의학 석사 학위논문

Volumetric Measurement of Posterior Cricoarytenoid Muscle: Implication for Prognosis of Unilateral Vocal Fold Paralysis

후윤상피열근 부피측정을 통한

일측성대마비 예후 분석

2021 년 2 월

서울대학교 대학원

의학과 이비인후과학 전공

조 성 동

후윤상피열근 부피측정을 통한 일측성대마비 예후 분석

지도교수 권 택 균

이 논문을 의학 석사 학위논문으로 제출함

2020 년 10 월

서울대학교 대학원

의학과 이비인후과학

조 성 동

조성동의 석사 학위논문을 인준함

2021 년 1 월

위원장	김 지 은	(인)
부위원장	권 택 균	(인)
위원	박 민 현	(인)

Abstract

Volumetric Measurement of Posterior Cricoarytenoid Muscle: Implication for Prognosis of Unilateral Vocal Fold Paralysis

Sung-Dong Cho

Department of Otorhinolaryngology

Seoul National University College of Medicine

Introduction: Vocal fold paralysis (VFP) refers to a condition in which one or both vocal cords do not move due to various reasons. Studies have been conducted to predict the direction of VFP and prognosis of VFP using computed tomography (CT). According to a recent study, in patients with unilateral VFP (UVFP), the lower the volume of the posterior cricoarytenoid (PCA) muscle on the affected side, the worse the laryngeal electromyography (LEMG) findings, the smaller the volume, and the less chances for UVFP to recover. However, there was no study that has quantitatively measured the volume of the PCA muscle and analyzed it as a continuous variable. Therefore, this study was conducted for the following purposes. First, the volume of the PCA muscle was measured using the ITK-SNAP program, and reproducibility was checked. Second, the PCA muscle volume ratio was calculated and analyzed to find whether there was a correlation with the result of LEMG findings. Third, we explored whether the PCA muscle volume ratio could be used as an index to predict permanent UVFP.

Methods: From 2005 to 2016, a retrospective medical record review of adult patients who visited the Seoul National University Hospital diagnosed with UVFP was performed. Patients with CT and LEMG performed at least 3 months after the onset of UVFP were analyzed. Cases in which the PCA muscle was indistinguishable from the surrounding structures by CT were excluded from the study. Through ITK-SNAP, the contours of the PCA muscle were specified in all planes where the PCA muscle was present. Based on the contour specified by the measurer, ITK-SNAP calculated the volume and PCA muscle atrophy ratio. The LEMG results were divided into 5 groups according to the severity. Subsequently, the correlations between the PCA muscle volume ratio and the LEMG as well as PCA muscle volume ratio and prognosis were analyzed.

Results: Analysis of 41 patients showed that the left side was more dominant (71%) with idiopathic VFP as the most common etiology. PCA muscle measured by two clinicians had significant reproducibility ($P<0.001$). The average PCA muscle volume ratio was 0.50, which had a negative correlation with LEMG grades (Rho=-0.351, P=0.024). However, as the PCA volume atrophy increased, the proportion of permanent UVFP significantly increased ($P<0.001$). When PCA muscle volume decreased by 82% or more compared to the normal side, the positive predictive value for permanent UVFP was 100%.

Conclusion: The quantitative volume measurement of the PCA muscle was highly reliable, and the PCA muscle volume ratio was significantly correlated with the LEMG results, which is a conventional tool for anticipating the prognosis. This was consistent with the findings of previous studies and can be used as an index for the prognosis of UVFP. Follow-up studies are required in which a greater number of patients are analyzed by the automated process so that the measured value can reach the true value.

Keywords: unilateral vocal fold paralysis, volumetric measurement, computed tomography, prognosis, laryngeal electromyography, ITK-SNAP

Student Number: 2019-26705

Contents

List of Figures

List of Tables

List of Abbreviations

VFP: Vocal fold paralysis

LEMG: Laryngeal electromyography

MUAP: Motor unit potential

CT: Computed tomography

UVFP: Unilateral vocal fold paralysis

PCA: Posterior cricoarytenoid

2D: 2-dimensional

PPV: Positive predictive value

3D: 3-dimensional

SNUH: Seoul National University Hospital

DICOM: Digital imaging and communications in medicine

PACS: Picture archiving and communication system

SD: Standard deviation

CTM: Cricothyroid muscle

TAM: Thyroarytenoid muscle

SLN: Superior laryngeal nerve

RLN: Recurrent laryngeal nerve

ROC: Receiver operating technique

AUC: Area under curve

NPV: Negative predictive value

Introduction

Vocal fold paralysis (VFP) refers to a condition in which the movement of one or both vocal folds is reduced or absent. The prevalence rate is known to be 0.001–0.400%.[1,2] VFP can be classified into central and peripheral types. While the central types are caused by neurological abnormalities in the central nervous system, the brain, and the spinal cord, the peripheral types are usually caused by dysfunction of the vagus nerve and its branches. Most of the patients who visit the laryngology clinic are ruled out as having central type VFP in other departments. The etiology of VFP includes direct damage to the nerves during cervical or thoracic surgery, compressed or infiltrated vagus nerve due to benign or malignant neoplasms, viral infection, and trauma.[3-5] Patients with VFP present symptoms such as aspiration or hoarseness due to increased mean flow rate.

Laryngeal electromyography (LEMG) is a verified tool to predict the prognosis of VFP. LEMG represents the measurement of the electric potential generated by muscle cells through a probe located in the muscle. These muscular signals overlap and generate compound potential and motor unit action potential (MUAP). The morphology and recruitment pattern of MUAP are both significant in evaluating the prognosis of VFP. Normal MUAP morphology has a duration of 2–10 ms and is triphasic. When MUAPs have more than 4 phases, it is called polyphasic. Polyphasic MUAPs occur in 10–20% of normal patients and appear in the early reinnervation phase.[6] The recruitment pattern is a phenomenon in which the motor units in the vicinity are excited simultaneously while the muscle strongly contracts. This pattern, also known as an interference pattern, is significant for predicting the recovery of VFP.

In LEMG findings, the presence of voluntary MUAP, lack of spontaneous activity, and near-normal unit recruitment indicate a good prognosis.[7-9] However, cases with the absence of voluntary MUAP or cases with fibrillation potential result in a poor prognosis.[10] Fibrillation potentials are spontaneous potentials observed in muscle fibers that lack innervation.[11] The mechanism of nerve regeneration is remyelination, generation of collaterals, and renewal from the proximal part of the nerve. The regeneration is initiated at least 2 weeks and up to 18 months from the date of paralysis.[12] Furthermore, some studies revealed that the normal potential of recovered VFP patients begins to appear 1–6 months after paralysis.[9,13] Therefore, LEMG conducted at least 1 month after the paralysis is considered to be a useful tool to predict the outcome of VFP.

Laryngeal computed tomography (CT), including the range from the skull base to the aortic arch, is performed to investigate the etiology of VFP. Due to the high accessibility of CT scans, efforts have been made to identify the laterality in unilateral VFP (UVFP) patients. The CT findings that infer on the side of UVFP include medially located vocal cords, enlarged ventricle, thickened unilateral aryepiglottic fold, and dilatation of unilateral pyriform sinus.[14,15]

In addition to the previous findings, it has been reported that the atrophy grade of posterior cricoarytenoid (PCA) muscle, which was subjectively estimated based on two-dimensional (2D) axial CT scans, helps to determine the direction of the VFP and analyze the prognosis.[16,17] According to Lee et al., the grade of PCA muscle atrophy and worse LEMG results showed a significant positive correlation and positive predictive value (PPV) of permanence with regard to a PCA muscle atrophy grade of 88%.[17] However, the grade of PCA muscle atrophy was subjectively assessed without calculating the cross-sectional area. Previously, there was no numeric analysis of the PCA muscle volume in a three-dimensional (3D) space.

The purpose of this study was, first, to quantitatively measure the exact volume of the PCA muscle with a 3D volumetric analysis software (ITK-SNAP), second, to analyze the correlation between PCA muscle volume ratio and LEMG grades, and third, to determine whether the measured volume can be used as a predictor of the UVFP recovery.

