International Journal of Clinical Oncology (2022) 27:1196–1201
https://doi.org/10.1007/s10147-022-02160-6

ORIGINAL ARTICLE

Efficacy of EUS-guided celiac plexus neurolysis in combination with EUS-guided celiac ganglia neurolysis for pancreatic cancer-associated pain: a multicenter prospective trial

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Received: 27 January 2022 / Accepted: 29 March 2022 / Published online: 12 April 2022

Abstract

Objectives This study evaluated the efficacy of endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) in combination with EUS-guided celiac ganglia neurolysis (EUS-CGN) for pancreatic cancer-associated pain.

Methods This multicenter prospective trial was registered in the University Hospital Medical Information Network (UMIN000031228). Fifty-one consecutive patients with pancreatic cancer-associated pain who presented at one of five Japanese referral centers between February 2018 and March 2021 were enrolled. EUS-CGN was added in cases of visible celiac ganglia. The primary endpoint was effectiveness, defined as a decrease in the numerical rating scale (NRS) by ≥ 3 points. NRS data were prospectively acquired at 1 week after the procedure to evaluate its effectiveness and the extent of pain relief.

Results The technical success rates of EUS-CPN and EUS-CGN were 100% and 80.4%, respectively. The overall efficacy rate was 82.4% [90% confidence interval (CI) 71.2–90.5, $P < 0.0001$]. The complete pain relief rate was 27.4%. The adverse events rate was 15.7%. The average pain relief period was 72 days. The efficacy rate was higher in the EUS-CPN plus EUS-CGN group than in the EUS-CPN alone group. EUS-CPN plus EUS-CGN was superior to EUS-CPN alone for achieving complete pain relief ($P = 0.045$). EUS-CGN did not improve the average length of the pain relief period.

Conclusions EUS-CPN combined with EUS-CGN is safe, feasible, and effective for pain relief in patients with pancreatic cancer. The patients who received additional EUS-CGN had a better short-term response.

Clinical trial number UMIN000031228.

Keywords Cancer-associated pain · Celiac ganglia neurolysis · Celiac plexus neurolysis · EUS · Pancreatic cancer

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Abbreviations

CI	Confidence interval
CPN	Celiac plexus neurolysis
EUS	Endoscopic ultrasonography
EUS-CGN	Endoscopic ultrasound-guided celiac ganglia neurolysis
EUS-CPN	Endoscopic ultrasound-guided celiac plexus neurolysis
NRS	Numerical rating scale
SD	Standard deviation
QOL	Quality of life

Introduction

Celiac plexus neurolysis (CPN) has been used worldwide as a treatment for cancer-related pain since the laparotomy procedure was first reported by Kappis in 1914 [1]. Computed

tomography-guided CPN is an established and highly effective treatment; however, serious complications such as weakness or paralysis of the lower limbs and/or pneumothorax occur in approximately 2% of cases [2]. Endoscopic ultrasound-guided CPN (EUS-CPN) was first reported by Faigel et al. and Wiersema et al. in 1996 [3, 4]. Because the target site is detected under EUS guidance, puncture and drug injection can be performed without risk of injury to blood vessels and other organs. The value of EUS-CPN for the management of pancreatic cancer-associated pain was reported previously [4–6]. EUS-guided celiac ganglia neurolysis (EUS-CPN) was developed to improve the efficacy of EUS-CPN [7, 8]. The present study prospectively evaluated EUS-CPN in combination with EUS-CGN for the treatment of pancreatic cancer-associated pain in a multicenter trial.

