

Peer Review File

Article information: <https://dx.doi.org/10.21037/gc-21-510>

Reviewer A

Material and methods:

Comment (1): In a retrospective study, we will compare the study group with a historical control because it will be more reasonable to change the behavior to a “better” approach. This would be the AA group, according to the authors. However, the author prospectively conducts the study group first and then compares the results with that of the future control group. It may result in a larger bias and made the results unconvincing.

Reply (1): Previously, we routinely transected ST muscle even the SH muscle during grossly enlarged thyroid surgery. Patients often complained about the postoperative changes in tone of voice, but the signal during intraoperative nerve monitoring indicated the functional integrity of laryngeal nerves. We postulated that the feature of ST muscle might contribute to voice changes after thyroidectomy. Thus, we developed anterolateral approach which combined lateral intervention with “classic” midline approach and were ready to put into practice in thyroid swelling surgery. From October 2018, every eligible patient was persuaded to receive anterolateral approach with a merit of preserving ST muscles, and finally achieved good compliance. We stick to this surgical method for one and a half years which facilitates the management of patients postoperatively, and ensure the skillful use of this technique. Then AA approach was found time-consuming and much patience was demanded in preservation of ST muscles. Meanwhile, for purpose of exploratory analysis and avoiding the bandwagon effect in patient’s decision making, we switch to conventional midline approach from March 2020 for more than a year. All the acoustic parameters was objectively collected by the DiVAS program without informing the speech pathologist and laryngologist about our research matters. Moreover, the baseline of demographic, operative, and pathological characters in two groups was proved comparable after analysis. In statistical analysis, self-control study was conducted in AA and MA group respectively without horizontal comparison. The voice change from baseline was calculated by the formula:

$$\Delta = 100\% \times (B - A) / A$$
 where each parameter of patients was normalized by their own

preoperative conditions. Although this is not a strictly designed study, we proved that this anterolateral approach is a patient-friendly technique, but not surgeon-friendly.

Changes in the text (1): We have modified our text as advised (see Page 7, line 130; Page 8, line 149; Page 10, line 197-198; Page 14, line 283-285). We added some data in Table 1.

Comment (2): The small sample size may result in a non-normalized distribution and needs different statistical analysis other than the "paired sample t-test." Could the author explain the use of the chosen statistical analysis?

Reply (2): The paired sample t-test was conducted to analyze the postoperative change of the parameters in AA and MA group respectively, each patient was served as his or her own control which may partially offset the defect of a non-normalized data

distribution. This statistical analysis was superior in detecting some delicate differences or tendencies rather than independent sample t-test. In Kolmogorov-Smirnov test, all the continuous baseline variables obey a normal distribution.

Result:

Comment (3): Review of the literature. Most articles concluded that there is no difference in voice outcome, whether the ST muscle is divided or not during a thyroidectomy (1,2). The result is different from this study. Could the author give us some recommendations?

Reply (3): In Ref.1 and Ref.2, authors did not report the extent of thyroid surgery, and the maximum thyroid specimen size was less than that of our study. Maybe we are less skillful in surgical techniques than the authors of those studies, which could potentially work on voice recovery. It is generally accepted that adult men have a low pitched voice and women a high voice. The authors did not analyze the measurements of F0, F0-Low and F0-High separately by genders. They did not validated the intact of EBSLN, RLN and cricothyroid muscle by IONM. It may result in a bias and made the results differ from us.

Comment (4): Although there is a statistical difference of F0 and F0-High change between the two groups, the subjective parameter G or clinical symptoms showed no difference. This means that the patient would not feel any urgency to enter a voice rehabilitation course because they felt normal. Therefore, the result may not impact on clinical practice. I would like to ask the author's opinion on this.

Reply (4): Sorry for the misrepresentation, patients would not enter a voice rehabilitation course. The auditory-perceptual parameters GRBAS only described the grade of hoarseness, but not the voice capability. Patients complained about the postoperative changes in tone of voice and failed to maintain the same habitual and maximum pitch as preoperatively, which was reflected by F0 and F0-High change.

