Prognostic Indication of Sarcopenia for Wound Complication After Total Laryngectomy

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**IMPORTANCE** Postoperative wound complications after total laryngectomy (TL) increase hospital stay, costs, and delay adjuvant therapy when indicated. Recently, sarcopenia has been identified as a predictor of postoperative complications in patients undergoing major surgery but has not been assessed in head and neck surgery patients.

**OBJECTIVE** To determine the incidence of sarcopenia in patients with squamous cell carcinoma (SCC) undergoing TL and evaluate its association with the development of postoperative wound complications.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective medical chart review of 70 patients with SCC who underwent TL with cross-sectional abdominal imaging obtained preoperatively from 2004 to 2016 in a tertiary care hospital. Patients were determined to have sarcopenia present if the skeletal muscle index was calculated to be less than 38.5 cm²/m² for women and 52.4 cm²/m² for men. Demographic data included age, sex, smoking history, Charlson Comorbidity Index (CCI) score, prior radiation history, tumor stage, body mass index (BMI), and preoperative albumin levels.

**MAIN OUTCOMES AND MEASURES** Measurements of abdominal wall and paraspinal musculature at the cross-sectional L3 vertebral body were performed, normalized for height, and compared with previously defined sex-specific cutoff values to identify sarcopenia. Postoperative complications including all complications, wound-related complications, and pharyngo-cutaneous fistula (PCF) were determined.

**RESULTS** Sarcopenia was identified preoperatively in 54 (77%) patients. There was not a significant difference between the sarcopenia group and the nonsarcopenia group for any data except BMI (Cohen 𝑑 = 1; 95% CI, 0.41-1.57) and preoperative albumin levels (Cohen 𝑑 = 0.69; 95% CI, 0.11-1.25). Of 70 patients, 13 (24%) in the sarcopenia group developed a PCF compared with 0 (0%) without sarcopenia (OR, 1.32; 95% CI, 1.13-1.53). Similarly, 35 (50%) patients in the sarcopenia group developed a wound complication compared with 2 (13%) in the nonsarcopenia group (OR, 7.54; 95% CI, 1.56-36.4). On univariate analysis, sarcopenia was the only predictive factor of any complication (OR, 6.53; 95% CI, 1.84-23.23) and any wound complication (OR, 7.54; 95% CI, 1.56-36.4). On multivariable analysis of preoperative albumin levels and preoperative sarcopenia, only sarcopenia was a significant predictor for all complications (OR, 7.96; 95% CI, 1.39-45.29).

**CONCLUSIONS AND RELEVANCE** Sarcopenia is an independent negative prognostic indicator for the development of all complications and wound complications after TL for the treatment of SCC.
Postoperative wound complications account for most complications after major head and neck surgery. These lead to increased length of hospital stay, increased hospital costs, and delayed initiation of adjuvant therapy when indicated. Poor wound healing is a major driver of wound complications, and the patient’s nutritional status is a key factor in normal wound healing. The head and neck cancer (HNC) population is especially vulnerable to malnutrition because many patients experience dysphagia and odynophagia as cancer-related symptoms secondary to primary tumor location. Even in the absence of these symptoms, patients may have poor nutrition secondary to lifestyle factors or other comorbidities that predispose them to wound healing problems.

Traditionally, nutritional status has been assessed via body morphology measures, such as body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), or laboratory studies, such as albumin and prealbumin levels. However, these measures are imperfect and may vary for reasons unrelated to a patient’s nutritional status. Recently, sarcopenia, defined as loss of skeletal muscle mass, has been identified as a negative prognostic factor in surgical patients leading to increased postoperative complications, including infection and poor wound healing. The term was initially coined in reference to older persons as an assessment of functional impairment and physical disability. Sarcomen can be present in the obese population and may be a better predictor of nutritional deficiencies.

Studies have found that sarcopenia can be assessed on cross-sectional body imaging by determining the mean muscle mass at L3 and accounting for stature. In 1 study, the sex-specific cutoffs for L3 skeletal muscle index associated with mortality ascertained by optimum stratification were 52.4 cm²/m² for men and 38.5 cm²/m² for women; patients below these values were classified as having sarcopenia. The population included patients diagnosed with cancers of the respiratory tract, colon or rectum, or other gastrointestinal sites (anus, pancreas, stomach, and esophagus). Median survival was also significantly associated with the presence of sarcopenia (P < .001; HR, 2.4; 95% CI, 1.5-3.9) and was 21.6 months (range, 16.9-26.3 months) for nonsarcopenic patients vs 11.3 months (range, 7.4-15.2 months) for sarcopenic patients.

