—Clinical Guideline—

Practice guidelines for endoscopic ultrasound-guided celiac plexus neurolysis

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ABSTRACT

Objectives: The objective of guideline was to provide clear and relevant consensus statements to form a practical guideline for clinicians on the indications, optimal technique, safety and efficacy of endoscopic ultrasound guided celiac plexus neurolysis (EUS-CPN). **Methods:** Six important clinical questions were determined regarding EUS-CPN. Following a detailed literature review, 6 statements were proposed attempting to answer those questions. A group of expert endosonographers convened in Chicago, United States (May 2016), where the statements were presented and feedback provided. Subsequently a consensus group of 35 expert endosonographers voted based on their individual level of agreement. A strong recommendation required 80% voter agreement. The modified GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria were used to rate the strength of recommendations and the quality of evidence. **Results:** Eighty percent agreement was reached on 5 of 6 consensus statements, 79.4% agreement was reached on the remaining one. **Conclusions:** EUS-CPN is efficacious, should be integrated into the management of pancreas cancer pain, and can be considered early at the time of diagnosis of inoperable disease. Techniques may still vary based on operator experience. Serious complications exist, but are rare.

Key words: Celiac plexus neurolysis, endoscopic ultrasound, guideline, pancreatic cancer

INTRODUCTION

Estimates for pancreatic cancer incidence and mortality for the US population in 2017 are 53,670 and 43,090, respectively. Pancreatic cancer accounts for 3% of all cancers in the US and 7% of all cancer deaths.[1] The overall 5 years survival remains only 7.7%; 29.3% for localized and 2.6% for metastatic disease which represent 9% and 52% of all diagnoses, respectively.[2] Substantial abdominal pain can be found in over 80% of pancreas cancer patients and frequently becomes difficult to control in those with unresectable disease.[3-5] Opiate-based systemic analgesic therapy (SAT) is often insufficient, requiring medication dose escalation, which may increase the frequency and severity of side effects. Furthermore, pain severity also correlates with decreased survival.[6] Celiac plexus neurolysis (CPN) involves injecting a neurolytic agent (*e.g.*, absolute alcohol, phenol) around and/or into the celiac plexus neural network of ganglia to prevent propagation of pain signals from the pancreas and nearby visceral organs. The goal of CPN is to lower abdominal pain levels, mitigate narcotic requirements, and therefore improve the quality of life. With the advent of endoscopic ultrasound (EUS) came a novel way to access the celiac plexus and to perform CPN. This guideline provides an evidence-based framework answering key questions on the utility and techniques of EUS-CPN.

METHODS

Three EUS journal editors (S. S., A. S., and M. G.) identified the need for comprehensive and evidence-based CPN practice guidelines. They created the CPN guideline international taskforce, a steering committee designed to develop these guidelines. An independent endosonographer (J. W.) was selected to spearhead this effort on behalf of the committee. Systematic literature searches of PubMed were performed by one voting (J. W.) and one nonvoting committee member (R. B.) using the search terms: EUS, endosonography, pancreas cancer, inoperable, chronic pancreatitis, neurolysis, celiac plexus, percutaneous, pain, bilateral, unilateral, central, ganglion (ganglia), broad, cytopathology (cytology), on-site, complication, adverse event, ethanol, phenol.

Level of evidence was graded by one voting (J. W.) and one nonvoting committee member (R. B.), using the online Grading of Recommendations Assessment, Development, and Evaluation (GRADEpro) free software and modules found at the Mac GRADE Centre (https://cebgrade.mcmaster.ca) published by McMaster University. Four levels of evidence were high, moderate, low, and very low. All voting members voted on each statement via an online survey program (www.surveymonkey.com) and collected by (S. S). There were six voting options.[7] A strong recommendation was defined *a priori* as 80% agreement with the consensus statement [Table 1]. The grade of recommendation was then formulated.

CONSENSUS STATEMENTS

Question 1: Can EUS-CPN be used safely and effectively to relieve pain due to chronic pancreatitis?

Statement 1: We recommend against EUS-CPN for the treatment of chronic pancreatitis (CP) pain.