Materials and Methods

Study design

A retrospective cohort study was conducted in a single tertiary referral center. Adults over 18 years of age who were diagnosed with UVFP in the Seoul National University Hospital (SNUH) outpatient clinic from November 2005 to December 2016 were included in the study. Subjects who underwent both CT and LEMG were selected. Since the volume of the limb muscle starts to decrease 3 months after a denervation injury, patients with CT at least 3 months after the UVFP were included.[18] Cases with CT cut thickness exceeding 5 mm were excluded due to the low resolution of the PCA muscle. Cases in which PCA muscle contours were difficult to evaluate due to artifacts or lack of fat pads were excluded from the study. Two operators first analyzed the CT and selected cases where the PCA muscle was not clearly visible. In case of disagreement between the two measurers, secondary opinions were exchanged and a consensus was reached to determine whether the measurement was possible.

Sex, age, the direction of paralysis, the onset of paralysis, etiology of UVFP, recovery date, last outpatient clinic follow-up date, and LEMG findings were obtained from the electronic medical records. The axial cut of the laryngeal CT with the format of digital imaging and communications in medicine (DICOM) was acquired from the picture archiving and communication system (PACS, Infinitt Co., Seoul, Korea). The date of the CT scan and thickness of the axial CT slice were also examined through the PACS.

PCA muscle volume measurements with ITK-SNAP

Principles of ITK-SNAP

ITK-SNAP is a software developed by Yushkevich et al., which includes a function that helps to perform an automated or manual segmentation analysis based on the DICOM files of axial CT scans.[19] In the manual segmentation method, which is the main tool for the analysis of PCA muscle volume, the number of voxels of the area selected by the user from each axial plane is measured and displayed. A voxel is a single unit containing graphic information in a 3D space, comparable with the concept of the pixel in two dimensions. As the size of the voxel gets smaller, it approaches the true value. This method of mensuration by parts is useful for the analysis of irregularly shaped objects.

Measurement protocol of the PCA muscle with ITK-SNAP

The method of acquiring PCA muscle volume from the ITK-SNAP is as follows. The latest software version was 3.6.0 at the time of analysis. Measurers selected "File-Open image" from the menu bar and then "Browse" from the popup window to open the DICOM files (.dcm). CT images of one subject usually contain hundreds of DICOM files (.dcm), and selecting only a single file from the software loads the entire CT. The main screen is divided into two horizontal rows and two vertical columns (Figure 1). The upper left is the axial plane in which we measure the PCA muscle volume. By clicking and dragging the right mouse button, we could zoom in or out and locate the PCA muscle at the center. Examiners selected "Tools-Image contrast-Contrast adjustment" from the menu bar. The image layer inspector popup appeared, and two red circles and one yellow circle in the "Curve-Based Contrast Adjustment" were manipulated (Figure 2). The width and level of the window were modified to make the PCA muscle visible (Figure 3B) compared to the initial non-adjusted image (Figure 3A). Examiners selected "Segmentation-Label editor" from the menu bar to designate the color and side of PCA muscle segments. The right and left PCA muscles were allocated red and blue, respectively (Figure 4). The smooth curve tool of the polygon mode in the main toolbar was selected (Figure 5). The segmentation label was changed to "Rt. PCA" when drawing the right PCA muscle contour and to "Lt. PCA" when drawing the left PCA muscle contour (Figure 5). The contours of the right and left PCA muscles were drawn with the free drawing tool (Figure 6). The PCA muscle lying over the posterior border of the cricoid was measured with effort taken for it not to be mistaken for the inferior constrictor muscle. While the area with high contrast enhancement showed both PCA muscle and inferior constrictor muscle, the area with low contrast enhancement indicated fat pad and pharyngeal mucosal space (Figure 7). After measuring the right and left sides, voxel count, volume (mm^3), and intensity mean ± standard deviation (SD) were obtained and analyzed by selecting the "Segmentation-volumes and statistics" from the menu bar (Figure 8). The examination was conducted such that the SD did not exceed 20, which we regarded as the threshold for the homogeneity of the muscle area contrast.

PCA muscle volume ratio

When measuring the PCA muscle volume, the direction of VFP, age, sex, etiology, date of paralysis, and presence of recovery were all blinded in an effort to eliminate performance bias. Two measurers examined the volume using the same method, and the average value of the two observers was defined as the “PCA muscle volume.” The value obtained by dividing the PCA muscle volume on the affected side by the PCA muscle volume on the normal side was designated as “PCA muscle volume ratio.” Values with a ratio exceeding 1 indicated a failure in direction prediction; thus, the ratio was set to 1.

LEMG

Preparation for the LEMG

Patients with UVFP underwent LEMG by electromyography at the rehabilitation medicine department, and the results were analyzed by medical doctors in an outpatient-based examination room. After positioning the patient supine, the neck was extended. Before performing the electromyography, clinicians analyzed the anatomy of the larynx using ultrasonography (Medison 128 BW prime, Samsung Medison Co, Ltd, Seoul, Korea). The height of the anterior part of the cricoid cartilage, length of the cricothyroid membrane, the height of the vocal cord from the cricoid upper border, and depth from the skin to the vocal cord were measured using ultrasound. Based on these measurements, the location and depth of the cricothyroid muscle (CTM) and thyroarytenoid muscle (TAM) were anticipated when the skin was punctured with the needle electrode.

Process of achieving LEMG signals

A ground electrode was attached to the skin above the clavicle so as not to obscure the laryngeal field. After sterilizing the skin with ethanol, the 26-gauze needle electrode was placed on either the CTM or TAM.

To identify the CTM, skin puncture was performed at the midline with the needle and followed the lower border of the thyroid cartilage. The examiner advanced the electrode posteriorly and laterally following the inferior border of the thyroid cartilage. CTM is innervated by the superior laryngeal nerve (SLN) and plays a role in increasing vocal muscle tone and length by tilting the thyroid cartilage forward. The electric signal was assessed by making /i/ pronunciation from low to high frequencies.

To approach the TAM, skin puncture was performed identically to the method for CTM. However, in contrast to CTM, the clinician punctured the cricothyroid membrane to access the TAM. The needle electrode was advanced in a superior and lateral direction. TAM is innervated by the recurrent laryngeal nerve (RLN), shortens the length of the vocal cords, and serves to reduce tension. The electric potential of TAM was investigated by making the /i/ sound comfortably.

Grading system of the LEMG recruitment pattern

The LEMG recruitment pattern was acquired, and grading was classified into 5 levels: 0=normal (Figure 9), 1=reduced, 2=discrete (Figure 10), 3=single fiber pattern (Figure 11), and 4=no activity (Figure 12) (Table 1).

Statistical analysis

When assessing the right and left PCA muscle volumes, the correlation between the two examiners was assessed with the intraclass correlation coefficient. Fisher's exact test was performed to obtain the prediction accuracy of the side with CT volume measurement. Investigation of the relationship between PCA muscle volume ratio and the LEMG recruitment grade was performed using the Spearman correlation analysis. To analyze whether the VFP was permanent or not according to the PCA trophy grade, binary logistic regression was utilized. The receiver operating characteristics (ROC) curve and area under the curve (AUC) were acquired for the PCA muscle volume measurement tool. Statistical results were analyzed using IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 365 (Microsoft, Redmond, WA, USA). P-values under 0.05 indicated statistical significance.

Results

Demographics and clinical characteristics

From November 2005 to December 2016, a total of 1264 patients were diagnosed with UVFP in SNUH. However, CT was not performed in 816 patients after the onset of UVFP. Of those on whom CT scans were performed, 398 subjects who did not take the CT at least 3 months after the onset were excluded from the data. Among the 49 subjects who had CT scans taken more than 3 months after the onset of UVFP, PCA muscles were not identified in 8 subjects; therefore, they were excluded. There were 5 cases of poor resolution and low shadow homogeneity in the 2D plane (Figure 13A), 2 patients with artifacts from spine surgery (Figure 13B), and 1 patient with an unidentifiable cortical bone of the cricoid (Figure 13C). The final analysis was performed on 41 subjects.

Of the 41 patients, 21 were males (51.2%) and 20 were females (48.8%), and the average age was 59.5 years (21–90 years). Laterality of the UVFP was 12 (29.3%) on the right and 29 (70.7%) on the left. The etiologies of UVFP were as follows: idiopathic (24, 58.5%), upper respiratory infections (6, 14.6%), postoperative status (5, 12.2%), mechanical or chemical trauma (3, 7.3%), tuberculosis (2, 4.9%), and direct invasion of cancer (1, 2.4%). Surgeries that resulted in UVFP were aortic valve replacement, aortic arch replacement, excision of mediastinal schwannoma, excision of orbital schwannoma, and thyroidectomy. Trauma events that brought about UVFP were slipping and falling with a toothbrush inside the mouth, strangulation, and accidentally drinking a chemical agent. Demographic values and clinical characteristics are described in Table 2.