Detecting sarcopenia in HNC patients preoperatively may be a useful predictor of complication risk and potentially guide physicians in preoperative nutritional optimization to decrease the rate of wound complications after surgery. Given that many patients diagnosed with squamous cell carcinoma (SCC) undergo staging abdominal cross-sectional imaging (PET-CT) as part of the metastatic workup prior to surgical consideration, sarcopenia measurements do not entail any additional testing for most patients. The objectives of this study were to determine the incidence of sarcopenia in patients undergoing total laryngectomy (TL) for the treatment of SCC and evaluate its impact on the development of all postoperative complications, wound complications, and pharyngocutaneous fistula (PCF).

**Key Points**

**Question** What is the incidence of sarcopenia in patients undergoing total laryngectomy for squamous cell carcinoma and how does it impact postoperative wound complications?

**Findings** This study of 70 patients undergoing total laryngectomy identified sarcopenia in 77% of patients and found that 50% of patients in the sarcopenia group developed wound complications vs 13% of patients in the nonsarcopenia group. Furthermore, 13 patients in the sarcopenia group developed a pharyngocutaneous fistula compared with 0 in the nonsarcopenic group.

**Meaning** Sarcopenia is a risk factor in the development of major wound complications after surgery, and early identification may lead to nutritional optimization before surgery.

**Methods**

**Patient Selection**

After approval by the institutional review board, a retrospective medical chart review was conducted of patients undergoing TL at Oregon Health and Science University between 2004 and 2016. Informed consent was waived and compensation was not offered given the retrospective nature of the study. Patients were included for analysis if cross-sectional abdominal imaging, typically a PET-CT, was available prior to surgery.

Patient demographic data including age, sex, BMI, smoking status, preoperative albumin levels, and Charlson Comorbidity Index (CCI) scores were collected, as well as stage and prior treatment history including chemotherapy and radiation. Use of a pedicled or free flap for reconstruction was included. A surgery-related complication was defined as an event occurring within 30 days after procedure. Data regarding postoperative non-wound-related complications, such as myocardial infarction (MI), urinary tract infection (UTI), *Clostridium difficile* colitis, and deep vein thrombosis (DVT) was collected as well as wound-related complications including infection, dehiscence, hematoma, and seroma (eTable in the Supplement). The number of PCF was recorded as well as the number of flap losses in cases of pedicled or free-flap reconstruction.

**Cross-sectional Measurement of Skeletal Muscle Mass at L3**

Muscle mass was measured by secondary analysis of abdominal cross-sectional images obtained preoperatively. The middle of the L3 lumbar vertebra was identified, and skeletal muscle was quantified by the use of Hounsfield unit (HU) thresholds (~29 to 150). The abdominal wall musculature is comprised of transversus abdominis, external and internal obliques, rectus abdominus, psoas, erector spinae, and quadratus lumborum. These muscles were outlined using free-hand region of interest with use of OsiriX software (version 5.8, Pixmeo SARL), by a trained head and neck surgeon (V.A.) with verification by a radiologist with 15 years of training in body radiology (A.G.). The sum of the cross-sectional area (cm²) of all of these muscles was calculated (Figure 1) and normalized for height to give an
L3 skeletal muscle index (cm²/m²). Previously published sex-specific cutoff values were used to define sarcopenia as less than 52.4 cm²/m² for men and less than 38.5 cm²/m² for women. These values are based on a cancer-specific population and were accepted by an international consensus group for the establishment of the diagnostic criteria of cancer cachexia.

**Statistical Analysis**

Statistical analysis was performed using SPSS statistical software (version 24, IBM SPSS). Fisher exact and χ² tests were used when appropriate. Univariate and multivariate analyses were conducted to determine differences between the sarcopenia and the nonsarcopenia group for 3 endpoints: all complications, wound complications, and PF. Data are reported as a mean with standard deviation (SD) or median with interquartile range (IQR). Effect size and 95% CIs around the effect size estimates are reported. For interpretation of Cohen's d, we used a d of less than 0.2 as a small effect, 0.5 as medium effect, and 0.8 or greater as a large effect.

**Results**

**Patient Characteristics**

After review of 122 patient medical records, 70 consecutive patients meeting inclusion criteria were included in the study. Overall, there were 58 men and 12 women with a mean (SD)
age of 66 (10) years. Sarcopenia was identified preoperatively in 54 (77%) patients. Cross-sectional abdominal imaging was obtained at a median of 30 days before surgery (IQR, 40 days). One patient with a history of SCC underwent TL for a nonfunctional larynx; pathologic T stage is provided for the remainder of the patients. The CCI was stratified into a low-risk category (<5) and a high-risk category (≥5) based on prior published studies. Preoperative serum albumin levels were collected for 48 patients (69%). Comparison of the sarcopenia and the nonsarcopenia groups did not show any statistically significant or clinically meaningful difference with respect to age, sex, smoking status, CCI, prior chemoradiation or radiation, or pathologic T stage (Table 1). Furthermore, there were no statistical or clinical differences between mean preoperative albumin levels or use of a free flap for reconstruction between the two groups. The mean (SD) BMI was found to be 22 (5) ibn the sarcopenia group vs 27 (5) in the nonsarcopenia group (Cohen $d = 1$; 95% CI, 0.41-1.57). Scatter plot graphs are depicted in Figure 2 with an $R^2$ value of 0.42 for BMI vs sarcopenia and a $R^2$ value of 0.08 for BMI vs preoperative albumin levels.

