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Significance of Anthropometric and Nutritive Factors in Oral and Oropharyngeal Cancer Patients Undergoing Free Flap Reconstruction

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Purpose: This study analyzed associations between preoperative nutritional status and the incidence of early postoperative complications as a primary outcome in patients with oral and oropharyngeal cancer undergoing free flap reconstruction. We hypothesized that preoperative nutritional status may be linked with specific complications, allowing for better preoperative risk assessment.

Patients and Methods: This longitudinal, retrospective cohort study encompassed 113 patients, all treated surgically for oral and oropharyngeal cancer in the period from March 2013 up to March 2018 in a tertiary referral center. Variables considered were preoperative and postoperative serum albumin and protein values; body mass index; waist-to-hip ratio; circumference of the neck, waist, hip, and thigh; number of cigarettes smoked per day during the 10-year period before surgery; average alcohol consumption; operative time; and postoperative albumin administration.

Results: Our study identified preoperative protein serum concentration (≤62 g/L), postoperative albumin administration (≥200 mL), number of cigarettes smoked per day (>20), and prolonged operative time (≥450 minutes) to be associated with postoperative complications.

Conclusions: This is the first study reporting cutoff values of clinical significance in assessing patient preoperative nutritional status in light of reducing postoperative complications after free flap reconstruction.

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According to the European Cancer Observatory yearly fact sheet, 99,630 persons are affected by oral cavity and oropharyngeal cancer, causing 43,662 deaths annually in Europe.[1] In oncologic surgery, free flaps have become the gold standard in head and neck defect reconstruction, most commonly immediately after tumor resection in an anatomically and functionally complex area. The ideal free flap must restore function and must remain vital and survive in a hostile environment, with minimal complications and a reasonable healing time.[2]

Head and neck cancer patients are frequently malnourished, at a rate of up to 35%.[3] "Malnutrition" is a general term used for all nutritional disorders and is defined as a state of energetic, protein, or nutritional deficiency that causes measurable changes in body functions, is associated with a worse outcome of disease, and is reversible by applying adequate nutritional support.[4]

There are 4 major factors of how cancer can contribute to malnutrition: *1)* Head and neck structures are essential in the feeding process, and disease presents a barrier to normal feeding; *2)* tumors have increased nutritional needs; *3)* tumors excrete substances that favor degradation of muscle tissue; and *4)* treatment processes may cause loss of taste and difficulty in swallowing.[5] Weight loss also may be due to cachexia, a cytokine-mediated paraneoplastic phenomenon resulting in metabolic derangements, cardiac dysfunction, and loss of lean body mass.[6] Whatever the mechanism, preoperative malnutrition is a well-described risk factor for perioperative complications and poor outcomes.[7] An additional factor affecting malnutrition is alcohol consumption. Alcohol is often a substitute for food, which leads to reduced input of other nutrients, and has an important role in the absorption of several nutrients, vitamins, and other elements.[8] Moreover, smokers not only are at greater risk of development of various diseases but also have a higher postoperative risk of development of various complications than nonsmokers. Complications are primarily related to problems of wound healing but also related to pulmonary and cardiac problems.[9]

Nutritional status can be assessed with biochemical and anthropometric measurements.[10] The serum albumin level is the most commonly used biochemical parameter and malnutrition indicator. Patients with hypoalbuminemia have greater mortality rates and longer hospital stays and are more likely to be readmitted to the hospital because of late complications.[11]

The most common anthropometric measurements used are height, body mass, body mass index (BMI), limb and body circumference, waist-to-hip ratio (WHR), and measurements of skin folds. BMI has long been thought of as a reliable predictor of overall death and morbidity, especially owing to an increased risk of cardiovascular disease, hypertension, and diabetes. It has recently been analyzed alongside other nutritional factors in the specific context of head and neck reconstructive surgery, with conflicting evidence about its impact.[12,13] There is a clear and pressing need to identify patients at risk of development of postoperative complications before free flap surgery, given that there are few reconstructive options after flap failure with similarly successful outcomes. The aim of this study was to evaluate associations between preoperative nutritional status and postoperative complications.

