**Neck muscle mass index as a predictor of post laryngectomy wound complications**

Gülpembe Bozkurt[1], Hassan Ahmed Elhassan[2], Abdullah Soydan Mahmutoğlu[3], İrfan Çelebi[4], Robert WJ Mcleod[5], Pınar Soytaş[6], Zeynep Nur Erol[7], Esra Sözen[8]

[1]*MD, Department of Otorhinolaryngology, Acıbadem University Hospital, Istanbul, Turkey, ORCID ID: 0000-0003-2100-023X*

[2]*FRCS DOHNS, Lewisham University Hospital, London, ORCID ID: 0000-0001-5378-8709, hassanelhassan@gmail.com*

[3]*MD, Department of Radiology, Istanbul Education and Research Hospital, Istanbul, Turkey, ORCID ID: 0000-0001-7987-0006, asmahmutoglu@yahoo.com*

[4]*MD, Department of Radiology, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey, ORCID ID: 0000-0003-2562-2482, irfancelebi@gmail.com*

[5]*MRCS PhD, Department of Otolaryngology, University Hospital of Wales, Cardiff, UK, mcleodrwj@gmail.com*

[6]*MD, Department of Otorhinolaryngology, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey, drpinarsoytas@gmail.com*

[7]*MD, Department of Otolaryngology, Hopa State Hospital, Artvin, Turkey, ORCID ID: 0000-0002-3680-4911, zneist11@hotmail.com*

[8]*MD, Department of Otorhinolaryngology, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey, esrasoz@gmail.com*

***Corresponding author for proofs and reprints:*** *Gulpembe Bozkurt MD, Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Acibadem University, Özel Acıbadem Atakent Hastanesi, Istanbul, Turkey*

*gptalayhan@gmail.com*

*Tel: +90 5325586990*

*Fax: +90 2124044445*

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**Objective**

We investigated the relationship between paravertebral muscle cross-sectional area (PVM CSA) at the third vertebra (C3) level using CT neck images, and its relationship with complications after total laryngectomy.

**Design**

Retrospective analysis of 60 advanced laryngeal cancer patients who underwent total laryngectomy was performed. The cross-sectinal areas of paravertebral neck muscles using neck computerized tomography (CT) at C3 level images obtained preoperatively were analysed.

**Results**

A significant difference in PVM CSA between complication and no complication groups [F(1,53=4.319, p=0.043] was identified by ANCOVA. There were no significant differences in between-subject effects: T-stage [F=1.652, p=0.204], BMI [F=0.889, p=0.35], Albumin [F0.359, p=0.552], Age [F=1.623 p=0.208], Smoking [F 4.319, p=0.41].

**Conclusion**

PVM CSA measured at C3 level on pretreatment CT may help identify patients at higher risk of postoperative wound complications after total laryngectomy and who may particularly benefit from pre-operative optimization of nutritional status.

**Keywords:** Total laryngectomy, lean muscle mass, sarcopenia, pharyngocutaneous fistula, cross-sectional area

**Neck muscle mass index as a predictor of post laryngectomy wound complications**

**Introduction**

Patients with laryngeal cancer experience loss of major weight and skeletal muscle mass (SMM), prior to and during therapy, which is associated with poor functional and survival outcomes.1 30–60% of head and neck cancer patients have malnutrition, related to the tumour and treatment.2 These patients have a high incidence of complications after major head and neck surgery that can delay the start of adjuvant therapy and add to the cost of health care.3 Pharyngocuteous fistule (PCF) and hematomas are the most common complications following total laryngectomy (TL).4,5 The PCF incidence varies from 2.6% to 65.5%.6 Factors associated with PCF formation include low body mass index (BMI), poor nutritional status as well as pre-operative radiotherapy and chemotherapy, male gender, increased age, tobacco and alcohol history, tumour site, size and stage, intra-operative flap reconstructions, tracheoesophageal puncture and pre-operative tracheostomy.7-10