Complications
Thirty-seven patients (69%) in the sarcopenia group developed a PCF compared with 0 in the nonsarcopenia group (Cohen $d = 1$; 95% CI, 0.41-1.57). Scatter plot graphs are depicted in Figure 2 with an $R^2$ value of 0.42 for BMI vs sarcopenia and a $R^2$ value of 0.08 for BMI vs preoperative albumin levels.

Discussion
Sarcopenia and its relationship to surgical morbidity is a relatively novel concept. It has been pioneered in general surgery patients, with a growing body of literature suggesting that it is a major factor in wound healing and complications. In many ways HNC patients are some of the highest-risk patients for sarcopenia given the adverse effect many head and neck tumors have on swallowing and nutritional intake. However, there is little data investigating the incidence of sarcopenia in head and neck surgery patients. In this study, we found sarcopenia to be quite common in patients undergoing total laryngectomy, and that sarcopenia was more strongly associated with postoperative complications than preoperative albumin levels or BMI. This is particularly relevant because occult sarcopenia may be present in patients with a normal or elevated BMI. Our results show that occult sarcopenia was present in patients with an elevated BMI owing to skeletal muscle attenuation and myosteatosis resulting in overall complications and wound complications.

Albunin levels have also been described as a valuable prognostic indicator in patients with head and neck cancer undergoing surgical resection. In the present study, the rate of complications was greatly elevated in patients with low preoperative albumin levels. However, owing to the small sample size, the precision of the estimate is low as evidenced by the wide CI, and no definitive conclusions can be made. Our results are in keeping with a retrospective study by Danan et al$^{19}$ which showed that the rate of wound infection was statistically higher in patients with hypoalbuminemia (univariate and multivariate analysis) and that a 1-point increase in serum albumin from 3 g/dL to 4 g/dL (to convert to g/L multiply by 10) decreased the risk of postoperative wound infection by 45%. In addition, we found that normal preoperative albumin values can be misleading and that a patient may be sarcopenic despite a normal serum albumin level. Overall, despite this limited data set sarcopenia was found to be a stronger predictor of wound complications, and this relationship between sarcopenia, albumin, and complications could be further elucidated in a prospective study.

Although, to our knowledge, this is the first study to date investigating the effect of sarcopenia on postoperative complications in head and neck surgery, there are a few recent re-
ports regarding sarcopenia in patients with HNC. One feasibility study assessed the correlation between skeletal muscle mass at C3 measured on a neck CT compared with abdominal muscle mass at L3 measured on an abdominal CT. The authors’ rationale was that few patients with HNC have cross-sectional abdominal imaging which would enable more traditional and validated measurements of sarcopenia. However, the authors failed to report the incidence of sarcopenia in an HNC population. With the increasing use of staging PET/CT, we have found that many patients do have preoperative cross-sectional abdominal imaging, hence sarcopenia can be measured reliably and without incurring any additional costs to the patient. Along these lines, another study used cross-sectional imaging of skeletal muscle mass at the L3 level to determine changes in body composition in patients with HNC undergoing radiation therapy (RT). While the rate of sarcopenia was not reported in this study, the authors demonstrated significant changes in lean body mass with RT, and demonstrated that cross-sectional imaging was superior to formulae based on patient height and weight.

Only one other study has reported the incidence of sarcopenia in patients with HNC. Grossberg et al investigated the incidence of sarcopenia and its effect on outcomes of patients with HNC treated with RT. Of a cohort of 190 patients, they identified sarcopenia in 35% of patients prior to treatment, and in 66% of patients after completing RT. Notably, patients with sarcopenia demonstrated decreased overall survival. Although the incidence of sarcopenia was less in this patient population than in the current study (77%), this difference is likely explained by the difference in study populations. Grossberg et al examined a heterogeneous group of patients with HNC (only about 10% laryngeal carcinoma), a wide range of cancer stages, and only about a third of patients in their study had prior surgery. In contrast, in the present study most patients had T3 or T4 tumors and had prior treatment with radiation or chemoradiation; these factors would be expected