Methods

Study design and patient enrollment

This study was approved by the Institutional Review Boards of all participating hospitals. All patients provided written informed consent. The trial was registered with the University Hospital Medical Information Network (number UMIN000031228). Consecutive patients with pancreatic cancer-associated pain who presented at one of five Japanese referral centers between February 2018 and March 2021 were prospectively enrolled. A numerical rating scale (NRS) was used to score the degree of pain with an 11-point scale from 0 to 10. Patients were included if they were > 20 years of age, had a pancreatic cancer-associated NRS ≥ 3, had a performance status ≤ 2, had no severe comorbidities, and had provided written informed consent. Patients were excluded if they had a high risk of bleeding (a platelet count < 50,000/mm^3 or PT-INR ≥ 1.5), had a performance status ≥ 3, or did not/could not provide informed consent. Although the timing of the procedure was not standardized, the research protocol stated the following as a guide for patient selection; "Patients who have difficulty in controlling pain with non- or weak opioid analgesics and are considering introducing or increasing the dose of opioid analgesics".

Outcome measures

EUS-CPN in combination with EUS-CGN was evaluated in terms of (i) technical success rate, (ii) efficacy rate (primary outcome), (iii) complete pain relief rate, (iv) adverse events rate, and (v) average length of pain relief period. Technical success was defined as successful puncture of the target and drug injection. The pain assessment as performed face to face by investigators who were not blinded to treatment group (CPN alone or CPN plus CGN). Effectiveness was defined as a decrease in NRS of ≥ 3 points 1 week after the procedure. Complete pain relief was defined as NRS = 0 at 1 week after the procedure. Adverse events were defined as procedure-related complications occurring within 30 days. The pain relief period was defined as the period from the date of the procedure until the date of NRS increase to the pre-treatment value, the introduction or increase in the dose of medications such as opioids, weak opioids, or non-opioid analgesics, or the time of death. In the present study, when the term opioid was used alone, it indicates a potent opioid in the present study.

EUS-CPN and EUS-CGN techniques

As described in a previous study, the procedures were performed by expert endosonographers who had performed more than 100 EUS treatments using a linear array echoendoscope (GF-UCT 260, Olympus Optical, Tokyo, Japan) [9]. EUS-CPN was performed using the central method with a 25- or 22-gauge needle. EUS-CGN was performed in addition to EUS-CPN if the celiac ganglia were visible (Figs. 1 and 2). For EUS-CPN, 20 ml of 99.5% absolute alcohol was injected at the level of the celiac artery after injection of 3 ml of 1% lidocaine to prevent transient neurolytic agent-induced pain. The celiac ganglia, hypoechoic nodular structures located between the aorta and the left adrenal grand, were identified. For EUS-CGN, 2–5 ml of 99.5% absolute alcohol was injected until it was sufficiently distributed.

Statistical analysis

A randomized multicenter trial in Japan reported that the efficacy rates of EUS-CPN and EUS-CGN were 45.5% and 73.5%, respectively [8]. The expected efficacy rate for EUS-CPN in combination with EUS-CGN in the present study was 75%, and the expected threshold efficacy rate

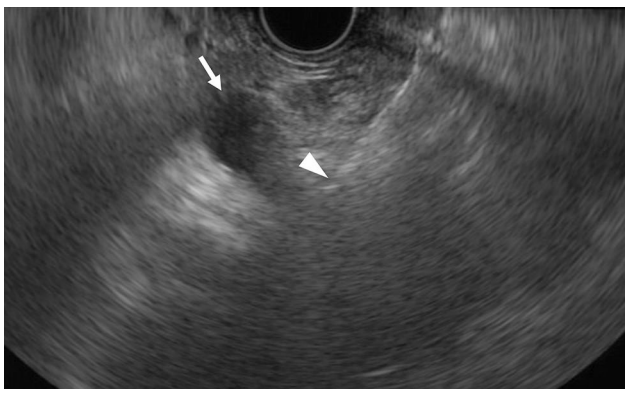

Fig. 1 EUS-CPN image showing the celiac artery (arrow) and a 22-gauge needle (arrowhead), which is positioned adjacent to the celiac artery origin