Table 1. Voting options and grades of recommendations

Voting options: Level of agreement[a]
Agree strongly (A+)
Agree with minor reservation (A)
Agree with major reservation (A−)
Disagree with minor reservation (D)
Disagree with major reservation (D−)
Disagree strongly (D+)
Grade of recommendation
Grade 1A: Strong recommendation, high-quality evidence
Grade 1B: Strong recommendation, moderate-quality evidence
Grade 1C: Strong recommendation, low-quality or very low-quality evidence
Grade 2A: Weak recommendation, high-quality evidence
Grade 2B: Weak recommendation, moderate-quality evidence
Grade 2C: Weak recommendation, low-quality or very low-quality evidence

[a]Adapted from Bitton *et al.*[7]

Vote: A+ =51%, A = 40%, A− =9%. Level of evidence: Very low

Grade of recommendation: 1C

An important distinction that must be made is between EUS-CPN and EUS celiac plexus block (CPB). The former classically involves destruction of the celiac plexus by injection of a neurolytic agent (with or without an anesthetic agent such as bupivacaine). The latter involves the injection of an anesthetic, with or without steroids, and no neurolytic agent. Neurolytic agents used during EUS-CPN induce a local inflammatory reaction, followed by fibrosis during the healing process. Since this local scarring may render surgery more difficult, it would appear prudent to reserve EUS-CPN for use in patients in whom surgery is formally contraindicated (ex: Unresectable malignancy) and to avoid its use in situations where surgery may eventually be indicated (ex: Potentially resectable cancers, CP).

Although CPN may be effective in CP pain from the perspective of biologic plausibility, there is a paucity of actual published data to confirm this. Levy *et al.*,[8] in the context of a study on the safety and efficacy of celiac ganglia neurolysis (CGN), included 5 patients with CP, in whom EUS-CPN was performed with absolute alcohol. Four patients (80%) who underwent EUS-CPN reported pain relief *versus* 5/13 (38%, $P = 0.11$) patients who underwent EUS-CPB with steroids. The alcohol volume ranged from 4 to 8 cc. Gress *et al.*[9] performed EUS-CPN with absolute alcohol in 2 CP patients, after incomplete response to CPB. One sustained a major complication (retroperitoneal bleeding due to post-EUS-CPN pseudoaneurysm). The only other published data on CP patients treated with CPN are case reports of serious complications,[10-13] which include deaths from end-organ ischemia and a brain abscess. Given how rarely EUS-CPN is used in CP and the relatively high proportion of reported significant complications, EUS-CPN for CP pain may (for unknown reasons) be riskier than EUS-CPN for malignancy.

Question 2: Which CPN technique is the most effective for pain due to pancreatic cancer: percutaneous (PQ) or EUS-guided?

Statement 2: Without availability of direct comparison between techniques, EUS-CPN appears equal or more effective in controlling pain.

Vote: A+ = 53%, A = 30%, A− = 15%, D = 3%. Level of evidence: Moderate.

Grade of recommendation: 1B

PQ-CPN can be performed under fluoroscopic, computerized tomographic (CT), or ultrasound guidance.[14-16] There is no trial directly comparing PQ-CPN with EUS-CPN for pancreas cancer pain. There are two randomized controlled trials (RCTs) comparing fluoroscopic and CT-guided CPB to EUS-CPB for pain due to CP but not EUS-CPN. These will be used as surrogates for a comparative efficacy analysis. An 18 patient unblinded study by Gress *et al.*, demonstrated significant postprocedure pain reduction in 50% *versus* 25% of patients and more persistent pain relief of 30% *versus* 0% at week 24 weeks for EUS-CPB compared to CT-guided CPB.[15] A single-blinded RCT by Santosh *et al.* with 56 patients also favored EUS-CPB over CT-guided CPB for initial pain relief (70% *vs.* 30%, $P = 0.044$) and a significantly longer duration of time.[14] Of note, bupivacaine and triamcinolone, but no alcohol was used in these CPB studies.

In a 2013 meta-analysis, Nagels *et al.*[17] included 5 RCTs (265 patients) demonstrating improved pain scores for PQ-CPN over SAT at 1–2 weeks of 0.87 (95% confidence interval [CI]: [−1.47, −0.28], $P = 0.004$), at 4 weeks of 0.47 (95% CI: [−0.71, −0.23], $P = 0.0001$). At 8 weeks, the significance of pain improvement in the combined studies was lost, with no individual study showing benefit at 12 weeks. A major confounder is opiate usage; and this systematic review found an absolute reduction in opioid use compared to SAT at 2 weeks

of −44.64 mg (95% CI: −72.74– [−16.54], $P = 0.002$), 4 weeks −72.41 mg (95% CI: −86.14 – [−58.68], $P < 0.00001$), 8 weeks −70.02 mg (95% CI: −104.05 – [−36.00], $P < 0.0001$) and one study at 12 weeks (105 ± 65 mg *vs.* 169 ± 71 mg, $P < 0.01$). Therefore, without multivariate analysis, we cannot conclude that the loss of pain improvement alone reflects poor performance of the PQ-CPN technique. It should be noted that one of these studies included intraabdominal malignancy pain in general in 98 patients, of which not all were pancreatic cancer.