Table 2. Univariate Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Complications</th>
<th>Wound Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Absent</td>
</tr>
<tr>
<td>No.</td>
<td>29 (55)</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Age &lt;70</td>
<td>16 (55)</td>
<td>24 (59)</td>
</tr>
<tr>
<td>≥70</td>
<td>13 (45)</td>
<td>17 (41)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (79)</td>
<td>35 (85)</td>
</tr>
<tr>
<td>BMI &lt;18.5</td>
<td>6 (21)</td>
<td>7 (17)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>13 (45)</td>
<td>23 (56)</td>
</tr>
<tr>
<td>≥25</td>
<td>10 (34)</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Former</td>
<td>22 (76)</td>
<td>29 (71)</td>
</tr>
<tr>
<td>Never</td>
<td>3 (10)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>&lt;5</td>
<td>27 (93)</td>
</tr>
<tr>
<td>≥5</td>
<td>2 (7)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Prior chemotherapy/XRT</td>
<td>18 (62)</td>
<td>30 (73)</td>
</tr>
<tr>
<td>Pathologic T stage</td>
<td>1</td>
<td>1 (3.5)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6 (21)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7 (24)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>14 (48)</td>
</tr>
<tr>
<td>NFL</td>
<td>1 (3.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sarcopenia present</td>
<td>17 (59)</td>
<td>37 (90)</td>
</tr>
<tr>
<td>Preoperative albumin levels</td>
<td>&lt;3.5</td>
<td>10 (34)</td>
</tr>
<tr>
<td></td>
<td>≥3.5</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Free flap for reconstruction</td>
<td>25 (86)</td>
<td>29 (71)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; NFL, nonfunctional larynx; XRT, prior radiation history.
Sarcopenia and Wound Complication After Total Laryngectomy

Research Original Investigation

Sarcopenia is an independent negative prognostic factor for the development of all postoperative complications and wound complications following TL. This is especially relevant in patients with prior organ preserving therapy because dysphagia associated with chemotherapy and radiation can lead to sarcopenia. In addition, sarcopenia can be detected radiographically in patients with otherwise normal BMI or serum albumin level, thus a normal serum albumin level or BMI may be misleading regarding the risk for complications. Future prospective studies examining the role of sarcopenia in head and neck surgery may point the way toward interventions to optimize nutritional status prior to surgery and improve patient outcomes.

LIMITATIONS

This study does have limitations that should be acknowledged. Most importantly, overall sample size was small as was the number of outcome events. Consequently, there were too few outcome events to include PCF in a univariate analysis. Furthermore, the number of independent variables that could be included in a multivariate analysis was also limited by the sample size, and the number of wound complications and PCF was not large enough to retain these in a multivariate model. Second, given its retrospective nature, only a subset of patients had cross-sectional abdominal imaging available to assess sarcopenia, and data collection on complications such as preoperative serum albumin levels was not complete. This study also only assessed patients undergoing TL to provide a more homogenous study population and consistency in complications, limiting its generalizability to other types of HNC. Further studies will be needed to examine the prognostic significance of sarcopenia for surgical outcomes in other head and neck procedures, and its broader role in overall oncologic treatment of patients with HNC.

CONCLUSIONS

Sarcopenia is an independent negative prognostic factor for the development of all postoperative complications and wound complications after major head and neck surgery. However, owing to the small sample size, the CI is very wide, preventing definitive conclusions. While our overall results may imply that sarcopenia is a superior predictor to preoperative albumin levels, prior radiation, or other risk factors, it is not possible to directly compare these variables with this limited data set.

Nutritional status, as measured by sarcopenia, may be a valuable measurement in patients prior to surgery because this is potentially a modifiable risk factor compared with other risk factors, such as age, smoking history, tumor stage, and prior chemotherapy and radiation exposure. Nearly 50% of patients with HNC experience malnutrition secondary to tumor burden, odynophagia, anorexia, and secondary effects from prior chemoradiation. Early identification of sarcopenia creates a potential window of opportunity between diagnosis and surgery whereby preoperative nutritional optimization may play a role in mitigating postoperative wound complications. Future studies will be needed to determine if targeting patients with sarcopenia for preoperative nutritional supplementation may reduce postoperative complications.

Table 3. Multivariable Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative complication of any kind</td>
<td>2.13 (0.57-7.99)</td>
</tr>
<tr>
<td>Preoperative albumin levels &lt;3.5</td>
<td>7.96 (1.39-45.29)</td>
</tr>
</tbody>
</table>

ARTICLE INFORMATION

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Author Contributions: Drs Achim and Clayburgh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Achim, Li, Wax, Andersen, Clayburgh.

Acquisition, analysis, or interpretation of data: Achim, Bash, Mowery, Guimaraes, Li, Wax, Clayburgh.

Drafting of the manuscript: Achim, Mowery, Guimaraes, Clayburgh.

Critical revision of the manuscript for important intellectual content: Achim, Bash, Guimaraes, Clayburgh.

Statistical analysis: Achim, Mowery, Clayburgh.

Administrative, technical, or material support: Achim, Guimaraes, Clayburgh.

Study supervision: Guimaraes, Clayburgh.

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REFERENCES