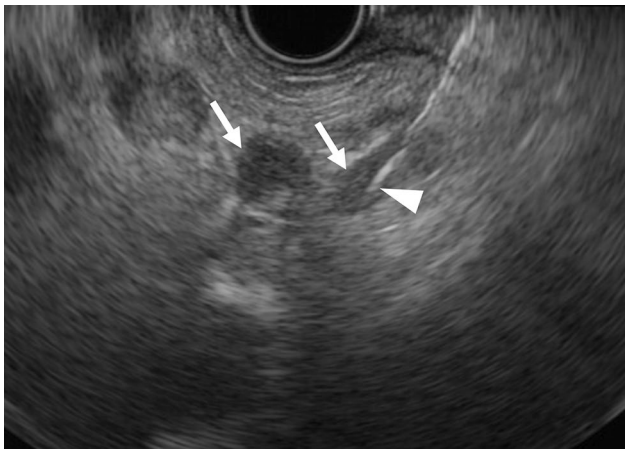

Fig. 2 EUS-CGN image showing celiac ganglia (arrows) and a 22-gauge needle (arrowhead), which punctured a celiac ganglion (arrow)

Table 1 Baseline characteristics of the patients

	Total, $n=51$
Age, median (range), years	69.1 (35 – 87)
Sex, male:female, *n*	31:20
Tumor size, mean ± SD, mm	42.7 ± 13.9
Stage (JPS 7th edition), *n*	
IIA	3
III	12
IV	36
NRS before the procedure, mean ± SD	6.2 ± 1.7
Undergoing chemotherapy, %	41.2 (21/51)
Subsidiary drug usage before the procedure, %	5.9 (3/51)
Non-opioid usage before the procedure, %	74.5 (38/51)
Weak opioid usage before the procedure, %	3.9 (2/51)
Opioid usage before the procedure, %	39.2 (20/51)

JPS Japan pancreas society, *NRS* numerical rating scale, *SD* standard deviation

for this procedure was 50%. Under this assumption, a type I error of 0.05 (one-sided), a power of 80%, and a sample of 42 patients would be required. Assuming a certain drop-out rate, a target sample size of 50 patients was established. If the lower limit of the 90% confidence interval (CI) was ≥ 50%, EUS-CPN combined with EUS-CGN would be considered valid. For reference, the 95% CI was also calculated. *P* values were calculated by performing the exact binominal test with a null hypothesis of 50%: a one-sided test with a 5% significance level was used. Continuous and categorical variables were analyzed using *t* tests and chi-square tests, respectively. Statistical analysis was performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Results

The study included 51 patients with unresectable pancreatic cancer (Table 1). Number of treatments at each facility and the selected treatment are shown in supplementary table. All patients had unresectable pancreatic cancer. Technical success rates of EUS-CPN and EUS-CGN were 100% (51/51) and 80.4% (41/51), respectively; celiac ganglia were undetectable on EUS in 10 patients. Outcomes of EUS-CPN and EUS-CGN are shown in Table 2. Overall efficacy rate was 82.4% (90% CI 71.2–90.5; 95% CI 69.1–91.6; $P<0.0001$). NRS decreased in almost all cases at 1 week after the procedure (Fig. 3). Efficacy rate of EUS-CPN plus EUS-CGN was higher than that of EUS-CPN alone ($P=0.061$). Complete pain relief rate was significantly higher for EUS-CPN plus EUS-CGN than for EUS-CPN alone ($P=0.045$). All adverse events were transient and did not require treatment. Pain relief lasted until death from the primary disease in six patients. There were no significant differences between cases with ($n=20$) and without ($n=31$) opioid usage before the procedure with regard to the rates of efficacy (75.0% vs. 87.1%, $P=0.289$), complete pain relief (15.0% vs. 35.5%, $P=0.198$), adverse events (10.0% vs. 19.4%, $P=0.456$), and average length of the pain relief period (45 days vs. 86 days, $P=0.100$).