Diagnostic accuracy of the UVFP side

The side with a lower volume of PCA muscle was regarded as the predicted side of UVFP. The predicted direction of paralysis was compared with the actual direction of paralysis. The prediction accuracy was 90.2% in measurer A (37 of 41, $P<0.001$) and 92.7% in measurer B (38 of 41, $P<0.001$). The result of estimating the laterality of paralysis by averaging the PCA volumes of the two researchers was an accuracy of 90.2% (37 of 41, $P<0.001$).

PCA muscle volume and ratio

The volume of the right PCA muscle was calculated as 53.8 mm^3 for measurer A and 75.2 mm^3 for B. Left PCA muscle volume measured by A and B were 36.1 mm^3 and 34.2 mm^3, respectively. The intraclass correlation coefficient of the PCA muscle volume between A and B was 0.703 ($P<0.001$, Figure 14). The PCA muscle volume ratios were 0.45 and 0.61 in A and B, respectively. The average muscle volume ratio was 0.50.

Correlation between PCA muscle volume and LEMG patterns

The relation between LEMG grade and PCA muscle volume ratio is displayed in a scatter plot (Figure 15) and a box plot (Figure 16). The horizontal bars inside the box plot depict the median value of the PCA muscle volume ratio. Under the assumption that the difference in prognosis between LEMG grades is equal, there was a significantly negative correlation between PCA muscle atrophy and LEMG recruitment grade. The Spearman correlation coefficient was -0.351 (P=0.024), and the Kendall correlation coefficient was -0.267 (P=0.027). However, there was no significant difference between the LEMG grade groups.

Prediction of permanent UVFP using the PCA muscle volume ratio

Thirteen subjects whose recovery of UVFP was identified during the follow-up were regarded as the “recovered UVFP” group. Patients with a follow-up period of more than 18 months without recovery of UVFP were considered the “permanent UVFP” group, and 17 patients met this criterion. The PCA muscle volume ratio was significantly higher in the recovered UVFP group than in the permanent UVFP group (0.60 and 0.34, P=0.044) (Table 3). The recovery rate was 43.3% (13 of 30). The recovery rate significantly decreased as the PCA muscle atrophy increased (P=0.009, Figure 17). The area under the curve was 0.817 (P=0.003), which is regarded as a very good quality test for predicting the recovery (Figure 18). When the cutoff value of the PCA muscle volume ratio was set to 0.18, the PPV was 100% and the negative predictive value (NPV) was 56.5% (Table 3).

Discussion

In this study, the PCA muscle volume ratio was calculated with quantitative values acquired from ITK-SNAP in UVFP patients. The lower the PCA muscle volume ratio, the higher was the LEMG grade and the lower was the probability of recovery. This is the first study to measure the volume of PCA muscle and use it as a predictor of UVFP recovery.

In this study, TAM, CTM, and PCA muscle were candidates for laryngeal muscles that can be measured by CT. However, TAM and CTM were ruled out due to the following reasons. The TAM is located underneath both the vocal fold mucosal layer and lamina propria layer without any fat pads; thus, distinguishing the muscle from the lamina propria was not possible. The CTM is located adjacent to the strap muscles, sternothyroid muscle, and sternohyoid muscle, lacking contrast difference. Our study group selected the PCA muscle as the adequate anatomic structure for volume measurement due to the reasons that a thin fat pad exists at the posterolateral side of the PCA muscle and that no other muscle is adjacent to the PCA muscle. The intraclass correlation coefficient of PCA muscle volume obtained by the two measurers had moderate reliability. The PCA muscle is well distinguished from the surrounding fat pads and inferior constrictor muscle; therefore, it is reliable even when measured by multiple people.

Several models exist for volumetric analysis: (1) water-immerse volumetry; (2) disk model; and (3) integration by parts. Water-immerse volumetry is a method in which an object is directly placed in a fully-loaded water tank and the volume of the exceeded water is calculated. However, when immersing objects with a small volume in water, the amount of water overflowing may be less than it is due to the water surface tension. Moreover, measurements using PCA muscles are not performed as they cannot be separated independently from the larynx.[20] Disk model is a method that involves grossly slicing an object into several plates. According to studies that measured limb volume, water-immerse volumetry and disk model showed a positive correlation coefficient of 0.93.[21] Disk model is utilized in cases with large volumes. For example, for the diagnosis of lymphedema, the volume of the upper or lower limbs can be approximated by measuring several cross-sectional areas with a consistent interval of height. Integration by parts is a method that includes reducing the height of the plates of the disk model to the minimum measurable unit.[22] Integration method, which is the method used in ITK-SNAP, allows researchers to obtain a volume closest to the actual volume. However, if the object is huge or there is no automated area segmentation tool in the software, integration methods are not appropriate due to high labor. PCA muscles are small enough to measure and usually require only about 10 slices of CT for the segmentation. Therefore, ITK-SNAP is an ideal tool for measurement.

It is difficult to acquire LEMG of the PCA muscle because it exists at the posterior part of the larynx, which is way too far for the needle to approach the muscle from the skin. In this study, LEMG grading was based on the recruitment pattern of TAM and CTM, not the PCA muscle. Although the roles of these three muscles are different, they are all innervated by the vagus nerve (Figure 16). Therefore, in this study, when the PCA muscle-based measurements were indirectly compared with those of other muscles, a significant correlation was demonstrated for prognosis and LEMG findings.

In the existing literature, PCA atrophy was graded as 0–3 based on “PCA muscle mass,” a subjectively identified thickness of PCA that is not based on the exact volume.[16,17,23] Since the “PCA muscle mass” was identified at the 2D CT plane and measured in a semi-quantitative means, it was not directly proportional to the volume. Contrary to previous studies, our study has an advantage in that the ratio of the affected side to the healthy side of the PCA muscle volume was obtained, and this ratio was expressed as a continuous variable rather than a categorical variable.

As PCA atrophy increased, the rate of permanent VFP increased significantly (Figure 17). In particular, when the PCA muscle volume ratio was less than 0.18, the UVFP in all patients did not recover and the AUC of the ROC curve was 0.817 (Figure 18). For these reasons, the PCA muscle volume ratio can serve as a marker for predicting whether the UVFP will persist.

The ratio in this study was found to be 0.50 on average, which is the first value to be reported in human PCA muscle volume. The ratio showed a similar trend to those obtained in previous in vitro and in vivo studies. According to Viguie, the muscle fibers of rats with nuclei decreased down to 51% in 12 months.[24] After denervation, the rat leg muscle volume compared to the initial state was reported to be approximately 50% at 2 weeks and was known to decrease to 20–40% after 4 months. [25-27] In addition to the previously described in vitro study, there was an in vivo study based on MRI, in which the volume of the sheep infraspinatus muscle decreased to 47% after 16 weeks of neurectomy.[28] Further studies with serial measurement of PCA atrophy over time will allow us to understand the overall trends of PCA muscle volume reduction derived from denervation.

CT findings such as pyriform sinus dilatation, medially positioned and thickened aryepiglottic fold, and enlargement of the laryngeal ventricle were observed in 77.5% of VFP patients.[15,29] According to Mengsteab, CT findings such as thyroarytenoid muscle atrophy and asymmetry of ventricular dilatation were significantly associated with permanent VFP. [30] In another study by Lee, when the PCA muscle contour was not traceable, the PPV was 100%.[17] The result of this study is in accordance with the results of previous studies. We suggest that the PCA muscle volume ratio can be used as a prognostic marker for permanent VFP.

The limitations in the measurement process of this study are as follows. The volume measurement method in the ITK-SNAP software was used to calculate the area by manually designating the area in all slices, and the same procedure was repeated for each slice. In addition, the window length and width were subjectively adjusted until the PCA was well recognizable. These manual operations are prone to measurement errors and lack consistency. In fact, automatically designating specific areas in ITK-SNAP is possible. However, since the PCA muscle is small and is sometimes hard to distinguish from adjacent structures, the automated mode was not accessible. It was difficult to visualize the PCA muscle in the elderly due to the beam hardening effect derived from the ossification of cartilage. Through further research, we intend to measure a large population in a more consistent and automated way to approach the true value of PCA muscle volume.

Conclusion

The PCA muscle volume ratio was acquired with ITK-SNAP. The process was reproducible and as the PCA muscle volume ratio decreased, the LEMG grade increased and the probability of recovery decreased, both significantly. Furthermore, a cutoff value for a positive prediction was presented. The results of this study suggest that PCA muscle volume can be considered as a reliable value for predicting the permanency of UVFP.

