December 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6788 - FINAL CPN Review edited.docx). ALL THE CHANGES ADDRESSED BELOW AND OTHERS ARE HIGHLIGHTED IN THE MAIN TEXT FOR EASY LOCALIZATION

Title: Celiac plexus neurolysis in the management of unresectable pancreatic cancer: when and how?

Authors: Jonathan M Wyse, Yen-I Chen, Anand V Sahai

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6788

The manuscript has been improved according to the suggestions of reviewers:

1) Format has been updated for authors and correspondence.
2) Short title, abstract, key words, and core tip were added to document.
3) References and typesetting were corrected
4) Revision has been made according to the suggestions of the **Reviewer #1:**

Good review. Please clarify that the pain the pancreatic cancer is multifactorial(eg liver capsule pain due to mets, etc) and therefore ablating the coeliac plexus is impossible to obtain perfect pain control. This is the reason for not achieving excellent pain control despite " perfect" coeliac plexus neurolysis.

Page 14: "One must note however, that pain due to pancreatic cancer is multi-factorial not only including celiac plexus pathways but also from for example, intestinal obstruction and liver capsule distention from metastases. CPN will only target some of these pain mechanisms and may play less of a role as disease progresses and other pain etiologies become more pronounced."

Also please make it clear that ideally if the ganglia are seen this should be the preferred method, followed by bilateral and midline however there are no head to head study to confirm this. The way it is written in the conclusion seems that you advocate bilateral over all other modalities.

Page 10: "Although there is no definitively proven superior technique, we favor the bilateral technique given the sum of the above evidence as well as the concept of wider distribution of the ethanol near areas where ganglia are most commonly found."

Page 11: "At this time we do not recommend CGN as a standard for CPN technique as it does not provide a wider distribution of the ethanol over the bilateral technique, but does add a degree of technical complexity and dependence on quality of equipment."

Page 13: "Given the sum of the evidence and with wider distribution of ethanol in areas where ganglia are known to reside, we favour bilateral CPN over central injection.

However this superiority is still controversial and central injections are certainly acceptable if the echoendoscopist is more comfortable with the latter. CGN cannot yet be recommended given inconsistent visualization of ganglia and the lack of trials compared to the bilateral technique which itself can be reproduced consistently in patients using only the celiac artery as a landmark."

At 8 weeks however, the statistical difference was lost -0.31 (95% CI -0.74, 0.12, P=NS) and no included study showed statistically improved pain control at 12 weeks (18). Please rephrase- second part of the sentence does not make sense

Page 4: "At 8 weeks however, the statistical difference was lost -0.31 (95% CI -0.74, 0.12, P=NS) and similarly no study showed benefit at 12 weeks [18]."

Under Bilateral vs. Unilateral/Central Neurolysis "In a prospective cohort study comparing unilateral vs. bilateral CPN or CPB, the bilateral technique achieved significantly more pain relief versus unilateral (mean percent pain reduction 70.4 % (61.0, 80.0) vs. 45.9 % (32.7, 57.4), P = 0.0016, at day 7 post treatment in short term (did not look at longer term)." Please rephrase

Page 10: "Although this is a short-term study the onset of neurolysis effect begins soon after the nerve ablation, therefore a comparison between two techniques at 7 days can still be revealing."

5) Revision has been made according to the suggestions of the **Reviewer #2:**

The article has not mentioned about IntraOperative Celiac Neurolysis. I have personally found that to produce excellent results. The caveat being that it is an option only for those patients who were not deemed inoperable preoperatively. Nevertheless that may also be mentioned.

Page 3: "Surgical splanchnectomy/intra-operative celiac plexus neurolysis can be performed on those not deemed inoperable preoperatively but will not be the reviewed in this paper."

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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