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Neurotization of the Radial Forearm Free Flap Improves Swallowing Outcomes in Hemiglossectomy Defects

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Funding Source: None

Running Title: Neurotization hemiglossectomy swallowing

Key Words: hemiglossectomy, sensate radial forearm free flap, nerve graft, neurotization of free flap, oral cavity

Conflicts of Interest: None

ABSTRACT

Background

We examined the effect of free tissue neurotization on speech and swallowing outcomes for patients undergoing reconstruction of hemiglossectomy defects with a radial forearm free flap (RFFF).

Methods

A retrospective study was performed in patients with oral cavity squamous cell carcinoma undergoing a hemiglossectomy and reconstruction with a RFFF. Functional outcomes including nutritional mode, range of liquids and solids and speech understandability were analyzed one-year post-treatment.

Results

Eighty-four patients were included in this analysis, 41 of whom had neurotized flaps (49%). No significant differences in demographic or clinical variables were seen between the neurotized and non-neurotized groups. On multivariate analysis controlling for BMI, flap area, and N-classification, patients with neurotized flaps were significantly more likely to have normal range of liquids and solids and less likely to have a G-tube.

Conclusions

Neurotization of RFFF reconstructing hemiglossectomy defects results in decreased G-tube dependence and improved range of liquids and solids.

Introduction

A variety of approaches to optimize reconstruction of patients with hemiglossectomy defects resulting from oral cavity cancer have been proposed.[1-4] All of these aim to restore the oral function of speech and swallowing and improve quality of life, which is a known predictor of survival in patients with head and neck cancer and has recently been incorporated in measures of oncologic success.[5,6] The radial forearm free flap (RFFF) has remained the workhorse for reconstructive surgeons in the setting of hemiglossectomy defects, in part due to its thin, pliable tissue quality, long, reliable pedicle, and the ability to be neurotized with the antebrachial cutaneous nerve.[7]

Prognostic factors associated with functional outcomes in oral cavity reconstruction are multifactorial, including both intrinsic and extrinsic factors such as tumor size, remaining native tissue, and postoperative adjuvant therapy.[8] While these factors cannot be modified, reconstruction is aimed at optimally addressing the resultant loss of sensory and motor function. Sensate free tissue, both via nerve graft coaptation and spontaneous recovery, has been studied in anticipation that it may modify functional outcomes.[9-11] Objectively, sensation has been shown to be improved by utilization of a neurorrhaphy, most commonly with the medial or lateral antebrachial cutaneous nerve, to the lingual or inferior alveolar nerve.[12] However, its implication for functional recovery is less clear.[10,13]

Studies investigating the role of free tissue transfer neurotization on functional outcomes in head and neck cancer and specifically for those with hemiglossectomy defects are limited by small, heterogenous study populations. Our goal was to examine the effect of free tissue neurotization on long-term speech and swallowing outcomes for patients undergoing reconstruction of a hemiglossectomy defect with a RFFF.

Methods

Study population

A cross sectional retrospective case series was performed including patients over the age of 18 years old who were diagnosed with oral cavity squamous cell carcinoma (OCSCC) and underwent a hemiglossectomy (with or without floor of mouth and glossotonsillar sulcus resection) and reconstruction with a RFFF between January 2000 and February 2019 at Michigan Medicine. This study was approved by the University of Michigan IRBMED (HUM00050982). From the electronic medical record, we identified 84 patients who met these inclusion criteria and who had greater than one year of follow-up with functional data available for analysis. Patients who were reconstructed with multiple flaps, those with defects larger than a hemiglossectomy or flaps other than the RFFF, and those who recurred before 12 months were excluded.