Figures and Tables

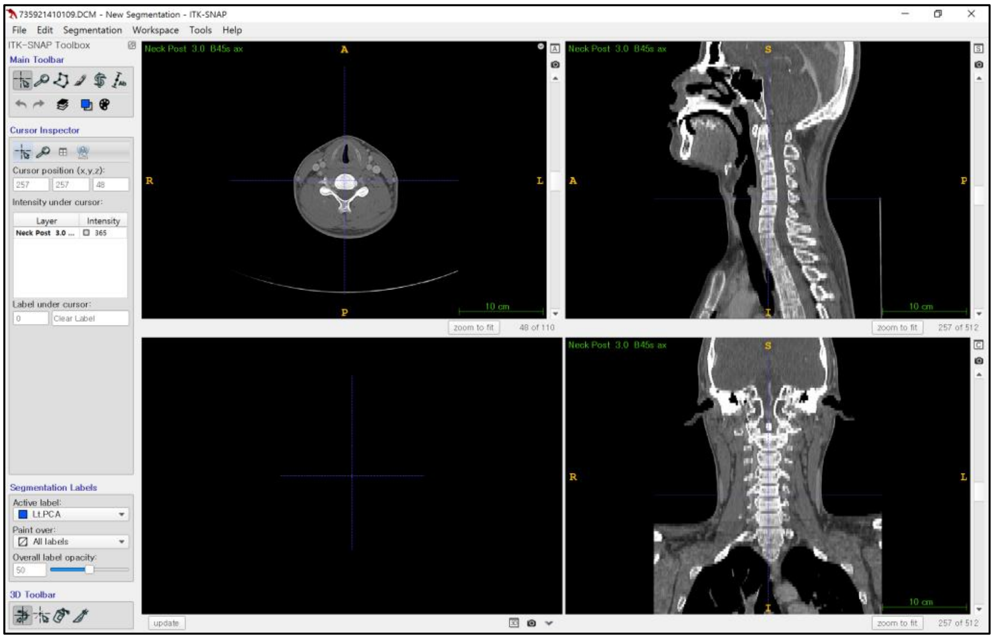


Figure 1. The main interface of ITK-SNAP.

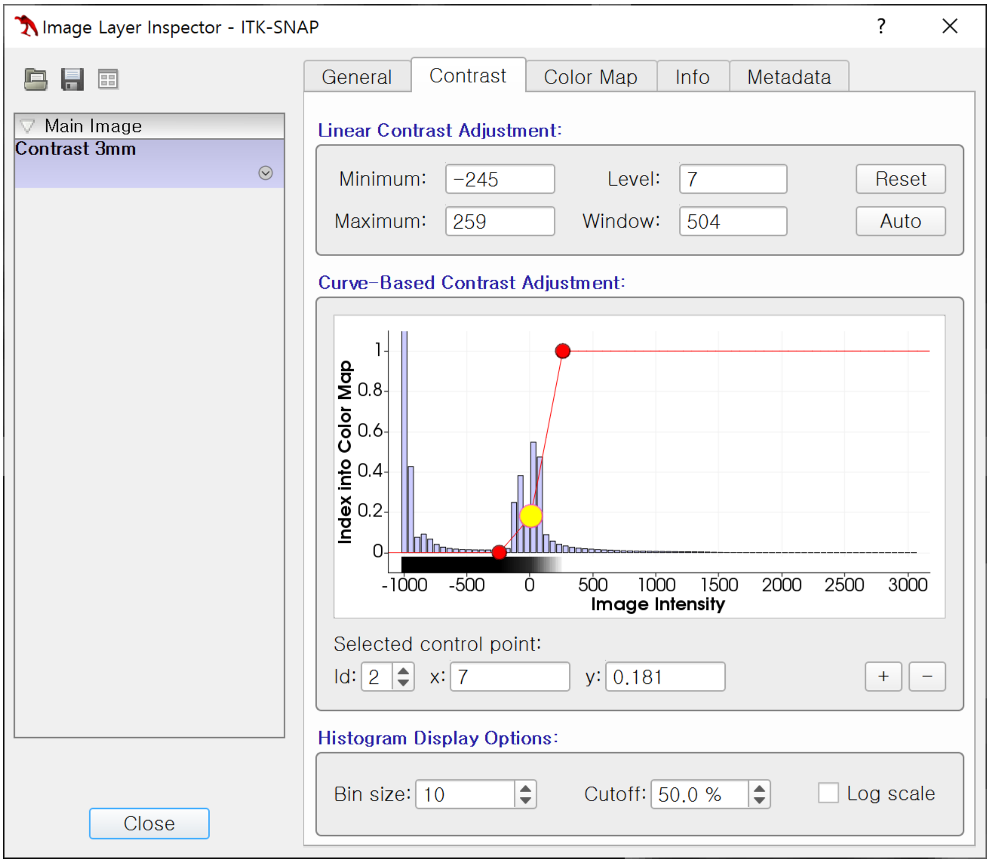


Figure 2. Image layer inspector.

By clicking the red and yellow circles, the window of the CT was adjusted to adequately view the PCA muscle

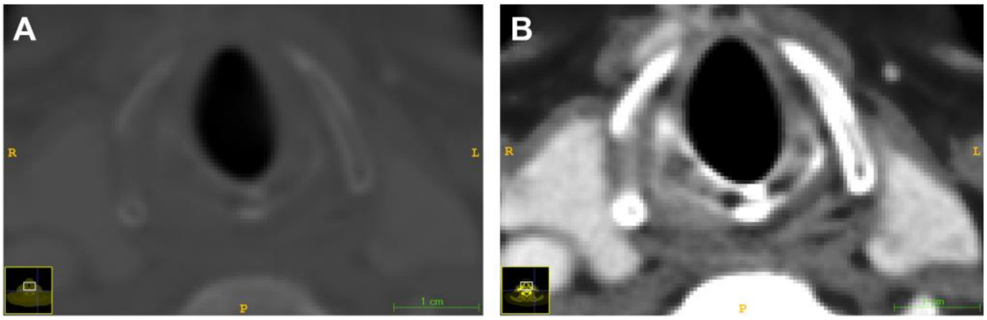


Figure 3. Curve-Based Contrast Adjustment.

(A) Pre-adjustment and (B) Post-adjustment state.

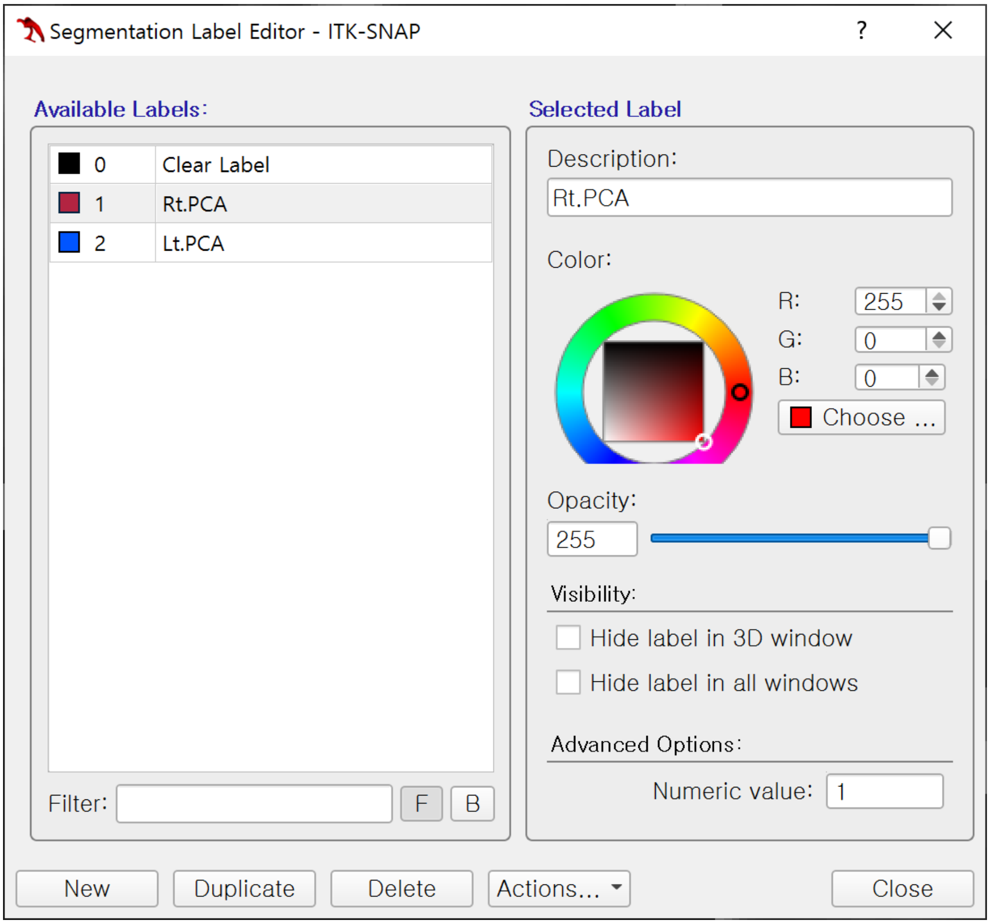


Figure 4. Segmentation Label Editor.

