EUS-guided celiac ganglion radiofrequency ablation versus celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial (with videos) CME

Ji Young Bang, MD, MPH, Bryce Sutton, PhD, Robert H. Hawes, MD, Shyam Varadarajulu, MD

Orlando, Florida, USA

Background and Aims: Although EUS-guided celiac plexus neurolysis (EUS-CPN) is frequently performed, its efficacy for palliation of pain in pancreatic cancer is suboptimal. Recently, EUS-guided radiofrequency ablation (EUS-RFA) has been proposed as a palliative treatment option for pancreatic neoplasms. We performed a single-blind, randomized trial to compare the effectiveness of EUS-CPN and EUS-RFA for palliation of pain in pancreatic cancer.

Methods: Patients with abdominal pain because of locally advanced or metastatic pancreatic cancer underwent EUS-CPN (n = 14) or EUS-RFA (n = 12). EUS-RFA was performed using a 1F monopolar probe passed via a 19-gauge FNA needle, by targeting the area of celiac plexus or visualized ganglia. Primary outcome was pain severity as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire pancreatic cancer module (PAN26) administered pretreatment and at 2 and 4 weeks post-treatment. Secondary outcome measures were comparison of quality of life as determined by the PAN26 and EORTC Quality of Life Questionnaire core questionnaire (C30) and opioid analgesia use between the 2 groups.

Results: Both the PAN26 (49.0 vs 57.0, $P < .001$) and C30 (51.9 vs 64.4, $P = .032$) revealed less pain for EUS-RFA than for EUS-CPN. Also, the EUS-RFA cohort experienced significantly less-severe GI symptoms, were able to plan more for the future, and had better emotional functioning compared with the EUS-CPN group.

Conclusions: Compared with EUS-CPN, EUS-RFA provided more pain relief and improved the quality of life for patients with pancreatic cancer. (Clinical trials registration number: NCT03152487.) (Gastrointest Endosc 2019;89:58-66.)

(footnotes appear on last page of article)

Pancreatic cancer is often associated with intense and refractory pain. Although non-narcotic medical therapies fail to control pain adequately, opioids induce side effects such as constipation, altered mental status, and respiratory depression.[1] The main advantage of administering a nonpharmacologic therapy such as celiac plexus neurolysis (CPN) is that both pain control and quality of life can be improved but without the attendant risk of medication-induced side effects.[2-4] CPN involves the destruction and subsequent fibrosis of the splanchnic nerve fibers by percutaneous or intraoperative injection of alcohol or a sclerosing agent.[5,6] The treatment has been shown to be significantly more effective than placebo, with pain relief lasting between 6 weeks and 6 months.

This video can be viewed directly from the GIE website or by using the QR code and your mobile device. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

The first report of EUS-guided CPN (EUS-CPN) via the transgastric route was published in 1996 and was shown to be safe, with significant improvement in pain scores in 88% of patients with pancreatic cancer or intra-abdominal metastases at a 3-month follow-up.[7] However, subsequent studies demonstrated substantial variation in the proportion of patients experiencing pain relief (24%-80%).[8-16] With the objective of improving treatment outcomes, the technique of neurolysis has undergone several iterations to include injection into both sides of the celiac trunk, broader injection to include the space around the superior mesenteric artery, and direct injection into the celiac ganglia.[17-20]

Radiofrequency ablation (RFA) is an electrosurgical technique that uses a high-frequency alternating current

to produce thermal coagulation of neoplastic lesions. RFA has also been shown to be effective in inducing splanchnic nerve blockade in patients with abdominal pain because of chronic pancreatitis and pancreatic or liver cancer.[21,22] Hitherto, RFA has been administered only by intraoperative or percutaneous techniques, but more recently, dedicated probes have been developed for RFA of pancreatic neoplasms under EUS guidance.[23-25] Despite limited data on their clinical effectiveness, preliminary evidence demonstrates good tolerability and an acceptable safety profile. Given the suboptimal treatment outcomes for EUS-CPN, we hypothesized that EUS-guided RFA (EUS-RFA) could potentially be superior to EUS-CPN for alleviation of pain in pancreatic cancer patients. This is because EUS-RFA likely results in more focused targeting of the celiac plexus of nerves, whereas injection of alcohol in EUS-CPN involves diffusion over a wide anatomic compartment. We therefore conducted a randomized trial to compare EUS-RFA and EUS-CPN for palliation of pain in patients with pancreatic cancer.

METHODS

Participants

After approval of the study by the Institutional Review Board, we attempted to recruit consecutive patients in the wards or preprocedure consultation rooms at a single tertiary referral center who presented with abdominal pain and pancreatic mass on CT or magnetic resonance imaging that was suspicious for locally advanced or metastatic pancreatic malignancy or those with previously diagnosed locally advanced or metastatic pancreatic adenocarcinoma. Patients aged <19 years, those who had undergone prior EUS-CPN, those with irreversible coagulopathy (international normalized ratio >1.5 or platelet count <50,000/mm^3), those in whom a preliminary diagnosis of adenocarcinoma could not be established intraprocedurally at EUS-guided FNA, or abdominal pain with etiology other than pancreatic malignancy were excluded. Informed consent was obtained from all patients.

Randomization and masking

Computer-generated randomization assignments were provided by the statistician using a block randomization method and placed in sequentially numbered, sealed, opaque envelopes that were opened by the research coordinator intraprocedurally to determine treatment allocation. Once the inclusion criteria were met, patients were randomized equally (1:1 allocation) to 1 of 2 treatment arms. Given the differences in procedural techniques, endoscopists were not blinded to the treatment allocation. However, study participants and research coordinators who conducted the outcome assessments were blinded to the type of intervention. No antibiotics were administered before or after the intervention. All authors had full access to the study data and have reviewed and approved the final manuscript.