Covariates and outcome measures

Data collection was performed by two study investigators. Clinical, oncologic, and reconstructive data, including preoperative body mass index (BMI), age, gender, tumor subsite, stage, adjuvant radiation therapy, total flap area, neurotization of free tissue transfer, and defect type were extracted from the electronic medical record. Neurotized flaps were harvested along with a branch of the antebrachial cutaneous nerve supplying the free flap skin paddle and neurorrhaphy was then performed to the transected lingual nerve. Patients were staged according to the American Joint Commission on Cancer (AJCC) 7th edition guidelines. Objective speech and swallowing outcomes were determined at approximately 12 months after the date of surgery. A modified Likert scale was utilized to collect these data (**Figure 1**).[8] Nutritional mode was graded as follows: complete tube feed dependence, combined oral intake and tube feeds, and oral intake alone. Range of liquids was graded as follows: no liquids by mouth, limited quantity of liquids by mouth, restricted range of liquid consistencies or bolus volume, and full range of liquids. Range of solids was graded as follows: no solids by mouth, pureed solids, soft solids, and full range of solids. Finally, understandability of speech was graded as follows: never understandable, difficult to understand, mostly understandable, and always understandable. At our institution, all patients undergoing hemiglossectomy with free flap reconstruction undergo speech-language pathology (SLP) evaluation at their first post-operative visit. Additional speech and swallowing therapy is rendered on an individualized basis guided by patients' needs. Thus, rates of SLP care is similar between our comparison groups.

Statistical analysis

Bivariate analysis was performed with t-tests or chi-square exact tests. Variables with trends for association ($p < 0.20$) with a speech or swallowing outcome were included for subsequent multivariable regression. The multivariate analysis was performed in two ways. First, conventional multivariable logistic regression was performed and hazard ratios were reported. For nutritional mode (G-tube dependence) and range of liquids (restricted), there were no events in the non-neurotized group. Therefore, a likelihood ratio test was also performed of nested multivariable models with and without neurotization included as a covariate to determine the effect, if any, of adding neurotization to the model predicting outcome. All statistical tests were conducted in SPSS version 26 (IBM) or SAS version 9.4 (Carey, NC).

Results

Eighty-four patients were included in this analysis, 41 of whom underwent a neurotized flap (49%). Patients presented at an average age of 55 years (± standard deviation 15 years) and had a male:female ratio of 1.6:1 (**Table 1**). The average preoperative BMI was 28 kg/m^2 (± standard deviation 5 kg/m^2). The cohort was dichotomized by T-classification with nearly half of the patients presenting with advanced (T3/4) tumors (46%, 39/84). The majority of patients were pN0 (58%, 49/84). Two-thirds of patients underwent adjuvant radiation therapy (66%, 55/84). There was no significant difference in these covariates between the neurotized and non-neurotized groups.

Swallowing outcomes were subsequently assessed and presented in **Figure 2A-C**. These data were then dichotomized and analyzed in **Table 2**. Neurotized patients were significantly more likely to have oral intake alone (100% [95% CI: (91,100)] vs 84% [95% CI: (69,93)] respectively (p = 0.002). Neurotized patients were significantly more likely to tolerate a full range of liquids (100% [95% CI: (91,100) vs 86% [95% CI: (72,95)] respectively (p = 0.004) and were significantly more likely to consume normal or minimally modified solid foods (90% [95% CI: (76,97)] vs 64% [95% CI: (48,78)] respectively (p = 0.005). Finally, speech understandability trended towards significance between the two groups with 72% (95% CI: 55,85) vs 51% (95% CI: 34,69) of patients being always understandable in the neurotized and non-neurotized groups, respectively (p = 0.07). (**Figure 3**)

Multivariable Modeling

Variables associated with a speech and swallowing outcome with a p value less than 0.2 were included in multivariable modeling. Conventional multivariable logistic regression was performed, and hazard ratios are reported, and a likelihood ratio test was also performed of nested multivariable models with and without neurotization included as a covariate to determine the effect, if any, of adding neurotization to the model predicting outcome (**Table 3**).