Patients and Methods

This was a retrospective observational study enrolling patients with oral cavity and oropharyngeal cancer undergoing surgical treatment and simultaneous microvascular free flap reconstruction from March 2013 up to March 2018. The patients were treated in a tertiary university referral center. The study was approved by the University Hospital Center Bioethical Board adhering to the 1989 revision of the Declaration of Helsinki. The inclusion criteria were advanced-stage disease (stage III of IV), no prior oncologic or surgical treatment, and a complete medical history. The procedures were performed by 2 surgeons. All patients signed informed consent forms after initial evaluation by a head and neck surgeon. The strict study protocol criteria excluded 12 patients because of incomplete documentation. All of the included patients' previous records were available, and data were collected from postoperative medical data, created through uniform follow-up forms. Patients' histories were searched for variables including gender; height; weight; BMI (in kilograms per square meter); neck, chest, waist, and thigh circumference; WHR; daily alcohol and cigarette consumption; preoperative serum protein and albumin levels; serum protein and albumin levels on the first and tenth postoperative days; and albumin administered postoperatively.

The occurrence of postoperative complications up to 14 days after surgery was considered a primary outcome measure, defined as the appearance of fistula, free flap necrosis, stasis of the flap blood supply, or complications at the donor site or the operative region. Flap failure and the need for revision surgery were considered major complications, whereas fistula formation, donor-site complications, and would infection not resulting in flap necrosis were considered minor complications. If 1 patient had several complications consecutively or simultaneously, these were noted as separate complications. The initial follow-up point was the patient's arrival in

the recovery room, and the endpoint was the end of the 14th postoperative day.

Data analysis was aimed at evaluating associations between nutritional and anthropometric variables and postoperative complications after free flap reconstruction. Tested variables were noted using standard descriptors (arithmetic mean and standard deviation or median). Associations between variables were assessed using a logistic regression model to test statistically significant correlations for the incidence of postoperative complications as a primary endpoint. All tests of statistical significance were performed using a 2-sided 5% type I error rate. Every variable that was significantly associated with postoperative complications was further analyzed with receiver operating characteristic (ROC) analysis, and a cutoff value for complication occurrence was identified using the Youden J index (measuring the sensitivity and specificity of a dichotomous tested variable). An area under the curve greater than 0.6 was considered statistically significant. $P \leq .05$ was considered statistically significant. Statistical analysis was performed with MedCalc software (version 11.2.1 [1993-2010]; MedCalc Software, Mariakerke, Belgium).

Results

In total, 113 patients (91 men and 22 women) with a median age of 59 years (range, 39 to 83 years) were included in the analyses. Of the patients, 38 (33.6%) underwent reconstruction with radial forearm free flaps; 35 (31%), anterolateral thigh free flaps; 15 (13.3%), vertical rectus abdominis muscle free flaps; 12 (10.6%), deep iliac circumflex artery free flaps; 9 (8%), fibula free flaps; 2 (1.8%), jejunum free flaps; and 1 (0.9%), a scapula chimera free flap.

The cumulative postoperative complication rate was 31.0%, of which 13.3% accounted for major complications, such as revision surgery and flap failure. The overall flap failure rate was 5.3%. Fistula formation was noted in 11.5% of patients, and 4.4% had transient venous stasis of the flap during the first postoperative week. Complications in the donor region occurred in 1.8% of patients (Table 1).

No significant associations were found between the outcome and the following variables: gender; height; weight; BMI (in kilograms per square meter); neck, chest, waist, and thigh circumference; WHR; alcohol consumption; preoperative albumin levels; and protein and albumin levels on the first and tenth postoperative days. However, logistic regression and subsequent ROC analysis identified significant correlations between the following parameters and the occurrence of early postoperative complications: preoperative protein serum concentration (cutoff value ≤ 62 g/L; $P = .03$; odds ratio [OR], 1.11; 95% confidence interval [CI], 0.524 to 0.711) (Fig 1); postoperative albumin administration (cutoff value ≥ 2 doses [ie, cutoff value ≥ 200 mL]; $P = .015$; OR, 1.31; 95% CI, 0.571 to 0.759) (Fig 2); number of cigarettes smoked per day (cutoff value > 20 per day; $P = .03$; OR, 1.04; 95% CI, 0.602 to 0.799) (Fig 3); and prolonged operative time (cutoff value ≥ 450 minutes; $P = .038$; OR, 1.38; 95% CI, 0.532 to 0.719; median, 450 minutes [range, 340 to 670 minutes]) (Fig 4, Table 2).