Study interventions

All interventions were performed using a curved linear-array echoendoscope (UCT140; Olympus America Corporation, Center Valley, Pa) under monitored anesthesia care using propofol with patients in the left lateral position. Lactated Ringer's solution was infused at a rate of 75 mL/h in all patients during the procedure. In patients without a prior tissue diagnosis, EUS-guided FNA of the pancreatic mass was first performed. Randomization was undertaken intraprocedurally only after a preliminary diagnosis of adenocarcinoma was rendered by an onsite cytopathologist and unresectability was confirmed.

The site of celiac artery take-off from the aorta was visualized endosonographically, and every attempt was made to identify the celiac ganglia, which were typically seen between the celiac artery and the left adrenal gland as hypoechoic, comma-shaped structures, often with an irregular edge. If more than 1 ganglia were identified, the larger ganglia were targeted for intervention. If ganglia could not be identified at EUS, then interventions were performed in the space located between the celiac trunk and the aorta. The procedures were performed by 1 of 3 endoscopists (S.V., R.H.H., J.Y.B.) who have all performed at least 2000 EUS procedures individually.

EUS-CPN technique. The tip of a 19-gauge FNA needle (Expect; Boston Scientific, Marlborough, Mass) was introduced into the celiac ganglia (Video 1, available online at www.giejournal.org) or the celiac plexus space (Video 2, available online at www.giejournal.org). Using both color Doppler and aspiration to confirm that the needle tip was not intravascular, we first injected 10 mL of .25% bupivacaine, followed by 20 mL of 98% dehydrated alcohol.

EUS-RFA technique. The Habib EUS-RFA catheter (EMcision Ltd, London, UK) is a 1Fr wire (.33 mm/.013 ins) with a working length of 190 cm. RF power was applied to the electrode at the end of the wire to coagulate tissue. The device was monopolar and used in conjunction with a grounding (diathermy) pad applied to the patient's lower back. The catheter was connected to an adaptor cable, which was then connected to a generator with power set at 10 W.

The stylet of a 19-gauge needle was removed and the RFA catheter gently inserted inside the hollow of the FNA needle until the needle tip was reached. The catheter was then withdrawn by a few millimeters so the catheter tip was located just proximal to the needle tip. The FNA needle containing the RFA catheter was then inserted into the working channel of the echoendoscope. After puncturing the celiac ganglia using the FNA needle, the RFA catheter was gently pushed into the ganglia until it could not be pushed in any further. The FNA needle was then withdrawn by 1 cm while at the same time advancing the RFA catheter within the ganglia to disengage the

