Smell and taste impairment after total laryngectomy

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Abstract

Objective. Aim of this observational study is the evaluation of olfactory and gustatory impairments in laryngectomized long-term survivors, comparing to control subjects. Correlation between smell and taste alterations, age and previous adjuvant treatments in laryngectomees was investigated.

Methods. Fifty control subjects and 50 patients who underwent total laryngectomy for advanced laryngeal carcinoma were evaluated. All subjects underwent symptoms evaluation, oropharyngeal exam, endoscopic fiber optic nasal examination, Taste Strips and Sniffin' Sticks tests.

Results. Hyposmia was reported by all laryngectomees and hypogeusia by 54% of patients. Sniffin' Sticks and Taste Strips tests demonstrated a statistically significant difference between controls and laryngectomees regarding olfactory threshold, odor discrimination and identification, TDI score, sour, salty and gustatory Total Taste score ($p<0.05$). Multivariate analysis for Total Taste score in laryngectomees showed a statistically significant correlation with aging, having an Odds Ratio of 0.127 for age ≥65 years, but not with TDI score, radiotherapy and follow-up time; whereas multivariate analysis for TDI score demonstrated no correlation with radiotherapy, age and follow-up time.

Conclusions. Total laryngectomy determines olfactory and gustatory impairments that should be taken into account in clinical practice. Relationships between sensorial alterations, aging, follow-up period and adjuvant treatments should be further evaluated in prospective studies.

Key words: Smell; Sniffin' sticks; Taste; Laryngectomy; Gustatory disorders; Olfactory disorders.

Introduction

Complete separation of upper and lower respiratory tract after total laryngectomy results in permanent effects on nasal cavities and tracheo-bronchial airways. In laryngectomees the air comes directly into trachea and nasal cavities are excluded from respiration and cannot carry out their physiological functions, such as filtering, heating and moistening of the inspired air and smell. Therefore hyposmia, impaired mucociliary function, cytological and histological alterations of nasal mucosa arise.[1-4] Currently, it is considered that total laryngectomy may cause olfactory changes due to loss of nasal airflow, as well as changes in the epithelial structure of nasal mucosa.[5,6]

Hypogeusia is also reported by laryngectomees.[7,8] Very few studies evaluated taste disorders and their relationships with smell and aging in laryngectomees.[7,9,10] Previous studies focused on smell disorders of these patients.[4]

The aim of this retrospective observational study was to evaluate sensorial impairments, by the means of standardized tests, as Sniffin' Sticks and Taste Strips, in laryngectomized long-term survivors, comparing to control subjects. Furthermore, correlation between smell and taste alterations, age and adjuvant treatments in laryngectomees was investigated.

Materials and methods

In this retrospective observational study, 50 control subjects and 50 long-term survivor patients who underwent total laryngectomy for advanced laryngeal carcinoma between 2003 and 2013 at our Division were enrolled. All laryngectomees included in the study were disease free at the time of engagement. Exclusion criteria were: chemotherapy or radiotherapy for second tumors or relapses, neurological diseases (i.e. degenerative and vascular diseases), use of drugs or occupational exposure to substances which could determinate gustatory and/or olfactory alterations, clinical evidence of infectious diseases involving oral and nasal cavities. Enrolled patients had at least a 2-year follow-up period (mean 61.96 ± 43.41 months, range 24-132 months) in order to evaluate stabilized late adverse effects.