This same review by Nagels *et al.* repeated the analysis with best available evidence for EUS-CPN. There were no RCTs available for EUS-CPN used for salvage therapy with only 5 case series included, of which only 2 studies comprising 122 of the 209 patients evaluated uniquely pancreatic cancer. A significant pain reduction was noted at weeks 2, 4, 8, and 12 with a mean difference in pain score of −4.26 (95% CI: −5.53 – [−3.00]), −4.21 (95% CI: −5.29 – [−3.13]), −4.13 (95% CI: −4.84 – [−3.43]), −4.28 (95% CI: −5.63 – [−2.94]), respectively. Absolute opiate usage was inconsistently reported in these studies but globally showed stable or slightly lower consumption in the face of these lower pain scores. An earlier meta-analysis on EUS-CPN by Puli *et al.*,[18] including only pancreas cancer patients, found a pooled proportion of patients with pain relief of 80.12% (95% CI = 74.47–85.22). To date, the only RCT evaluating the efficacy of EUS-CPN on pain, narcotic use and quality of life did not employ EUS-CPN for salvage therapy but early at time of pancreas cancer diagnosis and will be detailed in the section on early EUS-CPN timing below.[19]

Question 3: Which EUS-CPN technique is more effective: Bilateral or central injection?

Statement 3: Bilateral EUS-CPN (with needle advancement caudally, beyond the level of the celiac axis) is superior, but technical feasibility and operator comfort justify central injection as an acceptable option.

Vote: A+ = 53%, A = 29%, A− =12%, D = 3%, D− = 3%. Level of evidence: Moderate.

Grade of recommendation: 1B

The majority of celiac ganglia can be found between the celiac artery and the left adrenal gland.[20] Whereas the unilateral or central EUS-CPN technique involves a single injection of ethanol immediately cephalad into the celiac artery takeoff, the bilateral technique requires injection of the neurolytic agent on both sides of the artery. Sahai *et al.*, in a prospective cohort study including 160 patients, compared unilateral *versus* bilateral CPN or CPB. The bilateral technique achieved significantly more pain relief *versus* unilateral (mean percent pain reduction) 70.4% (95% CI: 61.0–80.0) *versus* 45.9% (95% CI: 32.7–57.4), $P = 0.0016$, at day 7 posttreatment.[21] The only predictor of a >50% pain reduction was bilateral injection (odds ratio 3.55, [95% CI: 1.72–7.34]). In a smaller randomized study with 50 patients by LeBlanc *et al.*, no statistical differences were found with pain relief in 69% central injection *versus* 81% in the bilateral group.[22] However, the techniques for bilateral injection differed importantly in these 2 studies. In the Sahai study, the needle was advanced lateral to the celiac artery and caudally, to the region lateral to the base of the SMA takeoff. Whereas, in Leblanc *et al.*, the methodology for bilateral describes injecting on both sides of the celiac artery with no needle advancement distal to the base of the celiac trunk.

Evidence for the superior efficacy of wider drug distribution was shown with EUS-broad plexus neurolysis (ethanol injected on either side of the SMA as opposed to celiac artery in EUS-CPN) with better 7 and 30-day pain relief dependent on the degree of ethanol spread.[23] Adequate depth of needle advancement, therefore, appears to be required to maximize the efficacy of the bilateral approach.

The meta-analysis by Puli *et al.*[18] also found that with bilateral injection the proportion of patients with pain relief was 84.54% (95% CI = 72.15–93.77) *versus* 45.99% (95% CI = 37.33–54.78) with unilateral.

Question 4: Should the celiac ganglion be targeted during EUS-guided neurolysis (CGN)?

Statement 4: There is no clear evidence that CGN is more superior to bilateral or broad plexus EUS-CPN (with needle advancement caudal to the base of the celiac axis). Therefore, EUS-guided CGN is not necessary.