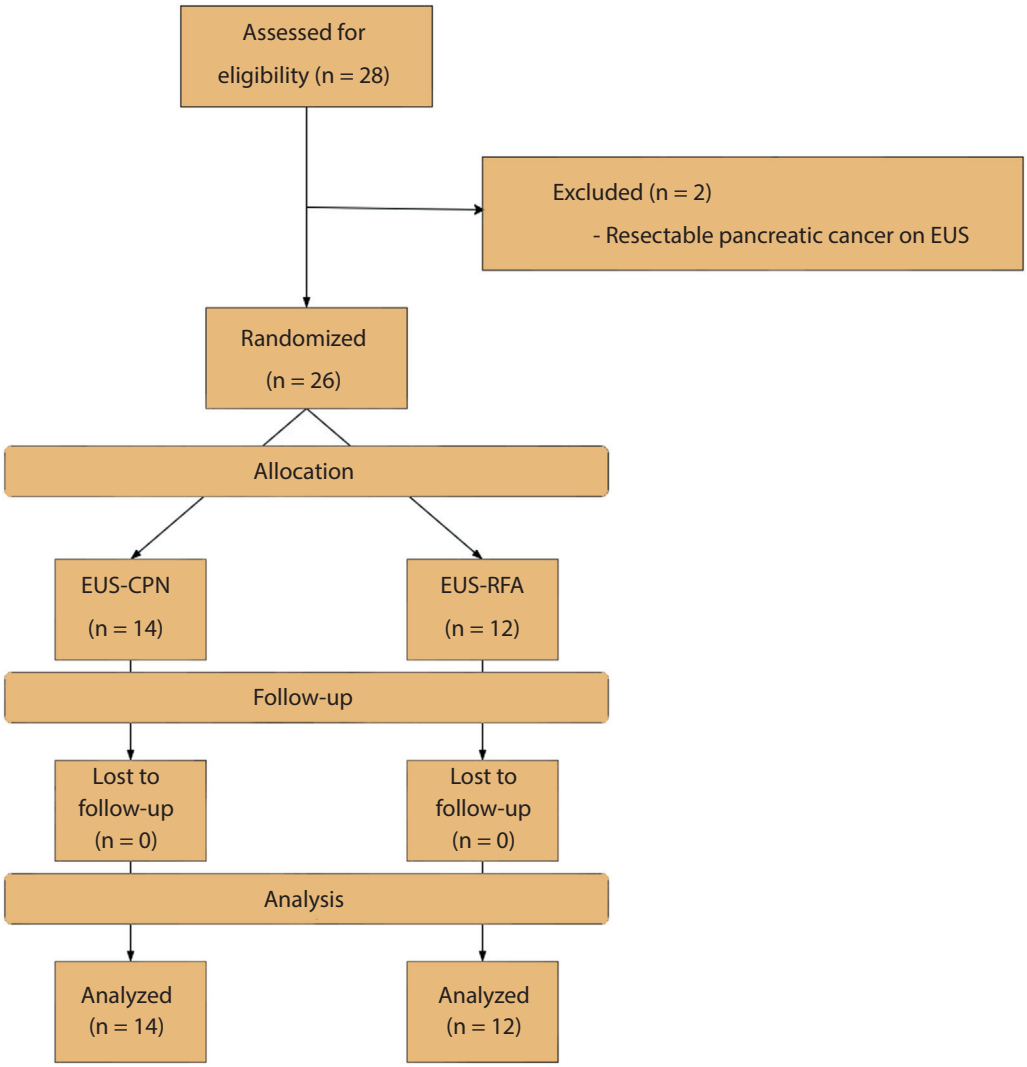

Figure 1. CONSORT flow diagram of patients undergoing EUS-guided celiac plexus neurolysis or radiofrequency ablation.

contact between the active part of the RF catheter and the metallic FNA needle. When required, fluoroscopy was used to enable visualization of the RFA probe protruding beyond the tip of the needle. RF energy was applied for 90 seconds at the set wattage. Application of RF energy was visualized sonographically as hyperechoic change within the ganglia. The RFA probe was then retracted and the needle repositioned to ablate another area of the ganglia (Video 3, available online at www.giejournal.org). This process was repeated 3 to 4 times to ensure complete ablation of the ganglia, as indicated by hyperechogenicity of the entire ganglion. When celiac ganglia were not visualized, the 19-gauge needle was positioned at the celiac plexus space and RF energy was administered at 2 locations, for 90 seconds per location (Video 4, available online at www.giejournal.org).

Postprocedure care

After completion of the procedure, patients were monitored for 2 hours before discharge. One liter of normal saline solution was administered in all patients during the recovery period unless contraindicated. Patients were crossed over to the alternate treatment arm if they reported persistent symptoms, and a repeat intervention was requested by their oncologists.

Assessment of outcome measures

For severity of pain and quality of life, 4 measures were used: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire pancreatic cancer module (PAN26), the EORTC Quality of Life Questionnaire core questionnaire (C30), the Brief Pain Inventory-Short Form (BPI), and the visual analog scale (VAS).

EORTC PAN26. The PAN26 was administered to all patients undergoing interventions. The instrument contains 26 items assessing pain, GI symptoms, oral intake, anorexia, cachexia, and emotional problems related to pancreatic cancer. The pancreatic cancer module is designed for patients at any stage of the disease and

TABLE 1. Patient characteristics and procedure details

Characteristic	Subgroup	CPN group (n = 14)	RFA group (n = 12)	*P* value*
Age, y	Mean (SD)	65.7 (12.1)	62.8 (13.7)	
	Median (IQR)	65 (57-74)	59 (52-75)	.520
Gender	Female	6 (42.9)	7 (58.3)	.431
	Male	8 (57.1)	5 (41.7)	
Race	Black	1 (7.1)	1 (8.3)	.720
	White	13 (92.9)	10 (83.3)	
	Other	0	1 (8.3)	
Duration of symptoms, wk	Mean (SD)	5.1 (3.7)	5.6 (3.1)	
	Median (IQR)	3.5 (3-6)	6 (3.5-7.5)	.406
Location of pancreatic mass	Head/uncinate	8 (57.1)	8 (66.7)	.701
	Body/tail	6 (42.9)	4 (33.3)	
Tumor stage	I	0	0	.360
	II	6 (42.9)	2 (16.7)	
	III	3 (21.4)	3 (25.0)	
	IV	5 (35.7)	7 (58.3)	
Tumor size, mm	Mean (SD)	32.5 (7.3)	29.6 (9.4)	
	Median (IQR)	30 (30-30)	27.5 (22.5-35)	.173
Tissue diagnosis	Established previously	5 (35.7)	7 (58.3)	.249
	Established at time of procedure	9 (64.3)	5 (41.7)	
Chemotherapy before CPN/RFA		3 (21.4)	6 (50.0)	.218
Technical success†		14 (100)	12 (100)	.999
Adverse events		5 (35.7)‡	5 (41.7)§	.999
Crossover to alternate arm		3 (21.4)	0	.225

Values are n (%) unless otherwise defined.
CPN, Celiac plexus neurolysis; *IQR*, interquartile range; *RFA*, radiofrequency ablation; *SD*, standard deviation.
*Comparison of continuous variables was performed using the Wilcoxon rank sum test.
†Celiac ganglia visualization: 5 (35.7%) in the CPN group, 4 (33.3%) in the RFA group.
‡Postprocedural adverse events in the CPN group: diarrhea (n = 1), fever (n = 1), nausea/vomiting (n = 1), and increase in abdominal pain (n = 2).
§Postprocedural adverse events in the RFA group: nausea/vomiting (n = 4), increase in abdominal pain (n = 1).

undergoing endoscopic, surgical, chemotherapy, or palliation. The PAN26 scales have been found to be both reliable and valid, and symptom scales are sufficiently sensitive to detect clinically meaningful differences in quality of life.[26,27] The instrument was scored according to developer guidelines in which linear transformations were applied to generate scales ranging from 0 to 100, with higher scores representing higher symptom severity. The PAN26 questionnaire was administered before CPN or RFA and then at 2 and 4 weeks after intervention. The pain score determined by PAN26 was taken as the primary outcome measure.