Laryngectomees who satisfied the inclusion criteria were informed about the study: 50 out of 53 (94%) alive patients accepted to participate. The control group consisted of patients with vocal fold Reinke's edema and without any disease interfering with taste and smell, except for high prevalence of smoke, similar to cancer patients. All patients gave their informed consent prior to their inclusion in the study. Institutional Review Board approval was obtained. Some of the laryngectomees were previously evaluated for nasal and tracheal microbial colonization and cytology at our Department.[11,12]

All subjects underwent symptoms evaluation (rhinorrea, hyposmia, hypogeusia), oropharyngeal exam and endoscopic fiber optic nasal examination. Gustatory and olfactory impairments were investigated with Taste Strips and Sniffin' Sticks tests.[13,14]

Taste Strips test (Burghart Messtechnik, Wedel, Germany) was based on filter paper strips, impregnated with tastant (4 concentrations each of the 4 basic taste qualities). The following concentrations were used: sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose; sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid; salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride; bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride. The strips were placed on the anterior third of the tongue. Before each administration of a strip, the mouth was rinsed with water. The tastes were presented in increasing concentrations and taste qualities were applied in a randomized fashion at each of the four levels of concentration. Patients had to identify the taste from a list of five descriptors: sweet, sour, salty, bitter and no taste (multiple forced-choice). To obtain an impression of overall gustatory function, the number of correctly identified tastes was added up to a “Total Taste score”. A taste score inferior to 12 is consistent with hypogeusia. Two interposed tasteless strips were used but they were not a component of the final score.[14]

Sniffin' Sticks test (Burghart Messtechnik, Wedel, Germany) was based on pen-like odor dispensing devices and consisted of three tests of olfactory function, namely tests for odor threshold, odor discrimination and odor identification.[13,15] Non-lateralized measures were used in the present analysis. Odor thresholds for n-butanol were assessed using a single-staircase of 16 dilutions, starting from a 4% n-butanol solution, with a three alternative forced-choice procedure. Three pens were presented in a randomized order, with two containing the solvent and the third the odorant. Subjects had to identify the odor-containing pen. Reversal of the staircase was triggered when the odor was correctly identified in two successive trials. Threshold was defined as the mean of the last four of seven staircase reversals. In the odor discrimination task, again using a three alternative forced-choice procedure, 16 triplets of pens were presented in a randomized order, with two containing the same and one a different odorant. Subjects had to determine which of three pens had the different odor. Odor identification was assessed for 16 common odors. Using a multiple choice task identification of individual odors was performed from lists of four descriptors each. Discrimination and identification results were reported as number of correct answers. Results of the three subtests were presented as a composite "TDI (Threshold Discrimination Identification) score", which was the sum of threshold, and correct answers in discrimination and identification subtests. A TDI score inferior to 30 is consistent with hyposmia.[16] No laryngectomized patient used nasal airflow-inducing maneuvre during testing.

All statistical analyses were carried out using Statistical Package for Social Sciences (SPSS), version 17.0. A descriptive analysis of all data was performed and they were reported as means or percentages and standard deviations. Since the Kolmogorov-Smirnov test demonstrated a non-Gaussian distribution of variables, nonparametric tests were used.

Differences between groups in the mean of continuous variables were assessed by the Mann-Whitney U-test. Linear association between variables (univariate analysis) was measured by the Bivariate Correlations procedure with Spearman's correlation coefficient. Logistic regression with Odds Ratios (OR) and its 95% Confidence Interval (95% CI) was used to perform multivariate analysis. A p value less than 0.05 was considered statistically significant.

Results

Mean age was 65.75 ± 8.76 years (range 53-76 years) for the control group and 67.54 ± 7.02 years (range 50-83 years) for laryngectomees. Table 1 shows socio-demographic and clinical characteristics, such as age and sex, tobacco, alcohol consumption, and allergies, and tumor related factors, such as histological type, TNM classification, grade, and stage. There were no clinical or demographic differences between controls and laryngectomees ($p>0.05$).

Bilateral selective neck dissection, associated to total laryngectomy, was performed in all patients. In 14% of cases total laryngectomy was performed as salvage surgery for local recurrence: in 4 patients after a previous laser cordectomy and in 3 patients after a partial supracricoid laryngectomy. Adjuvant radiation therapy (RT) or chemo-radiotherapy (CT-RT) was administrated in 16 and 4 patients respectively, because of histopathological adverse features (extracapsular nodal spread, positive margins, pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism).