In head and neck cancer, indicators of nutritional status including serum protein concentrations and serum albumin, when low, are associated adverse outcomes.1,11 Due to their variability these factors individually are unable to detect a patient's nutritional status.12 As such, there is a move away from these biomarkers and a focus towards patient energy intake, anthropometric measurements (BMI, body composition, weight) and functional measures.13,14

The loss of skeletal muscle mass (SMM) leads to objective weakness, is associated with functional impairment and disability15, a longer hospital stay16, higher economic burden, higher risk of nosocomial infections17, and decreased survival in both nonmalignant15,18 and malignant conditions19-21 and predicts chemotherapy toxicity22 and may be valuable in assessing patients prior to surgery. Although patients who lost more than 10% of their ideal body weight are at increased risk of postoperative complications23, weight loss alone poorly predicts outcome in head and neck cancer (HNC) patients when compared with depleted SMM.24 Low SMM is an independent predictive factor for chemotherapy toxicity in patients with advanced HNC treated with primary chemoradiotherapy. 25 Grossberg et al24 found that BMI and SMM depletion were powerful prognostic indicators of mortality. Nevertheless, BMI alone is not a reliable indicator of SMM.26

Sarcopenia was initially defined as muscle mass two standard deviations below that of a healthy adults27, there is now no clear definition of sarcopenia or one cut-off value for SMM that is valid for all oncological patients.28

The use of functional imaging techniques such as dual-energy X-ray absorption (DEXA) and magnetic resonance imaging (MRI), has improved the measurement of SMM. Studies using CT/MR imaging of the psoas muscle crosssectional area (CSA) at the level of the third lumbar (L3) vertebra28,29 have been used to estimate overall SMM. Assessing paravertebral muscle cross-sectional area (PVM CSA) on CT-scan at the third cervical (C3) vertebra appears to be a good alternative to abdominal CT-scans, based on the strong correlation between skeletal muscle cross sectional area at C3 and L3 vertebrae.30 The C3 level is preferred as it captures only the neck muscles. Higher cervical images include the tongue muscles while lower levels capture the trapezius muscle. The C3 level includes the following muscles, longus capitis, longus colli muscles located anterior to vertebrae and spinalis cervicis, semispinalis cervicis, semispinalis capitis, splenius capitis, and levator scapulae muscles.

There is currently little literature on the effect of sarcopenia on laryngeal cancer outcomes and no practical diagnostic tools for detecting sarcopenia. As laryngeal cancer staging includes cross sectional imaging of the neck as routine and a skeletal muscle mass estimate using C3 level CT-scans is practical and can be used to reliably to estimate SMM, this may be a cost effective and widely available tool to preoperatively assess patients prone to postoperative complications among HNC patients. Abdominal CT scans that include the third lumber vertebra (L3) and DEXA-scans are not routinely performed in HNC patients.

As sarcopenia and low SMM are associated with increased postoperative wound complications in patients with HNC31, we investigated the relationship between PVM CSA at C3 using CT neck images, and complications in advanced laryngeal cancer patients.

## Methods

A single-center-retrospective analysis of 77 laryngeal cancer patients who underwent total laryngectomy between January 1, 2010, to January 31, 2017 was performed. Data was collected from January 1, 2010, to March 31, 2017. Patients with wide tumor resections including skin, extended pharyngeal resection requiring flap reconstruction (n=3) and patients with positive surgical margins (n = 7) were excluded as these are risk factors for PCF32, 33, patients with missing pre-operative CT images (n=7) were excluded. Patients who had head and neck CT scans with a maximum interval of two months (n=2) prior to total laryngectomy surgery were included (n = 60). All patients were discussed at a multidisciplinary tumor board. Total laryngectomy was preferred in cases where lung capacity was insufficient for partial surgery (FEV1 < 60%), > 1 cm subglottic tumor extension, interaritenoid and postcricoid involvement, extralaryngeal extension, and vocal cord fixation due to cricoarytenoid joint invasion. The laryngectomies were performed with an open technique and simultaneous selective neck dissection (levels II-IV +/- IV); prophylactic (n=21) or therapeutic (n=39). Informed consent was obtained from 52 patients, 5 patients died and no contact information was available for 3. The institutional ethics committee approved the study.