Nutritional Mode

Covariates included in the model for nutritional mode were age, T-classification, flap area, and neurotization. In a multivariable logistic regression, smaller flap area was significantly associated with oral intake alone (0.92 [95% CI 0.84 – 0.98] $p = 0.02$). For neurotization, there were no events (G-tube dependence) in the non-neurotized group and no hazard can be reported. A likelihood ratio test for the addition of neurotization to the multivariate model showed performing neurotization is significantly associated with improved oral intake ($p = 0.009$).

Range of Liquids

Covariates included in the model for range of liquids were age, flap area, and neurotization. In a multivariable logistic regression, there were no variables that were significantly associated with improved range of liquids. For neurotization, there were no events (restricted range of liquids) in the non-neurotized group and no hazard can be reported. A likelihood ratio test for the addition of neurotization to the multivariate model showed performing neurotization is significantly associated with improved range of liquids ($p = 0.01$).

Range of Solids

Covariates included in the model for range of solids were age, BMI, T-classification, flap area, radiation, defect type and neurotization. In a multivariable logistic regression, neurotization was significantly associated with improved range of solids (4.59 [95% CI 1.1 – 23.38] $p = 0.05$).

Younger age was also significantly associated with improved range of solids (0.92 [95% CI 1.0 – 1.37] $p = 0.01$). A likelihood ratio test for the addition of neurotization to the multivariate model showed performing neurotization is significantly associated with improved range of solids ($p = 0.02$).

Speech Understandability

Covariates included in the model for speech understandability were BMI, flap area, and neurotization. In a multivariable logistic regression, there were no variables that were significantly associated with improved speech understandability. However, a likelihood ratio test for the addition of neurotization to the multivariate model showed performing neurotization is significantly associated with improved speech understandability ($p = 0.04$).

Discussion

The primary objective of this study was to investigate the impact of neurotization on functional outcomes in patients with OCSCC undergoing a hemiglossectomy and reconstruction with a RFFF. Given the complex and multifactorial nature of functional outcomes, we chose to narrow our study to this patient population to control for the large variability seen in patients with OCSCC undergoing surgical treatment. We determined that after controlling for covariates, neurotization of free tissue results in consumption of an improved range of liquids and solids, decreased likelihood of G-tube dependence, and improved speech intelligibility at one year postoperatively.

In 1989, Urken *et al* first described the RFFF for use in head and neck reconstruction.[7] In this study, he describes the ease of dissection of the medial and lateral antebrachial cutaneous nerves which can be identified “in the subcutaneous tissue near the proximal portion of the radial forearm skin paddle" [7] and can subsequently be coapted to the lingual nerve. The theoretical basis to support this concept was borne out by Kapur *et al* who showed that oral anesthesia following regional nerve block results in inferior masticatory efficiency.[14] Poorer outcomes following neurorrhaphy have been described when a recipient nerve other than the lingual or inferior alveolar nerve is utilized.[12] In our experience, neurotization does not result in increased risk of donor site morbidity for the patient or significant change in operative time. At the time of resection, it is important that the surgeon take care not to utilize electrocautery in transection of the lingual nerve to limit more proximal thermal injury and jeopardize the success of the neurorrhaphy.

Several objective measures have been examined to determine the success of neurotization of free tissue. These include light touch, 2-point discrimination, temperature, and pain sensation.[10,12] Boyd *et al* showed that in all domains tested, the neurotized flap outperformed the non-neurotized flap and was not statistically different in performance from the native side of the tongue.[15] The degree of recovery is, however, diminished by postoperative radiation therapy.[12] While these measures are critical when comparing techniques, they do not address important functional outcomes.