EORTC C30. The C30 is the core quality of life questionnaire for patients participating in clinical trials.[28] The C30 includes 9 multiple-item scales, 5 scales within the functional domain, 3 scales within the symptom domain, and 1 encompassing global health and quality of life. The functional scales address physical, cognitive, emotional, and social functioning. The symptom scales address pain, dyspnea, insomnia, appetite loss, fatigue, GI symptoms, and financial difficulties. The instrument was scored according to developer guidelines in which linear transformations were applied to generate scores ranging from 0 to 100. For functional scales, 0 represents poor function and 100 represents good function, whereas for symptom scales, higher scores represent higher symptom severity. The C30 was administered before CPN or RFA and then at 2 and 4 weeks after intervention.

BPI and VAS. The BPI was developed by the Pain Research Group at the University of Wisconsin-Madison and the Department of Symptom Research at the University of Texas MD Anderson Cancer Center with grant support from the National Cancer Institute and the Cancer Unit of the World Health Organization.[29] The instrument was developed specifically to measure self-reported cancer pain and consists of 9 items encompassing pain severity and pain interference. The questionnaire has been shown to have satisfactory to excellent test–retest reliability, construct validity, criterion validity, and sensitivity to change.[30-33]

The VAS for pain is a single dimension measure of current pain intensity or pain intensity in the last 24 hours,

TABLE 2. Comparison of the adjusted mean scores for PAN26 using generalized estimating equations (high score = high level symptomology)

	CPN group (n = 14)	RFA group (n = 12)	*P* value*
Pain	57.0	49.0	<.001
Restriction in oral intake	53.5	39.1	.031
Taste change	64.4	44.9	.280
Xerostomia	57.7	43.1	.032
Indigestion	51.0	20.6	<.001
Diarrhea and fecal urgency	24.8	16.9	.029
Jaundice	18.2	13.0	.002
Flatulence	33.5	16.0	<.001
Abdominal bloating	45.6	33.7	.015
Muscle weakness	48.2	33.6	.598
Weight loss	43.1	46.7	.525
Disinterest in sex/sexual enjoyment	65.2	72.9	.930
Dissatisfaction with body image	56.5	45.2	.426
Satisfaction with healthcare	81.1	81.6	.173
Burden of treatment	51.2	40.4	.470
Fear for future health	69.3	56.8	.001
Limitation in ability to plan for future	68.5	50.1	.003

PAN26, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-pancreatic cancer module; *CPN*, celiac plexus neurolysis; *RFA*, radiofrequency ablation.
**P* values reported for time and group interactions in the generalized estimating equation model using robust standard errors.

with scores ranging from zero ("no pain") to 10 ("worst possible pain"). The VAS scores were scaled from 0 to 100 to facilitate comparison with other reported pain measures. The BPI and VAS questionnaires were administered before CPN or RFA and then at 2 and 4 weeks after intervention.

Analgesia requirement

Information on the dose and frequency of opioid medications administered within 24 hours before the assignment intervention was collected and at 2 and 4 weeks after the procedure. The total dose of opioids administered was then converted into oral morphine equivalent dose for comparison (mg/24 hours). Management of patients' analgesic regimen was left to the discretion of a single physician, who was either the patient's primary physician or oncologist. This physician was solely responsible for opioid analgesia management, and no specific follow-up for opioid management was scheduled for study purposes.

Adverse events

Information regarding the incidence of any procedure-related adverse events was collected at 48 hours, 2 weeks, and 4 weeks after intervention.

Data collection and follow-up

A questionnaire comprising PAN26, C30, BPI, VAS, and opioid analgesia use in the previous 24 hours was completed by all patients themselves on the day of the procedure before undergoing EUS-CPN or EUS-RFA. After the procedure, a research nurse who was blinded to the assigned intervention collected the follow-up information in all patients via telephone calls at 48 hours, 2 weeks, and 4 weeks.

Outcomes measures

The primary outcome measure was to compare the difference in pain severity on the PAN26 between patients treated by EUS-CPN and EUS-RFA. The secondary outcome measures were comparison of quality of life as determined by the PAN26 and C30 and opioid use between the 2 groups.

Statistical analysis

The primary outcome, the PAN26 pain score, was used to determine the sample size for our statistical analysis using generalized estimating equations (GEEs). We based our sample size calculation using data from a prospective observational study of patients with abdominal pain caused by inoperable pancreatic cancer who underwent EUS-CPN.[34] To determine the required sample size, we ran simulations on random-effects models for our primary outcome because population-average models with exchangeable correlation structures are equivalent to random-effects models with just a random intercept. Based on these simulations, we determined that we could detect a 10-point difference in the PAN26 pain score (considered to be a small to moderate clinical effect based on prior studies)[27,35-37] with at least 82% power by enrolling a

TABLE 3. Comparison of the adjusted mean scores for C30 using generalized estimating equations

	CPN group (n = 14)	RFA group (n = 12)	*P* value*
Global health status (high score = high QOL)			
Global health status/QOL	32.7	39.6	.400
Functional scales (high score = high function)			
Physical functioning	57.4	64.5	.343
Role functioning	36.6	47.9	.243
Emotional functioning	54.3	75.8	<.001
Cognitive functioning	56.4	70.8	.052
Social functioning	47.4	49.4	.813
Symptom scales (high score = high level symptomology)			
Pain	64.4	51.9	.032
Fatigue	66.3	52.7	.057
Nausea and vomiting	33.8	22.8	.051
Dyspnea	24.7	21.2	.642
Insomnia	57.4	39.2	.062
Appetite loss	66.5	59.6	.459
Constipation	35.3	17.6	.020
Diarrhea	12.3	18.3	.242
Financial difficulties	46.5	38.7	.410

C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire; *CPN*, celiac plexus neurolysis; *QOL*, quality of life; *RFA*, radiofrequency ablation.
**P* values reported for time and group interactions in the generalized estimating equation model using robust standard errors.

minimum of 10 subjects per trial arm assuming assessments at baseline, 2 weeks, and 4 weeks, given the structure of our variance–covariance matrices for random effects and residuals. The GEE model was chosen because it allows for correlations in the repeated-response variable, requires fewer distributional assumptions, and provides consistent estimates when correlation structures are incorrectly specified.[38] The final sample size was set at 12 patients per group to account for a 20% drop-out rate.