### Patient demographics

Data including age, hospital stay time, BMI, smoking status, preoperative albumin levels, and co-existing morbidity (Charlson Comorbidity Index (CCI) scores34 were collected, as well as stage and prior treatment history including chemotherapy and radiation. The need of a pedicled or free flap for reconstruction was also included. Disease was staged per the American Joint Committee on Cancer using the TNM system.35 Advanced-stage laryngeal squamous cell carcinoma (LSCC) was defined as T3–T4 and any TN+, M+. Surgery-related wound complications (including infection, pharyngocutaneous fistula, dehiscence, hematoma, and seroma) defined as occurring within 30 postoperative days were recorded.

### Cross-sectional measurement of skeletal muscle index at C3

By calculating the cross-sectional area (CSA) of neck muscles using staging CT images obtained preoperatively and using the method devised by Swartz et al30 we estimated SMM. Swartz et al. recently presented a method to estimate skeletal muscle mass in routinely performed head and neck CT-scans; CSA at C3 strongly correlated with L3 muscle CSA. The middle of the C3 vertebrae was chosen as the reference point on sagittal reformatted image and CSA measurement undertaken on the axial image at this level.

Skeletal muscle was quantified by the use of standard Hounsfield unit (HU) thresholds (−29 to 150)36 Separately, the cross-sectional area of pixels that had a radiodensity between _29 and +150 HU was retrieved (further referred to as ‘‘HU muscle area”). Longus capitis, longus colli muscles, spinalis cervicis, semispinalis cervicis, semispinalis capitis, splenius capitis, and levator scapulae muscles were evaluated. The muscles were outlined using an image-processing system (PACS, Infinit Healthcare, South Korea, Guro-gu) by a single head and neck radiologist. The cross-sectional areas within the limits of the drawn boundaries was calculated using Xelis 3D software (V1.0.6.1, Infinit Healthcare, South Korea, Guro-gu ) were measured (Figure 2). The sum of the cross-sectional areas (mm2) of all muscles was calculated for each patient; the total area was then normalised for patient height (Cross Sectional Area (CSA) mm2/m2) to give a C3 skeletal muscle index.37

**Exclusion of sternocleidomastoid muscles**

Swartz et al. presented two methods to estimate skeletal muscle mass in routinely performed head and neck CT-scans. They assessed the correlation between CSA at L3 and PVM only and between L3 and the PVM and only a single SCM muscle. Swartz et al found significant correlation between the sum of the PVM and SCM muscles and L3 ($r = 0.785$, $p < 0.001$) and the PVM muscles only and L3 ($r = 0.778$, $p < 0.001$). However as the former was “the stronger correlation” they only performed further analysis on the sum of the PVM and SCM muscles.

This approach had several limitations that they alluded to in their section sub-titled ‘Clinically missing data’. In their study CSA assessment of one or both SCM muscles was impaired by lymph node metastases in 8 SCMs in 6 patients (7.6% of all HNC patient SCMs, 11.5% of all HNC patients, 17.6% of patients with neck metastases).

As such we agreed with Scwartz et al that CSA L3 correlated with CSA PVM alone, but disagreed with them that the PVM and SCM method of measuring neck CSA was best for further analysis. Stronger correlation is not reason enough to ignore the fact that in a significant proportion of patients data is not available, as the SCM muscles is invaded by lymph node metastases (Figure 1).

To minimise measurement inconsistency for our study we elected to use Schwartz et als first method that excluded the SCM muscles from the CSA calculations. Our study included 12 patients with N2c (bilateral) nodal involvement.