Hence, the cutoff values for all statistically significant associations between variables were as follows:

Table 1. POSTOPERATIVE COMPLICATION RATES

Variable	Complication Rate, %
Major complications	13.3
Flap failure	5.3
Revision surgery required	9
Minor complications	17.7
Fistula formation	11.5
Transient venous stasis of flap	4.4
Complications in donor region	1.8
Cumulative complication rate	31.0

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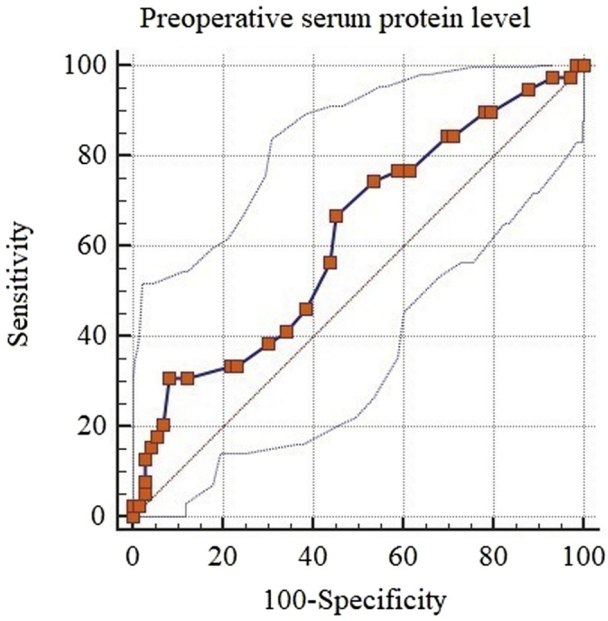

FIGURE 1. Association of preoperative serum protein levels and postoperative complications. Receiver operating characteristic analysis showed an area under the curve of 0.621, with $P = .03$. The Youden J index identified a cutoff value of 62 g/L or less, with a 95% confidence interval of 0.524 to 0.711, sensitivity of 30.77%, and specificity of 91.78%.

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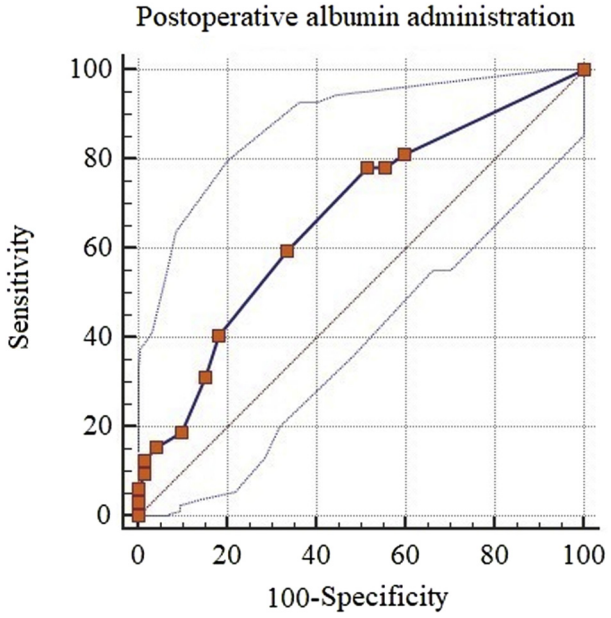

FIGURE 2. Association of postoperative albumin administration and postoperative complications. Receiver operating characteristic analysis showed an area under the curve of 0.670, with *P* = .003. The Youden J index identified a cutoff value of 2 or more doses (ie, ≥200 mL), with a 95% confidence interval of 0.571 to 0.759, sensitivity of 78.12%, and specificity of 48.61%.

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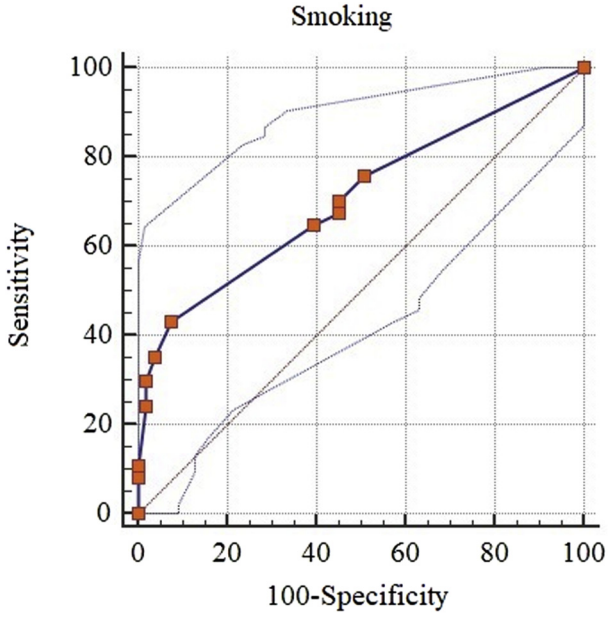

FIGURE 3. Association of smoking and postoperative complications. Receiver operating characteristic analysis showed an area under the curve of 0.707, with *P* = .0002. The Youden J index identified a cutoff value of greater than 20 cigarettes per day, with a 95% confidence interval of 0.602 to 0.799, sensitivity of 43.24%, and specificity of 92.45%.