Despite being first discussed nearly three decades ago, the value of neurotized free tissue on functional outcomes after oral cavity reconstruction still remains controversial. A recent systematic review evaluating 271 total tongue reconstructions did not find sufficient data to support a clear relationship with improved functional outcomes.[9] The inability to find a strong conclusion was in part due to the heterogeneity of the population. As such, we chose to limit our patient population to those with up to a hemiglossectomy defect reconstructed with a RFFF. In part, we utilized this methodology to exclude those patients who had small enough defects that were amenable to primary closure and large enough defects to necessitate a bulkier flap choice. We found that patients with a neurotized flap were significantly less likely to be G-tube dependent, more likely to have an improved range of both liquids and solids and have improved speech understandability. This finding persisted after controlling for BMI, flap area, and T-classification, which are surrogates for preoperative nutritional status, defect size, and extent of disease.

There were no patients in the neurotized group that required any degree of G-tube dependence at one year. This finding has significant implications for both healthcare costs and impact on patient quality of life.[16,17] Within the elderly population, one study estimated that one year of feeding via G-tube resulted in more than $30,000 in costs, placing a significant burden on the healthcare system.[16] Several studies have confirmed that long-term G-tube use has a detrimental effect on quality of life for patients with head and neck cancer, not only due to physical problems such as discomfort or leakage, but also as it relates to one's ability to engage in intimate relationships and hobbies.[18] Any opportunity to decrease the rate of long-term G-tube dependence in a population already at high risk for depression and psychosocial distress is critical.[19,20]

Speech understandability was significantly affected by neurotization of the RFFF in multivariate analysis, although a considerable proportion of patients in both the neurotized (28%) and non-neurotized (49%) groups had some degree of difficulty in understandability. While significantly different, this finding was not as strongly correlated to neurotization as the swallowing functional outcomes. We postulate that speech outcomes may be more appreciably affected by tongue elevation than sensation, and further research in this area will be necessary.[8]

In this study, we chose to evaluate only the RFFF to homogenize our cohort. However, there are other donor sites in which neurotization is possible including the anterolateral thigh, lateral arm, and rectus abdominis musculocutaneous free flaps, all of which are employed for glossectomy defects of various sizes.[21-23] Some of these options may be utilized for larger, subtotal and total glossectomy defects. In these instances, it is possible that neurotization may prove to be even more important due to a proportionally larger loss of mucosa within the oral cavity, but this will require further study.

This study is limited by the retrospective nature of data collection. Speech-language pathology notes were utilized to collect functional outcomes when available but often did not contain more granular information regarding tolerance of temperatures or spiciness. Further, there was a higher proportion of missing data for speech understandability (n = 10, 12.0 %) than outcomes of nutritional mode and range of solids and liquids. Additionally, objective data such as 2-point discrimination could not be determined in this patient population. Although attempts were made to create a homogenous cohort, there remain patients with varying sized defects which could have impacted outcomes. Finally, the decision to perform a nerve graft is surgeon-dependent, introducing inherent bias in the cohort.

Conclusions

The RFFF remains the primary choice for reconstruction of hemiglossectomy defects and can easily be neurotized when utilized in this manner. Neurotization results in decreased G-tube dependence, improved consumption of liquids and solids, and improved speech understandability.