Right and left PCA muscles were allocated with "Rt. PCA, red color" and "Lt. PCA, blue color", respectively.

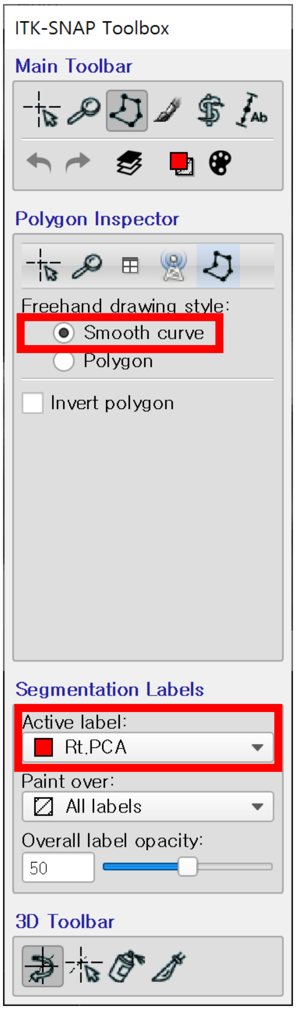


Figure 5. Polygon mode in the "Main Toolbar".

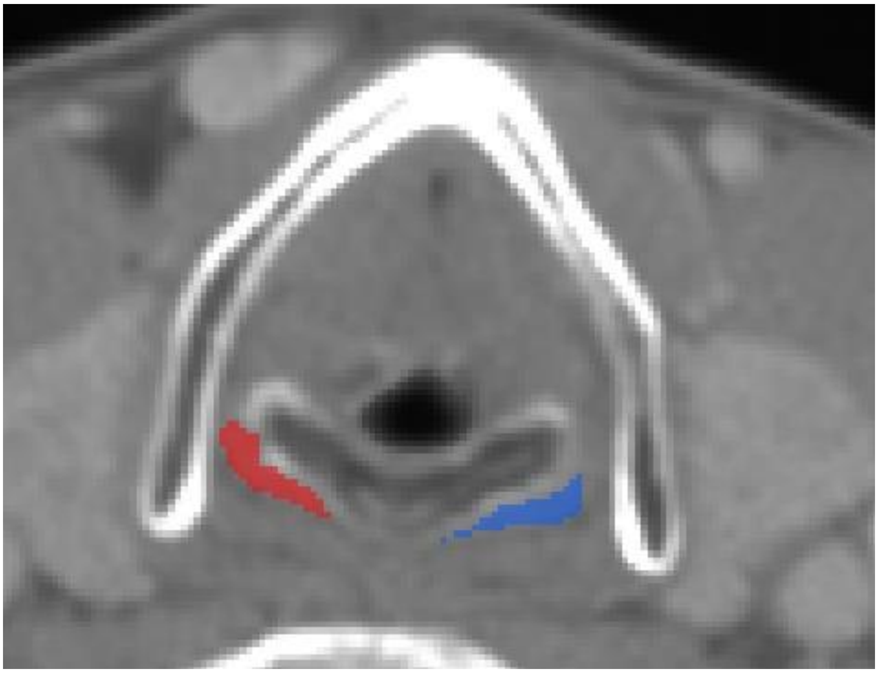
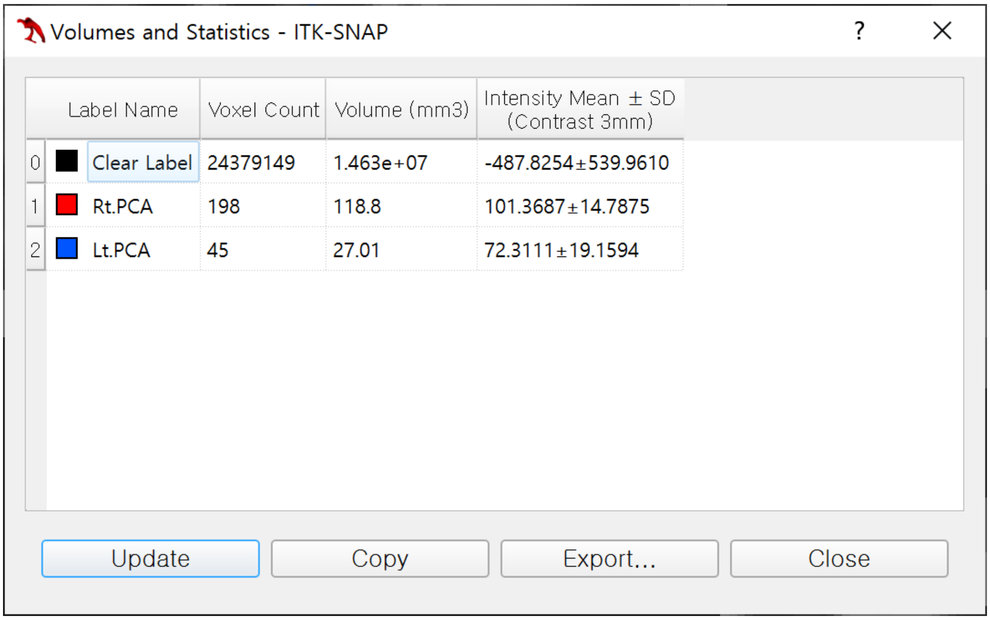


Figure 6. Segmentation of right and left PCA muscles.

Figure 7. Anatomy of adjacent structures around the PCA muscle.

Asterix indicates left PCA muscle; black arrowhead, fat pad covering PCA muscle; white arrowhead, pharyngeal mucosal space; white arrow, inferior constrictor muscle.



		Label Name	Voxel Count	Volume (mm3)	Intensity Mean ± SD (Contrast 3mm)
0		Clear Label	24379149	1.463e+07	-487.8254±539.9610
1		Rt.PCA	198	118.8	101.3687±14.7875
2		Lt.PCA	45	27.01	72.3111±19.1594

Figure 8. Volumes and statistics of right and left PCA muscles.

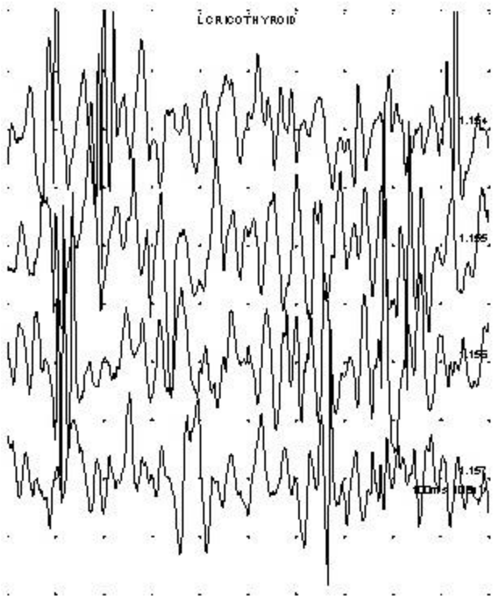


Figure 9. Normal LEMG recruitment pattern.