Discussion

The addition of EUS-CGN to EUS-CPN–related treatment has been reported to improve pain relief [8, 10]. Japanese randomized multicenter trials revealed that the positive response rate of EUS-CGN is significantly higher than that of EUS-CPN ($P=0.026$) [8]. Thus, EUS-CGN in combination with EUS-CPN-related procedures is becoming increasingly important. Sakamoto et al. reported that pain relief can be improved by distributing the drug solution over a wide area extending over the superior mesenteric artery, and concluded that broad neurolysis provided superior analgesia [11]. However, positioning the puncture needle around the superior mesenteric artery requires an experienced operator. There are various theories about the EUS-CPN methodology regarding the puncture site [12–15]. Two reports showed that bilateral injection, which involves injecting the drug solution into both sides of the celiac artery, is more effective than central or left injection [12, 13]. By contrast, two studies reported equal results of bilateral and central injection [14, 15]. Thus, bilateral vs. central injection remains controversial issue. With the hope that EUS-CPN–related procedures will be generalized in the future, we simplified the procedure in the present study, with the additional consideration

Table 2 Outcomes of CPN and CGN

	Total ($n=51$)	CPN plus CGN ($n=41$)	CPN alone ($n=10$)	P value*
Efficacy rate, %	82.4 (42/51)	87.8 (36/41)	60.0 (6/10)	0.061
Complete pain relief rate, %	27.4 (14/52)	34.1 (14/41)	0 (0/10)	0.045
Adverse events rate, %	15.7 (8/52)	17.1 (7/41)	10.0 (1/10)	1.000
Diarrhea, *n*	6	6		
Hypo tension, *n*	1	1		
Lower limb weakness, *n*	1		1	
Average length of pain relief period, days	72	69	88	0.576
Reduction rate of opioids, %	35.0 (7/20)	41.2 (7/17)	0 (0/3)	0.545

CGN celiac ganglia neurolysis, *CPN* celiac plexus neurolysis

*CPN plus CGN vs. CPN alone

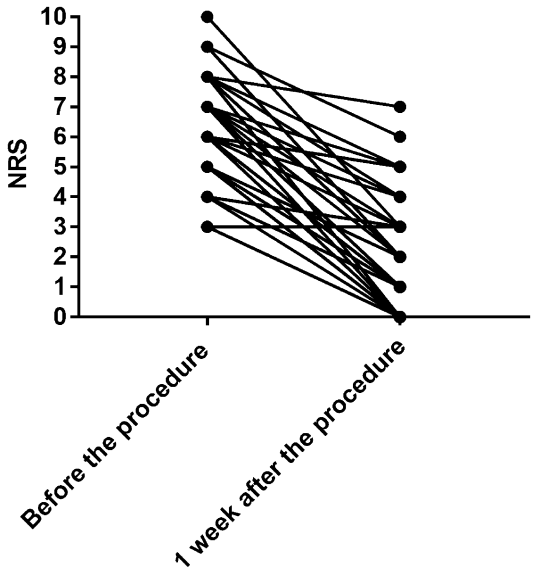

Fig. 3 Plot columns showing that NRS improved in almost all cases at 1 week after the procedure. The mean NRS with standard deviation before and at 1 week after the procedure was 6.2 ± 1.7 and 1.9 ± 1.8, respectively

that it was a multicenter study. We therefore, decided not to advance the puncture needle around the superior mesenteric artery and to perform central injection. Although there are few reports on the injection volume, one prospective pilot study showed that the safety and efficacy of 10 ml vs. 20 ml alcohol were comparable [16]. On the other hand, Kappelle et al. suggested that high-volume (4 ml per ganglion) is preferable to low-volume (1 ml per ganglion) in EUS-CGN [17]. Based on these previous studies, we assessed the efficacy of central EUS-CPN using 20 ml alcohol in combination with EUS-CGN using 2–5 ml alcohol in this multicenter prospective trial, expecting the high-volume to be more effective.