**Statistical analysis**

A one-way analysis of covariance (ANCOVA) was performed using SPSS statistical package for Mac version 23 (SPSS Inc., Chicago, Illinois) to investigate if there was a difference in LMM in complication and no complication groups. Statistical significance was defined as $p < 0.05$. Covariates included were BMI, albumin, age, T-stage (categorized as 2, 3 or 4) and smoking status. Complication or no complication groups were defined as the independent variable. This allowed the creation of 95% confidence intervals (CI) for the LMM dependent variable.

## Results

**Patient demographics**

Table 1 summarizes the clinical characteristics of 60 patients; all were men with a mean (SD) age of 59.4 (8.4) years. Hypoalbuminemia was identified preoperatively in 25 (41.6 %) patients. Among these study patients, 46 (76.6%) had locally advanced disease (T3–4), 14 (23.4 %) had T2 disease. Twenty one (35%) patients had N0 neck; 17 (28%), 5 (8%), 3 (13%), 12 (20%) and 2 (3%) patients had N1, N2a, N2b, N2c and N3 nodal involvement, respectively. None of the patients had detected distant metastasis. Nine patients (15%) had a history of prior chemo/RT.

**Wound Complications**

Wound complications occurred in 22 patients out of 60 (37%). One patient developed chyle leak, 1 had seroma, PCF, wound dehiscence and hematoma together, 1 had hematoma and seroma together, 8 had PCF, 3 had seroma, and 7 experienced dehiscence of their neck incision in the absence of a recognized salivary fistula (Table 2). PCFs occurred in 10 patients (16%); six (60%) were managed conservatively and four required surgical closure with pectoralis major flap. Regarding wound dehiscence (n=8), spontaneous closure with local wound care was noted in 6 (75%) patients whereas a surgical closure was necessary in two.

**Cross-sectional skeletal muscle index and postoperative complications**

Of the 60 patients 38 22 were categorized in the complications group and 22 38 in the no complications group. ANCOVA identified a significant difference in PVM CSA between complication and no complication groups [F (1,53=4.319, p=0.043] (Table 3). There were no significant differences in between-subject effects: T-stage [F=1.652, p=0.204], BMI [F=0.889, p=0.35], Albumin [F0.359, p=0.552], Age [F=1.623 p=0.208], Smoking [F 4.319, p=0.41]. Estimated marginal means accounting for covariates are shown in figure 3. Covariates in the model are evaluated at the following values: T stage = 3.0167, BMI = 23.5787, Albumin = 3.6492, Age = 59.3667, smoking = .50

**Postoperative complications related to other variables**

The focus of this study was the relationship between SMM, estimated by PVM CSA, and post operative complications. The relationship between postoperative complications and variables BMI and T-stage are widely known and we did not concentrate on within this study. However we analysed the data using t-tests looking for differences between the complication and non-complication within this study. Only BMI showed a significant difference between groups as an independent variable. This difference between groups is corrected for in the ANCOVA and not explored further.

**Discussion**

Postoperative wound complications account for most complications after major head and neck surgery.38 Adequate nutritional status is necessary to support wound healing and surgical recovery.39

Our study shows that lean muscle mass estimated by PVM CSA at C3 may be a potentially useful predictor of post-operative wound complications in in laryngeal cancer patients. We found that PVM CSA level below 815 mm2/m2 is a potential prognostic indicator of postoperative wound complication independent of other factors, such as BMI, hypoalbunemia, smoking history, and previous chemo/radiotherapy.

Grossberg24 et al reported that patients with HNSCC and low SMM at presentation or after treatment exhibit decreased overall and cancer-specific survival. Weight loss itself poorly predicts outcome in HNC patients when compared with depleted SMM. Therefore, weight loss alone cannot be used reliably to stratify by risk patients with larynx cancer undergoing laryngectomy. In our study, we also did not find a statistically significant difference between the complication and no complication groups using PVM CSA with regards to T-or N-stages, or low preoperative albumin.