Changes in the text (4): We have modified our text as advised (see Page 2, line 44; Page 10, line 194-196; Page 12, line 235-237).

Comment (5): Based on the experience of clinical practice, the damage from specific surgical procedure would be the most in the initial time and overcome after a period of healing process. It means it would be more reasonable to see difference in the 2 weeks after surgery rather than 3 months after surgery which is different from the result of the study. I would like to ask the author's opinion on this. Why we see the different in 3 months but not in 2 weeks?

Reply (5): Many factors may contribute to voice changes after thyroidectomy. The perturbation in voice would be the most in the initial time and overcome after a period of healing process. The general wound healing process is divided into three phases: inflammation, proliferation, and maturation. During surgery for thyroid swellings, the strap muscle is compressed by enlarged thyroid and becomes thick and thin. Removal of the thyroid gland modifies the vascular supply and venous drainage of the larynx. As the vocal fold inflammation and laryngeal nerve edema gradually resolved, other

latent factors contributing to voice changes are emerging, such as the slow involution of strap muscles.

Reference:

(1) Henry LR, Solomon NP, Howard R, Gurevich-Uvena J, Horst LB, Coppit G, Orlikoff R, Libutti SK, Shaha AR, Stojadinovic A. The functional impact on voice of sternothyroid muscle division during thyroidectomy. *Ann Surg Oncol*. 2008 Jul;15(7):2027-33. doi: 10.1245/s10434-008-9936-8. Epub 2008 May 6. PMID: 18459003.

(2) Lee HS, Kim SW, Park HS, Park CW, Kim JS, Hong JC, Kim YK, Baek SM, Lee KD. Partial cutting of sternothyroid muscle during total thyroidectomy: impact on postoperative vocal outcomes. *ScientificWorldJournal*. 2013 Sep 23;2013:416535. doi: 10.1155/2013/416535. PMID: 24174915; PMCID: PMC3794563.

Reviewer B

Comment (1): Why AA and MA were performed in different periods? If AA is a good method, why the author not keep performing this approach?

Reply (1): Previously, we routinely transected ST muscle even the SH muscle during grossly enlarged thyroid surgery. Patients often complained about the postoperative changes in tone of voice, but the signal during intraoperative nerve monitoring indicated the functional integrity of RLN. We postulated that the feature of ST muscle might contribute to voice changes after thyroidectomy. Thus we developed anterolateral approach which combined lateral intervention with “classic” midline approach and were ready to put into practice in thyroid swelling surgery. From October 2018, every eligible patient was persuaded to receive anterolateral approach with a merit of preserving ST muscles, and finally achieved good compliance. We stick to this surgical method for one and a half years which facilitates the management of patients postoperatively, and ensure the skillful use of this technique. Then AA approach was found time-consuming and much patience was demanded in preservation of ST muscle. Meanwhile, for purpose of exploratory analysis and avoiding the bandwagon effect in patient’s decision making, we switch to conventional midline approach from March 2020 for more than a year. Although this is not a strictly designed study, we proved that this anterolateral approach is a patient-friendly technique but not surgeon-friendly. It is relatively “good”.

Changes in the text (1): We have modified our text as advised (see Page 10, line 197-198; Page 14, line 283-285). We added some data in Table 1.

Comment (2): The patient collection in the second period is till Jun 2021, how the patients have a 3-month follow up?

Reply (2): Sorry for the misrepresentation. The anterolateral approach (AA) was performed on consecutive patients from October 2018 to January 2020, then the eligible cases hospitalized from March 2020 and followed up to June 2021 and receiving who received thyroidectomy via midline approach (MA) were served as controls.

Changes in the text (2): We have modified our text as advised (see Page 2, line 23-26;

Page 5, line 75-80).

Comment (3): What is the definition of “thyroid swelling”?

Reply (3): Thyroid swelling is used to describe the generalized enlargement of the thyroid gland, the pathological diagnosis include Graves’ disease, Hashimoto’s thyroiditis, diffuse or multinodular goiter, thyroid adenoma or follicular carcinoma.

Comment (4): The description about inclusion/exclusion is different in Method section and Figure 1, please clarify.

