Received: 16 July 2023 | Accepted: 13 August 2023
DOI: 10.1111/jocd.15973

JCD Journal of Cosmetic Dermatology WILEY

ORIGINAL ARTICLE

Safety considerations for treating the parotid and submandibular glands with neuromodulators for facial slimming

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Abstract

Background: Neuromodulators have predominantly been used for the treatment of upper facial lines, but their use has expanded to include lower face and neck treatments. However, the injection sites for these treatments are based on skin surface landmarks, which may pose risks to nearby structures and result in undesired outcomes.

Objective: To investigate the spatial relationship between the FDA-approved skin surface landmarks for neuromodulator injections in the parotid and submandibular glands and the topographical anatomy of critical facial structures such as the facial artery, facial vein, external carotid artery, and retromandibular vein.

Materials and methods: A cross-sectional retrospective analysis was conducted on contrast-enhanced cranial CT scans. The scans were analyzed for the morphology and location of the parotid and submandibular glands. Measurements were taken for gland volume, craniocaudal extent, anterior–posterior extent, and distances between the skin surface and gland capsule or nearby structures such as arteries.

Results: The study sample consisted of 53 subjects, including 7 males and 46 females, with a mean age of 36.91 years and a mean BMI of 23.28 kg/m^2. The mean volume of the parotid gland was 31.9 ± 3.0 cc in males and 28.5 ± 3.6 cc in females with $p < 0.001$, while the mean volume of the submandibular gland was 18.2 ± 2.0 cc in males and 14.5 ± 3.4 cc in females with $p < 0.001$. The mean distances between skin surface and the gland capsule were 5.98 ± 2.2 and 8.84 ± 4.0 mm for the parotid and submandibular gland, respectively. This distance increased with higher age and higher BMI values in a statistically significant manner with $p < 0.001$.

Conclusion: The distances between FDA-approved skin surface landmarks and the parotid and submandibular glands varied significantly depending on gender, age, and BMI. Optimal injection depth and location for neuromodulator treatments cannot be

Pavel Gelezhe and Konstantin Frank contributed equaly to this work.

generalized based on these landmarks alone, emphasizing the need for real-time ultrasound imaging guidance.

KEYWORDS
facial slimming, neuromodulators, parotid gland, safety, submandibular gland

1 | INTRODUCTION

Traditionally, neuromodulators were utilized to treat upper facial lines, to reduce the signs of skin aging, with major focus being placed on the forehead (frontalis muscle), glabella (procerus and corrugator supercilii muscles), and on lateral canthal lines (orbicularis oculi muscle).[1–3] With more acceptance of facial aesthetic treatments, neuromodulators were additionally utilized in the lower face and neck for the treatment of dysthymic facial expressions (depressor anguli oris), skin surface irregularities of the chin (mentalis muscle), or for platysmal banding (platysma muscle).[4–6]

Increasing anatomic knowledge of facial anatomy, resulted in the administration of neuromodulators to treat jawline contouring and midfacial volume loss (depressor anguli oris and platysma) or were utilized to indirectly treat temporal volume loss by targeting the masseter muscle.[7–9] The masseter muscle can also be targeted with neuromodulators for lower facial volume reduction and facial slimming; this is predominantly popular in Asian populations.[10,11]

However, reduction in lower facial volume can additionally be achieved by targeting the parotid and the submandibular glands with neuromodulators; this is a standard treatment for reducing excess saliva production (sialorrhea).[12,13] Despite several studies recommending to treat both glands for sialorrhea under ultrasound guidance, to increase treatment effectiveness and safety, some studies utilized the FDA-approved injection points which are based on skin surface landmarks. For the parotid gland, the skin surface landmark is 1 cm anterior to the mid-distance between tragus and mandibular angle, whereas the skin surface landmark for the submandibular gland is 1 cm caudal to the mid- distance between chin and mandibular angle.[14]