Radiologically assessed muscle mass has been suggested as a surrogate marker of functional

status previously.37,40 Published studies use criteria that are study specific, with some studies using imaging modalities such as CT or DEXA scans and others basing their criteria on muscle strength due to the cost effectiveness of the measurements.26-29,37 In the present study, Image analysis was performed as described in a previous report.16 For the purpose of comparing to literature values, measurements for skeletal muscle measured by CT were normalized to each patient’s height.41

Limitations of our study include, retrospective data collection, lack of female patients and sample size. Another limitation in our study in a few (n=2) patients, the interval between CT and laryngectomy was up to two months, and arguably there may have been significant weight loss in that time. The number of independent variables included in the ANCOVA was limited by the sample size, and the number of wound complications and PCF. This may explain why we did not have a significant difference between complications and disease stage. A larger and more homogeneous patient cohort is warranted.

This study, to our knowledge, is the first to investigate the role of PVM CSA measured at the C3 vertebrate level and postoperative wound complication rate among larynx cancer patients. The lower boundary of the 95% CI no complication rate is 815 mm2/m2 and the upper boundary of the 95% for the complication group is 850 mm2/m2. We propose that a neck muscle index below 815 mm2/m2 is considered as a risk factor for postoperative wound complications in head and neck patients that can be used as additional factor for stratifying low muscle mass and subsequent postoperative complication risk. We suggest this figure to research colleagues in head and neck surgery for future validation studies.

## Conclusion

Paravertebral muscle cross-sectional area (PVM CSA) at the third vertebra (C3) level may help predict patients at high risk of postoperative wound complications before total laryngectomy and who would particularly benefit from pre-operative optimization of nutritional status. The incorporation of CT-assessed muscle mass into routine pre-surgical assessment may aid nutritional status assesement.

***Abbreviations:*** *LMM: Lean muscle mass, SMM: Skeletal muscle mass, PCF: Pharyngocutaneous fistule, TL: Total laryngectomy, SCM: Sternocleidomastoid muscle, BMI: body mass index, DEXA: Dual-energy X-ray absorption, MRI: Magnetic resonance imaging, CT: Computed tomography, HNC: Head and neck cancer, PVM CSA: Paravertebral muscle cross sectional area, SM: Skeletal muscle, LSCC: Laryngeal squamous cell carcinoma*

***Compliance with Ethical Standards***

***CONFLICTS OF INTEREST:*** None.

***ACKNOWLEDGEMENTS:*** None

***ETHICAL APPROVAL:*** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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***Summary***

In larynx cancer patients, skeletal muscle mass can be estimated using neck muscle index from the PVM CSA at the C3 level and this tool may help predict patients at high risk of postoperative wound complications before total laryngectomy.

***Table Legends***

*Table 1: Patient characteristics (n = 60).*

*Table 2: Complications for surgical site (n = 22).*

*Table 3: Neck muscle index means for no complication and complications groups.*

***Figure Legends***

*Figure 1: Asymmetric enlargement of sternocleidomastoid muscle. Right sternocleidomastoid muscle shows asymmetric enlargement (white arrow) due to invasion by metastatic lymph node.*

*Figure 2: Paravertebral Muscles at C3 Depicted in green. Cross-sectional areas of the muscles outlined in green can be seen on axial CT image at C3 vertebrae level.*

*Figure 3: Box plot of PVM means between the two groups. Error bars depict 95% confidence intervals. Estimated marginal means of PVM between the two groups. Error bars depict 95% confidence intervals.*

