Peer Review File

Article information: https://dx.doi.org/10.21037/gs-21-708

Reviewer A

Comment 1. If the authors focused on iatrogenic RLNI in thyroid surgery, the title is not clear enough to indicate this issue. If author includes cancer patients with advanced feature who had RLN invasion, nerve tissue engineering technology should be very cautious. I don't suggest promoting it before more human evidence available.

Reply 1: Thanks for your revision advices to the paper. We agree with the reviewer that the title is not clear enough to indicate this issue, so we have already revised the title "A Narrative Review of Current Therapies in Unilateral Recurrent Laryngeal Nerve Injury Caused by Thyroid Surgery" of this review (see Page 1/Line1-3). In addition, we also think the more human evidence of nerve tissue engineering technology is needed. We referred this in the discussion "the safety and effectiveness in human need further validation" (see Page 11/Line230-233). Sometimes, nerve has to been resected for a distance due to tumor invasion, then the nerve tissue engineering technology is useful for repairing nerve. In other words, this exist of nerve tissue engineering can achieve the tumor R0 resection. Previous outcomes shown that nerve function will recover after nerve conduit therapy, and this will improve the tumor patient quality of life, especially for advanced tumor patients. It's not obviously reported the adverse reactions in these cases.
Changes in the text: Page 1/Line1-3; Page 11/Line230-233

Comment 2. The examples and citations in Table 1 are very weakly related to this article, even citing the case report, as the authors themselves mentioned in the direct suture section, misdirected regeneration in RLN makes it totally different from other peripheral nerves injury treatments.

Reply 2: As suggested by the reviewer, the table 1 is weakly related to this article, and we decided to delete the Table 1. Due to rare larger scale clinical trials in nerve regeneration, so we cited some case reports (see Page 17/Line444).
Changes in the text: Page 17/Line444

Comment 3. In the Introduction section, in terms of an article discussing RLNI therapies, it is inappropriate to comment the prophylactic effect of IONM. Furthermore, IONM shows mechanism/severity of RLNI and that is more helpful for choosing personalized treatment method.

Reply 3: We have re-written this part of IOMN according to the reviewer 's suggestions. Firstly, because the IONM is widely used for avoiding RLNI, we introduced the prophylactic effect of IONM briefly. Secondly, we added the content (see Page 3-4/Line60-68) that IOMN is

convenient for treatment by indicating the extent of nerve damage.
Changes in the text: Page 3-4/Line60-68

Comment 4. Transection and non-transection RLNI are completely different in terms of treatment considerations, and each issue has been discussed in many previous articles. Without the stratification in clinical situation, this review is only an introduction, which is not helpful for clinical selections.

Reply 4: We have made corrections according to the reviewer's comments. Considering the severity of transection, we introduced the treatment of transection RLNI. But we add content about non-transection RLNI in the introduction and discussion (see Page 3/Line57-59; Page 5/Line98-101; Page 5-6/Line105-115). In addition, we revised the objective of the review into "This review is a comprehensive summary of current therapies for unilateral recurrent laryngeal nerve injury" (see Page 2/Line24-27).
Changes in the text: Page 2/Line24-27; Page 3/Line57-59; Page 5/Line98-101; Page 5-6/Line105-115

Reviewer B

Comment 1. The causes of RLNI during thyroid surgery are manifold, most result from incorrectly performed surgical techniques such as stretching/traction, mechanical trauma (nerve blunt contusion, pressure, suction, or compression), electrocautery/ thermal, ligature entrapment or nerve transection. In recent years, the use of intraoperative neuromonitoring (IONM) during thyroid surgery has given surgeons a tool for better understanding of the possible mechanisms of RLN injury. Previously, a large cohort study (World J Surg. 2016 Jun;40(6):1373-81.) prospectively evaluated 6,093 nerves at risk during standardized monitored thyroidectomy and compared the recovery characteristics in 281 RLN injuries. Their results revealed the distribution of RLNI types, in order of frequency, was traction (71 %), thermal (17 %), compression (4.2 %), clamping (3.4 %), ligature entrapment (1.6 %), suction (1.4 %), and nerve transection (1.4 %). In addition, they noted different RNLIs induce different morphological alterations and have different recovery outcomes. Another recent study (Cancers. 2021 Oct 27;13(21):5379.) also report that different severity and mechanism of RLNI have different recovery and voice outcome, and thus may require different Therapeutic strategies. In this GS-21-708 "Narrative Review", it seems that the authors focus only on the therapies for the "transection" type of RLNI, which is account for less than 2% of RLNI in modern thyroid operation. To interest the readership and provide useful information for readers, this paper needs a major revision/rewriting with including the Review of Current Therapies for the "non-transection (>98%)" type RLNI, including mechanical (80%~traction/clamping.) & thermal (15-20%) types of RLNI. Different Therapeutic strategies for different types (mechanical/thermal/transection) should be provided.

Reply 1: Thanks for your revision advices to the paper. We agree with the reviewer that

therapeutic strategies of non-transection should be provided. According to the literature you provided and we searched, there seem to be hopeful that non-transection RLNI maybe recover themselves. We add content about non-transection RLNI in the introduction and discussion (see Page 3/Line57-59; Page 5/Line98-101; Page 5-6/Line105-115). Considering the severity of transection, we still emphatically introduce the treatment of transection RLNI. In previous studies, severity injury caused by thermal or severe mechanical damage, these therapy of transection RLNI are also applicable.
Changes in the text: Page 3/Line57-59; Page 5/Line98-101; Page 5-6/Line105-115

Comment 2. Speech therapy is an essential part of therapy for patient with Uni-RLNI after thyroid surgery (Gland Surg. 2017 Oct;6(5):501-509.). The author should include Speech therapy in the revised manuscript.

Reply 2: It is an important comment. As suggested by the reviewer, we added the content (see Page 9-10/Line200-211) of speech therapy in the discussion.
Changes in the text: Page 9-10/Line200-211