**Dear editors and reviewers,** *World Journal of Gastroenterology*

Thank you very much for your kind consideration and forwarding the reviewers' comments on our manuscript"Predictors of pain response after endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain caused by pancreatic malignancy" (Manuscript NO: 58049)". We appreciate your insightful suggestions and believe that these suggestions have improved the quality of our paper. We hope that the revised version of our manuscript meets your requirements for publication. The following comprises point-by-point replies to the reviewers' specific comments. Thanks again for your great efforts on our manuscript, thank you!

**Reviewers' comments:**

**The reviewer1's original comments:** Very interesting paper and very well written. However, there are many larger studies (multicentric) validating the role of EUS-CPN in pancreatic cancer. But the observation that patients with ganglia invisible and metastatic disease and celiac plexus invasion were significant factors for a negative response to EUS-CPN is relevant.

**Q1.** Have you tried celiac plexus block (other than neurolysis) in any of these patients or do you consider it only with chronic pancreatitis?

**A1 Reply:** Thank you for your valuable question. Yes, actually, we also have done the EUS-CPN, EUS-CGN and EUS-BPN. Unfortunately, the number of patients using EUS-CGN and EUS-BPN are not very large. It's difficult to compare the efficacy of the three methods. In addition, previous studies have also demonstrated that CGN did not improve pain, QOL, or adverse events, compared to CPN, such as the paper: *Combined Celiac Ganglia and Plexus Neurolysis Shortens Survival, Without Benefit, vs Plexus Neurolysis Alone*. *Clin Gastroenterol Hepatol. 2019 Mar;17(4):728-738.e9*. Finally, the major aim of this study was to identify the determinants of pain response in EUS-CPN for pancreatic cancer-associated pain. Therefore, we did not include these patients. Thank you very much!

**Q2.** How many patients needed fluid administration after hypotension following the procedure.

**A2 Reply:** Complications occurred in 6 patients (10.3%) of enrolled patients. No serious adverse events including ischemic, inebriation and acute paraplegia related to EUS-CPN were occurred. Most of the complications were minor and transitory self-limited, including hypotension (1.7%),

increase of pain (5.2%), and transient loose stools (3.4%). Actually, before EUS-CPN, every patient was hydrated with 500-1000mL saline solution during the procedure to minimize the risk of hypotension.

**Q3.** Do you suggest any modification of procedure in at least some sub set of patients who have high risk factors for no response?

**A3 Reply:** Thank you for your insightful question. Accord to our results, patients with ganglia invisible, metastatic disease and celiac plexus invasion were significant factors for a negative response to EUS-CPN. If the patient who need to use EUS-CPN to relieve the pain of pancreatic cancer, but he/she had at least some sub set, we would sign informed consent, tell the patient that the methods (including the efficacy) he/she could choose. We also might be use EUS-BPN, previous studies had demonstrated that patients with advanced abdominal cancer using EUS-BPN with better pain relief than standard EUS-CPN, and without incurring serious complications. (*EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. Am J Gastroenterol. 2010 Dec;105(12):2599-606.*).

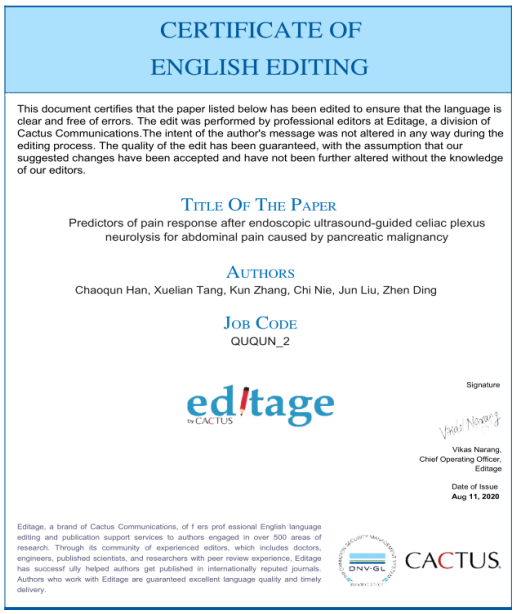
**Q4.** Do you suggest using a larger bore needle or larger amount of injection in those patients at high risk of having negative response.

**A4 Reply:** It's a very good question. From the current researches, the dose of alcohol used in EUS-CPN is not standardized. Most studies demonstrated that EUS-CPN using 10mL or 20 mL of alcohol is safe. Similar clinical outcomes were seen in both groups (*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.*). However, in my opinion, further investigations to confirm these findings are warranted. Recently, the papers indicated that endoscopic ultrasound-guided tumor ablation combined with celiac plexus neurolysis appears to be superior to celiac plexus neurolysis alone in terms of pain control and overall survival. (*Echoendoscopic ethanol ablation of tumor combined with celiac plexus neurolysis in patients with pancreatic adenocarcinoma. J Gastroenterol Hepatol. 2017 Feb;32(2):439-445.; EUS-guided celiac ganglion radiofrequency ablation versus celiac plexus neurolysis for palliation of pain in pancreatic cancer: a randomized controlled trial. Gastrointest Endosc. 2019 Jan;89(1):58-66. e3.*)

The method of endoscopic ultrasound-guided tumor ablation combined with celiac plexus neurolysis may be have a try.