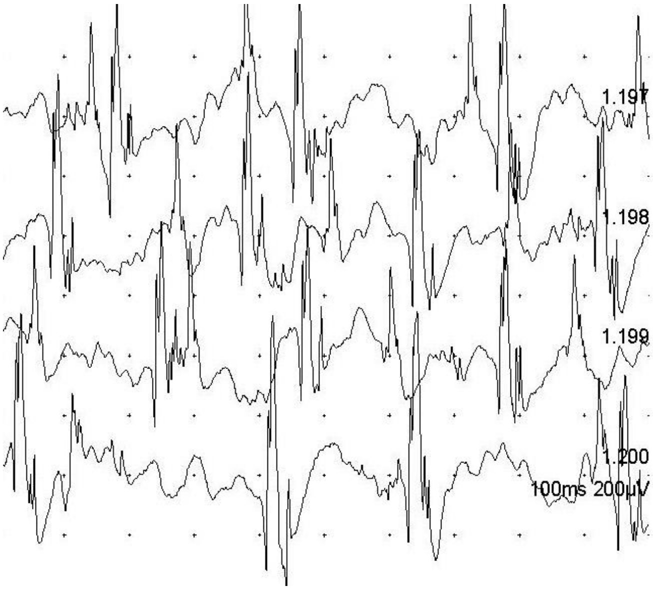


Figure 10. Discrete LEMG recruitment pattern.

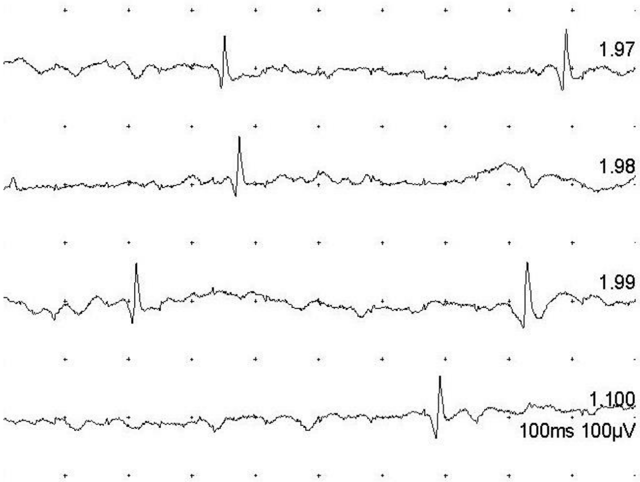


Figure 11. Single fiber pattern of LEMG recruitment.

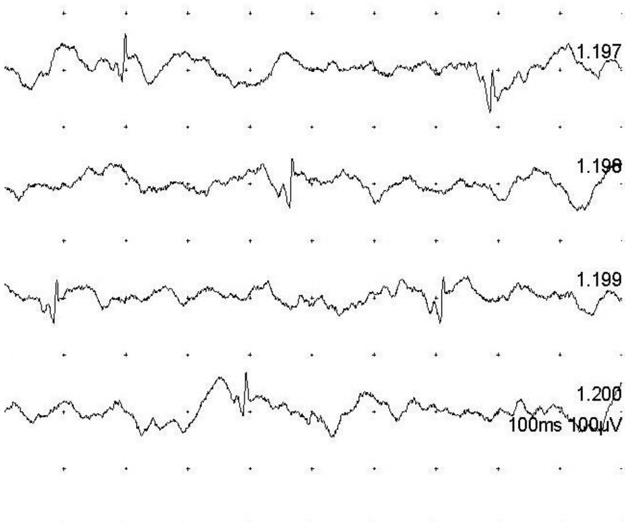


Figure 12. No LEMG recruitment activity.

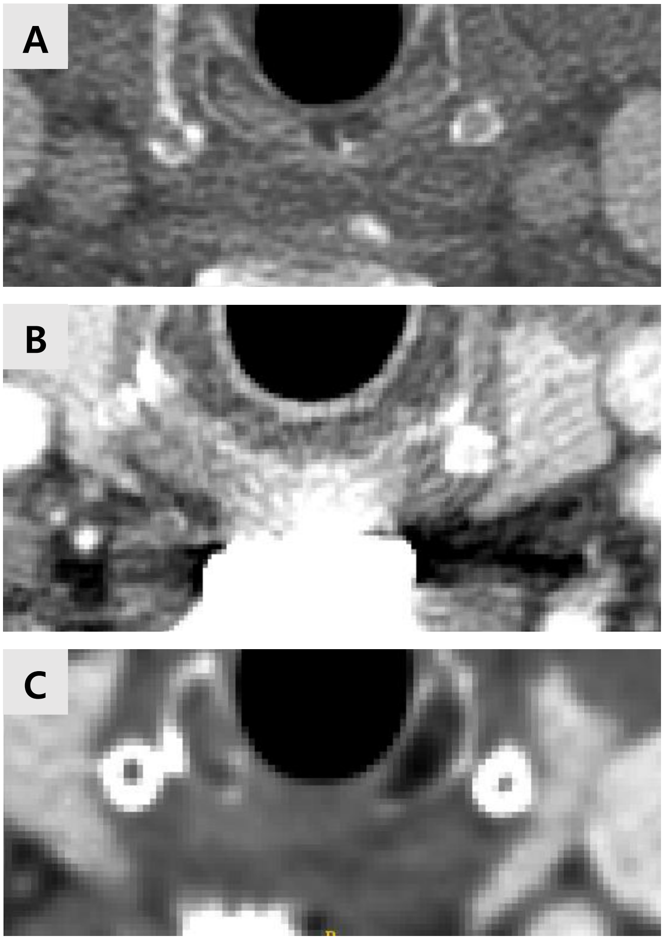


Figure 13. Representative examples of unevaluable CT findings.

(A) Unidentified PCA muscle due to poor resolution and low uniformity of contrast. (B) Unidentified PCA muscle due to artifacts. (C) PCA muscles were not distinguishable because of low cortication of the cricoid.

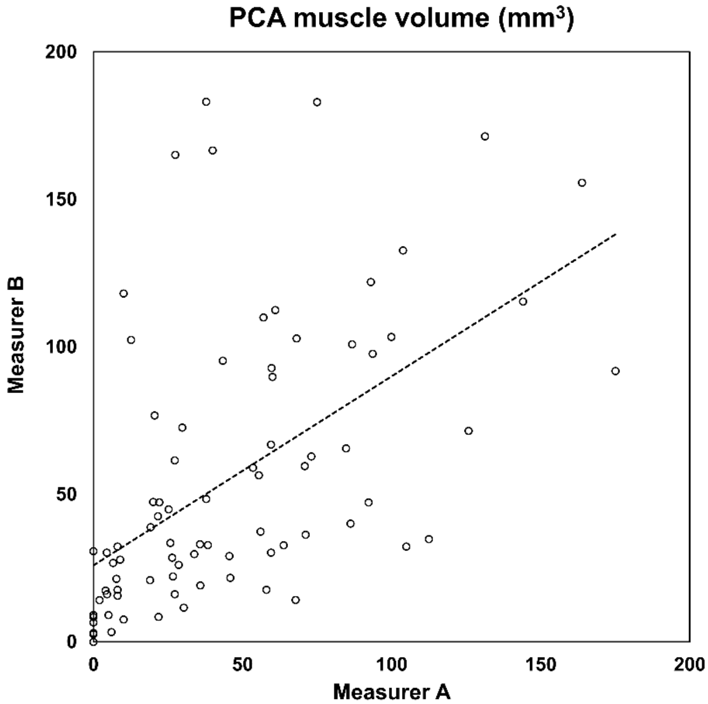


Figure 14. Reproducibility of the measurement by two examiners.

Two clinicians measured the volume of right and left PCA muscles. The intraclass correlation coefficient was 0.703 (P<0.001).

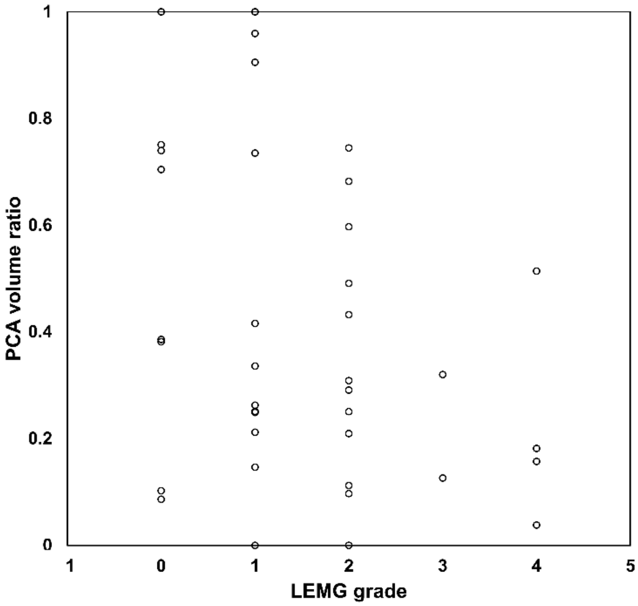


Figure 15. Scatter plot of the PCA muscle volume ratio according to LEMG grades.