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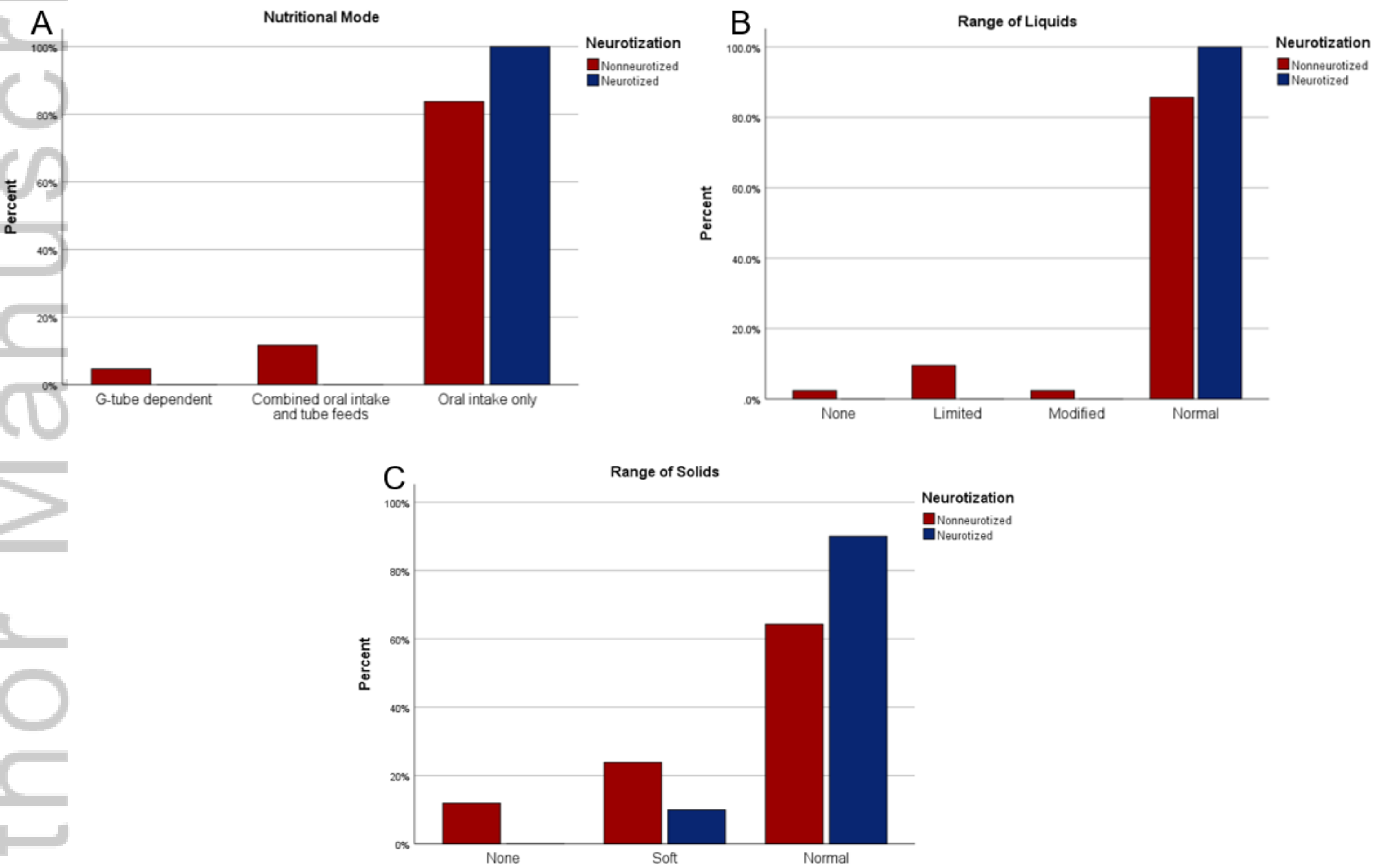
FIGURE LEGENDS:

Figure 1. Modified Likert scale utilized to measure functional outcomes.

Figure 2. Swallowing outcomes (A) Nutritional mode by neurotization (B) Range of liquids by neurotization (C) Range of solids by neurotization.

Figure 3. Speech outcomes by neurotization.