Descriptive data are presented as mean with standard deviation and median with interquartile range for continuous data or frequency with percentage for categorical data. Univariate group comparisons were performed by using the χ^2 or Fisher exact test for categorical variables and pooled Satterthwaite (unequal variance) *t* tests or Wilcoxon rank sum tests for continuous variables, where appropriate. The *t* tests were used to determine baseline differences between the 2 groups on summary scores for each instrument. For GEE models, the dependent variable was the summary score, and the independent variable of interest was the group and time interaction term. The group and time interaction allows statistical assessment of whether the treatment groups have different response curves over time. This also allows for flexibility in the response in which 1 endpoint may be identical but improvement in 1 group may occur more quickly over time. Other covariates included in the GEE models to control for the potential effects of confounding were age, gender, race, duration of symptoms, and undergoing chemoradiation therapy. Statistical significance was determined as $P < .05$ in 2-tailed tests. All analyses were conducted by using Stata 14 (Stata Corp, College Station, Tex). There was multiple testing of outcome data arising from individual patients, and therefore the results from the GEE analysis of PAN26 scores are to be taken as the main, definitive finding, with all other *P* values to be seen as descriptive only, uncorrected for multiple testing.

RESULTS

Patient characteristics and procedure details

Between April and October 2017, 28 patients were screened and 26 patients were enrolled in the study (EUS-CPN, n = 14; EUS-RFA, n = 12). Two patients were excluded before randomization because of resectable pancreatic adenocarcinoma on EUS (Fig. 1). The median tumor size was 30 mm (interquartile range, 25-30), and 46.2% had stage IV cancer at the time of enrollment. Twleve patients (46.2%) had a prior diagnosis of pancreatic cancer, of whom 9 were receiving chemotherapy. No patients were undergoing radiation therapy. There was no significant difference in the baseline patient or tumor characteristics between the 2 groups (Table 1). Baseline pain and quality of life scores are included in Supplementary Tables 1 to 3 (available online at www.giejournal.org).

TABLE 4. Comparison of the adjusted VAS and BPI scores and opioid use using generalized estimating equations (high score = high level symptomology)

	CPN group (n = 14)	RFA group (n = 12)	*P* value*
VAS (0-100)	57.3	30.1	.002
BPI (0-100)			
Pain severity	21.7	10.5	<.001
Pain interference	45.0	17.0	<.001
Opioid use (oral morphine equivalent dose in mg)	105.4	112.7	.583

VAS, Visual analog scale; *BPI*, Brief Pain Inventory; *CPN*, celiac plexus neurolysis; *RFA*, radiofrequency ablation.
**P* values reported for time and group interactions in the generalized estimating equation model using robust standard errors.

At the 4-week follow-up all patients were alive, with 16 patients (61.5%) undergoing chemotherapy (64.3% EUS-CPN vs 58.3% EUS-RFA, $P = .999$) and 1 patient undergoing radiation therapy. Three patients (21.4%) in the EUS-CPN group but none in the EUS-RFA group ($P = .225$) were crossed over to the alternate treatment arm for persistent abdominal pain on day 8 (n = 1) and day 15 (n = 2) after index intervention. All 3 of these patients did not require further intervention after crossover to the alternate arm.

Pain scores and opioid analgesia intake

At the 4-week follow-up, after adjusting for initial pain scores, patient demographics, symptom duration, and chemoradiation therapy using the GEE model, pain scores were significantly lower in the RFA group compared with CPN on the PAN26 (49.0 vs 57.0, $P < .001$) and C30 (51.9 vs 64.4, $P = .032$). Pain scores were also significantly lower in the RFA group compared with CPN on BPI and (10.5 vs 21.7, $P < .001$) and VAS (30.1 vs 57.3, $P = .002$) (Tables 2-4). However, there was no significant difference in the opioid analgesia use between the 2 groups at the end of follow-up (105.4 mg for CPN vs 112.7 mg for RFA, $P = .583$).

Quality of life

At the 4-week follow-up, the mean scores for several quality of life components in the PAN26 and C30 instruments were significantly better in the RFA group compared with the CPN group, when using the GEE model to adjust for baseline scores, patient demographics, symptom duration, and chemoradiation therapy. In the PAN26, patients in the RFA group had significantly less-severe GI symptoms that included restriction in oral intake, dry mouth, indigestion, diarrhea, jaundice, flatulence, and abdominal bloating and were able to plan more for the future (less fearful for future health and less limited in planning for future activities) (Table 2, Supplementary Table 4, available online at www.giejournal.org). In the C30, patients in the RFA group had better emotional functioning and less constipation compared with the CPN group (Table 3). Additionally, the internal reliability of the PAN26 as measured by Cronbach's alpha in our sample at both follow-up time points ranged from .22 to .96, which was consistent with previously reported measures (.09-.97) with the lower internal consistency corresponding to items related to jaundice.[27]

Adverse events

No intraprocedural adverse events were encountered in any patient. At 48 hours postprocedure, 10 patients developed procedure-related side effects, which included diarrhea in 1, fever in 1, nausea/vomiting in 5, and transient increase in abdominal pain in 3 patients. There was no significant difference in the incidence of side effects between the 2 groups (35.7% for CPN vs 41.7% for RFA, $P = .999$), and all these symptoms had resolved with conservative management at the 2-week follow-up (Table 1).