Concerning symptoms evaluation, anterior rhinorrhea was reported by 56% of laryngectomees, hyposmia by all laryngectomees and hypogeusia by 54% of patients. At fiber optic endoscopic evaluation, the main findings were turbinate hypertrophy (36%), pale nasal mucosa (42%) and serous nasal secretions (72%). Polypoid degeneration of nasal mucosa was seen in one case (2%). No statistically significant difference regarding nasal endoscopic findings was observed between laryngectomees and controls ($p>0.05$). Concerning objective examination of oral cavity, no hyperemic mucosa was observed (presence of mucositis was an exclusion criterion). Table 2 reports symptoms and endoscopic findings of laryngectomees and controls. No specific treatment for nasal and/or oral complaints was reported by patients. No endoscopic finding of acute or chronic rhinosinusitis was observed. No laryngectomee had tracheal cannula and/or tracheo-esophageal voice prostheses.

Sniffin' Sticks and Taste Strips tests demonstrated a statistically significant difference between controls and laryngectomees regarding olfactory threshold, odor discrimination and identification, TDI score, sour, salty and Total Taste score ($p<0.05$; Table 3 and Figure 1). Sweet and bitter tastes were only slightly impaired, without significant differences compared to controls with a similar age ($p>0.05$).

Analyzing olfactory and gustatory data of the entire sample of laryngectomees, no statistically significant correlation with physical findings (turbinate hypertrophy, pale mucosa, nasal secretions) has been found ($p>0.05$). Moreover, univariate analysis showed a statistically significant correlation between age and sensorial alterations (olfactory threshold, odor discrimination and identification, TDI score, gustatory total score) ($p<0.05$; Table 4) with a weak negative correlation (Spearman's rho between -0.393 and -0.222). Significant correlation between olfactory and gustatory functions was present in the control group. No statistically significant correlations between sensorial alterations and follow-up time and between olfactory and gustatory impairments were observed ($p>0.05$). No statistically significant correlation between age and follow-up time was present ($p>0.05$), so we could exclude differences in follow-up period as a bias.

Multivariate analysis for Total Taste score in laryngectomees showed a statistically significant correlation with aging, having an Odds Ratio of 0.127 for age ≥65 years (laryngectomees ≥65 years have a 7.87-fold risk to present a taste impairment, compared to those with less than 65 years). No statistically significant difference was observed analyzing TDI score, radiotherapy and follow-up time (Table 5). Multivariate analysis for TDI score in laryngectomees demonstrated no correlation with radiotherapy, age and follow-up time (Table 6). Smoking and chemotherapy was not considered in statistical analysis due to very small number of non-smokers (2 cases) and patients who received chemotherapy (4 cases).

Discussion

Total laryngectomy still represents a fundamental treatment for advanced laryngeal cancer. Permanent changes of airflow in nasal cavities and trachea, due to complete separation of upper and lower airways, result in loss of physiological nasal functions and presence of "unconditioned" inspired air in lower airways. Therefore, laryngectomees have olfactory impairments and often report gustatory alterations. In literature there are very few studies concerning taste changes after total laryngectomy and their relationship with smell and other factors, such as aging, radiotherapy and follow-up period.[7,9,10] In this study we reported olfactory and gustatory alterations of laryngectomees, by means of standardized tests, with a specific focus to possible confounding factors.

Hyposmia in laryngectomees is due to loss of nasal airflow and alterations of olfactory mucosa. Caldas, Facundes et al. reported that 88% of laryngectomees had hyposmia.[7] Olfactory acuity evaluated by Jet Stream Olfactometer, which spray odorants on olfactory epithelium, worsens 3 months post-operatively, while it recovers after 6 months.[17] Since hyposmia in laryngectomees is related to loss of nasal airflow, Hilgers et al. developed a nasal airflow-inducing maneuvre, the "polite yawning" technique, to be applied in the olfactory rehabilitation of laryngectomees. The technique is based on the repeated generation of a negative pressure in the oral cavity by simultaneously lowering the jaw, the floor of the mouth and the tongue with close lips. This maneuvre allowed about one-half of the laryngectomees to recover their sense of smell.[18] The impossibility to restore normal discrimination of olfactory function in all laryngectomees, in spite of restored airflow in the olfactory cleft, could be due to a damage to the neuroepithelial structure. Moreover, an abundant hyaline layer, showing heterogeneous positivity to both Alcian blue and PAS reaction, covers the tissue surface. This hyaline layer seems to be a result of the demolition of epithelium and Bowman's gland, rather than hypersecretion.[5]