The reduction in saliva production and flow is a desired treatment outcome when treating for sialorrhea, but is an undesired result when treating those glands for aesthetic facial slimming. In addition, the safety profile for such aesthetic procedures needs to be high and should mandate avoiding adjacent muscles (risorius muscle) and neighboring vessels: facial artery and vein, external carotid artery, and retromandibular vein.[15,16] With ultrasound imaging, these structures (muscles and vessels) can be identified reliably and neuromodulator treatments can be directed to avoid those danger zones. However, relying on skin surface landmarks poses a risk of injecting the neuromodulator agent into or in close vicinity to relevant structures. This can result in undesired outcomes like loss of effectiveness (due to a wash-out phenomenon), asymmetric smile (effect on the risorius muscle), or vessel injury (iatrogenic injury of arteries and veins).

To date, no study has investigated the spatial relationship between the FDA-approved skin surface landmarks for neuromodulator treatments of the parotid and submandibular glands and the location of the facial artery and vein, external carotid artery, and retromandibular vein. The results of such a clinically relevant study will help to guide practitioners to safer and more effective neuromodulator treatments of the lower face for facial slimming in cases when real-time ultrasound imaging is not available.

2 | MATERIALS AND METHODS

2.1 | Study sample

This study was designed as a cross-sectional retrospective analysis of routine contrast-enhanced cranial CT exams which were sampled from the database of the Research and Practical Center of Medical Radiology under the Department of Health Care in Moscow, Russia. CT scans were analyzed for the morphology and location of the parotid and submandibular glands between July 2022 and December 2022. The ethics committee of the Department of Health in Moscow, Russia (protocol number 5) approved the study, and patients provided informed consent for the use of their demographic information and CT scan data.

2.2 | Image analyses

CT scans were obtained according to a previously published protocol[17] using a Toshiba Aquilion LB scanner (manufactured by Toshiba Medical Systems Corporation located in Ōtawara, Tochigi, Japan) with the following scanning specifications: a voltage of 120 kV, slice thickness of 0.47 mm, field of view of 220 mm, and a tube current of 140 mA. CT scans had to provide full visibility of the parotid and submandibular gland without pathologic changes to the surrounding anatomy or to the glands themselves. Bilateral measurements were conducted utilizing the internal software tools of Intellispace 8.0 (made by Philips, Koninklijke) and used as skin surface reference points the previously FDA-approved landmarks for sialorrhea targeting the parotid and submandibular glands.[13,18] (Figure 1) The following parameters were evaluated bilaterally for both glands:

Parotid gland: (1) Volume, (2) Maximal craniocaudal extent, (3) Maximal anterior–posterior extent, (4) Distance between skin surface and parotid capsule, (5) Distance between skin surface and external carotid artery, and (6) Distance between skin surface and retromandibular vein (Figures 2 and 3).

Submandibular gland: (1) Volume, (2) Maximal craniocaudal extent, (3) Maximal anterior–posterior extent, (4) Distance between skin surface and submandibular capsule, (5) Distance between skin surface and facial artery, and (6) Distance between skin surface and facial vein (Figure 4).

2.3 | Statistical analyses

Descriptive and comparative analyses were conducted using SPSS Statistics 23 (IBM). Comparisons were performed between study participants of various age and body mass index (BMI) values using independent Student's *t*-test, Pearson bivariate correlation, and generalized linear models and results were considered statistically significant with $p<0.05$.