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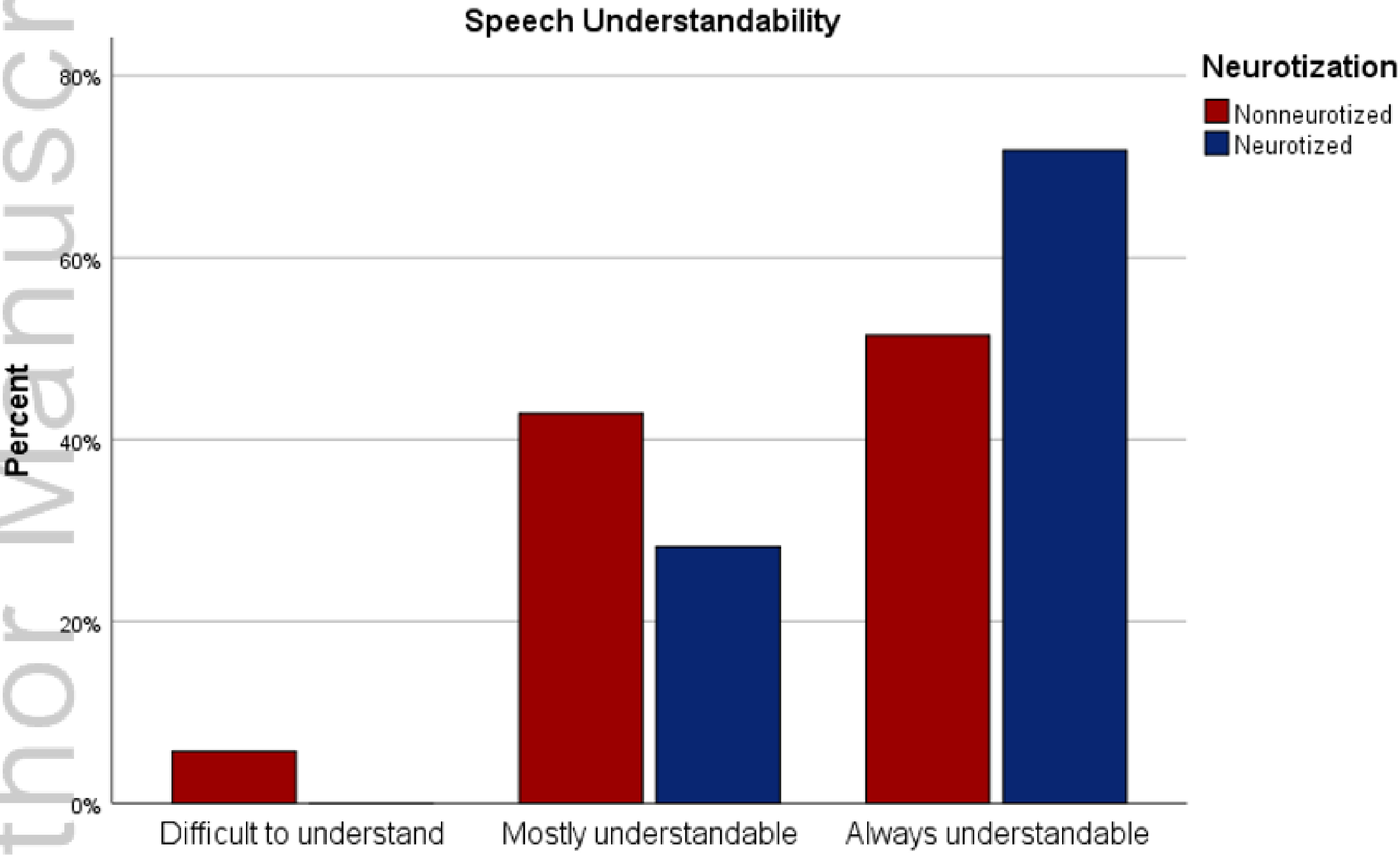

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Nutritional mode

1. Nothing by mouth; G-tube dependent
2. Combined oral and tube feeds
3. Oral intake alone

Range of liquids

1. No liquids by mouth
2. Limited quantity of liquids by mouth
3. Restricted range of liquid consistencies or bolus volume
4. Full range of liquids; no restrictions

Range of solids

1. No solids
2. Pureed solids
3. Soft solids
4. Full range or minimally restricted solids

Understandability of speech

1. Never understandable
2. Difficult to understand; may need face-to-face contact
3. Mostly understandable; occasional repetition necessary
4. Always understandable

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Table 1. Clinicopathologic Patient Characteristics.