In our study laryngectomees reported subjective hyposmia in 100% of cases and TDI score was greatly impaired (9.94 ± 7.88), compared to controls (32.42 ± 5.53). A TDI score less than 30 is considered significant for hyposmia.[13] Moreover, olfactory threshold, odor discrimination and identification were all impaired. The absence of statistically significant correlation with physical findings (turbinate hypertrophy, pale mucosa, nasal secretions) suggested that main causative factors for hyposmia are loss of nasal airflow and alterations of olfactory mucosa.

Hypogeusia is another complaint in laryngectomees, but it is still less investigated. Caldas et al. demonstarated that gustatory impairment evaluated by means of Taste strips was present in 80% of laryngectomees; bitter flavor showed no significant difference compared to a control group.[7] Gustatory alterations may be considered as a consequence of changes in smell.[19] Taste and smell intimately interact and this is reflected in patients with chemosensory dysfunction. Chemical senses seem to have no compensatory mechanisms, but rather mutual weakening, in contrast to other sensory modalities.[20] Gustatory and olfactory fibers are not intermingled at a peripheral level, thus hypogeusia after acquired smell disorders is probably due to central nervous changes. Amygdale, thalamus, insula and orbitofrontal cortex represent the most likely candidate regions.[20] Moreover, taste impairments are common in patients who underwent radiation and/or chemotherapy for head and neck malignancies and different alterations for specific tastes are reported in literature.[21-24] Fernando et al. showed a correlation between objective and subjective gustatory disorders and irradiated tongue volumes.[25] Radiation therapy determines a disappearance of taste buds, but not a damage to the taste nerves.[26-28] Furthermore, it is important to consider that chemotherapy may induce sensorial side effects. However, taste and smell alterations are generally transient after chemotherapy.[29]

Our laryngectomees reported subjective hypogeusia in 54% of cases, while Total Taste score at Taste strips was significantly lower (7.76 ± 3.11) compared to controls (11.56 ± 2.35). Sweet and bitter tastes were only slightly impaired, without significant differences compared to controls. We did not considered previous chemotherapy in statistical analysis due to very small number of patients who received chemotherapy (4 cases).

Cigarette smoking represents the main risk factor for laryngeal cancer and it is also associated with olfactory epithelium degeneration, destruction of taste buds, and neuronal damage, which may result in hyposmia and hypogeusia.[30,31] This finding should be considered in future studies, since this habit is significantly more frequent in the laryngectomees. We did not considered smoking in statistical analysis due to very small number of non-smokers (2 cases). However, we chose a control group with an high prevalence of smoking habits in order to avoid this bias.

Interesting relationships emerged from univariate and multivariate analysis of taste, smell and possible confounding factors in laryngectomees. Univariate analysis showed a significant correlation between sensorial scores (smell and taste) and laryngectomees' age, but not with follow-up period. Correlation with age was confirmed by multivariate analysis only for taste. No statistically significant correlation was observed for radiotherapy and follow-up period. Moreover, no statistically significant correlation was seen between taste and smell at univariate and multivariate analysis, as opposed to controls.

Concerning radiation therapy, nasal cavities are excluded from the radiated areas in all cases. Therefore, radiotherapy did not cause dysfunction of olfactory nerves. Similarly, radiation therapy did not impaired gustatory function.