PCA muscle volume ratio and LEMG grade was investigated with Spearman correlation analysis (Rho = -0.351, P=0.024) and Kendall rank correlation analysis (Tau-b = -0.267, P=0.027).

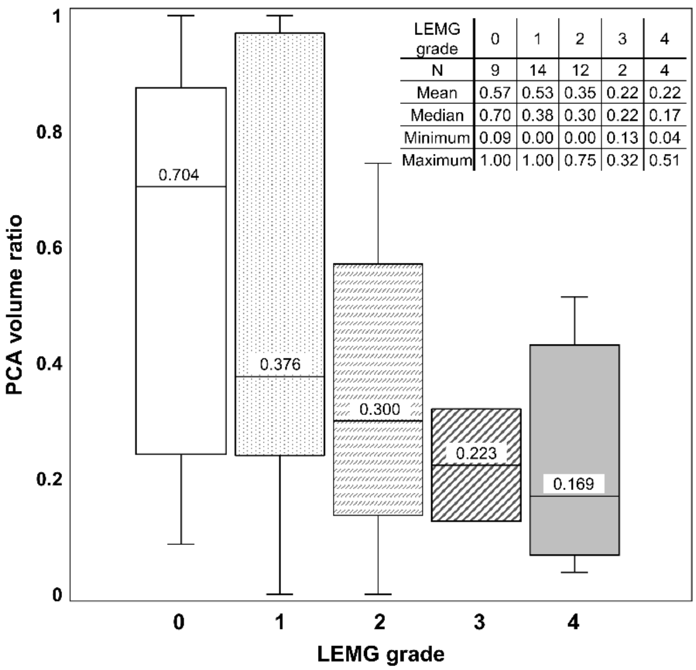


Figure 16. Box plot of the PCA muscle volume ratio according to LEMG grades. PCA muscle volume ratio and LEMG grade was investigated with Spearman correlation analysis (Rho = -0.351, P=0.024) and Kendall rank correlation analysis (Tau-b = -0.267, P=0.027). However, there was no significant difference between LEMG grade groups.

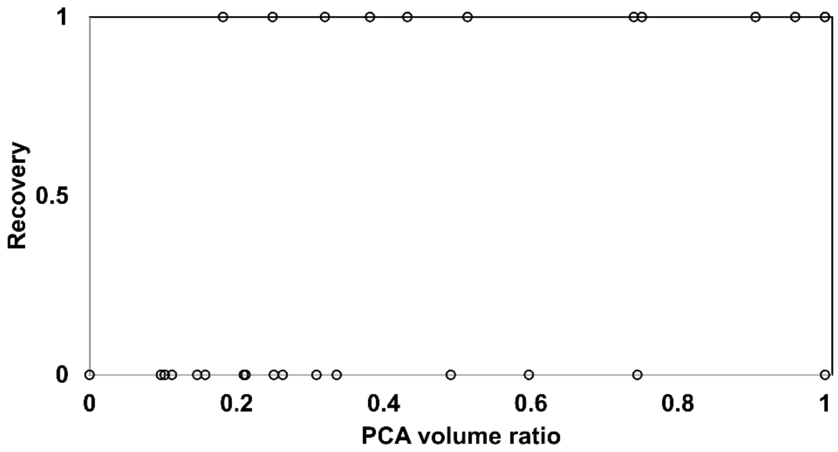


Figure 17. Plot of whether recovered or not according to PCA muscle volume ratio.

The chance of recovery was investigated with logistic regression (1: recovered, 2: not recovered). When the muscle atrophy increased, the chances of recovery decreased (OR = 46.8, P=0.009).

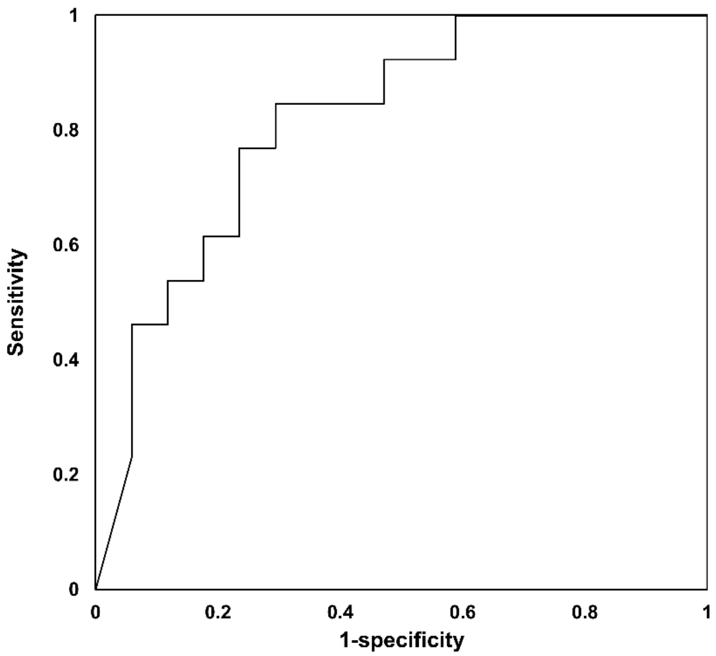


Figure 18. Receiver operating characteristic (ROC) curve analysis of the PCA muscle atrophy as a predictive tool for recovery rate.

ROC curve analysis reveals an AUC of 0.817, which is regarded as a very good quality test for predicting the recovery.

.

Table 1. LEMG recruitment grades

LEMG Recruitment Grade	Description
0	Normal
1	Reduced
2	Discrete
3	Single fiber pattern
4	No activity

Table 2. Demographic and clinical characteristics of the UVFP study population.

Characteristics	Value
Sex (male/female, N)	21/20
Age (years)	59.5 ± 14.7 (21-90) [a)]
Side of UVFP (right/left, N)	12/29
Interval between CT and onset (days)	1277.5±2070.3 (91-8949) [a)]
Interval between recovery and onset (days)	215.1±130.6 (105-484) [a)]
Etiology	
Idiopathic	24 (58.5) [b)]
URI	6 (14.6) [b)]
Postoperative status	5 (12.2) [b)]
Trauma	3 (7.3) [b)]
Tuberculosis	2 (4.9) [b)]
Cancer invasion	1 (2.4) [b)]

a) Mean ± SD (minimum-maximum)

b) Number (%)

Table 3. Predictive values of the PCA muscle volume ratio for permanency in UVFP.

	Recovered UVFP	Permanent UVFP	P-value or PPV/NPV
N	13	17	
PCA muscle volume ratio	0.60 ± 0.37	0.34 ± 0.26	0.044
PCA atrophy (-) (PCA ratio≥0.18)	13	10	100 / 56.5
PCA atrophy (+) (PCA ratio < 0.18)	0	7	

Reference

1. Masroor F, Pan DR, Wei JC, Ritterman Weintraub ML, Jiang N. The incidence and recovery rate of idiopathic vocal fold paralysis: a population-based study. *Eur Arch Otorhinolaryngol.* 2019;276(1):153-158.
2. Ahmad S, Muzamil A, Lateef M. A Study of incidence and etiopathology of vocal cord paralysis. *Indian J Otolaryngol Head Neck Surg.* 2002;54(4):294-296.
3. Pardo-Maza A, Garcia-Lopez I, Santiago-Perez S, Gavilan J. Laryngeal Electromyography for Prognosis of Vocal Fold Paralysis. *J Voice.* 2017;31(1):90-93.
4. Djugai S, Boeger D, Buentzel J, et al. Chronic vocal cord palsy in Thuringia, Germany: a population-based study on epidemiology and outcome. *Eur Arch Otorhinolaryngol.* 2014;271(2):329-335.
5. Ko HC, Lee LA, Li HY, Fang TJ. Etiologic features in patients with unilateral vocal fold paralysis in Taiwan. *Chang Gung Med J.* 2009;32(3):290-296.
6. Del Vecchio A, Negro F, Felici F, Farina D. Associations between motor unit action potential parameters and surface EMG features. *J Appl Physiol (1985).* 2017;123(4):835-843.
7. Rickert SM, Childs LF, Carey BT, Murry T, Sulica L. Laryngeal electromyography for prognosis of vocal fold palsy: a meta-analysis. *Laryngoscope.* 2012;122(1):158-161.