DISCUSSION

Given the poor prognosis of inoperable pancreatic cancer and the suboptimal pain control achieved with narcotics and CPN, there is a need for other low-risk therapies to mitigate symptoms. The present study is the first to suggest that EUS-RFA is an effective modality for alleviating pain and improving quality of life in pancreatic cancer.

Pharmacologic treatment of the celiac plexus using alcohol causes varying degrees of sympathetic denervation by inducing inflammation and necrosis on direct contact. However, the unpredictability of treatment effect is because of the varying diffusion of the injected agent within the anatomic compartment containing the nerve fibers. This diffusion, although uncommon, may induce nerve root damage causing secondary pain or paraplegia or could damage the surrounding vascular structures resulting in retroperitoneal or fatal bleeding.[39-43] With the application of RF energy, cellular proteins denature and cell membranes lose their integrity as their lipid components melt. Because of the predictability of ablation and size of necrosis being induced,[23] there has been a growing interest in the use of RFA for the neurolysis of splanchnic nerves. Another advantage is that, unlike alcohol and phenol, the symptom benefit is immediate. Two studies have demonstrated the effectiveness of percutaneous splanchnic nerve RFA for the treatment of chronic abdominal pain.[21,22]

Although EUS-RFA has been shown to be beneficial for the ablation of pancreatic neoplasms, data on their effectiveness to palliate pain in pancreatic cancer are limited. A report suggested that EUS-RFA of the celiac ganglia yielded better pain relief in a patient with pancreatic cancer

who failed initial treatment by EUS-CPN.[44] In the present study, although 21.4% of patients with persistent pain after undergoing EUS-CPN were treated by EUS-RFA, none of the patients treated by EUS-RFA required rescue therapy using CPN. Additionally, not only were the BPI and VAS pain scores significantly lower but also the adjusted scores for pain components of both the PAN26 and C30 were lower for EUS-RFA when compared with EUS-CPN. A significant difference in several quality of life components was also observed between the 2 groups, which is likely associated with the lower severity of pain in the EUS-RFA cohort.

Given these observations, how do we put the study findings into context when treating patients with pain from pancreatic cancer? It is clear that EUS-RFA affords some degree of pain relief and may be a treatment option, particularly when EUS-CPN is ineffective. However, before EUS-RFA can be advocated as a first-line treatment option, several questions and study limitations need to be addressed. First, although we chose 10 W, the ideal power setting and treatment endpoint for performing EUS-RFA need to be identified and then validated in large, prospective studies. Second, although we performed only 2 ablations in the celiac space, it may be safer and easier to ablate structures (ganglia) that can be visualized sonographically than applying energy at an ill-defined anatomic area. The challenge is that celiac ganglia were evident in only 35% of patients. However, the same limitation is encountered when performing EUS-CPN because the technique of injection is "semi-blind" as well. Third, it has been shown that the size and shape of necrosis during RFA depends on the probe gauge, length of the exposed tip, probe temperature, and duration of treatment. The probe used in the present study was only 1Fr in diameter and therefore was ideal for performing RFA in the celiac space. Although a larger diameter (18 or 19 gauge) probe may be more effective for ablating large tumors, they may result in perforation, vascular insult, or even parenchymal necrosis if the pancreas is accidentally targeted. Therefore, although no adverse events were observed with RFA in this study, the safety profile of EUS-RFA requires further validation in future studies. Fourth, the data presented herein pertain to a monopolar device and not a bipolar electrode or a system with internal cooling. Fifth, no structured follow-up was arranged for opioid management during the study period but rather was left to the discretion of the patients' primary physician or oncologist, which could have introduced variability. However, we believe that opioid management by nonstudy physicians who were blinded to the type of therapy performed minimized bias. Also, in this study, information regarding the preintervention opioid requirement was collected for the 24-hour period preceding the intervention and hence may have varied slightly if this information was collected over several days. However, we believe the difference would have been minimal because of the severity of the patients' symptoms before intervention. Finally, because the study follow-up period was until 4 weeks after intervention, the long-term treatment efficacy of EUS-RFA requires further evaluation.

In conclusion, preliminary evidence suggests that EUS-RFA may be superior to EUS-CPN for the palliation of pain and improvement in quality of life in patients with pancreatic cancer. However, the procedural technique needs to be standardized, and further technologic refinements may be required before its widespread adoption can be recommended.