The absence of correlation with age and follow-up period allows us to hypothesize that olfactory alterations are strictly related to total laryngectomy and post-operative loss of nasal airflow. Therfore, laryngectomees could not perceive possible smell worsening due to aging. It could be interesting to perform Sniffins' stick during nasal airflow-inducing maneuvre in future studies, to evaluate aging effects on olfactory function. On the contrary, age at total laryngectomy influences taste scores in these patients; however, no statistically significant correlation with follow-up period was observed. Therefore, we could hypothesize that post-operative taste impairment is probably related to pre-operative function and age of patients at total laryngectomy. In fact, we observed a worse gustatory function in older patients. Further prospective studies are needed to confirm or not these hypotheses.

Conclusions

Total laryngectomy determines olfactory and gustatory impairment that could compromise patients' quality of life and food intake. In clinical practice, it is relevant to evaluate these sensory functions and to develop rehabilitation programs for this population. In fact, smell and taste alterations may trigger changes in eating habits and impact food-related pleasure and nutritional status of these subjects. Relationships between sensorial alterations, aging, follow-up period and adjuvant treatments should be further evaluated in prospective studies.

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Tables

Table 1. Patients and tumor characteristics (Mann-Whitney U-test).

Characteristic	Number of subjects (%) Laryngectomees	Control group	p value
Sex			
Male	43 (86)	40 (80)	*0.215*
Female	7 (14)	10 (20)	
Smoker or former smoker			
Yes	48 (96)	45 (90)	*0.121*
No	2 (4)	5 (10)	
Previous alcohol consumption			
Yes	42 (84)	40 (80)	*0.302*
No	8 (16)	10 (20)	
Allergies			
Yes	4 (16)	12 (24)	*0.159*
No	21 (84)	38 (76)	
Tumor site			
Supraglottic larynx	14 (28)	-	
Glottic larynx	34 (68)	-	
Subglottic larynx	2 (4)	-	
Histological type			
Squamous cell carcinoma	50 (100)	-	
Tumor (pTNM VI ed.)			
T1	0 (0)	-	
T2	6 (12)	-	
T3	32 (64)	-	
T4	12 (24)	-	
Nodes (pTNM VI ed.)			
N0	32 (64)	-	
N1	8 (16)	-	
N2	10 (20)	-	
N3	0 (0)	-	
Distant Metastasis (pTNM VI ed.)			
M0	50 (100)	-	
M1	0 (0)	-	
Grade			
G1	2 (4)	-	
G2	14 (28)	-	
G3	34 (68)	-	
Stage			
I	0 (0)	-	
II	2 (4)	-	
III	26 (52)	-	
IV	22 (44)	-	

Table 2. Symptoms and objective findings for laryngectomees and controls (Mann-Whitney U-test).

Characteristic	Number of subjects (%)		p value
	Laryngectomees	Control group	
Symptoms			
Rhinorrea			
Anterior	28 (56)	10 (20)	***0.015***
Posterior	4 (8)	3 (6)	*0.426*
Hyposmia			
Yes	50 (100)	3 (6)	***0.001***
No	0 (0)	47 (94)	
Hypogeusia			
Yes	27 (54)	1 (2)	***0.012***
No	23 (46)	49 (98)	
Endoscopic findings - Nasal cavities			
Nasal septal deviation			
Yes	36 (72)	37 (74)	*0.447*
No	14 (28)	13 (26)	
Turbinates			
Hypertrophic	18 (36)	15 (30)	*0.201*
Normotrophic	30 (60)	35 (70)	
Atrophic	2 (4)	0 (0)	
Nasal mucosa			
Pale	21 (42)	11 (22)	*0.392*
Pink	29 (58)	39 (78)	
Hyperemic	0 (0)	0 (0)	
Secretions			
Dry nose	10 (20)	1 (2)	*0.456*
Serous	36 (72)	45 (90)	
Thick	4 (8)	4 (8)	
Purulent	0 (0)	0 (0)	
Polypoid degeneration of mucosa			
Yes	1 (2)	0 (0)	*0.438*
No	49 (98)	50 (100)	
Objective examination - Oral cavity			
Oral mucosa			
Pink	50 (100)	50 (100)	*0.500*
Hyperemic	0 (0)	0 (0)	

Table 3. Sniffin' Sticks and Taste Strips scores for laryngectomees and controls (Mann-Whitney U-test).

