS Contin consumption increased in 4 of these patients. The other patients re-

TABLE 2. Serum parameters before and after seed implantation

	Before implantation	After implantation
White blood cell count, $\times 10^9$/L	6.63 ± 1.45	6.01 ± 1.09
Serum amylase, U/L	72.08 ± 21.39	69.48 ± 15.26
Alanine aminotransferase, U/L	32.00 ± 7.23	33.66 ± 4.88
Blood urea nitrogen, mmol/L	4.86 ± 0.82	4.71 ± 0.66
$CD4^+/CD8^+$ T-cell ratio	1.47 ± 0.12	1.35 ± 0.92

There were no significant differences between before and after implantation by the Student *t* test. Values shown are ± standard deviation.

TABLE 3. Comparison of VAS score and MS Contin consumption before and after seed implantation

	VAS score*	No. of living patients	MS Contin consumption*
Before implantation	5.78 (4-8)	23	68.26 (40-90)
After implantation			
1 wk	6.09 (4-8)	23	71.74 (40-120)
2 wk	4.48 (3-7)†	23	55.22 (30-90)†
3 wk	3.39 (1-6)†	23	45.22 (20-80)†
4 wk	3.17 (1-6)†	23	42.17 (10-80)†
5 wk	2.96 (1-6)†	23	39.57 (10-70)†
6 wk	2.96 (1-6)†	23	39.13 (10-80)†
7 wk	2.91 (1-6)	22	40.45 (20-80)
8 wk	3.05 (1-6)	19	41.58 (10-80)
9 wk	2.79 (1-6)	14	40.71 (10-80)
10 wk	2.46 (1-5)	13	35.38 (10-70)
11 wk	2.00 (1-4)	10	32.00 (10-50)
12 wk	1.89 (1-4)	9	31.11 (10-50)
4 mo	2.00 (1-4)	5	30.00 (10-40)
5 mo	1.50 (1-3)	2	20.00 (10-30)

*Data shown are expressed as median (range).
†There were significant differences compared with before and 1 week after the procedure ($P < .05$, the general linear model). No statistical comparison could be made when only a few patients survived.

TABLE 4. The number and percentage of patients at each time interval who experienced partial pain relief

	No. of patients	No. of patients with partial pain relief	Percentage of patients with partial pain relief
1 wk	23	0	0
2 wk	23	1	4.34
3 wk	23	13	56.52
4 wk	23	14	60.86
5 wk	23	16	69.56
6 wk	23	16	69.56
7 wk	22	16	72.72
8 wk	19	12	63.15
9 wk	14	8	57.14
10 wk	13	8	61.53
11 wk	10	7	70.00
12 wk	9	7	77.77
4 mo	5	3	60.00
5 mo	2	1	50.00

ported no significant change in the VAS score, and analgesic consumption remained the same.

One week after surgery, the mean VAS score increased from 5.78 to 6.09, and MS Contin use increased from 68.26 mg to 71.74 mg, but no significant difference from before to 1 week after surgery. Two weeks after surgery, 82.6% (19/23) of patients reported pain relief, and 56.52% (13/23) experienced partial pain relief. For the group as a whole, from 7 to 14 days post-surgery, the mean VAS score decreased from 6.09 to 4.48, and the total amount consumed of MS Contin use also decreased significantly, from 71.74 mg to 55.22 mg, which has reached the statistical difference ($P < .05$). During the follow-up period, the mean VAS score and MS Contin use remained at relatively low levels and also reached the statistical difference compared with before and 1 week after surgery ($P < .05$). Twelve weeks after the procedure, 77.77% (7/9) of patients experienced partial pain relief, has reached its peak.

Five months after the procedure, 50% of patients still had partial pain relief (Tables 3 and 4, Fig. 3). However, none experienced complete pain relief in our study.

The mean survival time from enrollment was 79 days (range 43-156 days). Five patients reported constipation (21.7%; 95% CI, 0.07-0.43), 2 patients had nausea and vomiting (8.7%; 95% CI, 0.01-0.28). No other complications occurred.