REFERENCES

1. Schmidt-Hansen M, Bennett MI, Arnold S, et al. Oxycodone for cancer-related pain. Cochrane Database Syst Rev 2017;8:CD003870.
2. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 2011;29:3541-6.
3. Polati E, Finco G, Gottin L, et al. Prospective randomized double-blind trial of neurolytic coeliac plexus block in patients with pancreatic cancer. Br J Surg 1998;85:199-201.
4. Kawamata M, Ishitani K, Ishikawa K, et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. Pain 1996;64:597-602.
5. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial. Ann Surg 1993;217:447-55; discussion 456-7.
6. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA 2004;291:1092-9.
7. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc 1996;44:656-62.
8. Nagels W, Pease N, Bekkering G, et al. Celiac plexus neurolysis for abdominal cancer pain: a systematic review. Pain Med 2013;14:1140-63.
9. Gunaratnam NT, Sarma AV, Norton ID, et al. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. Gastrointest Endosc 2001;54:316-24.
10. Iwata K, Yasuda I, Enya M, et al. Predictive factors for pain relief after endoscopic ultrasound-guided celiac plexus neurolysis. Dig Endosc 2011;23:140-5.
11. Kaufman M, Singh G, Das S, et al. Efficacy of endoscopic ultrasound-guided celiac plexus block and celiac plexus neurolysis for managing abdominal pain associated with chronic pancreatitis and pancreatic cancer. J Clin Gastroenterol 2010;44:127-34.
12. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci 2009;54:2330-7.
13. Ramirez-Luna MA, Chavez-Tapia NC, Franco-Guzman AM, et al. Endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. Rev Gastroenterol Mex 2008;73:63-7.
14. Seicean A, Cainap C, Gulei I, et al. Pain palliation by endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. J Gastrointest Liver Dis 2013;22:59-64.
15. Si-Jie H, Wei-Jia X, Yang D, et al. How to improve the efficacy of endoscopic ultrasound-guided celiac plexus neurolysis in pain management in patients with pancreatic cancer: analysis in a single center. Surg Laparosc Endosc Percutan Tech 2014;24:31-5.
16. Wiechowska-Kozlowska A, Boer K, Wojcicki M, et al. The efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis for

treatment of pain in patients with pancreatic cancer. Gastroenterol Res Pract 2012;2012:503098.
17. Sahai AV, Lemelin V, Lam E, et al. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. Am J Gastroenterol 2009;104:326-9.
18. Leblanc JK, Rawl S, Juan M, et al. Endoscopic ultrasound-guided celiac plexus neurolysis in pancreatic cancer: a prospective pilot study of safety using 10 mL versus 20 mL alcohol. Diagn Ther Endosc 2013;2013:327036.
19. Sakamoto H, Kitano M, Kamata K, et al. EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. Am J Gastroenterol 2010;105:2599-606.
20. Ascunce G, Ribeiro A, Reis I, et al. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). Gastrointest Endosc 2011;73:267-74.
21. Raj PP, Sahinler B, Lowe M. Radiofrequency lesioning of splanchnic nerves. Pain Pract 2002;2:241-7.
22. Garcea G, Thomasset S, Berry DP, et al. Percutaneous splanchnic nerve radiofrequency ablation for chronic abdominal pain. Austr N Z J Surg 2005;75:640-4.
23. Lakhtakia S, Ramchandani M, Galasso D, et al. EUS-guided radiofrequency ablation for management of pancreatic insulinoma by using a novel needle electrode (with videos). Gastrointest Endosc 2016;83:234-9.
24. Song TJ, Seo DW, Lakhtakia S, et al. Initial experience of EUS-guided radiofrequency ablation of unresectable pancreatic cancer. Gastrointest Endosc 2016;83:440-3.
25. Pai M, Habib N, Senturk H, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg 2015;27:52-9.
26. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939-41.
27. Eaton AA, Karanicolas P, Johnson CD, et al. Psychometric validation of the EORTC QLQ-PAN26 pancreatic cancer module for assessing health related quality of life after pancreatic resection. J Pancreas 2017;18:19-25.
28. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
29. Cleeland CS. The Brief Pain Inventory user guide. 2009. Available at: https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf. Accessed March 5, 2018.
30. Erdemoglu AK, Koc R. Brief Pain Inventory score identifying and discriminating neuropathic and nociceptive pain. Acta Neurol Scand 2013;128:351-8.
31. Mendoza T, Mayne T, Rublee D, et al. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. Eur J Pain 2006;10:353-61.
32. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20:309-18.
33. Tan G, Jensen MP, Thornby JI, et al. Validation of the Brief Pain Inventory for chronic nonmalignant pain. J Pain 2004;5:133-7.
34. Bang JY, Hasan MK, Sutton B, et al. Intraprocedural increase in heart rate during EUS-guided celiac plexus neurolysis: clinically relevant or just a physiologic change? Gastrointest Endosc 2016;84:773-9.
35. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.
36. Epelboym I, Winner M, Dinorcia J, et al. Quality of life in patients after total pancreatectomy is comparable with quality of life in patients who undergo a partial pancreatic resection. J Surg Res 2014;187:189-96.
37. Billings BJ, Christein JD, Harmsen WS, et al. Quality-of-life after total pancreatectomy: Is it really that bad on long-term follow-up? J Gastrointest Surg 2005;9:1059-66; discussion 1066-67.
38. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology 2010;21:467-74.
39. Sahai AV, Lemedin V, Lam E, et al. Central vs bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. Am J Gastroenterol 2009;104:326-9.
40. Loeve US, Mortensen MB. Lethal necrosis and perforation of the stomach and the aorta after multiple EUS-guided plexus neurolysis procedures in a patient with chronic pancreatitis. Gastrointest Endosc 2012;77:151-2.
41. Gimeno-García AZ, Elwassiel A, Paquin SC, et al. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. Endoscopy 2012;44:E267.
42. Mittal MK, Rabinstein AA, Wijdicks EF. Acute spinal cord infarction following endoscopic ultrasound-guided celiac plexus neurolysis. Neurology 2012;78:e57-9.
43. Fujii L, Clain JE, Morris JM, et al. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. Endoscopy 2012;44:E265-6.
44. Jin ZD, Wang L, Li Z. Endoscopic ultrasound-guided celiac ganglion radiofrequency ablation for pain control in pancreatic carcinoma. Dig Endosc 2014;27:162-4.

Abbreviations: BPI, Brief Pain Inventory-Short Form; C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire; CPN, celiac plexus neurolysis; EORTC, European Organization for Research and Treatment of Cancer; GEE, generalized estimating equation; PAN26, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-pancreatic cancer module; RFA, radiofrequency ablation; VAS, visual analog scale.