	Cohort (No. of patients = 84)	Neurotized (No. of patients = 41)	Non-neurotized (No. of patients = 43)	*p* value
Age, years	55 (±15)	53 (±14)	56 (±15)	0.3
Gender, male	62 (52)	61 (25)	63 (27)	0.9
BMI, kg/m^2	28 (±5)	29 (±5)	27.3 (±5)	0.2
Flap area, cm^2	39 (±14)	37 (±11)	42 (±16)	0.1
Adjuvant radiation	66 (55)	68 (28)	63 (27)	0.6
T-classification				0.7
Early (T1/T2)	54 (45)	56 (23)	51 (22)	
Late (T3/T4)	46 (39)	44 (18)	49 (21)	
N-classification				0.2
N0	58 (49)	51 (21)	35 (15)	
N-positive	42 (35)	49 (20)	65 (28)	
Defect Type				0.5
Hemiglossectomy	25 (21)	23 (10)	27 (11)	
Hemiglossectomy with Floor of Mouth	50 (42)	56 (24)	44 (18)	
Hemiglossectomy with Floor of Mouth and Glossotonsillar sulcus	25 (21)	21 (9)	29 (12)	

Data are presented as mean (±SD) or no. of patients (%). Patients were staged according to the AJCC 7th edition guidelines

Table 2. Functional Outcome Measures. Data are presented as mean (±SD) or no. of patients (%).

	Cohort (No. of patients = 84)	Neurotized (No. of patients = 41)	Non-neurotized (No. of patients = 43)	*p* value
Nutritional mode				**0.002**
Any tube feed	8 (7)	0.0 (0)	17 (7)	
Oral intake only	92 (77)	100 (41)	84 (36)	
Range of liquids				**0.004**
Any restriction	7 (6)	0.0 (0)	14 (6)	
Normal	93 (36)	100 (40)	86 (36)	
Missing	(2)			
Range of solids				**0.005**
Any restriction	23 (19)	10 (4)	36 (15)	
Normal	75 (63)	90 (36)	64 (27)	
Missing	(2)			
Speech understandability				0.07
Any difficulty	38 (28)	28 (11)	49 (17)	
Always understandable	62 (46)	72 (28)	51 (18)	
Missing	(10)			

Table 3. Multivariable Regression for Swallowing and Speech Outcomes

Variable		Nutritional Mode		Range of Liquids		Range of Solids		Speech Understandability	
	unit	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Neurotization	Neurotized	--		--		4.59 (1.10 – 23.38)	0.05	2.18 (0.77 – 6.11)	0.1
	Non-neurotized	--		--		ref		ref	
Age	Years	0.89 (0.77, 0.98)	0.07	0.93 (0.84, 1.01)	0.12	0.92 (1.00, 1.37)	0.01		
BMI	kg/m^2					1.16 (0.99 – 1.31)	0.06	1.05 (0.95 – 1.16)	0.4
T-classification	Late	0.05 (0.001, 0.66)	0.07			0.29 (0.06, 1.29)	0.11		
	Early	ref				ref			
N-classification	N-positive								
	N0								
Flap area	cm^2	0.92 (0.84, 0.98)	0.02	0.97 (0.92 – 1.02)	0.25	0.96 (0.91 – 1.01)	0.09	0.96 (0.92 – 1.00)	0.06
Defect Type	Tongue + FOM + GTS					0.48 (0.04, 4.47)	0.67		
	Tongue + FOM					0.47 (0.04, 4.22)	0.64		
	Tongue	ref				ref			
Radiation Therapy						0.18 (0.02, 1.07)	0.08		
LRT for neurotization			**0.009**		**0.01**		**0.02**		**0.04**

Abbreviations: LRT = Likelihood Ratio Test (chi-square, 1 degree of freedom); BMI = body mass index; FOM=Floor of Mouth; GTS=Glossotonsillar sulcus.