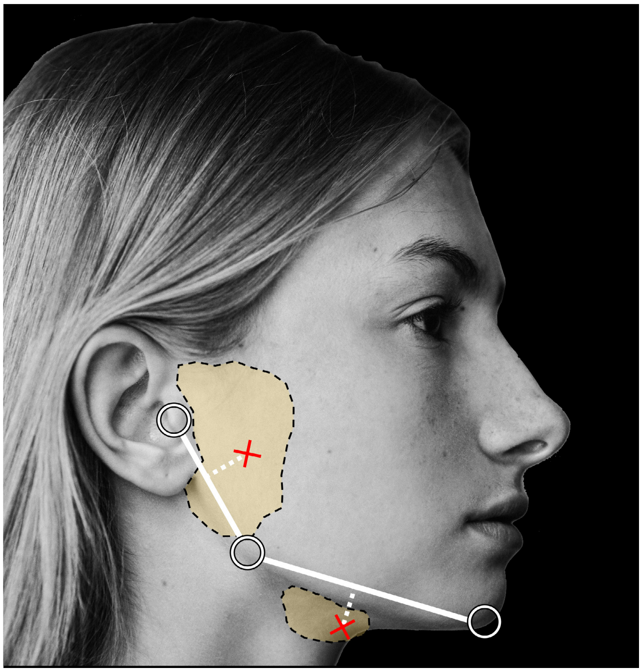

FIGURE 1 FDA-approved injection locations for the parotid and submandibular gland. Landmarks are indicated by white circles and injection points are indicated by red crosses.

3 | RESULTS

3.1 | Demographics

The retrospectively investigated 53 subjects consisted of 7 males (13.2%) and 46 females (86.8%) with a mean age of 36.91 ± 15.6 years (range: 14–78) and a mean BMI of 23.28 ± 4.3 kg/m^2 (range: 17.9–36.6). Males displayed a statistically significant higher age $p<0.001$) and BMI ($p=0.005$) when compared to females. Interestingly, a positive correlation was identified between age and BMI for the entire study sample with $r_p=0.341$ and $p<0.001$.

3.2 | Volume

3.2.1 | Parotid gland

Mean volume of the parotid gland was in males 31.9 ± 3.0 cc (range: 25.8–36.7) and was in females 28.5 ± 3.6 cc (range: 21.9–35.7) with $p<0.001$ for gender differences. A positive correlation was found between volume and age with $r_p=0.352$ and $p<0.001$ and between volume and BMI with $r_p=0.707$ and $p<0.001$.

3.2.2 | Submandibular gland

Mean volume of the submandibular gland was in males 18.2 ± 2.0 cc (range: 12.9–21.0) and was in females 14.5 ± 3.4 cc (range: 5.3–23.9) with $p<0.001$ for gender differences. A positive correlation was found between volume and age with $r_p=0.265$ and $p=0.006$ and between volume and BMI with $r_p=0.427$ and $p<0.001$.

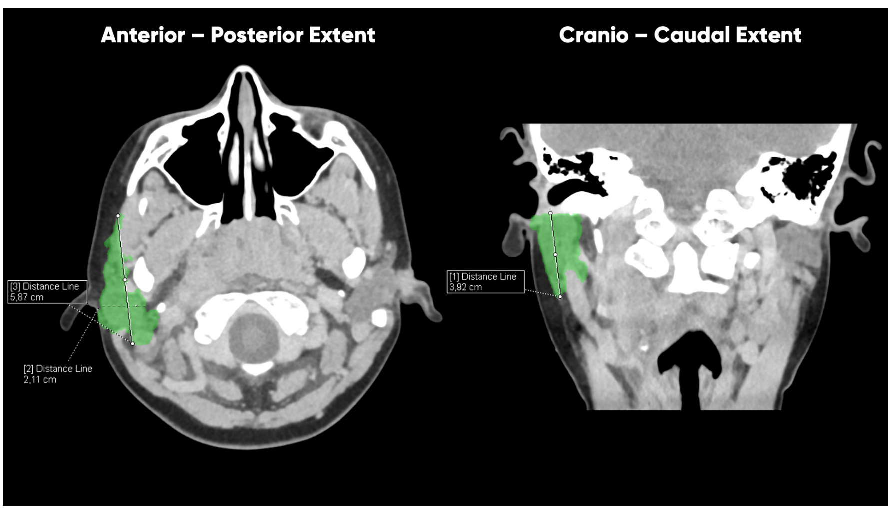

FIGURE 2 Computed tomographic scans showing the anterior–posterior extent of the parotid gland in the transverse view and the craniocaudal extent in the frontal view. The parotid gland is highlighted in green color.