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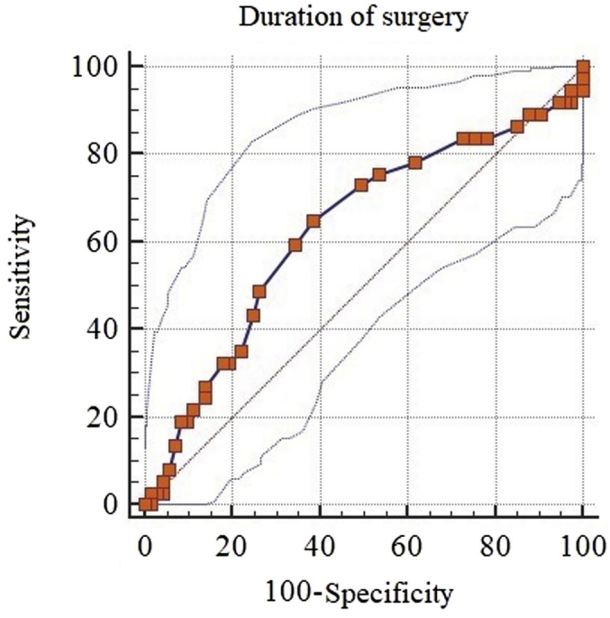

FIGURE 4. Association of prolonged operative time and postoperative complications. Receiver operating characteristic analysis showed an area under the curve of 0.629, with *P* = .0275. The Youden J index identified a cutoff value of 450 minutes or greater, with a 95% confidence interval of 0.532 to 0.719, sensitivity of 64.86%, and specificity of 61.64%.

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preoperative protein serum concentration of 62 g/L or less, postoperative albumin administration of 200 mL or greater, smoking of more than 20 cigarettes per day before surgery, and an operative time of 450 minutes or greater.

A comparison of all ROC curves clearly indicated that smoking more than 20 cigarettes per day before surgery showed the highest specificity for the occurrence of postoperative complications (91.78%) whereas postoperative albumin administration showed the lowest (48.61%). Postoperative albumin administration of 200 mL or greater showed the highest sensitivity for the occurrence of postoperative complications (78.12%), whereas preoperative protein serum concentration showed the lowest (30.77%).

Discussion

Among all analyzed variables, our study singled out duration of surgery, smoking, preoperative serum protein concentration, and postoperative albumin administration as factors associated with the occurrence of postoperative complications. Our study identified a duration of surgery of 450 minutes or greater as a cutoff value for postoperative complications. Similar studies also have found a link between length of surgery and an increase in postoperative complications,

Table 2. ANALYSIS OF ASSOCIATIONS BETWEEN NUTRITIONAL AND ANTHROPOMETRIC VARIABLES AND OCCURRENCE OF POSTOPERATIVE COMPLICATIONS USING LOGISTICAL REGRESSION MODEL

Variable	Statistical Significance: *P* Value	Odds Ratio
Gender	.74	
T tumor category	.28	
N tumor category	.51	
Free flap type	.12	
Height of patient (meters)	.26	
Mass of patient (kilograms)	.52	
Waist-to-hip ratio	.81	
Body mass index	.18	
Neck circumference	.93	
Waist circumference	.45	
Hips circumference	.37	
Thigh circumference	.60	
Preoperative smoking (number of cigarettes smoked per day)	.03	1.04
Alcohol (units consumed per day)	.54	
Preoperative serum protein concentration (grams per liter)	.03	1.11
Preoperative serum albumin concentration (grams per liter)	.77	
Concentration of serum proteins on first postoperative day (grams per liter)	.87	
Concentration of serum albumin on first postoperative day (grams per liter)	.81	
Concentration of serum proteins on tenth postoperative day (grams per liter)	.41	
Concentration of serum albumin on tenth postoperative day (grams per liter)	.62	
Postoperative albumin administration (number of 100-mL doses)	.015	1.31
Surgery duration (minutes)	.038	1.38