Reply (4): The exclusion criteria were some common factors that are likely to impact on the human voice, which are referred from several acoustic investigations. The exclusions in Figure 1 were the situations we've encountered in this study.

Changes in the text (4): We have modified our text as advised (see Page 6, line 94-97).

Comment (5): In Table 1, the author had description “unexpected malignancy”, which means there was patient selection in preoperative histologic survey, please clarify.

Reply (5): The indication for thyroid surgery in the study was that significant thyroid enlargement exhibits pressure symptom of airway or esophagus, as well as cosmetic deformity. Thyroid that were palpable were examined by ultrasound and CT only, FNA was not performed. In the cases of “unexpected thyroid malignancy”, the malignancies went clinically unrecognized according to preoperative imaging examinations until the final pathology report indicated the foci of papillary microcarcinoma or follicular carcinoma with capsular microinvasion in the enlarged lobes, in which total thyroidectomy is sufficient from perspective of radical cure.

Changes in the text (5): We have modified our text as advised (see Page 9, line 174-181).

Comment (6): The value gap of F0 high of female and male was too small, please clarify.

Reply (6): The generalized enlargement of the thyroid gland may have effect on preoperative F0 high, which may narrow the gap of F0 high between genders. The preoperative vocal capability of those patients is also pathological because of the compression symptoms. The sample size of male patients is small here and lacks representativeness. It is just descriptive statistics.

Comment (7): About the application of intraoperative neuromonitoring (IONM), did every patient in this study use this technique? If yes, how was the signal change of RLN? And if using IONM, please clarify “EBSLN identified during operation” is visualized or monitored.

Reply (7): Yes, we use IONM in every patient in this study. A >50% decrease in amplitude paralleled by a >10% increase in latency of EMG signals or loss of signal recorded during IONM which failed to restore during surgery were deemed as iatrogenic RLN damage. Those patients were excluded from the study. The EBSLN was visualized or monitored by stimulating the nerve from the point proximal to the

excision of the superior pole vessels with integral twitch of cricothyroid muscles, or with an electromyographic glottic response recorded through electrodes on endotracheal tube after safe and individual ligation of the superior pole vessels.

Changes in the text (7): We have modified our text as advised (see Page 7, line 118-127).

Comment (8): In this study, RLN/EBSLN identification should present as nerves/nerves at risk. This yield another issue, if thyroid swelling only occurs at one side, did the author still perform AA at the smaller side? Please clarify.

Reply (8): The inclusion criteria was thyroid swellings with relatively symmetrical type of thyroid growth. The study do not involve patients whose thyroid swelling only occurs at one side. If the patient had only one side of huge thyroid goiter and relative small nodule on the contralateral side, we did unilateral division of sternothyroid muscle. Some study indicated that there was a significant change in the vocal range compared with a separate group who had undergone unilateral division or no disruption. We speculated that unilateral division of sternothyroid muscle could be compensated by the unaffected side. Thus we did not put into research on those patients.

Changes in the text (8): We have modified our text as advised (see Page 5, line 89-90).

Reviewer C

Comment #1: The current study didn't show the significant differences between AA and MA thyroidectomy. To evaluate the voice outcome after thyroidectomy, there are possible factors that can affect postoperative voice quality. Therefore, the authors need to describe the details of clinical characteristics including tumor pathology, such as tumor size, thyroiditis, and the extent of thyroid surgery. Please describe in detail in the results section.

Reply #1: We had described the details of clinical characteristics in the results section according to your comments.

Changes in the text #1: We have modified our text as advised (see Page 9, line 171-181). We add some data in Table 1.

Comment #2: To show the voice outcome according to the different approaches between AA and MA, other important variables that can affect voice outcome need to be matched or clarified in the study. In the aspects of nerve damage, for the evaluation of voice outcome, the results of laryngoscopy or laryngeal ultrasound exam, which were used to evaluate the function of vocal cords, need to be included in the results section. Patients with vocal cord palsy could be classified as non-damaged.

Reply #2: We had described the laryngoscopy results in the results section according to your comments.

Changes in the text #2: We have modified our text as advised (see Page 9, line 171-172).