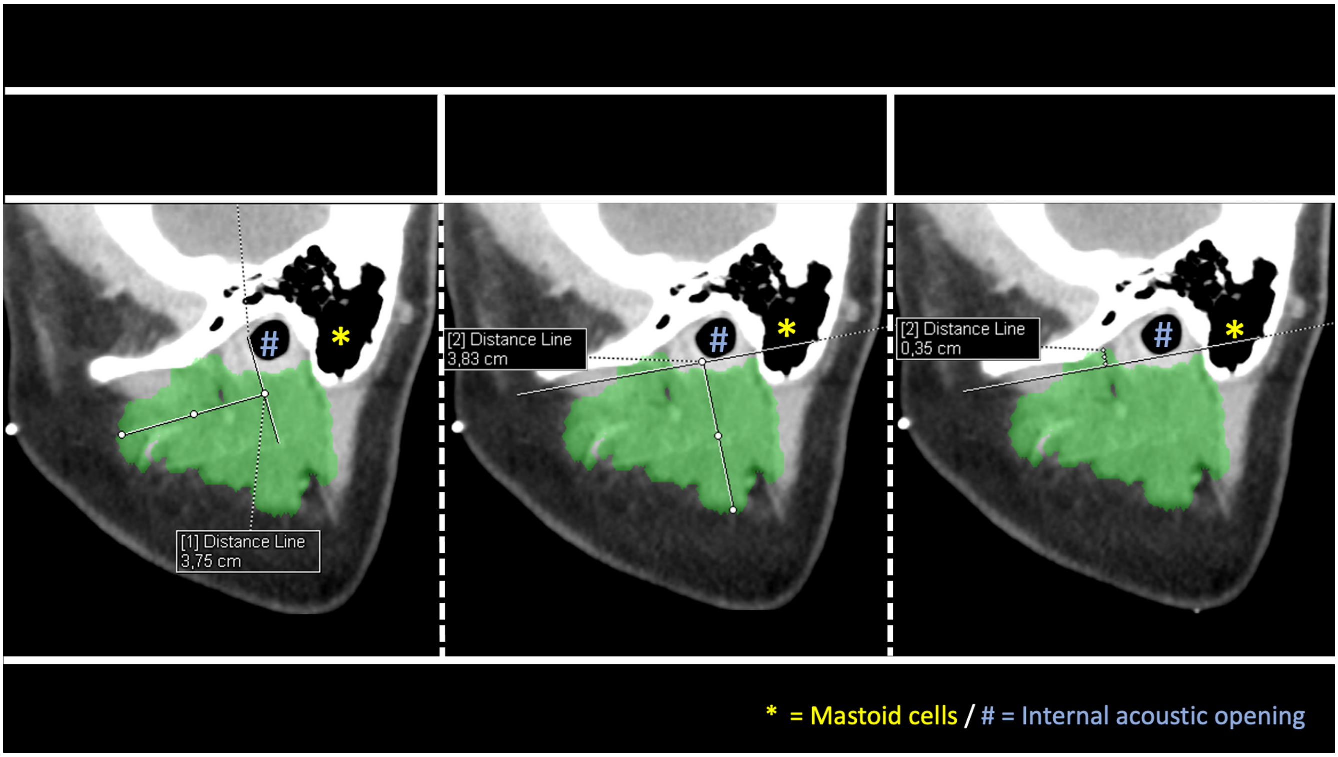

FIGURE 3 Computed tomographic scans showing the spatial relationships of the parotid gland and the mastoid cells (indicated by asterisk*) and the internal acoustic opening (indicated by number sign #).

FIGURE 4 Computed tomographic scans showing the dimensions of the submandibular gland in the sagittal and transverse view. The submandibular gland is highlighted in green color.