Characteristics	Mean score ± standard deviation Laryngectomees	Control group	p value
Sniffin' Sticks			
Threshold	1.42 ± 0.91	8.01 ± 2.36	***0.023***
Discrimination	3.88 ± 2.91	11.98 ± 2.82	***0.018***
Identification	5.04 ± 4.32	12.43 ± 1.99	***0.017***
TDI score	9.94 ± 7.88	32.42 ± 5.53	***0.010***
Taste Strips			
Sweet	2.48 ± 1.07	3.20 ± 0.73	*0.481*
Bitter	2.56 ± 1.15	2.65 ± 0.80	*0.709*
Sour	1.56 ± 1.15	2.69 ± 0.62	***0.036***
Salty	1.16 ± 1.13	3.02 ± 0.93	***0.041***
Total score	7.76 ± 3.11	11.56 ± 2.35	***0.021***

TDI = Threshold Discrimination Identification score

Table 4. Spearman's rho correlation (univariate analysis) in laryngectomees and control group.

	Laryngectomees		Control group	
	p value	Correlation coefficient	p value	Correlation coefficient
Total Taste score / TDI score	*0.327*	*0.141*	***0.029***	***0.258***
Total Taste score / Odor Threshold	*0.180*	*0.193*	***0.008***	***0.312***
Total Taste score / Odor Discrimination	*0.144*	*0.210*	***0.034***	***0.264***
Total Taste score / Odor Identification	*0.710*	*0.054*	***0.046***	***0.196***
Total Taste score / Age	***0.022***	***-0.222***	***0.013***	***-0.368***
TDI score / Age	***0.010***	***-0.362***	***0.009***	***-0.403***
Odor Threshold / Age	***0.018***	***-0.332***	***0.037***	***-0.275***
Odor Discrimination / Age	***0.047***	***-0.282***	***0.030***	***-0.294***
Odor Identification / Age	***0.005***	***-0.393***	***0.008***	***-0.416***
Total Taste score / Follow-up	*0.798*	*-0.265*	-	
TDI score / Follow-up	*0.644*	*-0.297*	-	
Odor Threshold / Follow-up	*0.854*	*-0.356*	-	
Odor Discrimination / Follow-up	*0.317*	*-0.292*	-	
Odor Identification / Follow-up	*0.983*	*-0.403*	-	

TDI = Threshold Discrimination Identification score

Table 5. Multivariate analysis (logistic regression) for Total Taste score in laryngectomees.

	Total Taste score < 8	Total Taste score ≥ 8	p value	OR (95% CI)
TDI score				
≥ 10	10	12	*0.187*	*0.421 (0.117 - 1.520)*
< 10	18	10		
Radiotherapy				
Yes	12	8	*0.929*	*0.940 (0.244 - 3.624)*
No	16	14		
Age				
≥ 65 years	16	20	***0.017***	***0.127 (0.023 - 0.691)***
< 65 years	12	2		
Follow-up				
≥ 5 years	14	12	*0.947*	*0.957 (0.957 - 3.505)*
< 5 years	14	10		

OR = Odds Ratio; ***CI*** = Confidence Interval; ***TDI*** = Threshold Discrimination Identification score