*Table 1*

| ***Characteristics*** | ***Datum (n, %)*** |
|---|---|
| **Total no. of patients** | 60 |
| **Age (year) (mean)** | 59.37 ± 8.40 (range 40–77) |
| **Flap** | 6 (10 %) |
| **Complication** | 22 (36,6 %) |
| **Prior Chemo/XRT** | 9 (15 %) |
| **T-staging**[a] | |
| • **T2** | 14 (23.4 %) |
| • **T3** | 30 (50 %) |
| • **T4** | 16 (26.6 %) |
| **Preoperative albumin** | 3,64±0.59 |
| • **<3,5 g/dL** | 25 (41.6 %) |
| • **≥3,5 g/dL** | 35 (58.33 %) |
| **CCI** | |
| • **<5/ ≥5** | 37/23 (61.6 % / 38.4 %) |
| **BMI**[b]**, (kg/m2)** | 23.57±5.13 |
| • **Underweight (<18.5)** | 5 (8.4 %) |
| • **Normal weight (18.5–24.9)** | 41 (68.3 %) |
| • **Overweight (25.0–29.9)** | 8 (13.3 %) |
| • **Obese (>30.0)** | 6 (10 %) |
| **PVM CSA ($mm^2/m^2$) (mean)** | 836.76±187.79 |
| **Smoking status** | |
| • **Current/former/never** | 28/30/2( 46,6% / 50% / 3,4%) |
| **Hospital stay time (day) (mean)** | 19.01±10.22 |

*Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); XRT, prior radiation history; CCI, Charlson comorbidity index; PVM CSA, Paravertebral muscle cross-sectional area*
*a Staging based on AJCC, American Joint Committee on Cancer (7th edition).*
*b Based on WHO BMI classification.*

*Table 2*

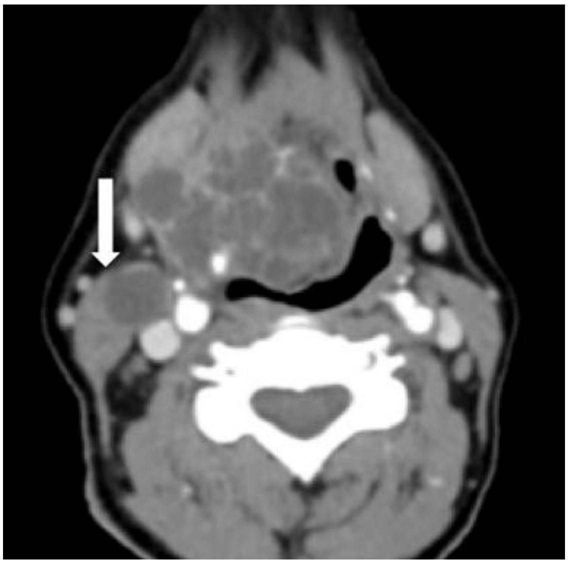
| ***Complications*** | ***n*** |
|---|---|
| Chyle leak | 1 |
| Seroma, PCF, wound dehiscence and hematoma | 1 |
| Hematoma and seroma | 1 |
| PCF | 8 |
| Seroma | 3 |
| Wound dehiscence | 7 |

*PCF: Pharyngocutaneous fistula*

*Table 3*

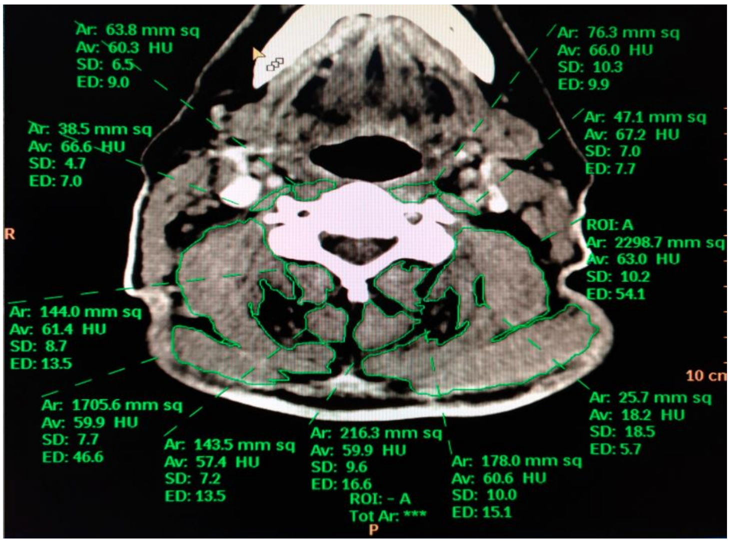
| | ***Neck muscle Index ($mm^2/m^2$)*** | ***95% Confidence Interval*** | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| **No complication** | 875, 108 | 815, 247 | 934, 968 |
| **Complication** | 770, 531 | 691, 160 | 849, 902 |