3.3 | Distances measured

3.3.1 | Parotid gland

Craniocaudal extent of the parotid gland was in males 67.29 ± 6.4 mm (range: 54.5–78.0) and was in females 60.0 ± 6.5 mm (range: 50.4–70.1) with $p < 0.001$ for gender differences, whereas the anterior–posterior extent was in males 39.63 ± 3.2 mm (range: 34.5–44.0) and was in females 37.51 ± 3.1 mm (range: 31.3–50.2) with $p = 0.021$ for gender differences. Independent of gender, both dimensions displayed a statistically significant correlation with age and BMI with $p < 0.001$.

3.3.2 | Submandibular gland

Craniocaudal extent of the submandibular gland was in males 35.45 ± 4.5 mm (range: 24.7–39.1) and was in females 30.05 ± 5.3 mm (range: 21.2–42.5) with $p < 0.001$ for gender differences, whereas the mean anterior–posterior extent was in males 37.29 ± 5.3 mm (range: 25.0–43.1) and was in females 30.48 ± 6.1 mm (range: 20.0–41.0) with $p < 0.001$ for gender differences. Independent of gender, both dimensions displayed a statistically significant correlation with age and BMI with $p < 0.001$ (Figure 5).

3.4 | Relationship with other structures

3.4.1 | Parotid gland

The mean distance between skin surface and parotid gland capsule was overall 5.98 ± 2.2 mm (range: 1.0–10.1) with $p < 0.001$ for gender differences. This distance significantly increased with higher age and higher BMI values with $p < 0.001$.

The mean distance between skin surface and the external carotid artery was overall 31.92 ± 5.1 mm (range: 21.7–42.0) with $p = 0.008$ for gender differences. This distance significantly increased for higher age and higher BMI values with $p < 0.001$.

The mean distance between skin surface and the retromandibular vein was overall 33.63 ± 4.0 mm (range: 25.9–41.7) with $p < 0.001$ for gender differences. This distance significantly increased for higher age and higher BMI values with $p < 0.001$.

3.4.2 | Submandibular gland

The mean distance between skin surface and submandibular gland capsule was overall 8.84 ± 4.0 mm (range: 1.0–17.3) with $p = 0.004$ for gender differences. This distance significantly increased for higher age and higher BMI values with $p < 0.001$.

The mean distance between skin surface and the facial artery was overall 15.83 ± 3.7 mm (range: 10.0–26.0) with $p < 0.001$ for gender differences. This distance significantly increased for higher age and higher BMI values with $p < 0.001$.

The mean distance between skin surface and the facial vein was overall 15.22 ± 2.9 mm (range: 10.9–21.0) with $p < 0.001$ for gender differences. This distance significantly increased for higher age and higher BMI values with $p < 0.001$ (Figure 6).

4 | DISCUSSION

This CT-scanning based study sought to investigate the distances between FDA-approved skin surface landmarks for neuromodulator injections and the parotid and submandibular glands, as well as critical facial structures like the external carotid artery and the