DISCUSSION

Chemotherapy is the first-line treatment in the majority of PC patients at a palliative stage and has been observed

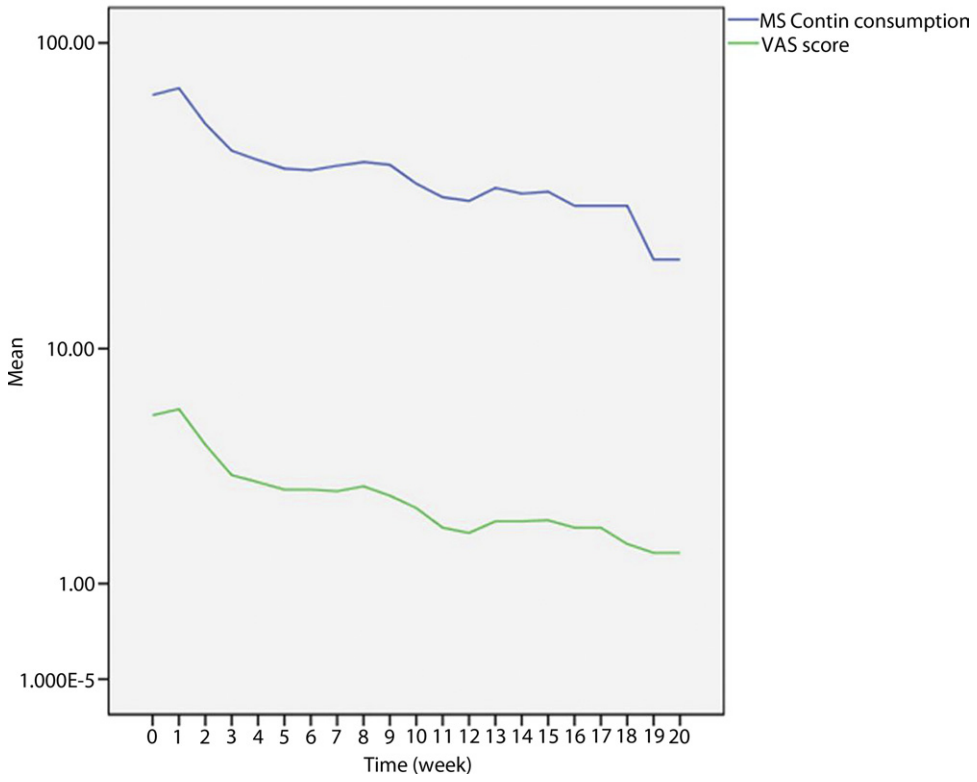

Figure 3. A semilogarithmic line graph showing the relationship between MS Contin consumption and Visual Analog Scale (VAS) score.

to have the ability to reduce pain, but the analgesic effect is limited and weak.[18] The standard approach to the management of cancer pain follows the WHO 3-step analgesic ladder, beginning with nonopioid analgesics, followed by weak opioids, and finally strong opioids as necessary.[13] Virtually all PC patients require increasing doses of opioids. Inevitably, intolerable adverse side effects limit their use.[19]

A previous study demonstrated that external radiation can play a role in the control of pain from PC.[20] Our previous study also indicated that EUS-guided interstitial implantation of ^{125}I seeds could improve pain control in PC patients.[21,22] These results suggest that radiotherapy might destroy intrapancreatic nerve fibers. Considering that EUS-guided celiac ganglion neurolysis (EUS-CGN) and ^{125}I seed implantation are 2 established minimally invasive techniques, we hypothesized that combining them might allow precise and safe implantation of radioactive seeds in the human celiac ganglia to manage pain.

In this study, ^{125}I seeds were successfully implanted the first time in all patients. Postoperatively, no abnormalities in white blood cell count, serum amylase, liver and kidney function, or immune function were detected, and no procedure-related complications occurred. During the follow-up period, there were no major complications. These data suggest that direct celiac ganglion irradiation with ^{125}I seeds is a safe and feasible procedure in patients with moderate to severe pain secondary to PC.

Because celiac ganglia can transmit pain signals from the pancreas and most of the upper abdominal viscera to the brain, neurolytic celiac plexus blockade (NCPB) has been developed to manage cancer pain by inhibiting the transmission of pain signals. A meta-analysis showed that at 24 hours after NCPB, there was a statistically significant improvement in pain control and decrease in opioid use compared with standard treatment. However, the overall benefit was limited, with a 6% reduction in mean VAS score compared with the baseline. The durability of pain control after NCPB was only 2 to 3 months.[23] In the current study, 82.6% of patients reported pain relief 2 weeks after the procedure. During the follow-up period, the mean VAS score and MS Contin use remained at relatively low levels. The cause of this difference was probably the different neurolytic agents used. Alcohol is favored as a neurolytic agent in NCPB, which can rapidly destroy the celiac plexus, but postmortem neurohistopathological examination of the celiac plexus has demonstrated that NCPB with alcohol is capable of partially destroying the epineurium with little effect on the perineurium and neurons.[24] Our previous study showed that ^{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. This damaging effect correlates positively with the duration of irradiation.