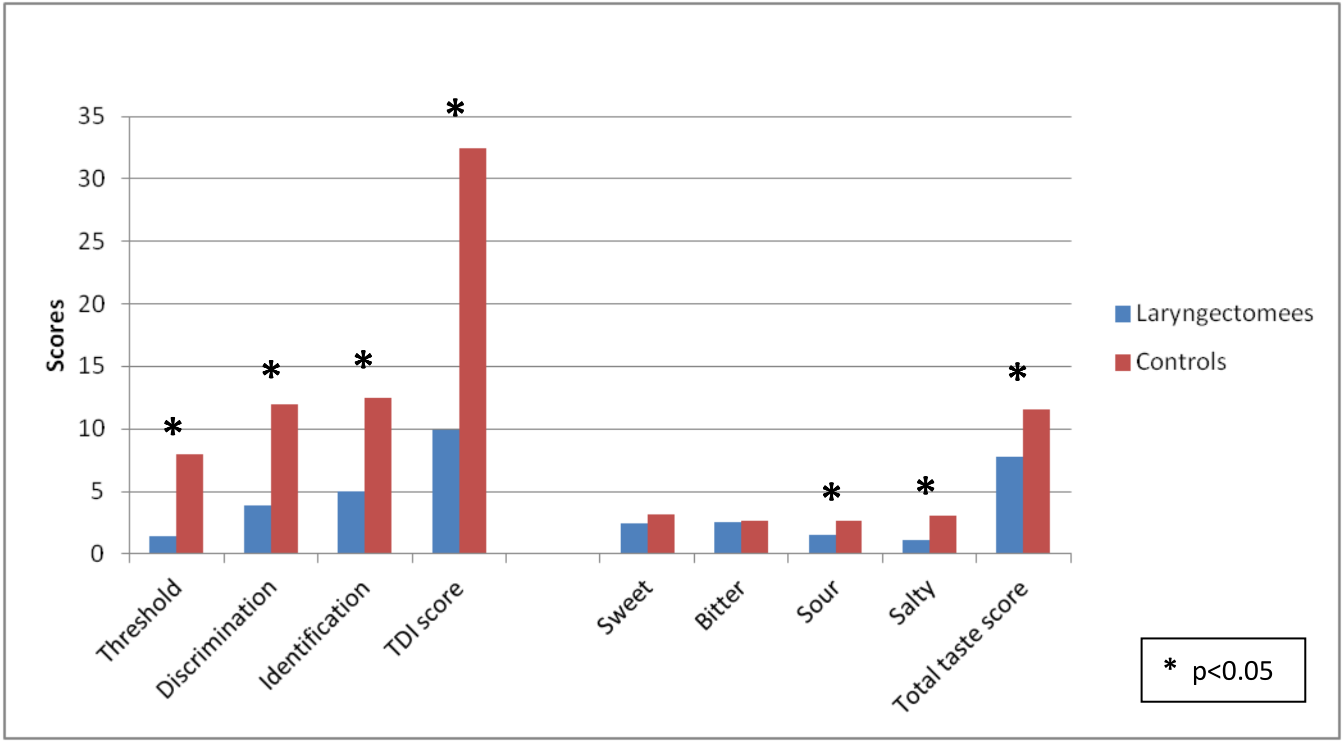
Table 6. Multivariate analysis (logistic regression) for TDI score in laryngectomees.

	TDI score < 10	TDI score ≥ 10	p value	OR (95% CI)
Radiotherapy				
Yes	12	8	*0.561*	*0.699(0.209 - 2.341)*
No	16	14		
Age				
≥ 65 years	20	16	*0.983*	*0.986 (0.279 - 3.486)*
< 65 years	8	6		
Follow-up				
≥ 5 years	14	12	*0.638*	*0.752 (0.229 - 2.468)*
< 5 years	14	10		

OR = Odds Ratio; ***CI*** = Confidence Interval; ***TDI*** = Threshold Discrimination Identification score

Figure legends.

Figure 1. Sniffin' Sticks and Taste Strips scores for laryngectomees and controls (Mann-Whitney U-test).



Scores
35
30
25
20
15
10
5
0
Threshold
Discrimination
Identification
TDI score
Sweet
Bitter
Sour
Salty
Total taste score
Laryngectomees
Controls
* p<0.05