Vote: A+ = 56%, A = 26%, A− = 9%, D = 3%, D− = 3%, D+ = 3%. Level of evidence: Moderate.

Grade of recommendation: 1B

Early studies on EUS-CGN[24,25] found celiac ganglia detection rates of at least one ganglion of 81% and

89%. The feasibility, safety, and efficacy of EUS-CGN was first reported by Levy *et al.* in 2008. In this series, 16 of 17 pancreas cancer patients (94%) reported "complete or partial" pain relief.[8] Of the patients who underwent EUS-CGN in this study (17 with pancreas cancer and 5 with chronic pancreatitis), 36% developed an initial pain exacerbation lasting a mean of 2.2 days. Subsequently, a multicenter RCT was performed comparing EUS-CGN with central EUS-CPN for malignant upper abdominal pain (almost all pancreatic cancer).[20] A drop of at least 3 points on a 10-point pain scale was significantly more frequent in the EUS-CGN group (73.5% *vs.* 45.5%; $P = 0.026$), and a complete response was also significantly higher in the EUS-CGN group (50.0% *vs.* 18.2%; $P = 0.010$). However, the control group in this study was central EUS-CPN and not bilateral EUS-CPN. Bilateral injection would have been a more appropriate control group since most ganglia are found lateral to the celiac artery. In fact, studies have produced almost the same results when comparing bilateral to central injection 70.4% (95% CI 61.0, 80.0) *versus* 45.9% (95% CI 32.7, 57.4) $P = 0.0016$.[21] Therefore, this study does not prove that EUS-CGN is more effective than bilateral EUS-CPN. Rather, it seems to confirm that central EUS-CPN is less effective than bilateral EUS-CPN.

Recently, a cadaver study compared EUS-CGN with EUS-CPN.[26] They demonstrated that ethanol spreads well beyond the targeted ganglia when CGN is performed, and the volume of injectate was key to ensure broad and bilateral spread. Of course, *in vivo* extrapolation is limited both in terms of volume of distribution and impact on pain. In the clinical portion of the study, EUS was shown to visualize a median of 2 ganglia per patient; with 29.9% left of celiac axis, 65.7% central, and 4.5% on the right side. However, the cadaver portion of the study demonstrated 3–5 ganglia per patient and large volume CPN had ethanol surrounding even those unseen, including right-sided. Minaga *et al.* found EUS-CGN added to EUS-BPN was the most efficacious but they were injecting more alcohol at more sites (EUS-BPN could deploy up to 40 cc of alcohol).[27] Again, the number of injection sites and volume injected seems to drive results.

Question 5: Is there a role for early EUS-CPN at the time of diagnosis of painful pancreatic cancer?

Statement 5: When on-site cytopathology is available, patients with painful inoperable pancreas cancer should undergo EUS-CPN at time of diagnosis (early).

Vote: A+ = 32%, A = 32%, A− = 15%, D = 15%, D− = 3%, D+ = 3%. Level of evidence: High.

Grade of recommendation: 2A (79.4% agreement)

There has only been one randomized double-blind controlled trial on EUS-CPN.[19] Since significant pain can be found in 80% of patients at the time of diagnosis, in this study, EUS-CPN was performed at the time of initial EUS in patients with pain, once nonresectable pancreas cancer was confirmed with on-site cytopathology. Over the 3 months trial beginning from diagnosis, pain would be expected to worsen, and narcotic requirements increase. When comparing EUS-CPN to SAT, pain relief was greater at 1 month (difference in mean percent change in pain score −28.9 (95% CI, −67.0, 2.8), $P = 0.09$) and significantly greater at 3 months −60.7 (95% CI, −86.6, −25.5), $P = 0.01$. The difference in absolute mean change in pain was larger in the CPN-EUS group at both 1 and 3 months (−1.0 [95% CI, −1.7 to −0.1], $P = 0.01$) and (−2.2 [95% CI, −3.1, −1.4, $P = 0.001$).

In the SAT group, morphine use increased compared with baseline at both 1 month (mean absolute change in MEQ consumption +54 mg [95% CI: +20, +96] and 3 months +100 mg [95% CI: +49, +180]. In the EUS-CPN group, morphine use also increased at 1 month +53 mg [95%CI: +28, +89], but increased no further by 3 months +50 mg [95% CI: +28, +79].