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especially among head and neck patients. Hardy et al[14] analyzed 1,753 patients undergoing reconstructive surgery and showed that there was no change in complication occurrence in the first quantile of operative time (<2.0 hours). However, for every extra hour after 3.1 hours of surgery, a 21% rise in morbidity was calculated (OR, 1.6; $P = .017$), with progressively greater rates of complications after 4.5 hours ($P < .0001$). The highest morbidity rate (43%) was found in the free flap group with surgery lasting over 8.35 hours (501 minutes), which is very similar to the results presented in our study. Hardy et al concluded that duration of surgery is the strongest independent predictor of complications. Offodile et al[15] analyzed 2,008 patients undergoing free flap reconstruction. A prolonged operative time also was associated with an increased risk of flap failure, with procedures lasting 6 to 12 hours showing an OR for complication occurrence of 4.64 and procedures lasting more than 12 hours showing an OR of 5.65 ($P = .014$). In addition, head and neck patients have been linked with a higher risk of postoperative complications.[16,17] Duration of surgery is a factor that is neither an anthropometric nor nutritive variable, but we considered it an important clinical parameter that could impact the incidence of postoperative complications. It is a variable that surgeons might find useful when planning their surgical procedures, and it may have substantial practical merit.

Our study has linked smoking over 20 cigarettes per day with an increase in postoperative complications ($P = .03$). Two published studies in patients with head and neck cancer and breast cancer support this finding, reporting that preoperative smoking cessation correlated with substantial risk reduction in managing postoperative complications,[18,19] but no single cutoff point has been identified to date. Sorensen et al[20] showed that smoking cessation 4 weeks before surgery may bring the risk of development of postoperative complications down to the nonsmoker level.[21] Haughey et al[22] analyzed 241 patients with head and neck cancer and free flap reconstruction and reported smoking to be directly linked to postoperative complications in free flap reconstruction, further supporting our results.

Although our results have not shown BMI to be associated with early postoperative complications, some large published studies have supported a correlation between BMI and the postoperative complication rate, whereas others have denied it. Patel et al[12] conducted a prospective study in 796 patients with head and neck cancer and free flap reconstruction and showed a positive association of low BMI with an increase in postoperative complications and prolonged

treatment. Similar results have been reported by Hyun et al[23] in a study in 259 patients with head and neck cancer and free flap reconstruction, further noting a greater likelihood of 5-year survival in patients with a high preoperative BMI. However, other studies in similar patient populations have not found BMI to be correlated with postoperative complications but have shown a higher incidence of venous thromboembolism in patients with a high BMI.[24-26] In the largest retrospective cohort study to date, comprising 1,921 patients, BMI was analyzed in 3 different groups of patients undergoing reconstruction (extremity, breast, and head and neck cancer), linking a high BMI to a greater risk of free flap failure in the breast reconstruction group (P = .004), with no significance in the head and neck cancer group.[13] Head and neck cancer patients tend to have a lower BMI than other patient groups owing to tumor localization–specific weight loss and cachexia, with few patients achieving high preoperative BMI values. This factor may reduce the importance of this variable in predicting postoperative complications compared with other cohorts. Our results showed a relatively low median BMI in our patient group (23.5), consistent with other published results.

A preoperative serum protein concentration of 62 g/L or less (P = .03; OR, 1.11) and a volume of albumin administered after surgery of 200 mL or greater (P = .015; OR, 1.31) showed strong associations with a rising rate of postoperative complications in our patient group. Tsai et al[27] analyzed 233 patients with advanced head and neck cancer and anterolateral thigh free flap reconstruction, showing that postoperative albumin values of less than 35 g/L showed a statistically significant association with the development of complications. They also found that preoperative hypoalbuminemia was associated with poor overall survival of patients. Another study has identified preoperative prealbumin serum levels as a possible measure of acute malnutrition, associated with overall survival.[28] The group of patients with poor nutrition at the time of surgery had a 3.9-fold increased risk of flap failure compared with patients with a normal nutritional status during the first postoperative month. No reports to date have discussed preoperative serum protein concentrations, giving additional importance to our results as possible predictors of outcome and enabling risk stratification for flap failure before surgery.

Most authors highlight the albumin value as an important measure of nutritional status, associated with early postoperative complications and overall patient survival. In our study, the preoperative albumin value was not associated with early postoperative outcomes, whereas a statistically significant association was found between preoperative total protein serum values and postoperative albumin administration, which further reinforces the well-established link between nutritional status and postoperative outcomes.

Head and neck cancer patients requiring free flap reconstruction have a higher complication rate and much longer hospitalization than patients undergoing other, more common procedures. Thus, the need to identify factors contributing to an adverse surgical outcome is evident. Our results emphasize the importance of a thorough evaluation of preoperative nutritional status in head and neck cancer patients to minimize postoperative complications while also identifying the specific cutoff values of clinical importance in estimating preoperative risk, as well as tailoring the type of reconstruction not only to the local extent of the lesion but also to the functional performance status of the patient.

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