**Q5.** Have you tried this procedure in other malignancies of pancreas- lymphomas and NET with significant pain? If so, what is your experience in comparison to pancreatic adenocarcinoma. I would also recommend language review by a Native speaker before resubmission I would suggest having the discussion part more concise and organized.

**A5 Reply:** Thank you for your question. It's very pity that we have no experience about the other malignancies of pancreas- lymphomas and NET with significant pain. However, we always use this procedure to treat insulinoma (pancreatic islet cell tumor) and get a very good curative effect. According to your suggestion, we submitted the article to the company for language editing. We didn't highlight them in revised paper because there were so many changes. We also upload the CERTIFICA TE OF ENGLISH EDITING. Thank you very much!



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TITLE OF THE PAPER

Predictors of pain response after endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain caused by pancreatic malignancy

AUTHORS

Chaoqun Han, Xuelian Tang, Kun Zhang, Chi Nie, Jun Liu, Zhen Ding

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**The reviewer2's original comments:** The manuscript by Han et al suggests that patients with pancreatic cancer have a statistically better response at 1 and 4 weeks if the tumor originated in the body or fail of the pancreas whereas patients with distant metastases, celiac plexus invasion, or ganglia that were indistinct or could not be seen by EUS were less likely to have pain relief (defined on an analog scale). The authors appropriately note that the small number of patients in this series and its retrospective nature makes conclusions tentative at best.

**Q1.** Patient numbers are too small to define outcomes in patients treated with 2 vs 20 cc of alcohol.

If efficacy is equivalent between these groups, the reviewer would wonder about beta error or the reproducibility of its subjective pain scale.

**A1 Reply:** Thank you for your question. Yes, the number of patients in this study was not very large. This is an inherent limitation that should be considered. From the current researches, most studies demonstrated that EUS-CPN using 10mL or 20 mL of alcohol is safe. Similar clinical outcomes were seen in both groups (*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.*). In additional, the major aim of this study was to identify the determinants of pain response in EUS-CPN for pancreatic cancer-associated pain. Therefore, we did not compare the efficacy between the groups who use different dose of alcohol. Thank you very much!

**Q2.** The very short follow-up (1 and 4 weeks) makes the reviewer question CPN efficacy, especially given small numbers and failure of the authors to report commonly described outcomes in pancreatic cancer. These include: a. Overall survival (OS) and b. Cancer-free survival (CFS) in those undergoing some form of palliative Rx. Did any of these patients have palliative chemo or radiation Rx?

**A2 Reply:** Thank you for your insightful question. Certainly, the present study has its inherent limitations that should be considered. the study is retrospective and the samples of patients are relatively small suggesting restricted application of the results. However, the present study was to explore determinants of pain response in EUS-CPN for pancreatic cancer-associated pain. The observation that patients with ganglia invisible, metastatic disease and celiac plexus invasion were significant factors for a negative response to EUS-CPN at 1 week and 4 weeks is relevant. These findings may be much helpful to endoscopists or oncologist to get correct practice scheme. The short duration of follow up is another limitation. Because beyond 4 weeks, there were fewer patients for analyzing these data. The more content we compared, with a limited number of examples, the results were less reliable. Therefore, we did not include any results about over survival in these patients. In order to reduce the bias (different chemoradiotherapy schemes may be used for different patients; individualize the treatment), the patients we included were not treated with any chemoradiotherapy, but only for end-stage pain relief. Therefore, a large group of multicenter, prospective, randomized trials are indeed required. Thank you very much!

**Q3.** Previous data by Cameron et al, Pitt et al, Lillemoe et al. as well as multiple additional reports by the Johns Hopkins surgical team suggest that survival in unresectable patients with pancreatic CA is a function of pain relief with CPN. Can the authors define survival outcomes in those who got significant pain relief vs those who do not?

**A3 Reply:** Thank you for your value question. Actually, overall survival in unresectable patients with CPN is variable. Different articles get different results. Previous data by Cameron et al, Pitt et al, Lillemoe et al. suggest that survival in unresectable patients with pancreatic CA is a function of pain relief with CPN. CPN is beneficial for the survival of pancreatic cancer. On the other hand, other papers also demonstrated that CPN did not affect survival for patients with unresectable pancreatic cancer, such as *Impact of Celiac Plexus Neurolysis on Survival in Patients with Unresectable Pancreatic Cancer: A Retrospective, Propensity Score Matching Analysis. Pain Physician. 2017 Mar;20(3): E357-E365*.Even some papers indicated that for patients who underwent celiac neurolysis, the median survival from the time of presentation was shorter compared with controls (193 vs 246 days; hazard ratio 1.32; 95% confidence interval, 1.13-1.54). Celiac neurolysis is an independent predictor of shortened survival in pancreatic cancer patients (Gastrointest Endosc. 2015 Jul;82(1):46-56. e2). There are also results even demonstrated that CGN to reduce median survival time without improving pain and adverse events compared to CPN. (*Combined Celiac Ganglia and Plexus Neurolysis Shortens Survival, Without Benefit, vs Plexus Neurolysis Alone. Clin Gastroenterol Hepatol. 2019 Mar;17(4):728-738.e9*). Therefore, in my opinion, the effect of CPN on survival may be related to the characters of pancreatic tumors. Considering the limitations of our paper (1. the number of patients; 2. retrospective design), a well-designed prospective design study should be conducted. We revise the limitations in the paper. Thank you very much!