Interestingly, since radiation and chemotherapy can improve pain and quality of life in pancreas cancer when stratified to those who did not receive such therapy, there were greater differences between EUS-CPN and SAT across all key variables. Because EUS-CPN was not performed as salvage therapy, these adjuvant therapies likely diluted the strength of results.[19]

Question 6: What are the risks associated with EUS CPN?

Statement 6: Although the evidence for efficacy outweighs the risks, the small incidence of serious adverse events should be disclosed to the patient.

Vote: A+ = 88%, A = 9%, A− = 3%. Level of evidence: Low.

Grade of recommendation: 1C

Most of the recognized side effects of CPN regardless of modality are believed to arise from unopposed parasympathetic activity following the sympathetic blockage of celiac plexus nerve ablation. An older meta-analysis from 2007 demonstrated that PQ-CPN compared to standard treatment had less constipation 0.67 (95% CI [0.49, 0.91]) and nonstatistical trends toward less nausea and vomiting 0.84 (95% CI [0.6, 1.19]), more hypotension 3.0 (95% CI [0.83, 10.88]), and more diarrhea 1.29 (95%CI [0.37–4.47]).[5] In their conclusion, they suggest a pooled adverse event rates across RCTs with PQ-CPN of diarrhea (9%), transient hypotension (8%), constipation (40%), nausea and vomiting (41%), and lethargy (49%). The aforementioned meta-analysis by Nagels *et al.* in 2013, found statistically more diarrhea occurred in PQ-CPN compared to standard care with risk ration (RR) 5.88 (95% CI 2.24, 15.44; $P = 0.0003$).[17] From 609 patients in various case series, 42% developed transient diarrhea. Constipation was again statistically less likely probably due to an opiate sparing effect with RR 0.34 (95% CI 0.24, 0.48; $P < 0.00001$). Nausea and vomiting was less with RR 0.44 (95% CI 0.29, 0.64; $P < 0.0001$) with case series reporting rates ranging from 3.6% to 32% for transient symptoms.

With only six case series and one case report assessing the side effects of EUS-CPN, Nagels *et al.* found an 18% incidence of diarrhea, transient hypotension of 11%–20% depending on the included studies, 9% with transient increase abdominal pain, and 8% signs of alcohol intoxication.[17] Given the presumed mechanism of these transient side effects, one can assume similar rates between PQ-CPN and EUS-CPN. Unfortunately, all RCTs reporting on them were PQ-CPN.

The difficulty, however, is determining the rate of serious adverse or fatal outcomes from EUS-CPN for pancreatic cancer pain. Publication bias likely impacts reported adverse event rates. Expanding to EUS-CPN performed for any indication this list includes infarction of spleen, pancreas and gastric antrum,[10] gastric ulceration,[28] fatalities from bowel infarction,[12,13,29] retroperitoneal abscess or bleeding,[9,30] permanent paralysis/paraplegia,[31-33] brain abscess (but unclear if CPB or CPN),[11] pulmonary embolus,[34] and bilateral diaphragm paralysis.[35] Paraplegia is felt to occur by inadvertent injection of ethanol into the artery of Adamkiewicz causing vessel trauma, thrombosis or vasospasm with anterior spinal artery infarction of the spinal cord. Similarly, injection into the celiac artery with vasospasm or thrombosis is felt to lead to multi-organ ischemia/infarction.

A recent review looking only at EUS-related safety found that in 661 EUS-CPN cases, 21% had minor and self-limited complications usually lasting <2 days and rarely up to 14 days.[36] Transient diarrhea, transient hypotension, and transient increased pain were experience in 7%, 4%, and 4%, respectively. Major complications mentioned above occurred in 0.2% of cases.

CONCLUSIONS

Although EUS is now part of mainstream medicine, the role of EUS-CPN is not well synthesized in the literature. These clinical practice guidelines recommend a consensus-guided approach to understanding EUS-CPN in the management of pancreas cancer pain. Topics examined were specifically the indications, optimal technique, safety and efficacy of the procedure.

EUS-CPN is efficacious, should be integrated into the management of pancreas cancer pain and can be considered early at the time of diagnosis of inoperable disease. Techniques may still vary based on operator experience. Serious complications exist but are rare. Studies with more robust methodology and higher level of evidence are needed to further strengthen and clarify these guidelines.

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Conflicts of interest

There are no conflicts of interest.

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