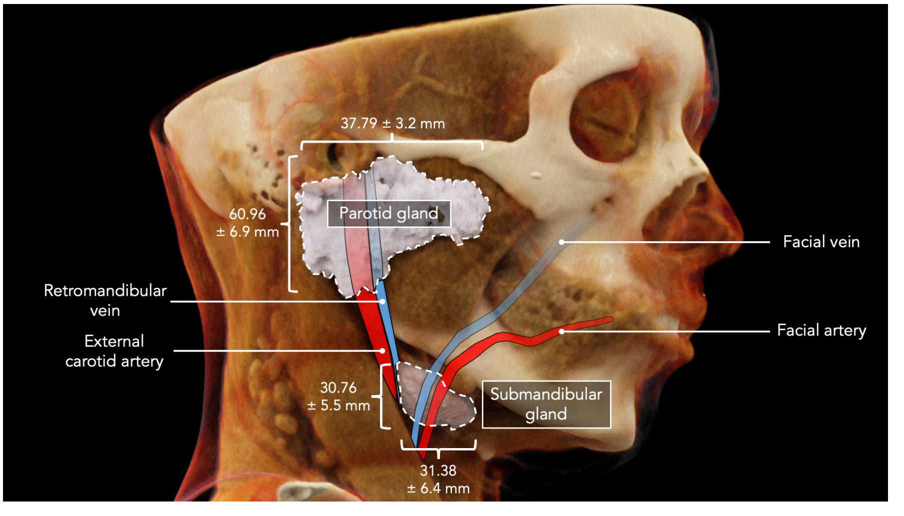

FIGURE 5 Horizontal and vertical extent of the parotid and submandibular gland and their topographical relationship to the retromandibular vein and external carotid artery as well as facial vein and facial artery, respectively.

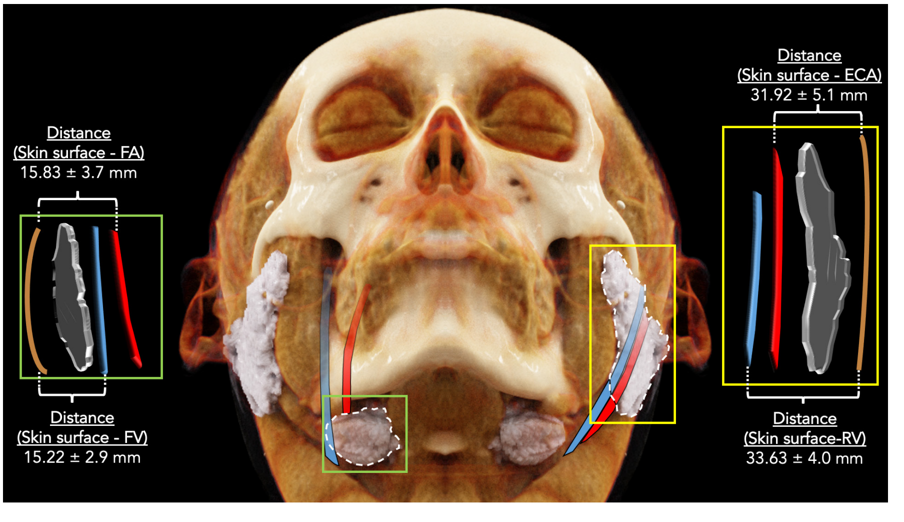

FIGURE 6 Topographical relationship and distance measurements between skin surface, gland capsule, and important vascular structures (i.e., facial artery/vein, external carotid artery, and retromandibular vein).

retromandibular vein (for parotid gland) and the facial artery and the facial vein (for submandibular gland). The results revealed that the distances between the FDA-approved skin surface landmarks and both glands vary highly depending on gender, age, and BMI with greater distances observed at higher age and with higher BMI (with $p<0.001$). The range of distance for the parotid gland was 1.0–10.1 mm whereas the range of distance for the submandibular gland was 1.0–17.3 mm. This indicates that optimal depth for administering neuromodulators safely and effectively into the body of the gland is highly variable and depends on the patient's individual demographic and body habitus data. Generalization of injection depth based on the results of this investigation is not possible and therefore real-time ultrasound imaging is recommended. This will allow injectors to identify the optimal depth of the gland for increased treatment outcomes. The depth measures obtained in this study also show that, in some instances, superficial product placement is needed; this results in greater risk to accidentally affecting the risorius muscle during parotid gland treatments.[19,20]

The volume of both glands was significantly greater in study participants of higher age ($p<0.001$) and of higher BMI ($p<0.001$) and displayed a highly positive correlation with $p<0.001$ for both glands. This is in line with previous publications which have revealed that the volumes of both glands increase when measured by CT scanning in a longitudinal study approach.[21,22] Not only the volume but also the craniocaudal and the anterior–posterior extent increased significantly at higher age and at higher BMI (all values $p<0.001$); this is interesting from a facial aging perspective. The age-related increase could potentially explain why, at higher age, a loss in mandibular angle and jawline contouring can be observed. The increase in gland volume and extent could camouflage the bony contours of the mandible and result in a smoothening in the transition between lower face and neck or between the ramus of the mandible and the peri-auricular area. This aspect emphasizes the need for individualized treatment strategies (i.e., injection depth and location) due to the age and body habitus-related changes. Therefore, generalized recommendations of injection locations should be replaced by real-time ultrasound imaging-guided injection procedures.