In the present study, the overall efficacy rates exceeded the expected value estimated when setting the number of cases. Similar to previous reports [18], the rate of visualization of celiac ganglia was 80.4% in the present study, the treatment was more effective for patients receiving the combination of EUS-CPN plus EUS-CGN. The rate of complete pain relief was 34.1%, and it was achieved only in patients who received EUS-CPN plus EUS-CGN. However, the length of the pain relief period did not differ between the combination group and the EUS-CPN alone group in the present or previous studies (2–3 months) [18]. Additional EUS-CGN may increase the responsiveness of patients only in the short term. The result that the average length of the pain relief period was shorter for EUS-CPN plus EUS-CGN than for EUS-CPN (69 vs. 88 days) was unexpected and the underlying of this mechanism is unknown. The number of patients who responded to EUS-CPN alone was only six in the present study; therefore, further examination on a large patient population will be needed to answer this question. The suitable timing of EUS-CPN or EUS-CGN has not been sufficiently investigated. Wyse et al. suggested that EUS-CPN should be performed at an early stage in patients with inoperable pancreatic cancer, such as at the time of diagnosis or cancer staging to improve pain relief [19]. Performing the procedure at an early stage would reduce the risk of a massive cancer involving ganglia. In the present study, the average pain relief period tended to be longer in patients who did not use opioids before the procedure that in those who did, although a tendency or significant difference in efficacy, complete pain relief, and adverse events between the two groups was not observed. This result suggests that the procedure should be performed as soon as possible.

The present study had several limitations. First, there was no control arm. A recent prospective randomized trial that evaluated the efficacy of EUS-CPN in 24 patients compared with medication alone in 22 patients with unresectable pancreatic cancer did not demonstrate the utility of EUS-CPN [20]. In this trial, there were no statistically significant differences in pain relief, quality of life (QOL), and opioid consumption between the groups. However, in the present study, the rate of reduction of opioid consumption was

41.2% for EUS-CPN in combination with EUS-CGN and 0% for patients treated with EUS-CPN alone, which might lead to improved QOL in patients with pancreatic cancer-related pain. Another recent prospective randomized study in patients with unresectable pancreatic cancer and abdominal pain reported that EUS-CPN combined with EUS-CGN reduced median survival time without improving pain, QOL, or adverse events compared with EUS-CPN [21]. The mechanism underlying the shortened median survival time was unknown and the authors concluded that further study was necessary. Thus, the combination of EUS-CPN with EUS-CGN should be performed with caution. The main differences in the EUS-CPN combined with EUS-CGN techniques between this randomized study and the present study are the use of bilateral vs. central methods, and whether EUS-CPN or EUS-CGN is performed first. In the randomized study, EUS-CGN was performed before EUS-CPN, and celiac ganglia were identified in 87.7% (50/57) of patients, which was higher than the result of the present study. Furthermore, the pain response was assessed 4 weeks after the procedure in the randomized study, whereas in the present study, it was assessed 1 week after the procedure because early pain relief was considered important for patients with pancreatic cancer-related pain. In the future, prospective randomized trials comparing EUS-CPN plus EUS-CGN vs. medication, EUS-CPN alone, or EUS-CGN alone, should be performed including a detailed evaluation of QOL, survival, or pain relief effects. In conclusion, EUS-CPN combined with EUS-CGN is safe, feasible, and effective for pain relief in patients with pancreatic cancer. EUS-CPN is less effective for patients who do not have a visible ganglion. Patients without a visible ganglion might have a massive cancer involving ganglia, resulting in a decreased response to EUS-CPN.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10147-022-02160-6.

Author contributions KK: wrote the manuscript, conceived and designed the study, and performed data collection and endosonography studies. MK, IK, HI, TO, HM, and KM: performed data collection, endosonography studies, and critically revised the manuscript with respect to important intellectual content. YC: performed statistical analysis of data. MT, MK, and MK: critically revised the manuscript with respect to important intellectual content.

Declarations

Conflict of interest All authors have no COI to disclose.

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