*Figure 1*



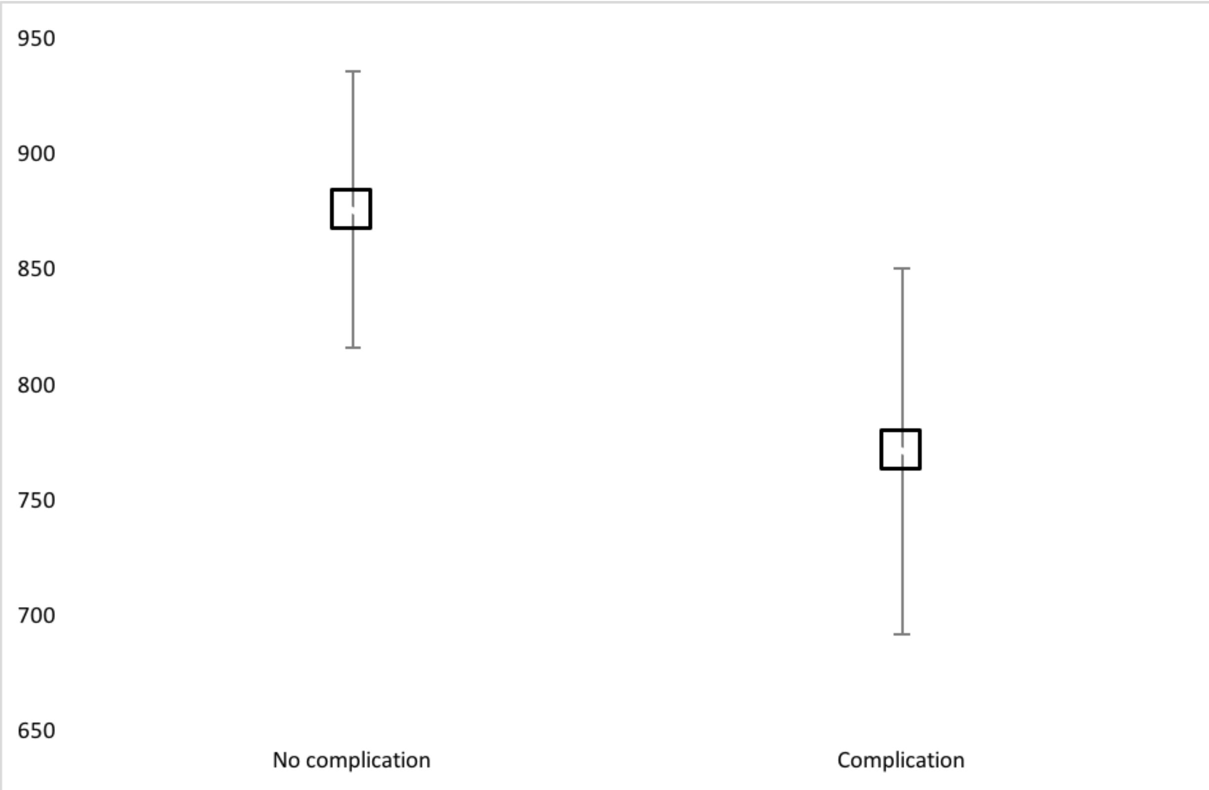
*Right sternocleidomastoid muscle shows asymmetric enlargement (white arrow) due to invasion by metastatic lymph node.*

*Figure 2*




*Cross-sectional areas of the muscles outlined in green can be seen on axial CT image at C3 vertebrae level.*

*Figure 3*




*Estimated marginal means of PVM between the two groups. Error bars depict 95% confidence intervals.*