DISCLOSURE: *The following authors disclosed financial relationships relevant to this publication: R. H. Hawes, S. Varadarajulu: Consultant for Boston Scientific and Olympus America. All other authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 188.

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2018.08.005

Received March 21, 2018. Accepted August 4, 2018.

Current affiliation: Center for Interventional Endoscopy, Florida Hospital, Orlando, Florida, USA.

Reprint requests: Shyam Varadarajulu, MD, Medical Director, Center for Interventional Endoscopy, Florida Hospital, 601 East Rollins Street, Orlando, FL 32803.

If you would like to chat with an author of this article, you may contact Dr Varadarajulu at svaradarajulu@yahoo.com.

SUPPLEMENTARY TABLE 1. Pretreatment scores for PAN26

	CPN group (n = 14)	RFA group (n = 12)	*P* value
Pain	78.0	73.6	.635
Restriction in oral intake	64.3	59.7	.751
Taste change	59.5	38.9	.204
Xerostomia	66.7	58.3	.556
Indigestion	61.9	27.8	.019
Diarrhea and fecal urgency	36.9	31.9	.722
Jaundice	29.8	27.8	.857
Flatulence	50.0	30.6	.140
Abdominal bloating	59.5	52.8	.667
Muscle weakness	42.9	47.2	.778
Weight loss	40.5	50.0	.578
Disinterest in sex/sexual enjoyment	63.1	68.1	.738
Dissatisfaction with body image	52.4	55.6	.825
Satisfaction with healthcare	75.0	84.7	.181
Burden of treatment	50.0	41.7	.533
Fear for future health	83.3	75.0	.379
Limitation in ability to plan for future	73.8	69.4	.709

PAN26, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-pancreatic cancer module; *CPN*, celiac plexus neurolysis; *RFA*, radiofrequency ablation.

SUPPLEMENTARY TABLE 2. Pretreatment scores for C30

	CPN group (n = 14)	RFA group (n = 12)	*P* value
Global health status (high score = high QOL)			
Global health status/QOL	28.0	31.9	.712
Functional scales (high score = high function)			
Physical functioning	61.9	53.9	.432
Role functioning	31.0	34.7	.727
Emotional functioning	41.1	61.1	.027
Cognitive functioning	46.4	51.4	.706
Social functioning	40.5	37.5	.802
Symptom scales (high score = high level symptomology)			
Pain	83.3	73.6	.239
Fatigue	68.3	63.9	.634
Nausea and vomiting	40.5	33.3	.595
Dyspnea	35.7	27.8	.514
Insomnia	76.2	63.9	.281
Appetite loss	69.0	69.4	.978
Constipation	50.0	22.2	.042
Diarrhea	14.3	19.4	.504
Financial difficulties	50.0	47.2	.859

C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core questionnaire; *CPN*, celiac plexus neurolysis; *QOL*, quality of life; *RFA*, radiofrequency ablation.

SUPPLEMENTARY TABLE 3. Pretreatment VAS and BPI scores and opioid use

	CPN group (n = 14)	RFA group (n = 12)	*P* value
VAS (0-100)	58.6	50.0	.344
BPI (0-100)			
Pain severity	22.1	19.8	.554
Pain interference	46.5	47.7	.843
Opioid use (oral morphine equivalent dose in mg)	95.0	125.8	.522

VAS, Visual analogue scale; *BPI*, Brief Pain Inventory; *CPN*, celiac plexus neurolysis; *RFA*, radiofrequency ablation.

SUPPLEMENTARY TABLE 4. Adjusted mean scores for PAN26 using generalized estimating equations with 95% confidence intervals (high score = high level symptomology)*

	CPN group (n = 14)	RFA group (n = 12)
Pain	57.0 (53.2-63.0)	49.0 (43.4-53.2)
Restriction in oral intake	53.5 (44.8-62.2)	39.1 (28.9-48.4)
Taste change	64.4 (53.3-72.3)	44.9 (31.7-51.8)
Xerostomia	57.7 (48.9-65.0)	43.1 (31.7-51.7)
Indigestion	51.0 (43.4-58.6)	20.6 (14.7-25.4)
Diarrhea and fecal urgency	24.8 (22.1-30.3)	16.9 (13.2-21.1)
Jaundice	18.2 (14.5-21.8)	13.0 (7.8-17.8)
Flatulence	33.5 (28.6-39.3)	16.0 (13.2-21.1)
Abdominal bloating	45.6 (37.6-53.2)	33.7 (25.2-39.6)
Muscle weakness	48.2 (39.0-57.6)	33.6 (23.1-44.0)
Weight loss	43.1 (32.9-52.2)	46.7 (36.1-57.8)
Disinterest in sex/sexual enjoyment	65.2 (58.3-72.4)	72.9 (64.5-80.7)
Dissatisfaction with body image	56.5 (47.7-62.5)	45.2 (37.3-51.9)
Satisfaction with healthcare	81.1 (74.6-84.8)	81.6 (76.8-85.7)
Burden of treatment	51.2 (43.3-56.9)	40.4 (33.5-45.6)
Fear for future health	69.3 (64.8-75.8)	56.8 (51.1-61.8)
Limitation in ability to plan for future	68.5 (59.1-76.6)	50.1 (44.1-54.1)

PAN26, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-pancreatic cancer module; *CPN*, celiac plexus neurolysis; *RFA*, radiofrequency ablation.

*Reported sample sizes are for the number of patients at baseline. Observations by item vary because of deaths from malignancy. Confidence intervals are for predicted mean scores by treatment group at 2 weeks with all other covariates held constant at their mean values.