If standardized injection locations are used, the product could end up either superficial or deep to the most optimal intra-glandular position. Too superficial injections into the parotid gland could potentially affect the risorius muscle whereas too superficial injections into the submandibular gland would result only in reduced effectiveness. However, injections performed into deeper planes might cause serious adverse events if crucial vasculature is inadvertently injured during the injection process for both glands. The depth of the external carotid artery, when measured as the distance between pre-auricular skin surface and the center of the vessel ranged between 21.7 and 42.0 mm, whereas the depth of the retromandibular vein ranged between 25.9 and 41.7 mm; both distances allow for sufficient space to position the product superficial to the vasculature. However, given the statistically significant dependency on age and BMI, with lower values, i.e., more superficial locations in younger study participants, the risk is not zero when injecting neuromodulators. The inserted needle could damage the vessel wall and arterial or venous blood could enter the parotid gland tissue and cause hematoma, facial nerve compression, or saliva flow obstruction.

The depth of the facial vessels, when measured from the skin surface of the infra-mandibular region ranged between 10.0 and 26.0 mm, whereas for the facial vein, it ranged between 10.9 and 21.0 mm. These distances showed a high degree of correlation with age and BMI, with younger individuals having a more superficial position of their vasculature. This could result in vessel damage or in reduced effectiveness as a consequence of product wash-out into the bloodstream if the product is administered in an intra-luminal location.

The results also indicate that real-time ultrasound guidance is recommended and should be state-of-the-art if neuromodulator treatments for the parotid and/or the submandibular gland are performed. The FDA-approved skin surface landmarks can provide a rough guide to treat both glands, however, the injector should be reminded that glandular injections are three-dimensional treatments that require both the knowledge of depth and the relevant vascular anatomy of the region. This is crucial if the optimal intra-glandular location is to be obtained and no adjacent vessels are to be harmed.

This study is not free of limitations. The sample size is limited to 53 subjects with only 7 males; this could be regarded as a shortcoming to represent a balanced patient sample. However, given the fact that the majority of aesthetic patients are females, the results are applicable to daily clinical practice. Further, the sample consisted of 100% Russian Caucasian individuals, and it is not known whether the results are applicable to the Asian, African American, or other ethnic groups. Future studies will need to elaborate on this issue. Further, ultrasound-guided measurements might have been more accurate due to their clinical applicability and non-radiation methodology. It must be noted that none of the CT scans was performed for the purposes of this study, but were conducted due to other medical reasons. The measurements performed were conducted after the CT scans were made available.

5 | CONCLUSION

The results of this CT-scanning-based investigation revealed that both the two-dimensional and three-dimensional measurements of both parotid and submandibular glands increase with higher age and BMI. This places younger aesthetic patients at a higher risk of having their crucial peri-glandular vasculature exposed in more superficial locations during neuromodulator treatments. Despite that skin surface landmarks are available and FDA-approved to target both the parotid and the submandibular glands, the depth of the peri-glandular vasculature varies with age, gender, and BMI. It is recommended, therefore, that real-time ultrasound-guided imaging is used to reduce the risk of iatrogenic vascular injury and to increase patient safety and treatment effectiveness.

FUNDING INFORMATION

This study received no funding.

CONFLICT OF INTEREST STATEMENT

None of the other authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author SC, upon reasonable request.

ETHICS STATEMENT

The ethics committee of the Department of Health in Moscow, Russia (protocol number 5) approved the study.

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How to cite this article: Gelezhe P, Frank K, Casabona G, et al. Safety considerations for treating the parotid and submandibular glands with neuromodulators for facial slimming. *J Cosmet Dermatol*. 2023;00:1-7. doi:10.1111/jocd.15973