8. Sittel C, Stennert E, Thumfart WF, Dapunt U, Eckel HE. Prognostic value of laryngeal electromyography in vocal fold paralysis. *Arch Otolaryngol Head Neck Surg.* 2001;127(2):155-160.

9. Guha K, Sabarigirish K, Singh SK, Yadav A. Role of Laryngeal Electromyography in Predicting Recovery After Vocal Fold Paralysis. *Indian J Otolaryngol Head Neck Surg.* 2014;66(4):394-397.

10. Wang CC, Chang MH, De Virgilio A, et al. Laryngeal electromyography and prognosis of unilateral vocal fold paralysis--a long-term prospective study. *Laryngoscope.* 2015;125(4):898-903.

11. Kraft GH. Fibrillation potential amplitude and muscle atrophy following peripheral nerve injury. *Muscle Nerve.* 1990;13(9):814-821.

12. Quan D, Bird SJ. Nerve conduction studies and electromyography in the evaluation of peripheral nerve injuries. *Univ Pa Orthop J.* 1999;12:45-51.

13. Yu PC, Gao N, Li XM, Zhao X, Sun GB. [The diagnostic value of laryngeal electromyography in vocal fold paralysis and arytenoid dislocation]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* 2018;32(6):420-423.

14. Paquette CM, Manos DC, Psooy BJ. Unilateral vocal cord paralysis: a review of CT findings, mediastinal causes, and the course of the recurrent laryngeal nerves. *Radiographics.* 2012;32(3):721-740.

15. Chin SC, Edelstein S, Chen CY, Som PM. Using CT to localize side and level of vocal cord paralysis. *AJR Am J Roentgenol.* 2003;180(4):1165-1170.

16. Romo LV, Curtin HD. Atrophy of the posterior cricoarytenoid muscle as an indicator of recurrent laryngeal nerve palsy. *AJNR Am J Neuroradiol.* 1999;20(3):467-471.

17. Lee DY, Kogay D, Song S, et al. Prognostic value of the posterior cricoarytenoid muscle atrophy in computerized tomography scans for unilateral vocal fold paralysis recovery. *Eur Arch Otorhinolaryngol.* 2020;277(3):827-832.

18. Giangregorio L, McCartney N. Bone loss and muscle atrophy in spinal cord injury: epidemiology, fracture prediction, and rehabilitation strategies. *J Spinal Cord Med.* 2006;29(5):489-500.

19. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage.* 2006;31(3):1116-1128.

20. Sitzia J. Volume measurement in lymphoedema treatment: examination of formulae. *Eur J Cancer Care (Engl).* 1995;4(1):11-16.

21. Kaulesar Sukul DM, den Hoed PT, Johannes EJ, van Dolder R, Benda E. Direct and indirect methods for the quantification of leg volume: comparison between water displacement volumetry, the disk model method and the frustum sign model method, using the correlation coefficient and the limits of agreement. *J Biomed Eng.* 1993;15(6):477-480.

22. Heymsfield SB, Fulenwider T, Nordlinger B, Barlow R, Sones P, Kutner M. Accurate measurement of liver, kidney, and spleen volume and mass by computerized axial tomography. *Ann Intern Med.* 1979;90(2):185-187.

23. Kano S, Horowitz JB, Sasaki CT. Posterior cricoarytenoid muscle denervation. *Arch Otolaryngol Head Neck Surg.* 1991;117(9):1019-1020.

24. Viguie CA, Lu DX, Huang SK, Rengen H, Carlson BM. Quantitative study of the effects of long-term denervation on the extensor digitorum longus muscle of the rat. *Anat Rec.* 1997;248(3):346-354.

25. Wu P, Chawla A, Spinner RJ, et al. Key changes in denervated muscles and their impact on regeneration and reinnervation. *Neural Regen Res.* 2014;9(20):1796-1809.
26. Wang H, Gu Y, Xu J, Shen L, Li J. Comparative study of different surgical procedures using sensory nerves or neurons for delaying atrophy of denervated skeletal muscle. *J Hand Surg Am.* 2001;26(2):326-331.
27. Pellegrino C, Franzini C. An Electron Microscope Study of Denervation Atrophy in Red and White Skeletal Muscle Fibers. *J Cell Biol.* 1963;17(2):327-349.
28. Gerber C, Meyer DC, Fluck M, et al. Muscle Degeneration Associated With Rotator Cuff Tendon Release and/or Denervation in Sheep. *Am J Sports Med.* 2017;45(3):651-658.
29. Kwong Y, Boddu S, Shah J. Radiology of vocal cord palsy. *Clin Radiol.* 2012;67(11):1108-1114.
30. Mengsteab PY, Kwon JY, Han TR, Kwon TK, Kim DH, Kim SJ. Factors associated with the improvement of vocal fold movement: an analysis of LEMG and laryngeal CT parameters. *J Electromyogr Kinesiol.* 2015;25(1):1-7.

Abstract in Korean (국문 초록)

서론

성대마비는 다양한 원인에 의해 한쪽 혹은 양쪽 성대가 움직이지 않는 상태를 말한다. 컴퓨터 단층촬영을 이용하여 성대마비의 방향 및 예후를 예측하려는 연구들이 선행되어 왔다. 최근 연구에 의하면 일측성대마비 환자에서 환측의 후윤상피열근의 부피를 건측과 비교하였을 때 부피가 작을 수록 후두근전도의 소견도 악화되었고, 일측 성대마비는 회복되지 않았다. 하지만, 이는 후윤상피열근의 부피를 정량적으로 측정한 연구가 아니었기에 다음과 같은 목적으로 연구를 시행하였다. 첫째, 후윤상피열근의 부피를 ITK-SNAP 프로그램을 이용하여 정량적으로 측정하고 재현성을 확인한다. 둘째, 측정한 후윤상피열근 부피의 환측 대 건측 비율을 구하여 근전도의 결과와 상관관계를 가지는지 분석한다. 셋째, 후윤상피열근의 환측 대 건측 비율이 영구적 성대마비를 예측할 수 있는 지표로 활용할 수 있을지 탐구해보고자 한다.

방법

2005 년부터 2016 년까지 서울대병원을 내원하여 일측성대마비로 진단받은 성인 환자를 대상으로 후향적 의무기록 분석을 시행하였다. 일측성대마비 발생 최소 3 개월 이후 시행된 컴퓨터 단층 촬영과 후두근전도가 있는 환자를 분석대상으로 하였다. 후윤상피열근이 컴퓨터 단층 촬영에서 주변 구조물과 구분이 되지 않는 경우는 연구대상에서

제외하였다. ITK-SNAP 을 통해 후윤상피열근의 윤곽을 후윤상피열근이 존재하는 모든 평면에서 지정을 하였다. 측정자가 지정한 윤곽을 바탕으로 프로그램이 후윤상피열근의 부피를 측정하였고, 환측 대 건측 비율을 구하였다. 후두근전도 결과는 정도에 따라서 5 개의 집단으로 구분하였다. 이후 환측 대 건측 비율과 후두근전도, 환측 대 건측 비율과 예후의 상관성을 분석하였다.

결과

총 41 명의 환자를 대상으로 분석하였으며 일측성대마비의 방향은 좌측(71%)이 우세하였으며 원인은 특발성인 경우가 가장 흔했다. 2 명의 분석자가 후윤상피열근의 부피를 측정하였으며 유의미한 재현성을 보였다. ($P<0.001$) 후윤상피열근의 환측 대 건측 비율은 0.50 이었으며 이는 후두 근전도 결과와 음의 상관관계를 가졌다. ($Rho = -0.351, P = 0.024$) 하지만, 후윤상피열근의 위축 정도가 증가할수록 즉 환측 대 건측 비율이 감소할 수록 영구적인 일측성대마비의 비율이 유의미하게 증가하였다. 후윤상피열근이 건측과 비교하여 82% 이상 감소한 경우에는 영구적 성대마비 양성예측도는 100%였다.

결론

후윤상피열근의 정량적인 부피측정은 신뢰도가 높았으며, 환측 대 건측 후윤상피열근의 비율은 기존의 예후 예측 방법인 후두근전도 결과와 연관성이 유의미하게 있었다. 이는 선행 연구와 일치하는 경향을

보이며, 향후 예측 지표로 활용 가능하다. 더 많은 환자군을 대상으로 자동화된 방법으로 분석하여 측정값이 참값에 근접할 수 있도록 후속연구가 필요하다.

주요어: 일측성대마비, 부피분석, 컴퓨터단층촬영, 후두근전도, 예후

학번: 2019-26705