Comment #3: Please clarify the identification methods of EBSLN or RLN whether using an intraoperative neuromonitoring system or visualization alone.

Reply #3: The EBSLN was visualized or monitored by stimulating the nerve from the point proximal to the excision of the superior pole vessels with integral twitch of cricothyroid muscles, or with an electromyographic glottic response recorded through electrodes on endotracheal tube after safe and individual ligation of the superior pole vessels. The RLN was visualized and monitored by IONM in every patient in this study.
Changes in the text #3: We have modified our text as advised (see Page 7, line 118-127).

Comment #4: Please check English proofreading

Reply #4: AME Editing Service had checked the English proofreading.

Reviewer D

Comment 1: All patients underwent total thyroidectomy in both study group (AA) and control group (MA). The bilateral sternothyroid muscles were routinely divided in the control group. If the patient had only one side of huge thyroid goiter (e.g. 7cm) and relative small nodule (e.g. 2.5cm) on the contralateral side, did bilateral division of sternothyroid muscle still perform? What is the rationale?

Reply 1: The patients recruited here were thyroid swellings with relatively symmetrical type of thyroid growth. The study do not involve patients whose thyroid swelling only occurs at one side. If the patient had only one side of huge thyroid goiter and relative small nodule on the contralateral side, we did unilateral division of sternothyroid muscle. Some study indicated that there was a significant change in the vocal range compared with a separate group who had undergone unilateral division or no disruption. We speculated that unilateral division of sternothyroid muscle could be compensated by the unaffected side. Thus we did not put into research on those patients.

Changes in the text 1: We have modified our text as advised (see Page 5, line 89-90).

Comment 2: Table 1 only showed the maximal length of thyroid gland, which might not be sufficient to know the real thyroid size in the study population. For example, an 8*2*3cm thyroid gland is significantly different from a thyroid gland of 8*4*6cm in size. The latter one is 4 times bigger and difficult to remove. Could you provide the estimated thyroid volumes ($0.479 \times \text{width} \times \text{length} \times \text{depth}$) or the thyroid specimen weight for both lobes?

Reply 2: We had provided the estimated thyroid lobe volume in Table 1 according to the record in ultrasonography report. The estimated thyroid lobe volumes were calculated using the following formula: $\pi/6 \times (\text{length} \times \text{width} \times \text{thickness})$.

Comment 3: The author's innovation is the anterolateral approach, which combines the traditional lateral intervention with midline approach. The lateral intervention allows easier access to the upper pole and superior thyroid vessel control in patients with large goiter. Could the author state more about the rationale and benefit of adding midline approach in their method?

Reply 3: When combining the midline approach, the early division of isthmus from the

tracheal endows great mobility of the thyroid lobe. During midline approach, the RLN could be dissected in anterograde fashion via medial approach after the upper pole was freed. Moreover, enlarged pyramidal lobe could be easily removed.

Comment 4: In the control group (MA), the upper part of sternothyroid muscle was divided and removed without suturing back. If the divided strap muscle was sutured back, would it partially restore the muscle integrity and improved the voice outcome? Furthermore, is it possible that the postoperative voice performance would become no difference between the two groups?

Reply 4: The upper part of divided sternothyroid muscle was denervated, of which vascular supply and venous or lymphatic drainage would be changed. Even if the divided strap muscle was sutured back, it would not work as well as preoperatively.

Changes in the text 4: We have modified our text as advised (see Page 15, line 296-297).

Comment 5: In the surgical technique described by the authors, it seemed that the ansa cervicalis was routinely identified and stimulated. Was the nerve identification rate 100%? The nerve stimulation was performed before the thyroid dissection or after the thyroid dissection? How did you know whether there was any nerve injury during the thyroid manipulation?

Reply 5: Yes, the ansa cervicalis was 100% identified and stimulated before and after the thyroid dissection. We did meticulous dissections in every ansa cervicalis and confirmed its integrity by corresponding strap muscle contraction after electro-stimulation, which imitated the procedure of RLN monitoring.

Changes in the text 5: We have modified our text as advised (see Page 6, line 107-110; see Page 7, line 118-127).