A previous meta-analysis showed that diarrhea (44%) and postural hypotension (38%) are 2 common post-NCPB adverse effects.[25] In the current study, no procedure-related complications, including diarrhea and postural hypotension, were observed. Alcohol can rapidly destroy the sympathetic nerves, induce parasympathetic nerve dominance, and thereby cause diarrhea and hypotension. Direct celiac ganglion irradiation with ^{125}I seeds avoids such complications because the dose of gamma rays continuously released by ^{125}I seeds is low and the body has adequate time to compensate for the damage to the sympathetic nerves. Actually, an earlier study indicated that tissue damage caused by ^{125}I seed irradiation reached the maximal level 14 days after implantation.[26]

The reported efficacy of direct CGN with alcohol varies from study to study. Levy et al[6] performed EUS-CGN in 18 patients with pain attributed to PC and found that pain relief was achieved in 17 (94%). However, they made no effort to calculate an analgesic-equivalent dose. Ascunce et al[27] retrospectively evaluated the efficacy of EUS-CGN in 64 PC patients and found a significant reduction in pain scores and narcotic use in 42 (65%) 1 week after the procedure; at 1 month, the response had persisted. In the current study, we found that the pain continued to improve over a long period of time, with a substantial drop in MS Contin consumption. We surmise that there are several possibilities to explain this phenomenon. First, the beneficial effect of this treatment may be attributed to the thorough destruction of the ganglion. Second, the primary purpose of the current study was the safety of direct celiac ganglion irradiation with ^{125}I seeds, which may bias the efficacy results. Third, there were also some patients who did not respond to the treatment, with a relatively low mean VAS score of 4.6 at baseline and shorter survival time (58 days compared with 79 days). Finally, the small sample and uncontrolled design may also cause bias. Of the patients, 82.6% (19/23) reported pain relief 2 weeks after the procedure, without an increase in MS Contin use. During the entire follow-up period, the relatively low VAS score and MS Contin use were maintained. In contrast, implanting the seeds in the tumor may also cause pain relief, but only briefly (VAS score decreased from 5.07 to 1.73 in 1 week and increased to 3.53 after 1 month[21]). The current method may cause an instant edema response to the seeds and a prolonged analgesic effect induced by the apoptosis of neural cells (VAS score increased from 5.78 to 6.09 in 1 week and decreased to 3.17 after 1 month). These findings suggest that EUS-guided celiac ganglion irradiation with ^{125}I seeds is a promising approach to the management of pain in PC patients.

Several mechanisms may explain the efficacy of celiac ganglion irradiation with ^{125}I seeds in PC patients. First, ^{125}I seeds may inflict significant damage to celiac ganglia, as demonstrated by our previous study.[11] Second, in PC patients whose celiac ganglia are invaded,[28] brachytherapy may induce apoptosis and necrosis of tumor cells, relieving the compression of celiac ganglia. Finally, concomitant use of chemotherapy may also improve pain control and enhance the effects of a celiac block.

Levy et al[6] reported that 34% of patients who underwent direct CGN experienced an initial pain exacerbation, which correlated with improved therapeutic response. But in another study published recently, such a phenomenon was not observed by Ascunce et al.[27] In the current study, we found that 26.1% of PC patients experienced a pain exacerbation lasting a mean duration of 8.5 days. However, initial pain exacerbation showed no relation to therapeutic response. It is still unclear why initial exacerbation of their pain developed in patients undergoing direct CGN. We surmise that the compression and stimulation of the celiac ganglia by ^{125}I seeds may partially explain this.

This study had some limitations. First, we cannot establish firm conclusions because of the small sample size and lack of controls. Second, the optimal dose of irradiation was not determined. We also did not investigate whether displacement or migration of radioactive seeds occurred for any reason during the follow-up period, which would further confirm the safety of this technique. Finally, patients in this study underwent chemotherapy, which has an analgesic effect and may make the results inconclusive. In the future, we want to design a controlled study to compare the efficacy and safety of celiac ganglion irradiation with ^{125}I seeds with those of drug therapy or CGN.

To the best of our knowledge, this is the first study that evaluates the efficacy and safety of direct celiac ganglion irradiation with ^{125}I seeds in the treatment of pain resulting from advanced PC. Our results suggest that EUS-guided celiac ganglion irradiation with ^{125}I seeds is safe, feasible, and effective in patients who have PC pain. Randomized, prospective, controlled, and comparative clinical trials are needed to confirm the safety and long-term effectiveness of this new approach to pain management, relative to conventional techniques.

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