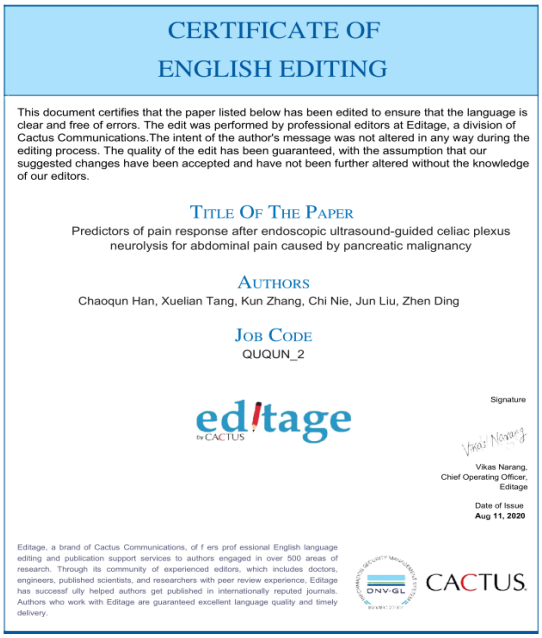
**Q4.** You mention opioid dose in the manuscript but fail to mention what opioid. You also talk about pain relief that responded from 1–16 weeks but fail to supply any results beyond 4 weeks.

**A4 Reply:** Thank you for your advice. We usually use tramadol for analgesia (50mg per time). We revise in the paper. We fail to supply any results beyond 4 weeks because over time, the efficacy of CPN became less. And the major aim of this paper was to identify the determinants of pain response

in EUS-CPN for pancreatic cancer-associated pain. We found that patients with ganglia invisible and metastatic disease were identified as significant factors for a negative response to EUS-CPN at 1 week and 4 weeks respectively, particularly for invasion of the celiac plexus. Beyond 4 weeks to 16 weeks, there were fewer patients for analyzing these data. Therefore, we did not include these patients who beyond the 4 weeks. The samples of patients are relatively small. However, the conclusion that patients with ganglia invisible, metastatic disease and celiac plexus invasion were significant factors for a negative response to EUS-CPN is relevant. Thank you very much!

**Q5.** The reviewer strongly suggests manuscript review by a native English speaker with a science background.

**A5 Reply:** Thank you for your advice. According to your suggestion, we submitted the article to the company for language editing. We didn't highlight them in revised paper because there were so many changes. We also upload the CERTIFICA TE OF ENGLISH EDITING. Thank you very much!



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Predictors of pain response after endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain caused by pancreatic malignancy

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Thank you very much for your time and insightful suggestion! Thanks again for your great efforts on our manuscript!

Yours Faithfully,

Chaoqun Han

Dear editors and reviewers, World Journal of Gastroenterology

Thank you very much for your kind consideration and forwarding the reviewers' comments on our manuscript" Predictors of pain response after endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain caused by pancreatic malignancy"(Manuscript NO: 58049)". We appreciate your insightful suggestions and believe that these suggestions have improved the quality of our paper. We hope that the revised version of our manuscript meets your requirements for publication. The following comprises point-by-point replies to the reviewers' specific comments.

Thanks again for your great efforts on our manuscript, thank you! Reviewers' comments: The reviewer1's original comments:

1. The manuscript and grammar are improved, but the reviewer still has multiple minor changes to suggest. Please see the returned manuscript with some suggestions.

2. You mention following up patients for 16 weeks but provide no data on how many you followed or their response to CPN at that time. Either provide the data, eliminate the statement, or as suggested in your paragraph on efficacy note ("Data not shown").

**Reply:** Thank you for your insightful question. We revise them in the paper. Certainly, the short duration of follow up is our limitation. We fail to supply any results beyond 4 weeks because over time, the efficacy of CPN became less. Actually, the major aim of this paper was to identify the determinants of pain response in EUS-CPN for pancreatic cancer-associated pain. We found that patients with ganglia invisible and metastatic disease were identified as significant factors for a negative response to EUS-CPN at 1 week and 4 weeks respectively, particularly for invasion of the celiac plexus. Beyond 4 weeks to 16 weeks, there were fewer patients for analyzing these data. Therefore, we did not include these patients who beyond the 4 weeks. The samples of patients are relatively small. However, the conclusion that patients with ganglia invisible,

metastatic disease and celiac plexus invasion were significant factors for a negative response to EUS-CPN is relevant. We add the comments on the DISCUSSION section. Thank you very much!

Thank you very much for your time and insightful suggestion! Thanks again for your great efforts on our manuscript! Yours Faithfully, Chaoqun Han